Research Protocol

Version-2

A Randomized, Double-Blind Placebo Controlled Clinical Trial of Ivermectin plus Doxycycline for the Treatment of Confirmed Covid -19 Infection

Principal Investigator

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Trial Registration: ClinicalTrials.gov Identifier: NCT04523831.

Document date: 26.08.20

Amendment Approval

Office of the Ethical Review Committee

Dhaka Medical College Hospital

Dhaka, Bangladesh

Approval of Amendment

Ref-Application from principal investigator of an ongoing trial "**A Randomized, Double-Blind Placebo Controlled Clinical Trial of Ivermectin plus Doxycycline for the Treatment of Confirmed Covid -19 Infection".**

Trial No-117

The amendment proposed by the trial team in the second version of the trial protocol"**A Randomized, Double-Blind Placebo Controlled Clinical Trial of Ivermectin plus Doxycycline for the Treatment of Confirmed Covid -19 Infection"**was verified. It is believed that these non-substantial change will not affect the quality of the trial .So the ethicalcommittee approve the following amendment in the version 2 of the trial protocol.

1. Co- Investigators List of the Protocol
2. Objective of the Protocol
3. Outcome measures of the Protocol

26/08/2020

Professor Dr. SM Shamsuzzaman

Head, Department of Microbiology and

Chairman, Ethical review committee and Data safety monitoring Board,

Dhaka Medical College

Dhaka, Bangladesh

Part A

Project Title: A Randomized, Double-Blind Placebo Controlled Clinical Trial of Ivermectin plus Doxycycline for the Treatment of Confirmed Covid -19 Infection

1. **Principal Investigator:**

Name	Designations & place of posting
Dr. Reaz Mahmud	Assistant Professor, Department of Neurology, Dhaka Medical College

2. **Co-Principal investigators:**

Name	Designations & place of posting
Professor Mujibur Rahman	Professor and Head, Department of Medicine, Dhaka Medical College
Dr. Iftikher Alam	Assistant Professor, Department of Neurology, Dhaka Medical College
Dr. Kazi Gias Uddin Ahmed	Associate Professor and Head, Department of Neurology, Dhaka Medical College
Dr. AKM. Humayon Kabir	Associate Professor, Department of Medicine, Dhaka Medical College

3. Co-investigators:

Name	Designations& place of posting
Dr. S. K Jakaria Been Sayeed	Indoor Medical Officer, Department of Medicine, Dhaka Medical College.
Dr. Mahfuzul Haque	Assistant Professor, Department of Medicine, Dhaka Medical College
Dr.MD. Shahidul Islam	Junior Consultant, Medecine, Sarkari Karmachari Hospital, Dhaka.
DR. Mohammed Monirul Islam	Assistant Surgeon, MoHFW
Dr. Mohammad Aftab Russel	Medical officer, OSD, MD Thesis part student, Department of Neurology, Dhaka Medical College
Dr. Anindta Barshan	Indoor Medical Officer, Department of Medicine, Dhaka Medical College
Dr. Farhana Binte Monayem	Medical Officer, Sarkari Karmachari Hospital,Dhaka.
Dr. Mohammad Zaid Hossain	Associate Professor, Department of Medicine, Dhaka Medical College
Dr. Mohammad Abdullah Yusuf	Assistant Professor, Department of Microbiology, National Institute of Neurosciences and Hospital.

4. Place of the study/Institution(s):

   Covid-19 Dedicated Unit, Dhaka Medical College Hospital.

5. Sponsoring/Collaborating Agencies:

   None

6. Duration:

   03 months (June 2020 to August 2020).

7. Date of Commencement:
   01, June 2020
8. Date of Completion:
   25, August 2020
9. Total Cost: Not estimated

10. Other Support for Proposed Research:

(1)	Is this research project being supported by any other source?	No
(2)	Has an application for funding of this project been submitted to any other organization(s)?	No

11. Date of Submission : 16-06-2020

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PART – B

PRINCIPAL INVESTIGATOR(S) INFORMATION SHEET

1. (i) Name :**Dr. Reaz Mahmud**

(ii) Designation: Assistant Professor, Neurology

(iii) Official Address with telephone: Dhaka Medical College Hospital, Dhaka.

