Statistical Analysis Plan (SAP)

COVID-19-associated ARDS treated with DEXamethasone (CoDEX).

COALITION COVID-19 BRAZIL III

Version: 2.0 – May 28, 2020

Refers to protocol version 5.0

This document is confidential and its use, reproduction, dissemination and publication are restricted to the main investigators and sponsors.

Coalition Covid-19 Brazil (Steering Committee)

Hospital Israelita Albert Einstein:

Otávio Berwanger

Henrique Fonseca

Remo Holanda Furtado

Ary Serpa-Neto

Thiago Correa

Cláudio Galvão

Leonardo Rolim Ferraz

Guilherme Schettino

Luiz Vicente Rizzo

HCor:

Alexandre Biasi Cavalcanti

Fernando Godinho Zampieri

Thiago Lisboa

Israel Silva Maia

Letícia Kawano Dourado

Hospital Sírio Libanes:

Luciano Cesar Pontes Azevedo

Eduardo Leite Vieira Costa

Bruno Martins Tomazini

Hospital Moinhos de Vento

Régis Rosa

Maicon Falavigna

Hospital Alemão Oswaldo Cruz

Álvaro Avezum

Beneficência Portuguesa

Viviane Cordeiro Veiga

Danielle Leão

João Prats

Philip Scheinberg

BRICNet:

André Gobatto

Cintia Grion

Felipe Dal Pizzol

Fernando Augusto Bozza

Flávia Machado

Flavio Geraldo Rezende de Freitas

Glauco Westphal

Hugo Urbano

Régis Rosa

Rodrigo Biondi

Rodrigo Cruvinel Figueiredo

Viviane Cordeiro Veiga

BCRI

Renato Delascio Lopes

Responsible Statistician: Lucas P Damiani
E-mail: ldamiani@hcor.com.br

ClinicalTrials.gov identifier:

SAP version: 2.0

Date: May 28, 2020

Authors: Bruno M Tomazini
Luciano C P Azevedo
Lucas P Damiani

89

Table of contents

1. Introduction

The infection caused by the SARS-CoV2 (COVID-19) spread world-wide and is now considered a pandemic[1]. The most common manifestation of COVID-19 Is viral pneumonia with varying degrees of respiratory compromise and up to 40% of hospitalized patients might develop Acute Respiratory Distress Syndrome (ARDS)[2]. Several clinical trials evaluated the role of corticosteroids in ARDS with conflicting results[3]. Given the hyperinflammatory state associated with COVID-19[4] and possible benefit of early corticosteroids in ARDS[5] we postulated that early treatment of moderate or severe ARDS with dexamethasone, a potent anti-inflammatory drug, might increase ventilator-free days at 28 days in this population.

2. Study objectives

a. Primary outcome

Our primary objective is to evaluate the effectiveness of early intravenous (IV) dexamethasone administration on the number of days alive and free of mechanical ventilation within 28 days after randomization in adult patients with moderate or severe ARDS due to confirmed or probable COVID-19.

b. Secondary outcomes

Secondary objectives are to evaluate the effect of dexamethasone treatment plus standard treatment versus standard treatment alone on the following:

- All-cause mortality rates at 28 days after randomization
- Clinical status of patients at 15 days after randomization using the World Health Organization 6-point Ordinal Scale for clinical improvement
- Number of days of mechanical ventilation from randomization to day 28
- ICU free days within 28 days
- Change in the Sequential Organ Failure Assessment (SOFA) Score 48h, 72h and 7 days after randomization

We will also evaluate the medium and long-term consequences on morbidity and mortality, activities of daily living, psychological health and quality of life of patients, assessed at 3, 6, 9 and 12 months:

- Mortality from any cause
- Rate of hospital readmission for any cause
- Need for home respiratory support (oxygen therapy, non-invasive ventilation or mechanical ventilation)
- Physical-functional capacity measured through the Modified Barthel Index and Lawton's Instrumental Activities of Daily Living
- Anxiety and depression symptoms measured using the hospital anxiety and depression scale (HADS) and post-traumatic stress symptoms measured using the revised event impact scale (HEI-R).
- Health-related quality of life measured using the EQ-5D-3L scale.
- Return to work or studies in 3, 6, 9 and 12 months

3. Study design

The COVID-19-associated ARDS treated with DEXamethasone: CoDEX is a pragmatic, prospective, randomized, stratified, multicenter, open-label, superiority, controlled trial including 350 patients with moderate or severe ARDS due to confirmed or probable COVID-19 in 53 Intensive Care Units in Brazil.

