Unique Protocol ID: COVID20

Brief Title: ARB, ACEi, DRi Effects on COVID-19 Course Disease (BIRCOV)

Official Title: Effects of RAS Inhibitors (ARB, ACEi, DRI) in People with Hypertension 1-2 Stages on the Course of COVID-19 (BIRCOV Trial: ARB, ACEI, DRi Effects on COVID-19)

registered in ClinicalTrials.gov (NCT04364984).

The study begun on April 1 2020, primary completion was achieved on July 24, 2021, and final results were available on August 1, 2021 [9].

Document date 27.01.2022

January 27, 2022: Document updated for additional results

December 01, 2021: Document updated for Delayed Results.

April 16, 2020: Modified Outcome Measure Description definition to describe when the Description is required.

March 20, 2020: Clarified that Document Upload Information (Study Protocol, Statistical Analysis Plan, Informed Consent Form) should be the version reviewed by a human subjects protection review board (if applicable) and must include a cover page.

June 23, 2020: Minor editorial changes.

October 31, 2020: subanalysis for CKD.

Background

Current international guidelines suggest continuing the usage of antihypertensive drugs, in particular inhibitors of renin-angiotensin-aldosterone system, in people with hypertension who become ill with COVID-19 [1] with no differences between 5 classes of anti-hypertensive agents [2].

It is well-known that the SARS-CoV-2 uses an ACE2 receptor and furin to enter the cell [3-5]. So if ACE2 levels are higher or lower in some hypertensive subjects, then the severity of disease and blood pressure (BP) level might be different [6]. It is natural to assume that SARS-CoV-2 can affect the state of the iRAS.

Although most studies do not point out a negative effect of the virus on blood pressure levels, there is information about the different effects of different RAS inhibitors. Mandeep R et al (2020) found some differences between ACEi (Angiotensin-converting enzyme inhibitors) and ARB (Angiotensin receptor blockers) [7]. Probably, there also could be a difference for DRi (Direct renin inhibitor) [8].

In this regard, in March 2020, we initiated a study which **was aime**d to pinpoint possible clinical and laboratory differences in people with hypertension who received iRAS and suffered coronavirus infection.

Study protocol. POEM (Patient-Oriented Evidence that Matters) [10] intervention was performed as an open prospective randomized two medical centers trial in subjects suffering with COVID-19 who have been receiving iRAS, either ACEi, ARB or DRi as basic antihypertensive therapy.

120 people with stage 1-2 hypertension and COVID-19 have been screened, 108 was enrolled the trial which has been formed 2 clinical arms: clinical arm, consists of 108 people, and kidney arm, consists of 85 people with chronic kidney disease.

Study Population: patients with proved COVID-19 and preliminary stage 1-2 hypertension receiving iRAS at the onset of COVID-19 had been inspected for 24 weeks.

Details about the collection method: documents and records.

Sampling Method: Non-Probability Sample. Minimum Age:18 Years, Maximum Age: 90 Years,

