Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Collaborators' Meeting

29/30th June 2020

Agenda

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1. Introductions
2. Update on progress
3. Hydroxychloroquine
4. Dexamethasone
5. Lopinavir-ritonavir
6. Future plans
7. Q&A

Introductions

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- One of the central study team will talk to the agenda
- If you have questions please enter them into the “Q&A” on the right side of your screen.
- Questions may be answered directly or to the whole group

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PROGRESS UPDATE

Current trial design

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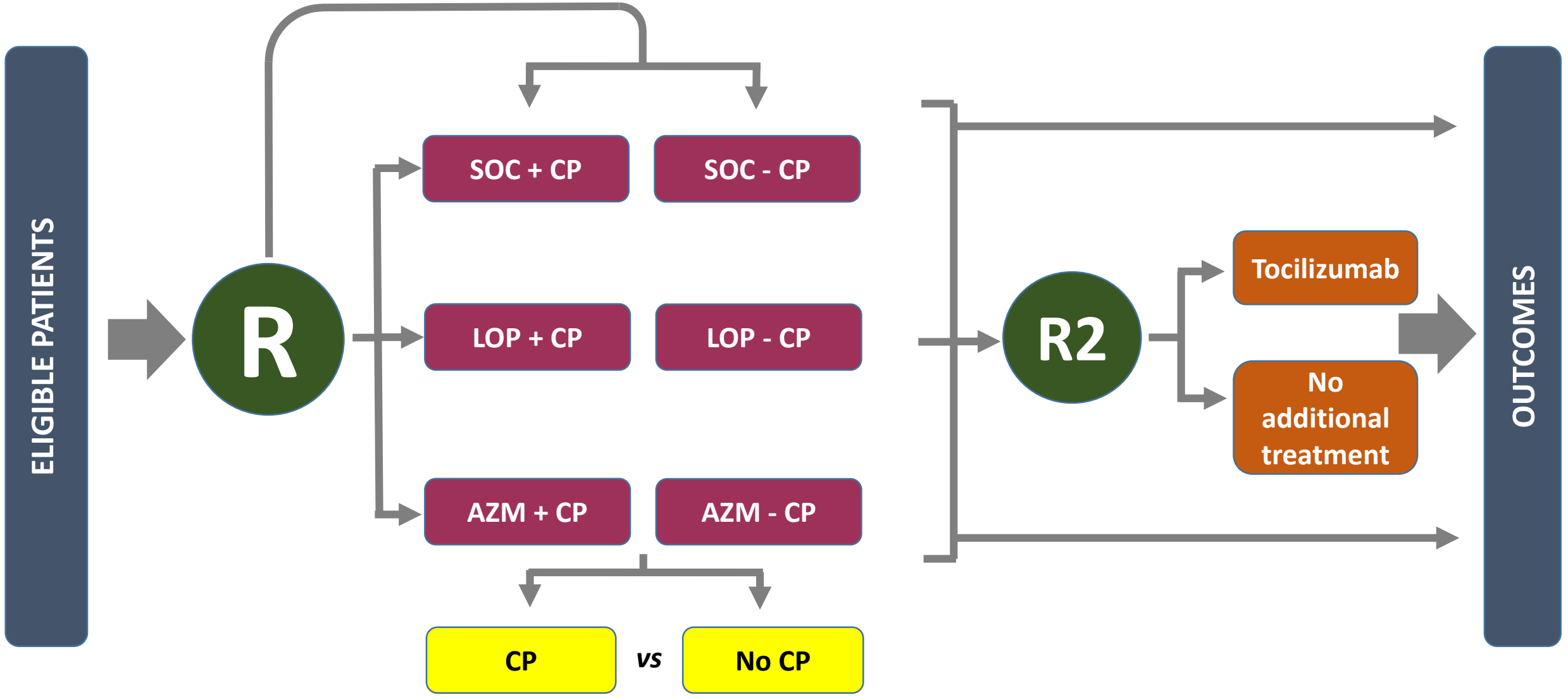