4. Study population

a. Inclusion criteria

- Age ≥18 years old
- Probable or confirmed infection by SARS-CoV2
- Intubated and mechanically ventilated
- Moderate or severe ARDS according to Berlin criteria[6]
- Onset of moderate or severe ARDS in less than 48h before randomization

b. Exclusion criteria

- Pregnancy or active lactation
- Known history of dexamethasone allergy

- Daily use of corticosteroids in the past 15 days
- Indication for corticosteroids use for other clinical conditions (e.g refractory septic shock)
- Patient is expected to die in the next 24 hours
- Consent refusal for participating in the trial
- Patients who did use corticosteroids during hospital stay for periods equal or greater than two days
- Use of immunosuppressive drugs
- Cytotoxic chemotherapy in the past 21 days
- Neutropenia due to hematological or solid malignancies with bone marrow invasion

5. Intervention

Patients in the intervention group are receiving after randomization dexamethasone 20mg intravenously once daily for 5 days, followed by dexamethasone 10mg IV once daily for additional 5 days or until ICU discharge, whichever occurs first. Patients in the control group are not receiving dexamethasone. Patients in the control group will not receive dexamethasone.

6. Study hypothesis

Treatment with dexamethasone in patients with moderate or severe ARDS due to COVID-19 increases the number of days free from mechanical ventilation from randomization to day 28.

7. Statistical analysis

a. Sample size and power

There is a lack of reliable data available in patients with ARDS due to COVID-19 to allow an accurate sample size calculation. We therefore used data from a randomized controlled trial in non-COVID-19 ARDS patients[7], a well-designed multicenter trial that is representative of ARDS outcomes in Brazil, to calculate the

sample size. We assumed a mean of VFD at 28 days of 8 days ± 9 days (standard deviation) in the control group. With a two-sided type I error of 0.05 and power of 80% to identify a difference in three days free of mechanical ventilation between groups, a sample size of 290 patients would be needed. However, after discussing the protocol with the Data Monitoring Committee (DMC), the Steering Committee decided to increase the sample size based on the following rational: Given the uncertainty regarding the normality of distribution of VFD, based on the Pitman Asymptotic Relative Efficiency[8], the sample size should be increased by 15% to preserve study power coupled with a 4% increase considering possible lost to follow-up and withdrawal of consent. Therefore, a final sample size of 350 patients is needed.

Also, due to the lack of data about ventilator free days in COVID-19 patients, the sample size will be updated using the pooled standard deviation of ventilator free days of the first interim analysis, unless by the time of the first interim analysis all patients have been recruited.

The minimal clinically important difference of three days for VFD was chosen based on other trials[9,10] along with what is perceived as a significant improvement to the in-hospital complications, costs, and intensive care unit availability, especially in countries with limited resources.

b. Primary outcome analysis

The main analysis study population will comprise all patients who have been randomized (intention-to-treat population), using the group allocated as variable, regardless of the medication administered or treatment adherence. Baselines characteristics will be displayed as the shown in Table 1.

The primary objective is to evaluate the effectiveness of early intravenous (IV) dexamethasone administration in ventilator-free days at 28 days after randomization, defined as alive and free from mechanical ventilation in adult patients with moderate or severe ARDS due to confirmed or probable SARS-CoV2 infection. Patients discharged from the hospital alive before 28 days will be considered alive and free from mechanical ventilation at day 28. Number of days free from mechanical ventilation will be presented as mean and standard deviation. The treatment effect will be presented as mean difference, with 95% confidence interval and p-value. We will use a generalized linear model with beta-binomial distribution or zero/one inflated beta distribution, with

center as random effect and adjusted for age and PaO_2/FiO_2 ratio. In case of loss of follow-up missing data on the primary outcome will be dealt with using the multiple imputations technique.

c. Secondary outcomes analysis

All-cause mortality rates at 28 days will be analyzed using a mixed Cox model, with centers as random effects (frailty model). The treatment effect on SOFA Score 48h, 72h, and 7 days after randomization will be analyzed by a linear mixed model with centers as random effects. For the clinical status of patients, an ordinal logistic regression will be used. The results will be presented as a proportional odds ratio comparing two combinations: Intervention versus Control. The probability ratios will be derived from a mixed logistic regression of proportional probabilities adjusted for age and PaO_2/FiO_2 ratio, with random intercepts for the center. The cumulative ordinal scores will be presented separately, as well as the main secondary results. Each odds ratio will be estimated using mixed logistic regression. The same models will be used to compare the effects of treatment on the follow-up. In case of the proportional odds assumption is not met, categories of the Ordinal scale 1-4 will be grouped as a single category for the analysis. All secondary outcomes are exploratory and no adjustment for multiple testing will be made.