Sex: All

Inclusion Criteria: Hypertension, stage 1-2

Exclusion Criteria: Hypertension, stage 3, HF (NYHA) 3-4

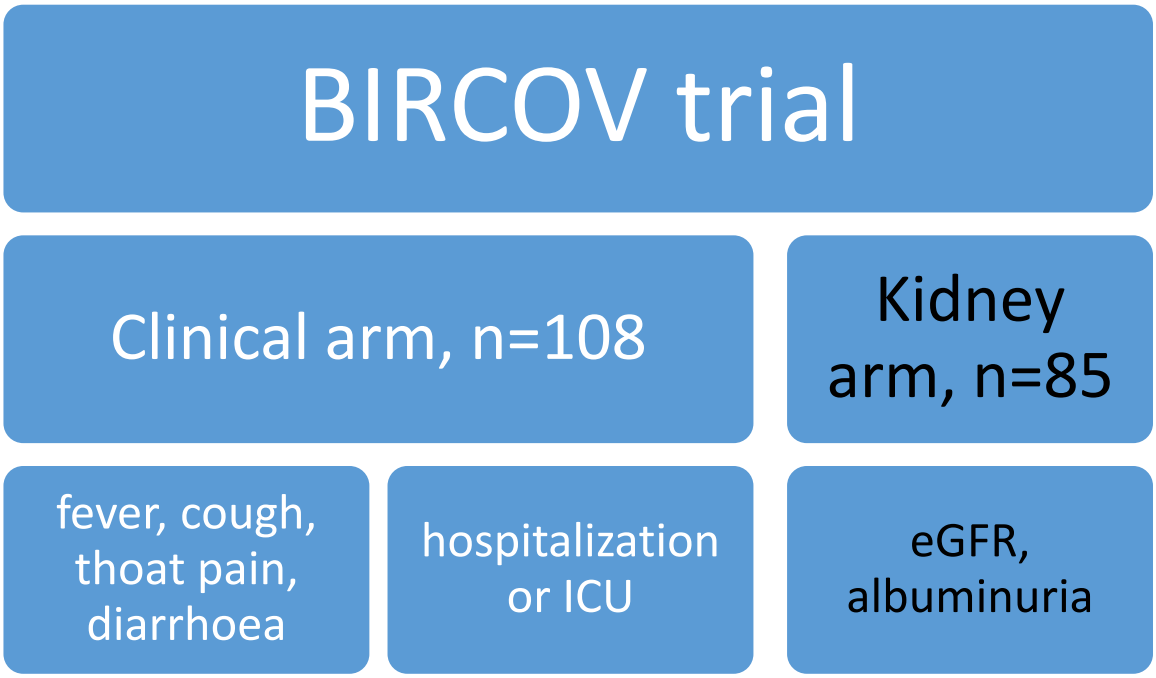
COVID-19 was confirmed by a PCR test, the disease follow-up was divided into 2 periods: up to 12 weeks and up to 24 weeks.

Primary Outcome Measure: BP was known one week before COVID-19 and was tested during the disease onset on weeks 2, 4, 12, 24. Secondary Outcome Measures: number of patients with fever (above 37.2C) up to 3 weeks after COVID-19 onset, number of patients with cough (Time Frame: 12 weeks), number of patients with throat pain (Time Frame: 2 weeks), number of patients with diarrhoea (Time Frame: 2 weeks) and number of patients who needed hospital admission and intensive care unit (Time Frame: 24 weeks).

Informed Consent Form - optional under 42 CFR Part 11, all patients gave their oral consent to submit personal data.

BIRCOV trial included sub analysis of CKD patients - kidney arm, with primary endpoint: BP and eGFR measures and secondary endpoint: albuminuria grade (picture 1).

Picture 1. BIRCOV trial



Hydration status was elevated according to Ivanova MD et al [11]. Risk of progression to kidney failure requiring dialysis or transplantation (using the Kidney Failure Risk Equation) [13] have been calculated for all patients of kidney arm on 2, 4, 12 and 24 weeks from COVID-19 onset.

The protocol was approved by a human subjects protection review board.

Outcome Measures

A table of data for each primary and secondary outcome measure by arm (that is, initial assignment of participants to arms or groups) or comparison group (that is, analysis groups), including the result(s) of scientifically appropriate statistical analyses that were performed on the outcome measure data.

Outcome Measure Type

Primary

Definition: Blood pressure.

Outcome Measure Description

Definition: mm Hg

2 characters: systolic and dyastolic.

Outcome Measure Time Frame through study completion, on 2, 4, 12, 24 week after COVID-19 onset

Arm/Group Information

Arm/Group Title: 3 groups: patients who were taken ARB (1), ACEi (2) or DRI (3).

Definition: Blood pressure, in mm Hg, 2 characters: systolic and diastolic blood pressure

Analysis Population Information

Overall Number of Participants Analyzed is 108, for each outcome measure and each arm/group are 32 (group 1), 34 (group 2) and 31 patient (group 3).

Type of Units Analyzed: sex, age, level of blood pressure

Count of Participants: Number

Count of Units of blood pressure: median

Measure of Dispersion/Precision

Standard Error

95% Confidence Interval

Number of Units Analyzed: absolute number of patients

Statistical Analyses [*]

Definition: Results of scientifically appropriate tests of statistical significance of the primary and secondary outcome measures. Such analyses include: pre-specified in the protocol and statistical analysis plan.

Statistical Analysis Overview

Definition: Summary description of the analysis performed.

Comparison Group Selection: 3 mentioned groups

Type of Statistical Test

Superiority

Statistical Test of Hypothesis

Definition: Procedure used for statistical analysis of outcome measure data and the calculated p-value.