Recruitment by site and by time

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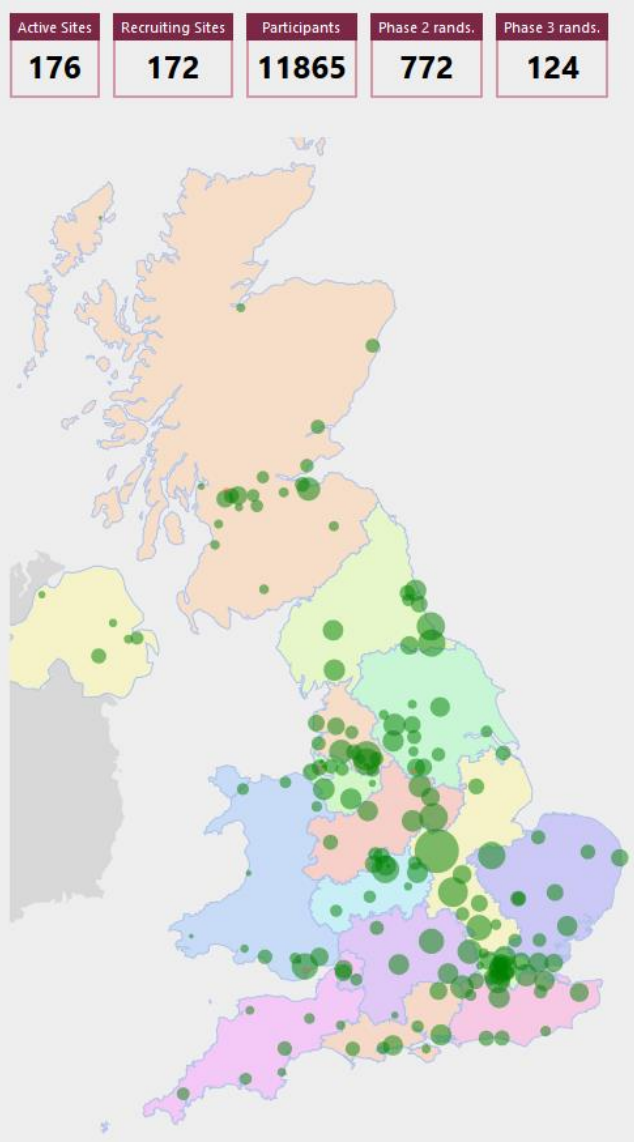