Phone: 01912270803

(iv) Present Residential Address with telephone: Road # 07, House # 13
Abdullah bagh, Uttar Badda, Badda Dhaka.

4. Academic Background:

Degree	University	Field	Year
MBBS	Dhaka University		May,2003
FCPS	BCPS	Medicine	January,2013
MD	Dhaka University	Neurology	June,2015

5. Field of Specialty:

Medicine & Neurology

6. (a) Research Experience :

1. **Association between Hypertensive retinopathy and Lacunar stroke.**	Done for FCPS Dissertation
2. **Risk Factors and Morphological Differences of Ruptured Saccular Aneurysm in different sites of Anterior Circulation in Patients presenting with Subarachnoid Haemorrhage**	Done for MD thesis
3**. Recent sensitivity Pattern of Salmonella Typhi in a private hospital.**	Done for Research

(b) Other Experience:

Teaching:

1. Assistant Registrar cardiology NICVD, 03-08-09 to 21-06-10
2. Assistant Registrar Medicine, Faridpur Medical college Hospital, Faridpur 23-06-10 to 31-06-12

Administration:

Work as a Departmental Head, Critical Care Medicine, Sarkari Karmachari Hospital from 01-11-2016 to 04-12-2019

Others:

5. **Number of Scientific Publications:**

Sl No	National/ International	Original/ review	Authorship	Reference
1	National	Original	Co-author	Ali M Y, Mahmud R. A case report on Lepra Reaction Type II. Faridpur Medical college journal 2012; 2 : 93-97
2	National	Original	Author	Mahmud R, Ali MY, Islam MS, Shanewaz S, Rabbani G, Manayem FB. Association Between Hypertensive Retinopathy and Lacunar Infarct- A Study in Faridpur Medical College Hospital. DCIMC J 2016; 3(2):27-33
3	National	Original	Co-author	Saha R, Mahmud R, Hossain MZ,Sarker PK. Families with Neurocutaneous Syndrome:Report of two cases.Dhaka Med Coll J 2013; 22(1): 102-107.
4	National	Original	Author	Mahmud R, Habib M, Uddin S,Risk Factors and Morphological Differences of Ruptured Saccular Aneurysm in Different Sites of Anterior Circulation in Patients Presenting with Subarachnoid Haemorrhage. Journal of National Institute of Neurosciences Bangladesh. January 2017; 3(1):21-28.
5	National	Original	Author	Islam K, Mahmud R. Recent sensitivity Pattern of Salmonell Typhi in a private hospital.J Medicine 2018; 19: 15-17
6	National	Original	Author	Mahmud R, Habib M. Huntington's Disease with Retinitis Pigmentosa- a Case Report. Faridpur Med. Coll. J 2017;12(1):50-52.
7	National	Original	Co-Author	Ghose, S., Ahmed, K. G., Chowdhury, A., Hasan, A., Saha, K., Mahmud, R., Joy, N., Biswas, R., Sarkar, M. S., Rahman, M. M., Sina, H., Arifuzzaman, M., Alam, I., Hossain, M. M., Karim, A., & Habib, M. (2018). Assessment of Initial Stroke Severity by National Institute Health Stroke Scale (NIHSS) Score at Admission. *Journal of Dhaka Medical College*, *26*(2), 90-93. https://doi.org/10.3329/jdmc.v26i2.38765

PART - C

Project Title: A Randomized, Double-Blind Placebo Controlled Clinical Trial of Ivermectin plus Doxycycline for the Treatment of Confirmed Covid -19 Infection.

1. Summary:

On 31 December 2019, the World Health Organization (WHO) was formally notified about a cluster of cases of pneumonia in Wuhan City, China. On 7 January the responsible virus was isolated and its genome sequence was shared on 12 January. It was named as COVID-19, a novel Coronavirus, SARS-CoV-2. It is a member of the Corona virus family which is RNA enveloped viruses.

