

# Clinical Trial Protocol

## Iranian Registry of Clinical Trials

23 Jun 2026

### The effect of the bromhexine-hydrochloride plus hydroxychloroquine on outcome of patients with COVID-19: A randomized, triple-blind, placebo-controlled trial

#### Protocol summary

##### Study aim

To find out the clinical efficacy of synergistic action of bromhexine hydrochloride and hydroxychloroquine or each drug alone in comparison to placebos on outcome of patients with COVID19 in a controlled and randomized clinical trial

##### Design

Triple blind randomized trial of two drugs in combination and each drug alone compared to placebo in four groups of COVID19 patients receiving, Bromhexine hydrochloride plus Hydroxychloroquine, either drug alone plus placebo of other drug, or two placebos.

##### Settings and conduct

EmamReza Hospital of Tabriz, Iran

##### Participants/Inclusion and exclusion criteria

COVID19 patients of 18 years and older admitted to hospital fulfilling the enrolment criteria and free of specified exclusion criteria

##### Intervention groups

Four groups of COVID19 patients receiving: group 1) Bromhexine hydrochloride 16 mg q 8 h for 16 days + Hydroxychloroquine, bromhexine 200 mg tablets two tablets q 12 h first day and one tablets q 12 h day 2 to 5, group 2) bromhexine plus placebo of other drug, group 3) hydroxychloroquine + placebo of other drug, group 4) placebos for both of the drugs.

##### Main outcome variables

intensive care transfer, intubation and mechanical ventilation, and survival or death

#### General information

##### Reason for update

##### Acronym

##### IRCT registration information

IRCT registration number: **IRCT20200818048444N4**

Registration date: **2021-11-28, 1400/09/07**

Registration timing: **registered\_while\_recruiting**

Last update: **2021-11-28, 1400/09/07**

Update count: **0**

##### Registration date

2021-11-28, 1400/09/07

##### Registrant information

###### Name

Khalil Ansarin

###### Name of organization / entity

###### Country

Iran (Islamic Republic of)

###### Phone

+98 41 3337 8093

###### Email address

dr.ansarin@gmail.com

##### Recruitment status

**Recruitment complete**

##### Funding source

##### Expected recruitment start date

2021-11-11, 1400/08/20

##### Expected recruitment end date

2022-05-01, 1401/02/11

##### Actual recruitment start date

empty

##### Actual recruitment end date

empty

##### Trial completion date

empty

##### Scientific title

The effect of the bromhexine-hydrochloride plus hydroxychloroquine on outcome of patients with COVID-19: A randomized, triple-blind, placebo-controlled trial

##### Public title

Efficacy of bromhexine-hydrochloride plus hydroxychloroquine on outcome of patients with COVID-19

## Purpose

Treatment

## Inclusion/Exclusion criteria

### Inclusion criteria:

COVID19 diagnosis by a physician on the basis of history and physical examination and compatible imaging and PCR testing as: 1, Having symptoms of COVID19 disease: FEVER (measured or subjective), COUGH, DYSPNEA, DIFFICULTY BREATHING, SORE THROAT, NEW OLFACTORY OR TASTE DISORDERS, SEVERE LASSITUDE OR FATIGUE, MYALGIAS, HEADACH, GI SYMPTOMS plus having compatible imaging or positive PCR testing for SARS virus COVID19 2, Being free of chronic respiratory or other illnesses with symptoms confused with symptoms of COVID19 disease AND 3 , Signed consent form.

### Exclusion criteria:

Major Exclusion Criteria: --1-1- Age: less than 18 years; justification: adult hospital with not enough young patients to compare and follow up 2- Pregnant or breast feeding woman: for fetal safety 3- Severe liver disease and severe renal failure: being confounding - 4- Serious eye disease with visual loss or cardiac conduction defects: as a confounder in side effects of drugs. 5- Subjects on immune modulating drugs for other diseases for: as confounding 6- Subjects already on bromhexine hydrochloride or hydroxychloroquine. 7- Subjects with history of allergy to bromhexine hydrochloride or hydroxychloroquine. 8- Subjects in other clinical trials for COVID-19 within 30 days before or after this trial: for being confounding. 9- Direct admission of patient to ICU at the the time of screening: because of the conflict with one of outcomes. 10- Having other subject characteristics (not thought to be related to underlying COVID-19) that portend a very poor prognosis (e.g, severe liver failure, severe renal failure, malignancies, and etc.) that may impact primary and other clinical endpoints. 11-Impending death at the time of admission on the judgement of physician. 12- Other uncontrolled disease, as judged by investigators influencing study endpoints.

## Age

From **18 years** old

## Gender

Both

## Phase

3

## Groups that have been masked

- Participant
- Care provider
- Investigator
- Outcome assessor
- Data analyser
- Data and Safety Monitoring Board

## Sample size

Target sample size: **800**

## Randomization (investigator's opinion)

Randomized

## Randomization description

After the recruitment of the subject on the basis of the inclusion and exclusion criteria, centralized web-based randomization, through random allocation by balanced block method, individuals are divided into four groups of controls and experimental. Using Random Sequence Generator, groups are created and people are placed in one of these four groups based on the reference sequence.

## Blinding (investigator's opinion)

Triple blinded

## Blinding description

Using placebos and actual drugs blind to the investigator, patient, and care givers except for the person providing drug which is not associated with any of the three. This is a triple blinded study in which the investigator, the patient, and providers of the care all will be blind to the drug received by the patient. The drugs or placebos prepared in 4 similar packages with different codes will be delivered to patient by a member of the team as pharmacist and the data regarding the nature of the packages will not be will be revealed to providers.