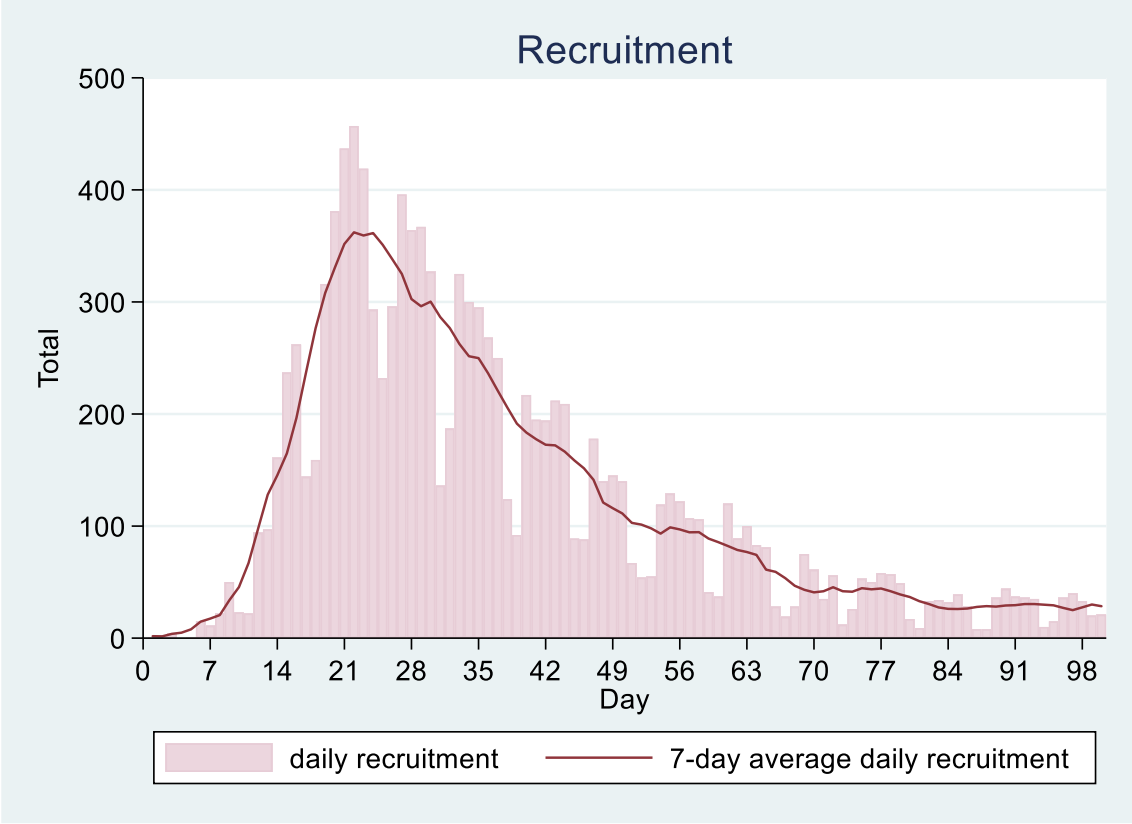

Recruitment: the first 100 days

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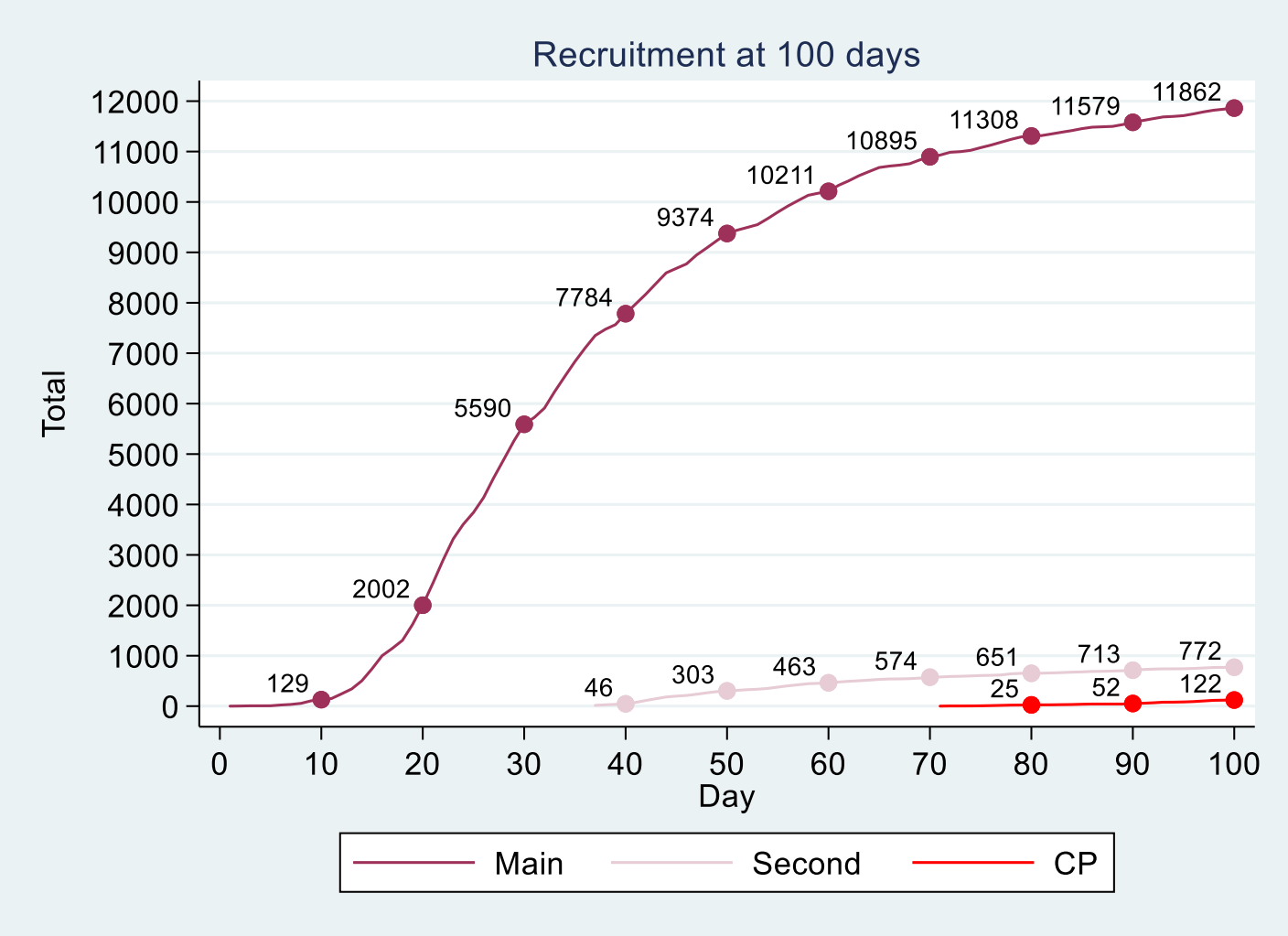

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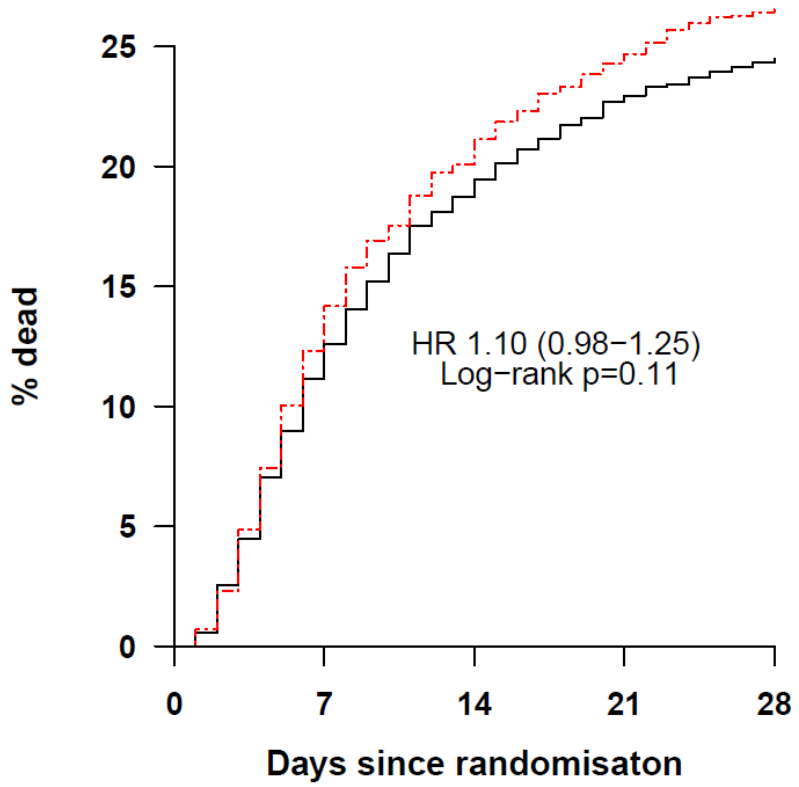
RESULTS AND IMPLEMENTATION