Very rapidly the virus emerged as pandemic. Now it is dominating the lives of every people of this universe. Till date **75,53,182 confirmed cases** of COVID-19, including 4,23,349 **deaths,** reported to WHO. In Bangladesh cases as well as the death tolls are also increasing exponentially (84,379 cases and 1,139 death).

Management of the COVID-19 relies on mainly supportive care and oxygen supplementation via non-invasive or mechanical ventilation in critical cases. Patients who are critically ill may also require vasopressor support and antibiotics for secondary bacterial infections.

There is no vaccine or highly effective antiviral drugs for COVID-19. Currently there is a tremendous effort around the world to develop effective preventive and therapeutic treatment for this disease.

World Health Organization has launched a non-blinded clinical trial (SOLIDARITY) to evaluate four candidate treatments (remdesivir, lopinavir/ritonavir, lopinavir/ritonavir/ interferon beta-1a, and chloroquine or hydroxychloroquine) versus standard of care in 18 countries worldwide. RECOVERY trial one of the largest trials to see the efficacy and safety of hydroxychloroquine revealed that they are no clear cut clinical benefit for COVID-19. Other drugs in the SOLIDARTY trial are quite expansive for resource limited countries like Bangladesh.

Study Published in the American Journal of Tropical Medicine advocates further research into Ivermectin for COVID-19 Treatment. The spotlight on Ivermectin was brought by Australian researchers from Monash University who demonstrated its efficacy against the SARS-CoV-2 coronavirus in vitro studies.

In a recent international, multicenter, propensity-score matched case- controlled study using prospectively collected data on patients diagnosed with COVID 19 by Patel et al, observed substantial benefit using Ivermectin over standard care.

In different study Doxycycline also showed promising results in treatment of COVID 19 infection. It is highly lipophilic antibiotics that are known to chelate zinc component of matrix metalloprotienases (MMP). Corona viruses are known to rely heavily of MMPs for survival, cell infiltration and replication. It also has an anti-inflammatory effect which might be effective in combating cytokine storm of Covid-19 infection.

So it have been planned to conduct an experimental clinical trial using combination of ivermectin and doxycycline for treatment of COVID 19 along with the other standard care. It would be a randomized double blind placebo controlled Trial. The study would be conducted on 200 confirmed cases of Covid- 19. Another 200 patients will receive placebo.

The primary outcome would be the Days required for the Clinical improvement of the patients from the day of randomization.

Data will be analyzed using SPSS 20. Unpaired t-test would be used for testing quantitative data and for testing qualitative data two sample z- test would be used. For the comparison between two groups Hazard ratio, Kaplan-Meire curve, binary logistic regression would be used to see the outcome. Result of the study and statistical analysis will be presented by tables, figures, graphs, diagrams, charts and photographs. All these will have own legends (i.e. title) and will be serially numbered. Discussion will be done on the basis of result obtained from the study and comparing with similar studies done at home and abroad. Summarization will be drawn after discussion. Conclusion will be drawn depending upon the results and discussion.

PART - D

INTRODUCTION

On 31 December 2019, the World Health Organization (WHO) was formally notified about a cluster of cases of pneumonia in Wuhan City[1]. On 7 January the causative virus was isolated and its genome sequence was shared on 12 January. The cause of the severe acute respiratory syndrome that became known as COVID-19 was a novel corona virus, SARS-CoV-2[2]. The virus Spread quickly through out the universe in quick succession. The World Health Organization (WHO) on March 11, 2020, has declared the novel Corona virus (COVID-19) outbreak a global pandemic[3].

Phylogenetic analysis suggests that SARS-CoV-2 originated in animals, probably bats, and was transmitted to other animals before crossing into humans at the Huanan wet market in Wuhan City[4-5]. It was the year 1918, when a new flu pandemic launched worldwide The pandemic infected 3% to 5% percent of the world's population including remote Pacific islands and the Arctic. The Life expectancy dropped by about 12 years[6]. The fatal casualties of the diseased had reached the number of the fifty million victims[7].

