Appendix 2: Outcomes included, Covid-19 RCTs, Paediatric RTI RCTs, Excluded RCTs

CONTENTS

1 Critical and important outcomes

All studies
Critical
1. Change in health-related quality of life score
2. Number of participants with a severe adverse event
3. Number of participants with any adverse effects
4. Number of withdrawals from the study due to an adverse event
Important
5. Number of participants who experienced different types of adverse effects*
Prevention of viral respiratory tract infections (RTIs)
Critical

1. Number of participants with one or more RTIs (per person or person-months/years)
2. Number of RTIs (episodes)
3. All-cause mortality

Important

4. Number of RTI symptomatic days per person or episode
5. Severity of RTI symptoms*
6. Proportion of participants with complications from RTIs, including non-respiratory*
7. Proportion of participants with RTIs requiring hospital admission

Treatment of mild to moderate viral respiratory tract infections

Critical

1. Symptomatic survival (i.e. remaining symptomatic) from onset of symptoms
2. Symptom severity score at the time when symptoms most commonly peak for the specific viral infection (e.g. day 3 of symptoms for common cold [61])
3. Average daily symptom severity score during the study period
4. Complication-free survival (not progressing to severe/critical illness, non-respiratory complications*, or all-cause mortality) up to 60 days from onset of symptoms

Important

5. Number of days from onset of symptoms to symptomatic recovery from RTI or other non-respiratory complications
6. Number of days from onset of symptoms to negative PCR result
7. Number of participants with complications (e.g. progressing to severe/critical, non-respiratory complications, or deceased from any cause) during the study period
8. Number of participants requiring hospital admission

Treatment of severe to critical viral respiratory tract infections (RTI)

Critical

1. Overall survival (all-cause mortality) up to 60 days from study enrolment
2. All-cause mortality rate up to 60 days during study period
3. Complication-free survival (not progressing from severe to critical, requiring mechanical ventilation, or all-cause mortality) up to 60 days from study enrolment
4. Number of participants with complications (e.g. progressing from severe to critical, requiring mechanical ventilation, non-respiratory complications*, deceased from any cause) during the study period
5. Symptomatic survival (i.e. remaining symptomatic, including from non-respiratory complications*) from onset of illness

Important

6. Number of days on mechanical ventilation
7. Number of days requiring critical/intensive care
8. Number of days from study enrolment to symptomatic recovery from RTI or other non-respiratory complications
9. Number of days from study enrolment to negative PCR
10. Number of days from study enrolment to absorption/resolution of pulmonary infiltration

* added post-protocol following blinded feedback from consumer advocates

2 Studies pending results: Randomized control trials (RCTs) investigating zinc for SARS-CoV-2, registered on clinical trial registries.

2.1 Coronavirus 2019 (COVID-19) - Using Ascorbic Acid and Zinc Supplementation (COVIDAtoZ)

Registration no.	NCT04342728
Registration date	8 April 2020
Completion date	30 December 2020
Location	US
Setting	Community health clinics and hospital outpatients, Ohio and Florida
Design	Multicentre, open label RCT, 4 arms
Sample size	N=520
Demographics	Adults, including women of child-bearing potential
Inclusion criteria	Confirmed diagnosis of SARS-CoV-2 not requiring hospitalisation
Exclusion criteria	1. SARS-CoV-2 detected during hospitalisation 2. Pregnant and lactating 3. CKD 4. Liver disease (waiting transplant) 5. Calcium oxalate stones
Zinc intervention (elemental dose)	1. Zinc gluconate 50mg (7mg)/day for 28 days 2. Zinc gluconate 50mg (7mg)/day + vitamin C 8000mg /day for 28 days
Comparator	1. Usual (standard) care 2. Vitamin C alone
Primary Outcomes	Days to 50% reduction of symptoms
Secondary Outcomes	1. Symptom resolution (fever, cough, shortness of breath, fatigue) 2. Total symptom score on day 5 3. Hospitalisation 4. Adjunctive medicines 5. Adverse events
Follow-up time	28 days

2.2 High-dose intravenous zinc (HDIVZn) as adjunctive therapy in COVID-19 positive critically ill patients: A pilot randomized controlled trial