Hydroxychloroquine



Hydroxychloroquine	1561	1325	1202	1134	1089
Control	3155	2741	2491	2354	2278

- Added to protocol on 21 March 2020
- Recruitment stopped on 5 June (+76 days)

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Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June 2020

No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19

- US FDA revoked Emergency Use Authorisation on 15 June (+86 days)

Dexamethasone

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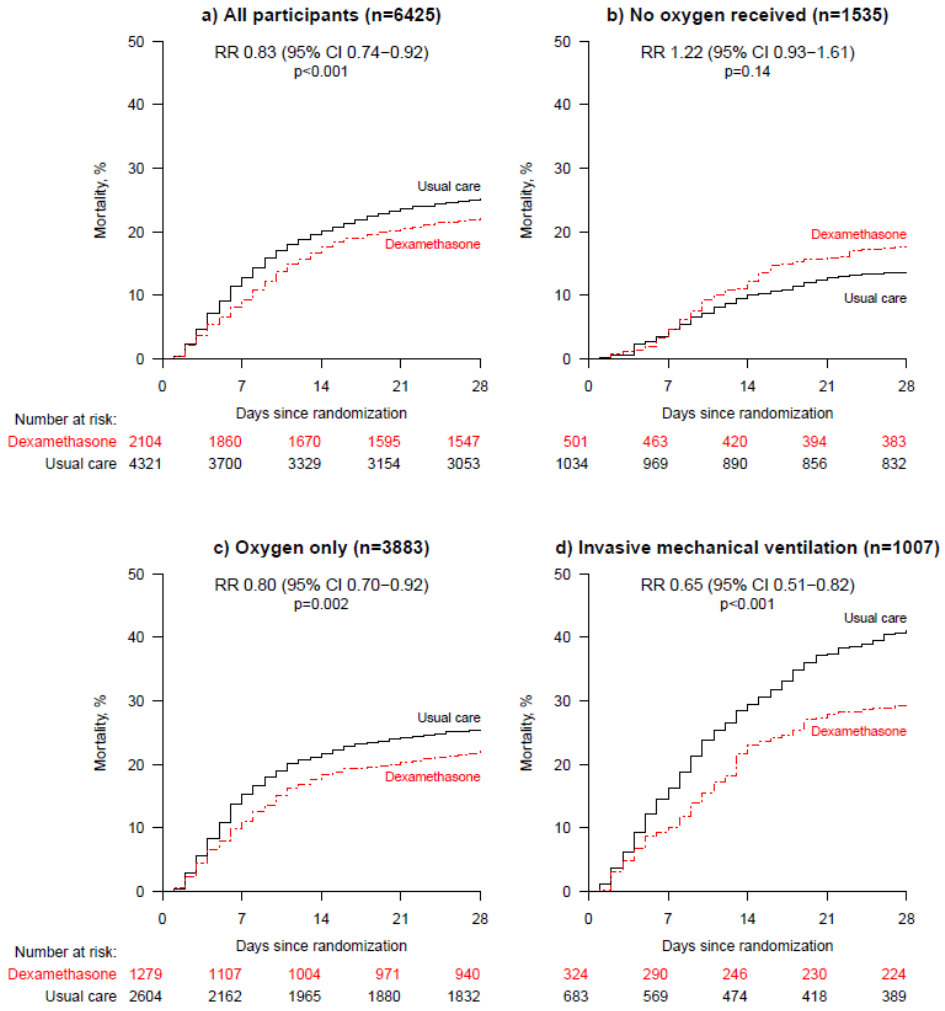

- Included in original protocol (13 March)
- Recruitment stopped on 8 June (+87 days)
  - Stopped blind to outcome because recruitment sufficient

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Oxford University News Release

EMBARGOED UNTIL 16 June 2020, 13:00 (UK Time)

Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19

- Results announced on 16 June (+95 days)

Dexamethasone

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- The guideline writers are going to be busy…

Table 5 | Recommendations for use of corticosteroids for covid-19 in global guidelines produced early in pandemic