That dreadful experience might be compared with the recent ongoing pandemic. By 13 june 2020, there have been 75,53,182 confirmed cases of COVID-19, including 4,23,349 deaths, reported to WHO[8]. Most of the countries of the word are in strict lockdown state. Now it is dominating the lives of every people of this universe. The Economy of the world also constricted. In Bangladesh cases as well as the death tolls are also increasing exponentially. Our Economy is also shrinking day by day.

While the clinical presentation of COVID-19 ranges from asymptomatic to fulminant and fatal, severe cases of infection can develop pneumonia, acute respiratory distress syndrome, sepsis and/or multiple organ failure which are not unique to coronavirus[9].

Death is due to pneumonia and possibly hyper-inflammation associated with cytokine storm syndrome[10].

Management of the COVID-19 relies on mainly supportive care. Approximately 14% of the Covid-19 patients develop severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit[11].

There is no vaccine or specific antiviral drug for COVID-19 for which the people of the world are craving.

Worldwide the scientific community has focused on developing and/or repurposing medicines that can target SARS-Cov 2 and help control the pandemic of COVID-19.

Repurposing currently available medicines against COVID-19 has led to the development of hundreds of trials worldwide. Therapeutics under investigation includes various antiviral and immunomodulatory medicines[12].

Table: 1 All drugs used for COVID-19 in vitro lab and in vivo (clinical) human studies published from January 2020[13].

Name of the Drug	Name of the Drug	Name of the drug
Meplazumab(monoclonal antibody)	Darunavir(antiviral)	Umifenovir/arbidol(antiviral).
Ivermectin	Nelfinavir(antiviral)	Lopinavir/ritonavir(LPV/r)protease inhibitor
Siltuximab(monoclonal antibody).	Remdesivir(antiviral)	Interferon-alphaα
Danoprevir(antiviral)	Corticosteroids .	Interferon-beta β.
Tocilizumab/IL-6(monoclonal antibody).	Chloroquine/hydroxychloroquine	Heparin
Favipiravir(antiviral)	Convalescent Plasma	α-Lipoic acid

Many studies carried out independently in small group of people but there is a risk that the trials will lack statistical strength.

World Health Organization has launched a nonblinded clinical trial (SOLIDARITY) to evaluate four candidate treatments (remdesivir, lopinavir/ritonavir, lopinavir/ritonavir/ interferon beta-1a, and chloroquine or hydroxychloroquine) versus standard of care in 18 countries worldwide[14].

Recently a publication in lancet journal claimed that they were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19. The Findings were controversial.

Other drugs in the SOLIDARTY trial are quite expansive as well as toxic for resource limited countries like ours. Study Published in the American Journal of Tropical Medicine advocates further research into Ivermectin for COVID-19 Treatment. It could emerge as a good drug candidate. It is cheap and less toxic. Dosing regimen is also simple.

The spotlight on Ivermectin was brought by Australian researchers from Monash University who demonstrated its efficacy against the SARS-CoV-2 coronavirus in vitro studies[16].

Ivermectin has a broad spectrum antiviral activity. Recently it is found to be effective to

combat infections of RNA viruses like human immunodeficiency virus (HIV)-1, influenza, west nile virus , Zika virus and dengue virus(DENV)[17].

Caly L etal demenostrate ivermectin has antiviral action against the SARS-CoV-2 clinical isolate *in vitro*, with a single dose able to control viral replication within 24–48 h in their system[16].

Importin (IMP) α/β1 30 is a heterodimer that binds to the SARS-CoV-2 cargo protein and moves it into the nucleus which reduces the host cell antiviral response. Ivermectin destabilizes the Impα/β1 heterodimer, prevents it from viral protein binding and thus from entering the nucleus.[16, 17].