Adverse events will be expressed as counts and percentages and compared between groups using the Chi-square test. The main results will be displayed as the shown in table 2. The significance level for all analyses will be 0.05. There will be no adjustment for multiple testing. All analyses will be performed using the R software[11] (R Core Team, Vienna, Austria, 2020).

d. Additional analysis

Sensitivity analyses

We plan to perform analyses to assess treatment effects on the primary and secondary outcomes considering only patients that received the proposed treatment in the intervention group and patients that not received corticosteroids in the control group (per protocol analysis). Additionally, we will also perform sensitivity analysis for the primary outcome in the following groups:

1. Confirmed COVID-19 infection
2. Confirmed and probable COVID-19 infection
3. Patients which received corticosteroids and patients which did not received corticosteroids (as treated analysis)
4. Patients which received the proposed treatment in the intervention group and patients that not received corticosteroids in the control group (Per protocol analysis)

Subgroup Analyses

Will also perform subgroup analysis adding an interaction parameter with group in the main model for (Table 3):

1. Age, years (<60 and ≥60)
2. PaO_2/FiO_2 ratio, mmHg (≤100 and >100)
3. SAPS3, points (<50 and ≥50);
4. Duration of symptoms at randomization, days (≤7 and >7)
5. Duration of moderate or severe ARDS to randomization, hours (≤24h and >24h to 48h)
6. Position at randomization; (prone or supine)
7. HScore (≥169 and <169)
8. Use of corticosteroids before randomization
9. Use of vasopressors at randomization

Gene expression analyzes will be carried out together with the company Endpoint Health (Palo Alto, California, USA).

e. Interim analysis

Two interim analyses are planned for safety and efficacy evaluation, after 96 (one third of planned sample size) patients and 234 (70% of the re-estimated sample size) patients with the complete follow up to the primary outcome. Since the recruitment rate for the study is expected to increase giving the increase in number of cases of COVID-19 in Brazil it is possible that by the time all the patients for the second interim analysis have completed the follow-up for the primary outcome, the

entire sample has already been recruited. Therefore, in this specific situation, the second interim analysis will be cancelled.

We will use the Haybittle–Peto boundary stopping rule for both safety and efficacy based on the evidence of significant differences between intervention or control group regarding ventilator free days at day 28, mortality or adverse events. The stopping rule for safety will be a p-value <0.01 and for efficacy p-value <0.001. The Haybittle–Peto boundary is a conservative stopping rule at interim analysis that has minimal impact in increasing type I error in two-arm trials[12]. We will not adjust the final tests for sequential analysis. The interim analyses will be performed by an external and independent DMC.

8. Treatment adherence

Adherence to protocol and corticosteroids use in both groups is accessed daily. The use of corticosteroids in the control group is not forbidden since critically ill patients might have another indication for corticosteroid use during their ICU stay. However, any use of corticosteroids for treating ARDS and or refractory hypoxemia in the control group is considered protocol deviation. Changes in dosage of dexamethasone or early interruption in the intervention group will also be considered protocol deviation.

9. Safety

Unexpected serious adverse events directly related to the study should be reported. Unexpected serious adverse events directly related to the study are defined as adverse events that meet the following two criteria:

1) Any fatal or life-threatening event (immediate risk of death) or that leaves a sequel or permanent disability or that prolongs hospitalization; AND

2) The attending physician believes that the event is related to inclusion in the study. Serious adverse events will be considered “study-related” if the attending physician judges that the event was probably caused by the study medication and follows a plausible time sequence since the administration of the study drug.

The most common adverse effects of corticosteroids use are hyperglycemia and possible increase in infections rates. Data on glycemic control is collected daily until day 14 and data on the development of new infections is collected daily until day 28. For any other adverse events a specific form is available on the eCRF and the data is sent in real time to the coordinating center.

10. Tables

Table 1: Demographic and clinical characteristics of patients at baseline

	Dexamethasone (Dex.)	Control (Cont.)
	n=xxx	n=xxx
Age, mean (SD)	xx.x ± xx.x	xx.x ± xx.x
Female sex, N (%)	xx.x (xx.x)	xx.x (xx.x)
SAPS3 score, mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Number of nonpulmonary organ failures, median [IQR]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Time since onset of symptoms, median [IQR], days	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Days intubated prior to randomization, median [IQR]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
COVID-19, N (%)		
Positive	xx.x (xx.x)	xx.x (xx.x)
Negative	xx.x (xx.x)	xx.x (xx.x)
In analysis	xx.x (xx.x)	xx.x (xx.x)
Not collected/Unavailable	xx.x (xx.x)	xx.x (xx.x)
Comorbidities, N (%)		
Hypertension	xx.x (xx.x)	xx.x (xx.x)
Diabetes	xx.x (xx.x)	xx.x (xx.x)
Former smoker	xx.x (xx.x)	xx.x (xx.x)