Origin	Corticosteroid recommendations	Evidence base	Antimicrobials notes
WHO	Corticosteroid therapy contraindicated	Stockman LJ et al,[27] Rodrigo C et al,[28] Delaney et al,[29] Arabi YM et al[30]	Give empirical antimicrobials to treat all likely pathogens causing SARI
Italy	Not recommended for confirmed covid-19 patients, but low dose dexamethasone may be considered in patients with confirmed ARDS on ICU clinicians' indication	World Health Organization interim guidance,[9] Villar J et al[31]	Add antibiotic (empirical or targeted) according to clinical indications, health policies, or protocols in use
US CDC	Corticosteroids should be avoided unless indicated for other reasons (eg, COPD exacerbation or septic shock)	Zumla A et a,l[32] Arabi YM et al,[30] Russell et al,[33] Metlay JP et al[34]	
India	Not recommended for viral pneumonia or ARDS outside of clinical trials, unless indicated for other reason	No link to supporting evidence provided	Antibiotics not recommended/covered
Turkey	Not recommended routinely	No link to supporting evidence provided	Give empirical antimicrobials to treat all likely pathogens causing SARI
South Korea	Steroids not indicated in general but may be considered for other conditions, such as septic shock	No link to supporting evidence provided	Empirical antimicrobials for possible pathogens are recommended
France	Steroids not indicated for SARS-CoV-2 infection alone	Stockman LJ et al[27]	Routine use of antibiotics for treatment of covid-19 not recommended. However, antibiotics may be used if accompanying bacterial infection is suspected
Brazil	Not recommended for viral pneumonia or ARDS outside of clinical trials, unless indicated for other reasons	No link to supporting evidence provided	
Taiwan	Not recommended for viral pneumonia or ARDS outside of clinical trials, unless indicated for other reasons	No link to supporting evidence	Systematic coverage of bacterial infection/superinfection recommended in severe forms
Indonesia	Not recommended for viral pneumonia or ARDS outside of clinical trials, unless indicated for other reasons	No clear link to supporting evidence	
Spain	Not recommended	No clear link to supporting evidence	Give empirical antimicrobials to treat all likely pathogens that cause SARS
Malaysia	Not recommended unless indicated for other reasons (eg, COPD, septic shock)	No clear link to supporting evidence	Consider giving empirical antibiotics to treat other possible bacterial infection
Germany	Not recommended without clear indication	No clear link to supporting evidence	Give empirical antibiotics based on likely aetiology

ARDS=acute respiratory distress syndrome; COPD=chronic obstructive pulmonary disease; ICU=intensive care unit; SARI=severe acute respiratory illness; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Dagens *BMJ* 2020

Dexamethasone: into practice <100 days after the trial started

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Department of Health & Social Care

MHRA

NHS

COVID-19 Therapeutic Alert

Original Issue date: 16 June 2020.
This version published on 24 June 2020. The paragraph at the end of the Clinical Guidance section has been updated to include updated information on the interaction between remdesivir and dexamethasone. This update appears in red text.
Alert ref: CEM/CMO/2020/026

Dexamethasone in the treatment of COVID-19
Implementation and management of supply for treatment in hospitals

Summary

For immediate action

Dexamethasone has been demonstrated to have a clear place in the management of hospitalised patients with COVID-19.

There were no excess harms identified in using this dose of dexamethasone in this patient population. Dexamethasone was not used in pregnant women.

Clinicians should therefore consider dexamethasone for the management of hospitalised patients with COVID-19 who require oxygen or ventilation.

Out of hospital treatment is not appropriate.

There is no current or anticipated constraint on supply of the medicine in the UK.

World Health Organization

Health Topics | Countries | Newsroom | Emergencies

Home / Newsroom / Detail / WHO welcomes preliminary results about dexamethasone use in treating critically ill COVID-19 patients

WHO welcomes preliminary results about dexamethasone use in treating critically ill COVID-19 patients

16 June 2020 | News release

The World Health Organization (WHO) welcomes the initial clinical trial results from the United Kingdom (UK) that show dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill with COVID-19. For patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth, according to preliminary findings shared with WHO.

The benefit was only seen in patients seriously ill with COVID-19, and was not observed in patients with milder disease.

"This is the first treatment to be shown to reduce mortality in patients with COVID-19 requiring oxygen or ventilator support," said Dr Tedros Adhanom Ghebreyesus, WHO Director-General. "This is great news and I congratulate the Government of the UK, the University of Oxford, and the many hospitals and patients in the UK who have contributed to this lifesaving scientific breakthrough."