Registration no.	ACTRN12620000454976
Registration date	8 April 2020
Completion date	NI
Location	Australia
Setting	Austin Hospital, Victoria
Design	Pilot RCT
Sample size	N=160
Demographics	Adults
Inclusion criteria	Hospitalised with confirmed SARS-CoV-2 infection (PCR or other laboratory confirmed) of any duration. SaO2: ≤94% or Pao2:Fio2 ≤ 300 mg Hg. Ventilated or non-ventilated.
Exclusion criteria	1.CKD 2. Pregnant or lactating

	3. Allergy to Zinc 4. Severe hepatic impairment 5. eGFR ≤ 30 mL/min/1.73 m2 6. Organ transplant 7. CPR within 14 days 8. DNR or DNI orders 9. Imminent or inevitable death 10. Dialysis 11. HIV infection 12. Known or suspected history of oxalate nephropathy or hyperoxaluria, scurvy, chronic iron overload, G-6PD deficiency
Zinc intervention (elemental dose)	Zinc 0.5mg/kg/day intravenous infusion (saline 250ml/day) over 3-6 hrs for 7 days
Comparator	Saline solution 250ml/day infused over 3-6 hrs for 7 days
Primary Outcomes	For non-ventilated patients: mean change in the worst (highest) level of oxygenation (flow in litres/min). For ventilated patients: mean change in the worst (lowest) PaO2:FiO2(mmHg). Feasibility: blinding; drug availability; GCP; protocol compliance; costs; SOP
Secondary Outcomes	1.Mortality 2.Duration of mechanical ventilation 3.Duration of oxygen therapy
Follow-up time	28 days

2.3 HCQ and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers (COVID-Milit)

Registration no.	NCT04377646
Registration date	4 May 2020
Completion date	31 July 2020 (not confirmed)
Location	Tunisia
Setting	Tunisia Military Academy
Design	Multicentre, double-blind RCT, 3 arms
Sample size	N = 660
Demographics	Military professionals aged 18-65
Inclusion criteria	At risk of infection by SARS-CoV-2 at 2 levels
Exclusion criteria	1. Allergy to medications 2. Heart rhythm disturbances 3. Severe hepatic impairment 4. Retinal pathology 5. Epilepsy 6. Myasthenia 7. Psoriasis 8. Methemoglobinemia 9. Porphyria 10. Pregnant or lactating women 11. Concomitant treatments
Zinc intervention (elemental dose)	Zinc capsules 15mg/day + HCQ 400mg on day 1 and 2 and HCQ 400mg/week for 2 months
Comparator	1. Placebo zinc, 1 per day for 28 days + HCQ 400mg on day 1 and 2 and 400mg/week for 2 months

	2. Placebo zinc, 1 each day + placebo HCQ on day 1 and 2 and weekly for 2 months
Primary Outcomes	Incidence of SARS CoV2 infection
Secondary Outcomes	1. Incidence of any COVID-19 related symptoms 2. Adverse events
Follow-up time	28 days

2.4 Hydroxychloroquine, Azithromycine and Zinc for the treatment of SARS-Cov2 infection in Senegal. (ESHAZ trial)

Registration no.	PACTR202005622389003
Registration date	14 May 2020
Completion date	NI
Location	Senegal
Setting	Community health centre – Centre for epidemic treatment, Aerogare Yoff, Health District of Yoff, Dakar
Design	RCT three arms
Sample size	N= 384
Demographics	Adults
Inclusion criteria	Patients confirmed SARS-CoV-2 infection less than 72 hours prior to randomisation without chronic disease and without danger signs (e.g. respiratory distress, requiring mechanical ventilation or supplemental oxygen, encephalitic disorders and/or renal function failure.
Exclusion criteria	1.Known allergy to any of the study medication 2.Pregnancy or breastfeeding 3.ECG abnormality at admission 4.Patients with ALAT/ASAT higher than 3 times the upper limit of normal on admission 5.Patients with known chronic kidney diseases 6.Patients with known retinal diseases.
Zinc intervention (elemental dose)	Zinc tablets: 20mg per day for 7 days
Comparator	1.Hydroxychloroquine: 600 mg daily for 6 days plus Azythromycine: 500 mg on day 1 followed by 250 mg daily from day 2 to day 5 2.Hydroxychloroquine: 400 mg daily for 6 days (200 mg twice per day) plus Azythromicine: 500 mg on day 1 followed by 250 mg from day 2 to day 5
Primary Outcomes	Percentage with undetectable viral load 7 days after treatment initiation.
Secondary Outcomes	Time to first PCR negative after treatment initiation. Biochemical parameters from baseline to day 7 after treatment initiation. Haematological parameters from baseline to day 7 after treatment initiation. Proportion with ECG abnormality after treatment initiation
Follow-up time	7 days