Active smoker	xx.x (xx.x)	xx.x (xx.x)
Obesity	xx.x (xx.x)	xx.x (xx.x)
Solid Tumor	xx.x (xx.x)	xx.x (xx.x)
Hematologic Malignancy	xx.x (xx.x)	xx.x (xx.x)
Heart Failure	xx.x (xx.x)	xx.x (xx.x)
COPD	xx.x (xx.x)	xx.x (xx.x)
AIDS	xx.x (xx.x)	xx.x (xx.x)
Chronic Renal Failure	xx.x (xx.x)	xx.x (xx.x)
Chronic dialysis	xx.x (xx.x)	xx.x (xx.x)
Cirrhosis	xx.x (xx.x)	xx.x (xx.x)
Asthma	xx.x (xx.x)	xx.x (xx.x)
Neuromuscular Disease	xx.x (xx.x)	xx.x (xx.x)
Previous MI	xx.x (xx.x)	xx.x (xx.x)
Clinical Characteristics		
Systolic BP, mmHg, mean (SD)	xx.x ± xx.x	xx.x ± xx.x
Diastolic BP, mmHg, mean (SD)	xx.x ± xx.x	xx.x ± xx.x
HR, bpm, mean (SD)	xx.x ± xx.x	xx.x ± xx.x
SpO_2, %, mean (SD)	xx.x ± xx.x	xx.x ± xx.x
HScore ≥169, N_0 (%)	xx.x (xx.x)	xx.x (xx.x)
Respiratory Measures (mean, SD)		
PaO_2/FiO_2	xx.x ± xx.x	xx.x ± xx.x
Tidal volume, ml/kg predicted body weight	xx.x ± xx.x	xx.x ± xx.x
Plateau Airway Pressure, cmH_2O	xx.x ± xx.x	xx.x ± xx.x
Minute Ventilation, L/min	xx.x ± xx.x	xx.x ± xx.x
Respiratory rate, breaths/min	xx.x ± xx.x	xx.x ± xx.x
Driving Pressure, cmH_2O	xx.x ± xx.x	xx.x ± xx.x
Positive End Expiratory Pressure, cmH_2O	xx.x ± xx.x	xx.x ± xx.x
Respiratory system static compliance, ml/cmH_2O	xx.x ± xx.x	xx.x ± xx.x

Intravenous sedation, N (%)	xx.x (xx.x)	xx.x (xx.x)
Richmond Agitation Sedation Scale, median [IQR]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Treatment during study period, N (%)		
Vasopressors	xx.x (xx.x)	xx.x (xx.x)
Renal Replacement Therapy	xx.x (xx.x)	xx.x (xx.x)
Use of neuromuscular blocking agents	xx.x (xx.x)	xx.x (xx.x)
ECMO	xx.x (xx.x)	xx.x (xx.x)
Prone Position	xx.x (xx.x)	xx.x (xx.x)
Blood Sample		
Creatinine, mg/dL, mean (SD)	xx.x ± xx.x	xx.x ± xx.x
D-dimer, ng/dL, mean (SD)	xx.x ± xx.x	xx.x ± xx.x
Hemoglobin, g/dL, mean (SD)	xx.x ± xx.x	xx.x ± xx.x
Total leucocyte count, µg/mL, median [IQR]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Platelets, /mm^3, mean (SD)	xx.x ± xx.x	xx.x ± xx.x
Lymphocytes, µg/mL, median [IQR]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Lactate (mg/dL)	xx.x ± xx.x	xx.x ± xx.x
Troponin, median [IQR]	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]
Additional Medication, N (%)		
Hydroxychloroquine	xx.x (xx.x)	xx.x (xx.x)
Azithromycin	xx.x (xx.x)	xx.x (xx.x)
Other antibiotics	xx.x (xx.x)	xx.x (xx.x)
Oseltamivir	xx.x (xx.x)	xx.x (xx.x)
Lopinavir+Ritonavir	xx.x (xx.x)	xx.x (xx.x)
Use of corticosteroids before randomization, N_0(%)	xx.x (xx.x)	xx.x (xx.x)

Table 2: Outcomes, adverse events, and complications

Outcomes	**Dex.**	**Cont.**	**Treatment Effect**
			Dex. vs Cont.

	n=xxx	n=xxx	[IC95%]	p
Primary Outcome				
N_o Ventilator free days from 1 to 28 d, mean (SD)	xx.x ± xx.x	xx.x ± xx.x	x.xx [x.xx; x.xx]	x.xx
Secondary Outcomes				
Clinical Status at day 15, N (%)				
Category 1-5 vs. 6 (alive vs dead)	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Category 1-4 vs. 5-6	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Category 1-3 vs. 4-6	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Category 1-2 vs. 3-6	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Category 1 vs. 2 to 6 (at home vs. hospital or dead)	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
All-Cause Mortality at 28 days	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Number of days of MV from 1 to 28 d	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
ICU free days at 28 days	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
SOFA scores				
48 h	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
72 h	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
7 days	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Adverse events				
New diagnosis of infection until day 28, N (%)	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Insulin use for hyperglycemia, N (%)	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx

Table 3 – Effect of dexamethasone vs control on ventilator free days according to subgroups

Subgroups	**Dex.**	**Cont.**	**Treatment Effect**	
			Dex. vs Cont.	
	n=xxx	**n=xxx**	**HR [IC95%]**	**p**
Age				
< 60 years	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
≥ 60 years	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
PaO_2/FiO_2				

≤ 100 mmHg	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
> 100 mmHg	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
SAPS 3				
< 50	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
≥ 50	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Duration of symptoms at randomization, d				
≤ 7	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
> 7	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Duration of moderate / severe ARDS to randomization, h				
≤24	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
>24 to 48	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Position at randomization				
Supine	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Prone	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
HScore				
< 169	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
≥ 169	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Use of corticosteroids before randomization				
Yes	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
No	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
Use of vasopressors at randomization				
Yes	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx
No	x.xx (x.xx)	x.xx (x.xx)	x.xx [x.xx; x.xx]	x.xx

11. Data Monitoring Committee Charter

Version 1.1

June 10, 2020

CONTENT	CHARTER DETAILS
INTRODUCTION	
Name of the trial	COVID-19-associated ARDS treated with DEXamethasone: CoDEX Trial **Trial Intervention** Intravenous dexamethasone
Objectives	**Primary objective** 1. Evaluate the effectiveness of early intravenous (IV) dexamethasone administration in ventilator-free days at 28 days after randomization in adult patients with moderate or severe ARDS due to confirmed or probable SARS-CoV2 infection **Secondary objectives** 1. All-cause mortality rates at 28 days after randomization 2. Clinical status of patients at 15 days after randomization using the 6-point Ordinal Scale 3. Number of days of mechanical ventilation from randomization to day 28 4. ICU free days at day 28 5. Change in the Sequential Organ Failure Assessment (SOFA) Score 48h, 72h and 7 days after randomization
Outline of scope of charter	The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, decision-making of the DMC for the CoDEX Trial, including the timing of meetings,

	methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees
ROLES AND RESPONSABILITIES	
A broad statement of the aims of the committee	To protect and serve the CoDEX Trial patients regarding safety and to assist and advise the Academic Steering Committee to protect the validity and credibility of the CoDEX Trial. To safeguard the interests of the CoDEX Trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the CoDEX Trial.
Terms of reference	The DMC should receive and review the progress and accruing data of the CoDEX Trial and provide advice on the conduct of the trial to the Academic Steering Committee. The DMC should inform the Academic Steering Committee if, in their view: I. The results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm, or a subset of trial population, is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management**.**
Specific roles of DMC	The DMC will assess and provide recommendations on the study protocol, DMC Charter, Statistical analysis plan and collected data and safety. The DMC will review the trial data after 96 patients and 234 of patients with complete follow up to the primary outcome. The review of the trial's progress will include data quality, and main endpoints

	(ventilator free days at 28 days and all-cause mortality at 28 days), including safety data.
BEFORE OR EARLY IN THE TRIAL	
Whether the DMC will have input into the protocol	All potential DMC members should have sight of the protocol before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the sponsor, scrutiny by other trial committees, a research ethics committee (REC), Medicines and Healthcare products Regulatory Agency (MHRA) and Health Research Authority. Therefore, if a potential DMC member has major reservations about the trial, they should report these to the Academic Steering Committee and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Whether the DMC will meet before the start of the trial	The DMC will meet early in the course of the trial, to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the Academic Steering Committee.
Any issues specific to the disease under study	Issues specific to the disease under study should be described.
Any specific regulatory issues	The DMC should be aware of any regulatory implications when making recommendations.
Any other issues specific to the treatment under study	Issues specific to the treatment under study should be described.