Lopinavir-ritonavir

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- Lopinavir is a protease inhibitor used to treat HIV
  - Combined with ritonavir as ritonavir inhibits metabolism of lopinavir so increases its half-life
- Found to inhibit SARS-CoV *in vitro*
- Also inhibits MERS-CoV *in vitro* and in animal model

Lopinavir-ritonavir: conclusions

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- No meaningful effect on all-cause mortality by 28 days
- No evidence of any difference in effect in different types of participant (e.g. those with earlier stage disease)

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TOCILIZUMAB

Tocilizumab

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- Added to protocol on 14 April as a second randomisation for deteriorating participants
  - Hypoxia (or significant systemic disease with persistent pyrexia in children)
  - Inflammation (CRP ≥75 mg/L)

- Nearly 800 participants recruited to date

- Two other tocilizumab trials due to present results at the end of July
  - COVACTA: Roche's own trial of 450 participants
  - BACC study: 243 participants

Tocilizumab

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- Other trials very unlikely to have power to demonstrate effect on mortality
- Effects of tocilizumab in presence of dexamethasone is now an important question
- Please keep recruiting into this arm
- If your site is not included yet but would like to be, please e-mail recoverytrial@ndph.ox.ac.uk

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FOLLOW-UP

Completeness is key

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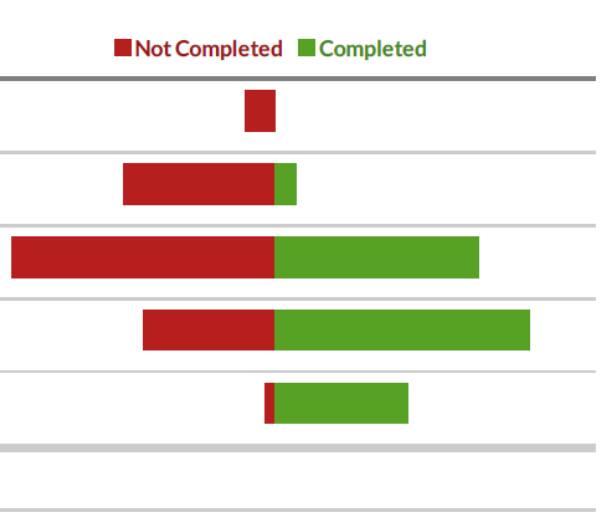
- Weekly reminders will be sent out by trial team to PI and staff with responsibility for completing Follow-up forms, highlighting participants randomised >28 days ago without complete form

- Please do complete these as soon as possible

Follow-up form completion summary

Days Since Rand.	FU Not Completed	FU Completed	Total Rands.
7 ≤ 14	3 (100.0%)	0 (0.0%)	3
14 ≤ 21	15 (88.2%)	2 (11.8%)	17
21 ≤ 28	26 (56.5%)	20 (43.5%)	46
28 ≤ 35	13 (34.2%)	25 (65.8%)	38
> 35	1 (7.1%)	13 (92.9%)	14
Total	**58 (49.2%)**	**60 (50.8%)**	**118**



Follow-up completeness

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- Particular plea for the **72 hour convalescent plasma safety forms**
- These are used by DMC to assess safety of convalescent plasma
- Need to be completed for participants receiving convalescent plasma **and** those assigned standard care in that comparison

Data queries

- Trial management team (Lucy, Karen, Sarah, Richard, Wojtek and Ayten) may be in touch about “data queries”

- Please respond as quickly as possible in order to get data ready for publications

SAE reporting

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- Please remember that adverse events only need to be reported if they are **both**:
  - SERIOUS (e.g. prolong admission, require significant intervention to avoid life-threatening situation)

  AND
  - RELATED with reasonable probability to study treatment

- Please contact coordinating centre if such an event occurs.
- Please do not use “yellow card” system

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FUTURE PLANS

Current protocol

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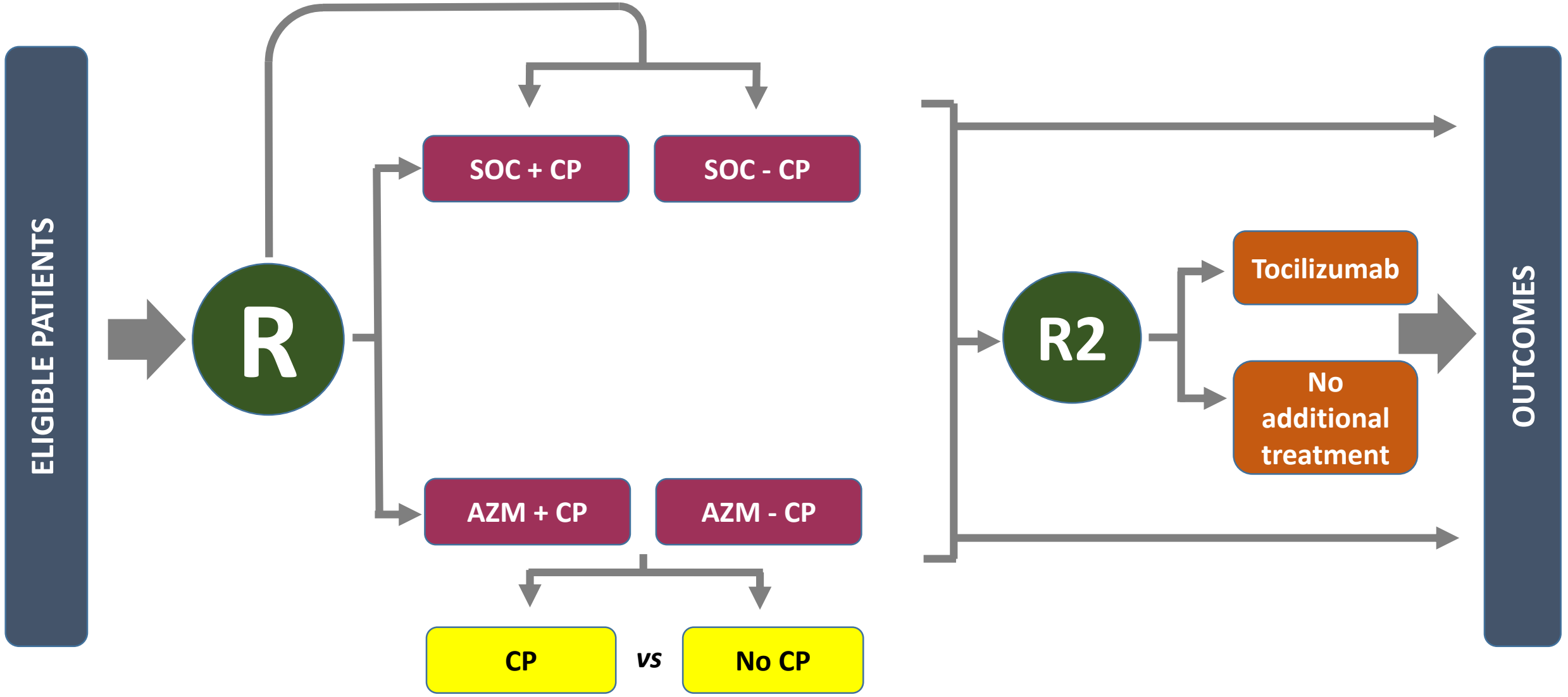