2.5 The effect of zinc on the treatment and clinical course of patients with SARS-cov2 (COVID-19)

Registration no.	IRCT20180425039414N2
Registration date	31 May 2020
Completion date	NI
Location	Iran
Setting	Amin Hospital, Isfahan
Design	Open label RCT, 2 arms
Sample size	N=80
Demographics	Adults
Inclusion criteria	Hospitalised with confirmed SARS-CoV-2 infection (RT, PCR and CT scan of the lungs). Blood oxygen levels: 90-3%; Breathing rate 20-24 breaths/min; Heart rate 100-130 bpm
Exclusion criteria	1.Intubation 2.Blood oxygen below 90% Breathing rate equal to 30 or more breaths per minute 3. Allergic to interventions 4.Cardiogenic pulmonary oedema associated shortness of breath 5.Pregnancy and lactation 6. Oxygen therapy at home 7. End stage lung, malignant, G6PD deficiency, diabetic ketoacidosis, cardiac arrhythmia
Zinc intervention (elemental dose)	Zinc tablets 440mg/day + HCQ sulphate tablets 400mg every 12 hours on day 1 and 200mg every 12 hours during hospitalisation
Comparator	HCQ sulphate tablets 400mg every 12 hours on day 1 and 200mg every 12 hours during hospitalisation.
Primary Outcomes	Clinical course defined as: 1. Resolution of symptoms (fever, shortness of breath, cough), SaO2 and hemodynamic parameters 2. Mortality 3. Days in hospital
Secondary Outcomes	None
Follow-up time	During hospitalisation

2.6 Zinc with chloroquine/hydroxychloroquine in treatment of COVID-19

Registration no.	NCT04447534
Registration date	23 June 2020
Completion date	1 October 2020
Location	Egypt
Setting	Tanta university hospital
Design	Phase 3, RCT double blind
Sample size	N= 200
Demographics	Adults (aged over 18 years) any gender
Inclusion criteria	Patients with positive COVID-19
Exclusion criteria	Contraindications or hypersensitivity to chloroquine.
Zinc intervention (elemental dose)	Zinc with Chloroquine NI
Comparator	Chloroquine alone
Primary Outcomes	The number of patients with mortality

	The number of patients with negative PCR
Secondary Outcomes	
Follow-up time	Two weeks
2.7 To study the role of Zinc combined with standard treatment for COVID-19	
Registration no.	CTRI/2020/07/026340
Registration date	2 July 2020
Completion date	NI
Location	India
Setting	Hospital
Design	RCT
Sample size	N= 100
Demographics	Adults
Inclusion criteria	Diagnosed with COVID-19
Exclusion criteria	1.Pregnant or lactating women 2. End stage CKD 3. Patients with dementia, learning disability, mental health needs 4. Unable to understand the procedures and protocol 5. Deemed unfit for the study according to the investigator
Zinc intervention (elemental dose)	Zinc sulphate 100mg once daily plus standard treatment NI
Comparator	Standard treatment alone
Primary Outcomes	Symptom severity reduction Duration of hospitalisation, ICU admission, ventilator requirement, complications, discharge timepoint: Baseline, day 1, day 5, day 7, day 14 or till discharge
Secondary Outcomes	Symptom resolution
Follow-up time	Day 1, day 5, day 7, day 14 or till discharge

6GPD Glucose-6-phosphate dehydrogenase deficiency**; CKD:** chronic kidney disease; **CPR** cardiopulmonary resuscitation; **CT** computerized tomography; **DNR** do not resuscitate; **DNI** do not intubate; **eGFR** estimated Glomerular Filtration Rate; **GCP:** Good Clinical Practice **FiO2** fraction of inspired oxygen**; HCQ:** hydroxychloroquine: **ICU:** intensive care unit; **NI:** no information**; PaO2** Partial pressure of oxygen; **PCR:** Polymerase Chain Reaction; **RCT:** randomised controlled trial; **RT** Rapid Test; **SaO2** Oxygen saturation; **SOP** standard operating procedures

3 Articles pending analysis: Randomized control trials (RCTs) investigating zinc for treatment or prevention of viral respiratory tract infections in children or adolescents

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4 Articles published in English that were excluded at full-paper screening

Each article is cited once and was categorised in the following order.

4.1 Reason for exclusion: study design

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