Whether members of the DMC will have a contract	DMC members do not formally sign a contract but formally register their assent to join the group by confirming (1) that they agree to be on the DMC and (2) that they agree with the contents of this Charter. Any competing interests should be declared at the same time.
COMPOSITION	
Membership and size of the DMC	Membership will consist of three members, which include at least one clinician experienced in the clinical area and at least one experienced clinical statistician. Additional members experienced in clinical trials should reflect the other specialties involved in the trial. The DMC will be formed only by overseas members. The members should not be involved with the trial in any other way nor have competing interests that could impact on the trial. Any competing interests, both real and potential, must be declared. Although members may be able to act objectively despite such connections, complete disclosure enhances credibility. The members of the IDMC for this trial are: (1) Professor Carol Hodgson (Chair) (2) Professor Michael Bailey (Statistician) (3) Professor Theodore Iwashyna
The Chair, how they are chosen and the Chair's role	The Chair should have previous experience of serving on DMCs and experience of chairing meetings and be able to facilitate and summarize discussions. The Chair will be chosen by the Academic Steering Committee and will be responsible for choosing the other two DMC members. The Chair is expected to facilitate and summarize discussions and keep copies of all reports and communications. Other Chair's roles are:

	1. Hold all DMC meetings and ensure that all relevant data is reviewed 2. Ensure that only DMC members are present during the analysis and deliberation of the DMC data 3. Approve written minutes of all closed sessions of the DMC meetings 4. Create and archive written minutes of all executive sessions of DMC meetings. These minutes will remain confidential only to DMC members until after the database has been blocked and the sponsor's disclosure. 5. Arrange additional consultations with subject matter experts as needed.
The responsibilities of the DMC statistician	The DMC statistician will be chosen by the DMC Chair and will provide independent statistical expertise. The statistician appointed by the DMC Chair will perform independent statistical analyses and have unlimited access to the entire study database. However, the analysis plan of the independent statistician of the DMC should follow the same principles described in the statistical analysis plan of the study.
The responsibilities of the Steering Committee	The responsibilities of the Academic Steering Committee are: 1. Monitor the conduct of the study, as well as the collection and quality of the study data 2. Review scheduled DMC reports, with aggregated hidden data (i.e. all subjects, not separated by treatment group) 3. Provide joint review and approval of minutes of open and final sessions of the DMC data review meetings 4. Accept or reject DMC recommendations. The DMC shall

	be notified in writing of the response to any recommendations, including the reasoning in which the recommendations are not accepted 5. Communicate the recommendations of the DMC for changes in the conduct of the study to the researchers, who in turn communicate them to the Ethics Committees of each site and to the National Council of Ethics in Research (CONEP) and to the National Health Surveillance Agency (ANVISA). Communication on the DMC with researchers will be limited to formal requests for changes in the conduct of the study and will not include information on the conduct of DMC meetings 6. The implementation of changes to the protocol is in accordance with the DMC recommendations.
RELATIONSHIPS	
Role of the funding source	The COVID-19 Brazil Coalition III is a partnership of academic leaders who designed a study initiated by a double-sponsored researcher, the Coalition in conjunction with Aché Pharmaceuticals which provided the study drug, the drug logistics distribution to the study centers and insurance for the study patients. However, Aché will have no participation or interfere with the trial design, enrolment, analysis, manuscript writing, or publication, it will have no role in the DMC´s choices, in appointing members, or in the design of this regulation. The decision to interrupt or continue the trial on the recommendation of the DMC will be entirely the responsibility of the Academic Steering Committee, without influence or supervision of the Aché. However, Aché will be notified of any decision of the steering committee as soon as the decision is made.

Payments to DMC members	Each DMC member will receive a payment of US$ 1000 (One thousand United States Dollars). DMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
ORGANISATION OF DMC MEETINGS	
Expected frequency of DMC meetings	DMC members will meet once at the beginning of the study, at each interim analysis and whenever they deem it necessary or at the request of the Academic Steering committee, especially when new evidence emerges about the therapy being studied or when adverse events are reported.
Whether meetings will be face-to-face or by teleconference	All meetings will be held by videoconference.
How DMC meetings will be organized, especially regarding open and closed sessions, including who will be present in each session	The meetings will consist of open and closed parties. During the initial open part of the meeting, a steering committee member will conduct a brief presentation related to the status of the trial, its conduct, and any concerns, and will be available for questions from DMC members. The closed session, which will take place immediately after, and will be attended only by DMC members.
TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION	
Confidentiality regarding trial's information	To protect the scientific integrity of the study under review, all members of the DMC agree to keep all information in absolute secrecy and will not disclose data, findings, or decisions outside the scope of communication defined in this Charter. Materials provided to DMC for analysis are highly confidential and should not be