Future protocol

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- Purpose of a platform trial is that drugs may be added
  - Anticoagulation comparison
  - Synthetic antibodies

- Although pandemic is relatively quiet in the UK, this allows an opportunity to prepare treatments for large-scale implementation in a ‘second wave’
  - Convalescent plasma is an example of this

Carry on recruiting!

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- Need to continue recruitment and collection of follow-up information to provide DMC with information about efficacy and safety of study treatments

- As admission rates fall, please focus efforts on recruiting as many admitted patients as possible

- Thank you!

Randomised Evaluation of COVID-19 Therapy: the RECOVERY trial

Paediatric Collaborators' Meeting

30th June 2020

Agenda

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1. Update on progress
    1. Hydroxychloroquine and lopinivir-ritonovir
    2. Dexamethasone
    3. Convalescent plasma - children
    4. Tocilizimab
2. PIMS-TS Delphi and RECOVERY - now
3. PIMS-TS Delphi and RECOVERY - future

Hydroxychloroquine and Ritonivir-lopinivir

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- **HYDROXYCHLOROQUINE**

Recruitment stopped on 5th June

- **LOPINIVIR- RITONIVIR**

Recruitment stopped on 29th June

Dexamethasone

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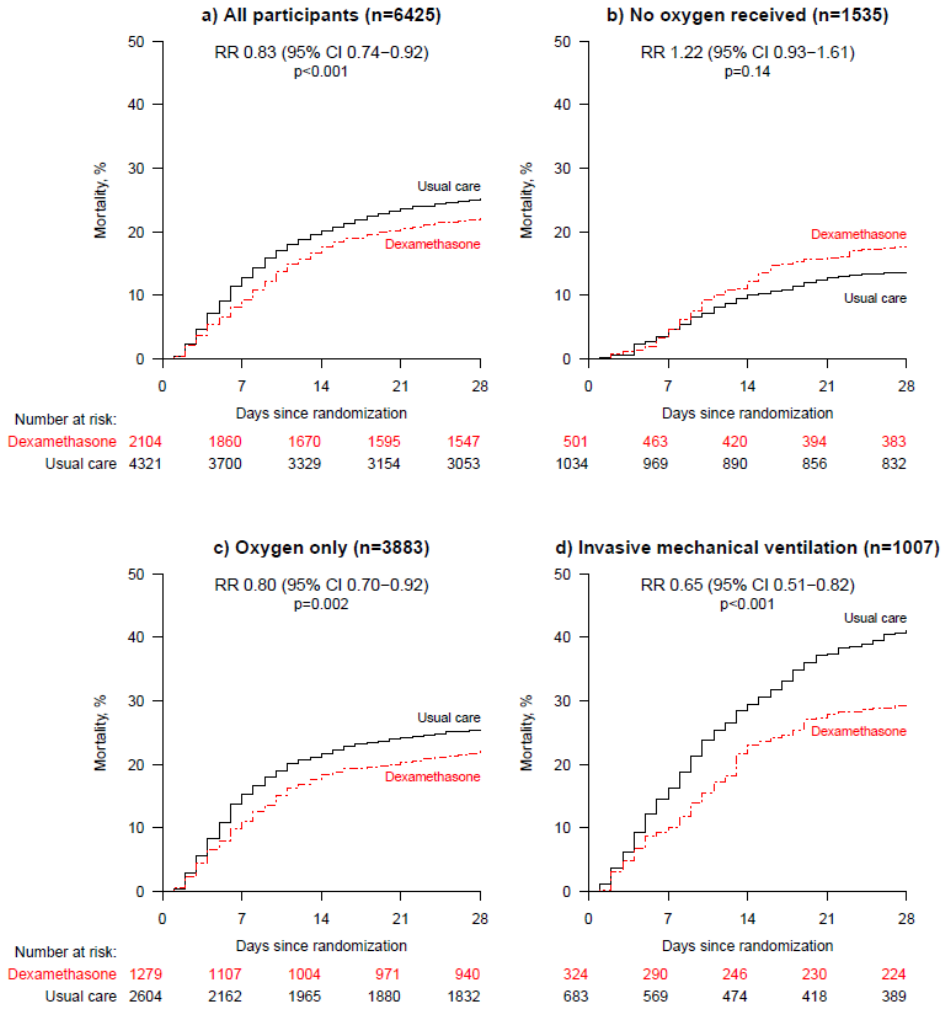