## Placebo

Used

## Assignment

Parallel

## Other design features

## Secondary Ids

empty

## Ethics committees

### 1

#### Ethics committee

##### Name of ethics committee

Regional Committee for Research Ethics(Human Subject Studies(91000001))

##### Street address

Third Floor, Tabriz University of Medical Sciences, Central Building Golgasht St.

##### City

Tabriz

##### Province

East Azarbaijan

##### Postal code

5166614766

#### Approval date

2021-10-25, 1400/08/03

#### Ethics committee reference number

IR.TBZMED.REC.1400.656

## Health conditions studied

### 1

#### Description of health condition studied

COVID19

#### ICD-10 code

U07.1

### ICD-10 code description

SARS-associated coronavirus as the cause of diseases classified elsewhere CODE: U07.1

## Primary outcomes

### 1

#### Description

ICU transfer

#### Timepoint

28 days after the start of the disease

#### Method of measurement

Patient hospital medical record

### 2

#### Description

Intubation and mechanical ventilation

#### Timepoint

28 days after the start of the disease

#### Method of measurement

Patient hospital medical record

### 3

#### Description

Survival or death of the patient

#### Timepoint

28 days after start of the disease

#### Method of measurement

Patient hospital medical record

## Secondary outcomes

empty

## Intervention groups

### 1

#### Description

After selection and enrolment and after obtaining and informed consent subjects will be assigned to one of four groups to receive, in addition to the usual care as directed by national guideline, one of the four treatments. In GROUP1 the subject will receive bromhexine hydrochloride tablets 16 mg every 8 hours for 14 days plus hydroxychloroquine tablets 400mg every 12 hours on day 1 and 200 mg every 12 hours on days 2 to five.

#### Category

Treatment - Drugs

### 2

#### Description

Intervention group 2: After selection and enrolment and after obtaining and informed consent subjects will be assigned to one of four groups to receive, in addition to the usual care as directed by national guideline, one of 4 treatments. In GROUP 2 the subject will receive

bromhexine hydrochloride tablets 16 mg every 8 hours for 14 days plus placebo of hydroxychloroquine tablets for five days.

#### Category

Treatment - Drugs

### 3

#### Description

Intervention group 3: After selection and enrolment and after obtaining and informed consent subjects will be assigned to one of four groups to receive, in addition to the usual care as directed by national guideline, one of the four treatments. In the group 3 the subject will receive hydroxychloroquine tablets 400mg every 12 hours at day one and 200 mg every 12 hours at days 2 to five + placebo of bromhexine for 14 days.

#### Category

Treatment - Drugs

### 4

#### Description

Control group: After selection and enrolment and after obtaining and informed consent subjects will be assigned to one of four groups to receive, in addition to the usual care as directed by national guideline, one of the four treatments. In the control group (group 4) the individual will receive just placebo for bromhexine hydrochloride for 14 days and hydroxychloroquine for 5 days.

#### Category

Placebo

## Recruitment centers

### 1

#### Recruitment center

##### Name of recruitment center

EmamReza Hospital, Tabriz University of Medical Sciences

##### Full name of responsible person

Khalil Ansarin, MD

##### Street address

Daneshgah Avenue

##### City

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##### Province

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##### Email

imamreza@tbzmed.ac.ir

##### Web page address

<https://imamreza-en.tbzmed.ac.ir/>

## Sponsors / Funding sources

### 1

#### Sponsor

**Name of organization / entity**

Tabriz University of Medical Sciences

**Full name of responsible person**

Khalil Ansarin

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Number 24 Gholghasht st.

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**Grant name**

Donation

**Grant code / Reference number**

N/A

**Is the source of funding the same sponsor organization/entity?**

Yes

**Title of funding source**

Tabriz University of Medical Sciences

**Proportion provided by this source**

100

**Public or private sector**

Private

**Domestic or foreign origin**

Domestic

**Category of foreign source of funding**

*empty*

**Country of origin****Type of organization providing the funding**

Other

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## Person responsible for scientific inquiries

**Contact****Name of organization / entity**

Tabriz University of Medical Sciences and Ministry of health

**Full name of responsible person**

Khalil Ansarin

**Position**

Professor of Meidine

**Latest degree**

Subspecialist

**Other areas of specialty/work**

Pulmonary disease and Sleep Medicine

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## Person responsible for general inquiries

**Contact****Name of organization / entity**

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**Full name of responsible person**

Khalil Ansarin

**Position**

Professor of Medicine

**Latest degree**

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**Other areas of specialty/work**

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## Person responsible for updating data

**Contact****Name of organization / entity**

Tabriz University of Medical Sciences

**Full name of responsible person**

Khalil Ansarin

**Position**

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**Other areas of specialty/work**

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## Sharing plan

### **Deidentified Individual Participant Data Set (IPD)**

Yes - There is a plan to make this available

### **Study Protocol**

Yes - There is a plan to make this available

### **Statistical Analysis Plan**

Yes - There is a plan to make this available

### **Informed Consent Form**

Yes - There is a plan to make this available

### **Clinical Study Report**

Yes - There is a plan to make this available

### **Analytic Code**

Yes - There is a plan to make this available

### **Data Dictionary**

Yes - There is a plan to make this available

### **Title and more details about the data/document**

All data can be shared without names of participating subjects

### **When the data will become available and for how long**

Summer of 2022

### **To whom data/document is available**

Researchers can reach the data after their request and approval

### **Under which criteria data/document could be used**

In order to use or control data the researchers should send their request of the data and the data will be delivered to them after approval of their request.

### **From where data/document is obtainable**

Through the email of: or kansarin@tbxmed.ac.ir or dr.ansarin@gmail.com or the postal code: 5142954481

### **What processes are involved for a request to access data/document**

The researcher should send his/her request of data to our group and data will be sent as a Excel or SPSS file.

### **Comments**