Ivermectin has an established safety profile for human use although there is not enough evidence to make conclusions about the safety profile in pregnancy[18].

However, the in vivo antiviral potential of ivermectin has only been reported against the pseudorabies virus [19] and parvoviruses [20].

Considering the promising result of the in vitro study, the clinical benefit of ivermectin therapy was evaluated in an observational registry-based study involving critically ill SARS-CoV-2-infected patients. Treatment with ivermectin at a dose of 150 µg/kg was found to be associated with a lower mortality rate and reduced healthcare resource use[21]

The clinical efficacy and utility of ivermectin in SARS-CoV-2-infected patients are unpredictable at this stage, as we are dealing with a completely novel virus.

The exact mechanism behind ivermectin is still under investigation but studies have found that a single treatment of ivermectin in a COVID-19 patient can cause the effect of a ~5000-fold reduction in viral RNA at 48 hours[16.22]. Due to an immensely significant decrease in viral load with just one dose, ivermectin holds a significant amount of promise and thus, warrants further investigation in humans.

In a recent international, multicenter, propensity-score matched case- controlled study using prospectively collected data on patients diagnosed with COVID 19 by Patel et al, observed substantial benefit using Ivermectin over standard care[16]. They found that fewer patients died in the ivermectin group (7.3 versus 21.3 percent) and overall death rates were lower with ivermectin (1.4 versus 8.4 percent).

Tetracyclines are antibiotics that are generally well-tolerated and widely available. They are generally used as broad spectrum antibiotics to treat different bacterial diseases as well as some atypical infection[23].

However, several authors have suggested they may be effective against different viruses as well. In a recent article, Mohit Sochi and Mahiyar Etminan , have suggested that they may be effective against COVID 19[24].

Tetracyclines are highly lipophilic antibiotics that are known to chelate zinc component of matrix metalloprotienases(MMP)[25]. Corona viruses are known to rely heavily of

MMPs for survival,cell infiltration and replication, many of which have zinc as part of their MMP complex[26]. It may be possible that zinc chelating properties of tetracyclines may aid in inhibition of COVID 19 infection in humans. Some in vitro studies also suggested that tetracyclines may inhibit RNA replication on positive sense single stranded RNA viruses, like COVID 19.

Second, teracyclines have well known anti-inflammatory effects. The anti-inflammatory mechanism of tetracyclines is complexe and not fully understood. However, it probably involves inactivation of MMPs, serine proteases and decrease production of inflammatory cytokines such as TNF-alpha, interleukin beta and IL-6[27]. It has been suggested that cytokines play an important role in the pathogenesis of COVID 19 including exacerbation of lung damage[28,29]. Several authors have suggested that tetracyclines may be used to treat inflammatory disorders including those caused by Corona viruses.

Third, as they are highly lipophilic drugs, tetracycline has good tissue penetration in the lungs .This, along with their anti- inflammatory properties, might allow them to inhibit viral replication in the lung and reduce lung damage. The recommendation of using tetracyclines as treatment for Corona virus was previously suggested given that chemically modified tetracycline can prevent septic shock induced by ARDS[30].

Based on the evidences, Mohit Sodhi et Al strongly urged international research groups to consider investigating the potential therapeutic efficacy of tetracycline in treating COVID 19.

Compared with the original tetracycline, the synthetics, including minocycline and doxycycline, show a better pharmacokinetic profile than the first-generation tetracyclines when used orally, being rapidly and completely absorbed, even in elderly populations, with a longer half-life and excellent tissue penetration, with almost complete bioavailability[31]

The rationale of using combination of ivermectin and doxycycline for treatment of COVID 19 is based on their antiviral and anti-inflammatory properties. Since the two drugs have different mode of action, their synergistic effect would be of value to contain the viral infection by targeting different sites of the pathogenesis of the disease.

2. OBJECTIVES:

General objectives:

To observe the benefit (clinical and microbiological) of Ivermectin and Doxycycline in Confirmed Covid 19 cases.