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Dexamethasone

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Dexamethasone is now the NHS standard of care for patients with COVID-19 needing oxygen. Why is dexamethasone still part of the RECOVERY protocol for children?

- Children (outside of the neonatal period) admitted to hospital with acute COVID-19 respiratory disease requiring oxygen should be considered for treatment with dexamethasone as part of standard of care (and the steroid arm should be selected as unsuitable in RECOVERY randomisation 1 for these children).
- However, where a child has been diagnosed with PIMS-TS, the NHS England Delphi process (publication pending) has demonstrated equipoise regarding the role of steroids. In PIMS-TS, steroid can still be an option (along with azithromycin) for the first randomisation in RECOVERY.

Convalescent plasma

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Can children be randomised to the convalescent plasma arm of RECOVERY?

Acute respiratory presentation of COVID-19:

Yes, children can be to randomised to receive convalescent plasma or standard of care as part of RECOVERY for any neonate or child diagnosed with acute COVID-19, if available at the research site and local investigators consider this appropriate for that child.

Children with PIMS-TS:

Individual investigators may choose to randomise patients with PIMS-TS to convalescent plasma, where it is available in a specific research site and local investigators consider this appropriate for that child.

Tocilizumab

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- Other trials very unlikely to have power to demonstrate effect on mortality in adults
- Effects of tocilizumab in presence of dexamethasone is now an important question in adult COVID-19
- Please keep recruiting into this arm, including PIMS-TS as appropriate

Current options

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SOC vs

- Corticosteroid (neonates and PIMS-TS phenotype)
- Azithromycin

+/-

- Convalescent plasma

SOV vs

- Tocilizumab

PIMS-TS Delphi and RECOVERY

- **A national consensus management pathway for Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS): The results of a national Delphi process**

- Submitted to ADC

- Rachel Harwood, Benjamin Allin, Simon Kenny

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Box 4: Research for children with PIMS-TS

RECOVERY trial

RECOVERY is an adaptive trial and based on this Delphi process, the Trial Steering Committee are considering a PIMS-TS specific first randomisation protocol amendment.

1. All children who meet the criteria for inclusion in the RECOVERY trial should be offered the opportunity to enter and be randomised in the first stage.

2. For a future amendment in RECOVERY or a future research trial there is equipoise for children with both phenotypes of PIMS to receive methylprednisolone OR IVIg as a first line treatment within a research study.

3. Children enrolled in the RECOVERY trial should be offered the opportunity to enter the 2nd stage intervetions arm (Tocilizumab vs standard of care) if they have been discussed by a MDT and the decision made to commence biological therapy.

Future protocol

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- Purpose of a platform trial is that drugs may be added
- Although pandemic is relatively quiet in the UK, this allows an opportunity to prepare treatments for large-scale implementation in a ‘second wave’
- TSC very receptive to a paediatric specific amendment for PIMS-TS

RECOVERY for PIMS-TS

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Aim: compare steroids vs SOC (in presence and absence of IVIg) and IVIg vs SOC (in presence and absence of steroids).

Design being discussed will:

- Allows investigators to use no treatment, IVIg or steroids or as standard care if deemed necessary
- Allows effects of steroids and IVIg to be compared with SOC separately (in presence and absence of other drug)
- Allows wide spectrum of severity to be recruited because some treatment can be guaranteed but not absolutely required
- Second randomisation to tocilizumab is still available. Can collect baseline use of steroids/IVIg at second randomisation too (in case clinicians go off-protocol in-between two randomisations)

Carry on recruiting!

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- The current protocol can be used for PIMS-TS as per the current guidance document (will be updated tomorrow to v5.0 to incorporate changes discussed today).

- Potential amendment will be discussed by the paediatric working group and TSC this week, followed by MHRA/HRA and REC.

- Planning for second wave / local spikes or waves

- Thank you!