Pre-planned meta-analysis of randomised trials of sofosbuvir-daclatasvir, to evaluate clinical benefits and survival

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Introduction

There are currently no effective therapies for COVID-19 in tablet form. Repurposed therapies are already mass produced, are readily available and are safe. SOF/DCV has shown *in-vitro* efficacy against COVID-19, and a number of clinical trials around the world are investigating its effects on clinical recovery.

Objective

To estimate the effect of SOF/DCV compared with standard of care on: (i) clinical recovery from COVID-19 and (ii) all-cause mortality.

Study design

Prospective meta-analysis of RCTs. Double blind and open-label trials are eligible.

Intervention and comparator

Intervention groups receive 400mg/60mg of SOF/DCV daily. Comparator groups receive standard of care or placebo.

Search strategy

Trials were systematically identified from: ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), WHO International Clinical Trials Registry Platform (ICTRP), Chinese Clinical Trials Registry (ChiCTR) and the Oxford COVID-19 Trials Tracker.

Statistical methods

Inverse-weighted random-effects meta-analysis will be conducted using the Paule-Mandel estimate of heterogeneity and Hartung-Knapp adjustment. Heterogeneity between trials will be quantified using the I^2 statistic. Evidence for subgroup effects will be quantified by ratios of odds ratios comparing effects in the subgroups.

Interim analysis

We will use the O'Brien Fleming boundary to conduct two analyses:

(1) An interim analysis in Nov 2020;

(2) A final analysis in Jan 2021.

Figure 1. Power calculations assumed 80% power, 5% significance and used existing small-scale trials to set expected odds ratios (ORs). Our study will have >95% power to detect effects on clinical recovery and 84% power to detect changes in survival. Power analysis assumes moderate heterogeneity between trials.

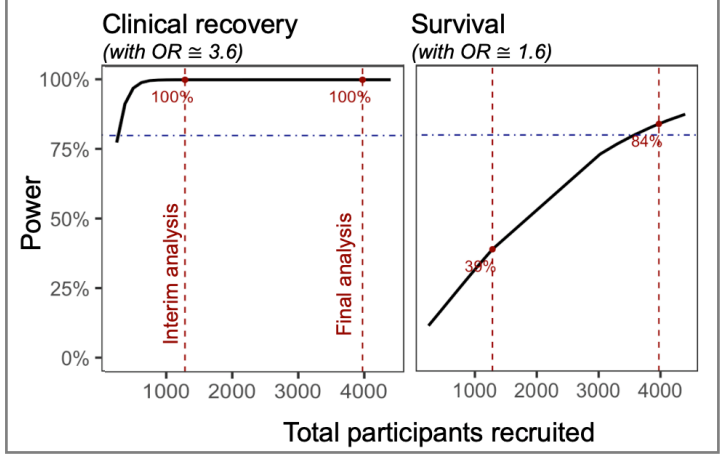

Table 1. Studies to be included in the first interim analysis in November 2020

	Iran Sari	Iran Tehran	PHARCO	DISCOVER	Algeria
Trial ID	IRCT20200328046886N1	IRCT20200128046294N2	DRKS00022203	IRCT20200624047908N1	TBC
Location	Iran	Iran	Egypt	Iran	Algeria
Sample size	48	66	90	1000	80
Trial type	Open-label RCT	Open-label RCT	Open-label RCT	RCT	Open-label RCT
Recruitment start	Complete	Complete	Complete	TBC	Sep 2020
Intervention	SOF/DCV + RBV	SOF/DCV + HCQ + LPV/r	SOF/DCV	SOF/DCV	DOF/DCV
Control	HCQ + LPV/r + RBV	HCQ + LPV/r	Standard of care	Placebo	Standard of care

Table 2. Studies to be included in the final analysis in Jan 2021. These studies will be in addition to those at interim (Table 1)

	India	REVOLUTIOn	SODA CAN	Egypt	SAVE	South Africa
Trial ID	TBC	NCT04468087	TBC	NCT04460443	TBC	NCT04532931
Location	India	Brazil	iran	Egypt	Egypt	South Africa
Sample size	134	126	2000	60	120	250
Trial type	RCT	Adaptive Phase II/III RCT	Outpatient RCT	Open-label RCT	Open-label RCT	Outpatient Open-label RCT
Recruitment start	TBC	Sep 2020	TBC	TBC	TBC	TBC
Intervention	SOF/DCV	SOF/DCV	SOF/DCV	SOF/DCV	DOF/DCV	SOF/DCV
Control	Placebo	Placebo	Placebo	Active comparator	TBC	Standard of care

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