	disclosed in any way to unauthorized third parties.
Will the IDMC be blinded to the treatment allocation	The DMC will not be blinded to the treatment allocation.
To whom the DMC will communicate the decisions/ recommendations that are reached	DMC recommendations duly voted and approved are transmitted in writing or by teleconference from the President of the DMC to the Academic Steering committee expeditiously, at the latest within the established deadline.
PROPOSAL OF THE STATISTICAL ANALYSIS PLAN	
General principles and interim analyses	There will be two pre-planned interim analyses for safety and efficacy evaluation, after 96 patients and 234 of patients with the complete follow up to the primary outcome. Since the recruitment rate for the study is expected to increase giving the increase in number of cases of COVID-19 in Brazil it is possible that by the time all the patients for the second interim analysis had completed the follow-up for the primary outcome, the entire sample has already been recruited. Therefore, in this specific situation, the second interim analysis will be cancelled. We will use the Haybittle–Peto boundary stopping rule for both safety and efficacy based on the evidence of significant differences between intervention or control group regarding ventilator free days at day 28, mortality or adverse events. The stopping rule for safety will be a p-value <0.01 and for efficacy p-value <0.001. The Haybittle–Peto boundary is a conservative stopping rule at interim analysis that has minimal impact in increasing type I error in two-arm trials.
Primary outcome analysis	The locking of the database will be performed after obtaining 28

and All-cause mortality analysis	days of follow-up of all patients and all the necessary actions to obtain follow-up are performed. The main analysis will be made considering the intention to treat principle. The primary outcome is to evaluate the effectiveness of early intravenous (IV) dexamethasone administration in ventilator-free days at 28 days after randomization, defined as alive and free from mechanical ventilation in adult patients with moderate or severe ARDS due to confirmed or probable SARS-CoV2 infection. Patients discharged from the hospital alive before 28 days will be considered alive and free from mechanical ventilation at day 28. Number of days free from mechanical ventilation will be presented as mean and standard deviation. The treatment effect will be presented as mean difference, with 95% confidence interval and P-value. We will use a generalized linear model with beta-binomial distribution or zero/one inflated beta distribution, with center as random effect and adjusted for age, corticosteroid use before randomization and PaO2/FiO2 ratio. All-cause mortality rates at 28 days will be analyzed using a mixed Cox model, with centers as random effects (frailty model).
Safety and stopping standards	If there is a general increase in severe adverse events at 28 days with a two-tailed alpha threshold <0.01, the DMC will consider efficacy data together with safety information to consider stopping the study, also the DMC can choose to wait for the next interim analysis for weighting. To do this, the DMC will have access to the entire study database required for this specific intermediate analysis and may request additional data if necessary. If the study is not interrupted after any intermediate analysis, the alpha thresholds for severe adverse events will not be adjusted in the final statistical analysis.

	The occurrence of other non-severe adverse events (hyperglycemia) will also be weighted by DMC. Additionally, the DMC will consider other factors outside the rigid limits mentioned above to prepare a recommendation on the study. Safety and efficacy findings often need to be weighed along with external evidence outside the rigid limits. We believe that the DMC is free to carry out such consideration and provide its opinion in these terms.
DECISION MAKING	
What decisions/recommendations will be open to the DMC	DMC will recommend one of the following written actions to the Academic Steering Committee: 1. Continue the study according to the protocol and any related changes 2. Modify the study protocol. Modifications may include, but are not with others, changes in inclusion/exclusion criteria, frequency of safety monitoring, changes in study procedures 3. Pause inclusion, with pending resolution of a specified problem 4. Interrupt the study
How decisions or recommendations will be reached within the DMC	DMC members formally vote on all recommendations to be submitted to the steering committee. To vote, a Member of the DMC must be present at the meetings convened. A simple majority vote of the members transmits a proposal, motion or recommendation to the Academic Steering Committee.
REPORTING	
To whom will the DMC report their recommendations/decisions, and in what form	The DMC will report their recommendations/decisions to the Academic Steering Committee through a letter or e-mail within one week after the DMC meeting. A copy of the DMC recommendation will be stored in the trial master file.

356

357

12. References

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. WHO. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published 2020. Accessed March 25th, 2020.
2. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med.* 2020.
3. Lewis SR, Pritchard MW, Thomas CM, Smith AF. Pharmacological agents for adults with acute respiratory distress syndrome. *Cochrane Database Syst Rev.* 2019;7:CD004477.
4. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020.
5. Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med.* 2020;8(3):267-276.
6. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA.* 2012;307(23):2526-2533.
7. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial I, Cavalcanti AB, Suzumura EA, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA.* 2017;318(14):1335-1345.
8. Lehmann EL, D'Abrera HJM. *Nonparametrics: Statistical Methods Based on Ranks.* Holden-Day; 1975.
9. Rice TW, Wheeler AP, Thompson BT, et al. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA.* 2011;306(14):1574-1581.
10. Hodgson CL, Cooper DJ, Arabi Y, et al. Maximal Recruitment Open Lung Ventilation in Acute Respiratory Distress Syndrome (PHARLAP). A Phase II,

Multicenter Randomized Controlled Clinical Trial. *Am J Respir Crit Care Med.* 2019;200(11):1363-1372.