Specific objectives:

1. To observe the clinical outcome in trial group and the placebo group.
2. To observe the duration require for the recovery in the trial and placebo group
3. To compare the outcome between the two groups.

3. RATIONALE:

Covid-19 is an emergent pandemic, threatens the life of millions of the people throughout the globe. There is increasing effort of the scientist to unveil a remedy of covid-19. Still it is unsuccessful. At present there is no other alternative other than experimenting the existent drug against the virus. There are several trials going throughout the globe. Among them Ivermectin showed good efficacy in vitro trial. Some clinical trial also proved it beneficial. The Doxycycline also has some anti-viral role with its prominent anti-inflammatory role. Synergistic action of the two drugs might be proved some benefit in clinical trial. As both drugs are cheap and less toxic, if it does, it would be the blessing for the poor people of the globe.

4. METHODOLOGY:

Study type: Interventional Clinical trial

Estimated enrollment: 200 participants per group

For superior trial, the formula is:

$$N = \frac{1}{2} \times \left(\frac{Z_{\frac{\alpha}{2}} + Z_{\beta}}{\arcsin\sqrt{p} - \arcsin\sqrt{P_0}} \right)^2$$

N=size per group; p=the response rate of standard treatment group; p_0= the response rate of new drug treatment group; z_x= the standard normal deviate for a one or two sided x; d=

the real difference between two treatment effect; δ_0= a clinically acceptable margin; S^2= Polled standard deviation of both comparison groups.

All parameters were assumed as follows: p =0.40; p0=0.58; α=0.05;β=0.20; δ=0.18; δ0=0.10.

$$N_{\text{statistical superiority}} = \frac{1}{2} \times \left(\frac{1.96 + 0.845}{\arcsin\sqrt{0.40} - \arcsin\sqrt{0.58}} \right)^2 = 121$$

However, we are assuming that lost to follow up or refuse to include in trial will be 20%, that means 24. So at least 150 patients will be allocated randomly and power of this study will be 80%.

Allocation:

Randomized: Block randomization (Computer generated randomization code)

Intervention model: Parallel assignment

Intervention model description: Patient will be randomized 1:1 to placaebo with standard care and combined doxycycline and ivermectin with standard care.

Blinding: Double blind (The participant and the clinicians/data collectors will be unaware of the treatment the participant receives)

Primary purpose: Treatment

Official title: A phase III trial to promote recovery from covid 19 with combined Doxycycline and Ivermectin along standard care.

Provider of placebo and active ingredients: Popular pharmaceutical limited

Dosage of the drugs: Ivermactin 6 mg 2 tab stat, cap Doxycycline 100 mg 1 cap BD 5 days

Content of the placebo:

Placebo description of Ivermectin: Attached with Annexure 1

Product Name: Placebo Tablet of Imec 6 Tablet

Batch No.: PB029 **Mfg. Date:** JUN 2020 **Exp. Date:** MAY 2022

Appearance: A pale yellow colored, round, standard bi-convex uncoated tablet with a bre line on one side and other side plain

Composition:

SL. No.	MATERIAL NAME	QUANTITY PER TABLET	PERCENTAGE PER TABLET
1.	Microcrystalline Cellulose (PH102)	93.325 mg	74.644 %
2.	Pregelatinised Starch (Starch 1500)	20.000 mg	16.000 %
3.	Sodium Starch Glycolate (Type A)	9.375 mg	7.500 %
4.	Anhydrous Citric Acid	0.013 mg	0.010 %
5.	Butylated Hydroxyanisol (BHA)	0.012 mg	0.010 %
6.	Pigment Blend Yellow PB3071	0.045 mg	0.036 %
7.	Colloidal Anhydrous Silica (Aerosil 200)	0.500 mg	0.400 %
8.	Magnesium Stearate	1.750 mg	1.400 %