P-Value

Definition: Calculated p-value given the null-hypothesis

Method

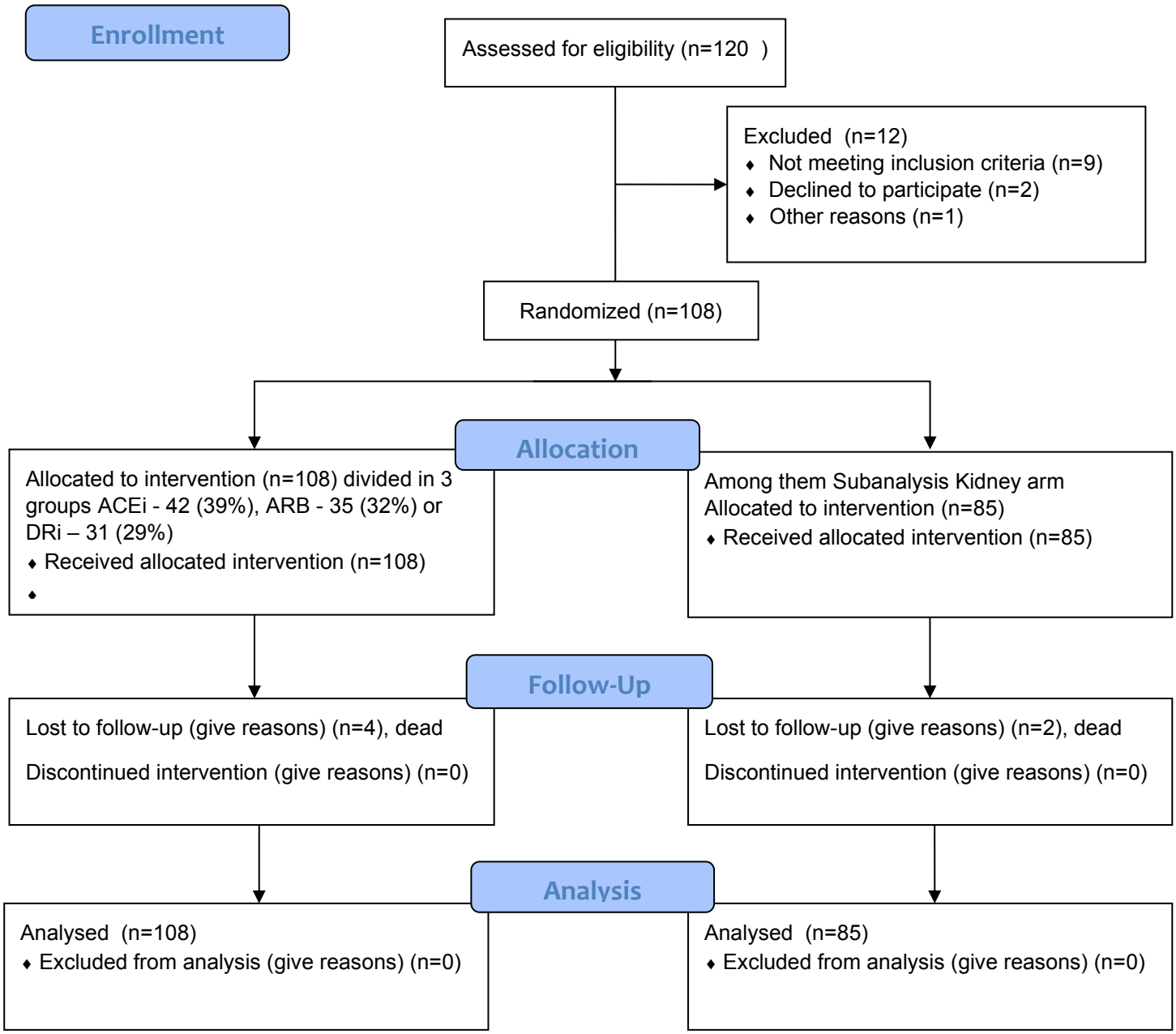
Definition: The statistical test used to calculate the p-value, if a P-Value is ANOVA

Method of Estimation

Definition: Procedure used to estimate effect of intervention. Estimation Parameter is Cox Proportional Hazard

Parameter Dispersion Type is Standard Deviation

BIRCOV trial (ARB, ACEI, DRi in COVID-19) registered in ClinicalTrials.gov (NCT04364984) Diagram of **Statistical Analysis Plan**



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