11. *R: A Language and Environment for Statistical Computing* [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2019.

12. Blenkinsop A, Parmar MK, Choodari-Oskooei B. Assessing the impact of efficacy stopping rules on the error rates under the multi-arm multi-stage framework. *Clin Trials.* 2019;16(2):132-141.

Statistical Analysis Plan (SAP)

COVID-19-associated ARDS treated with DEXamethasone (CoDEX).

Summary of Changes

Versions and dates

Statistical Analysis Plan version 1.0
Version date: March 26, 2020
Refers to protocol version 1.0

Statistical Analysis Plan version 2.0
Version date: May 28, 2020
Refers to protocol version 5.0

Summary of changes from version 1.0 to version 2.0

Additional information on the content of each change can be found in the file SAP_comparison_v1_v2.

Header

Changes: Logotype inclusion of the new collaborators (Hospital Moinhos de Vento, Hospital Alemão Oswando Cruz, Beneficência Portuguesa and BCRI).

Cover and footers

Changes: Update with the new version and date.

Steering Committee and its components

Changes: Inclusion of the researchers (Régis Rosa, Maicon Falavigna, Álvaro Azezum, Viviane Cordeiro Veiga, Danielle Leão, João Prats, Philip Scheinberg and Renato Delascio Lopes) from the new collaborators (Hospital Moinhos de Vento, Hospital Alemão Oswando Cruz, Beneficência Portuguesa and BCRI).

Page 5

Changes: Update on version and date.

Secondary outcomes

Changes:

1- *Exclusion from the secondary outcomes: Ventilator-free days in the subgroup of patients with secondary hemophagocytic lymphohistiocytosis and Ventilator-free days in patients with laboratory-confirmed SARS-CoV2. Since the HScore for diagnosis of secondary hemophagocytic lymphohistiocytosis needs additional laboratory exams which might not be available in all centers we changed this secondary outcome to an additional analysis. The investigators believe that in patients with ARDS during the pandemic will have in the majority SARS-CoV2 infection. This outcome will be explored in a sensitivity analysis.*
2- *Inclusion of ICU free days within 28 days as a secondary outcome. Given the lack of ICU beds during the pandemic, we believe that this is a meaningful outcome, especially in developing countries.*
3- *Inclusion of the long-term outcomes of the study.*

Study Design

Changes: Change in the sample size (from 290 to 350) and in the number of ICUs participating in the trial (64 to 53).

Inclusion Criteria

Changes: Change in the time limit of the onset of moderate or severe ARDS for the inclusion in the trial from 24h to 48h. The rationale for this modification was due to most centers receiving patients intubated in the ICU already with ARDS diagnosis and more than 24 hours of mechanical ventilation, which shortened the time window for recruitment.

Exclusion Criteria

Changes: Change in the exclusion criteria. Given the widespread use of corticosteroids before ICU admission in Brazil, we allowed inclusion of patients who have previously received less than two days of corticosteroids during hospital stay, which was not allowed at first. The exclusion criteria were refined by adding three more criteria: use of immunosuppressive drugs, cytotoxic chemotherapy in the past 21 days, and neutropenia due to hematological or solid malignancies with bone marrow invasion.

Sample size and power

Changes:

1. *Change in the sample size after discussion with the Trial Steering Committee and Data Safety Monitoring Committee, before the first interim analysis, the final sample size was changed. Given the uncertainty regarding the normality of distribution of VFD, based on the Pitman Asymptotic Relative Efficiency, the sample size should be increased by 15% to preserve study power coupled with a 4% increase considering possible lost to follow-up and withdrawal of consent. Therefore, a final sample size of 350 patients is needed. Also, due to the lack of data about ventilator free days in COVID-19 patients, the sample size will be updated using the pooled standard deviation of ventilator free days of the first interim analysis, unless by the time of the first interim analysis all patients have been recruited.*
2. *Justification for the chosen minimal clinically important difference was added.*

Secondary outcomes analysis

Changes: Addition of the planned backup analysis in case of the proportional odds assumption is not met for the analysis of the Ordinal scale.

Additional analysis

Changes:

1- Definition of the proposed sensitivity analysis.

2- Definition of the subgroup analysis.

Interim analysis

Changes:

1- *Adjustment in the timing of the second interim analysis after the sample size re-estimation.*
2- *Addition of a statement clarifying that the second interim analysis might not be performed due the increase in the number of cases in Brazil with the end of recruitment before the second interim analysis.*

Safety

Changes: Addition of the definitions of severe adverse events.

Tables

Changes:

1. *Update of tables 1 and 2.*
2. *Inclusion of table 3.*

Data Monitoring Committee Charter

Change: Addition of the Data Monitoring Committee Charter.

References

Change: Update of references.