Placebo Description of Doxycycline: Attached with Annexure II

Product Name: Placebo Capsule of Doxibac 100 Capsule

Batch No.: PB030 **Mfg. Date:** JUN 2020 **Exp. Date:** MAY 2023

Appearance: Hard gelatin capsule shell size #2 having white opaque body imprinted with popular logo in black ink and dark blue opaque cap containing white granular powder

Composition:

SL. No.	MATERIAL NAME	QUANTITY PER CAPSULE	PERCENTAGE PER CAPSULE
1.	Anhydrous Lactose	247.000 mg	88.448%
2.	Microcrystalline Cellulose (PH102)	7.350 mg	2.629%
3.	Sodium Starch Glycolate (Type A)	20.000 mg	7.143%
5.	Magnesium Stearate	5.000 mg	1.786%
6.*	EHGC Shell Size #2 (Body: White Opaque, Cap: Dark Blue Opaque)	1 Pc.	---

Estimated study date: 01 June, 2020

Estimated primary completion date, 25 August 2020

Estimated study completion date: September, 2020

Inclusion Criteria:

- At least 18 years of age
- COVID-19 infection, confirmed by polymerase chain reaction (PCR) test within 3 days from enrollment
- Only mild and moderate COVID-19 infected cases
- Able to provide informed consent

Exclusion Criteria:

- Unable to take oral medication
- Pregnant or breast feeding lady
- Patients with severe COVID symptoms or admission in ICU/HDU

- Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN)
- On non-invasive positive pressure ventilation or mechanical ventilation at time of study entry
- Known hypersensitivity to Doxycycline or ivermectin or its components.

Research instruments:

1. Informed consent form.
2. Case record form

Primary Outcome Measure:

The number of days required for clinical improvement

1. Early Clinical improvement of the patients
How many days it requires to become the patient completely symptoms free
[Time Frame: 7 days]

2. Late clinical recovery
How many days the symptoms persist
[Time Frame: 12 days]

Secondary Outcome Measure:

1. Percentage of patients having clinical deterioration.
Patients deteriorating to next level of severity, like moderate, severe and death
[Time Frame: 1 month]

2. Persistently positive for RT-PCR.
Percentage of Covid-19 Patients repeatedly become positive for RT-PCR for Covid-19
[Time Frame: 14 days]

Data collection technique:

Data will be collected by assigned. trained data collectors (Physician).
Patient will be enrolled according to defined inclusion and exclusion criteria in the current research. Informed written consent will be obtained from the patient or their relatives. Each patient participating in the trial will be uniquely identified, and information such as his name, address is recorded in the trial 'subject number list'. Only the principle investigator will be aware about the allocation of the drugs. The patients

and the data collectors will be unaware about the group allocation of the drugs. The Data will be reviewed by the co-investigators. It will be managed by principle and co-principle investigators in designated computer.
Clinical assessment (fever, cough, Anorexia, Temperature, pulse, blood pressure, respiratory rate, oxygen saturation) will be done every day. Routine investigation (CBC, ESR, CRP, Creatinine, RBS, SGPT, chest x-ray, D- Dimer) will be done at admission and at day 3, 5, 7, 10 and 14 day. In case of the clinical deterioration it would done according to necessity. RT-PCR will be done at day-0, Day 5, day 7 and day 14.

Standard care: both the experimental and placebo will receive the available standard of care, like-

- Paracetamol, Antihistamine, Cough suppressant, Vitamins
- Oxygen therapy according to indication and need
- Low molecular weight heparin according to indication
- Appropriate other broad spectrum antibiotics
- Other drugs for associated co- morbid condition

Management of the adverse events:
Drugs adverse effect will be monitored by a defined committee. The patient experiencing adverse effect of the drugs will be discontinued from the study. It will be managed with priority to the highest possible level by the hospital authority as well as the investigators.

If the patient progresses from mild to moderate or severe disease, the study will be continued and available management of the appropriate severity will be immediately started. The patient will be monitored closely.

Data analysis:
Data will be analyzed by computer with the help of SPSS (Statistical Package for Social Sciences) version 20. To compare mean of the two group chi square will be used. Comparing drug outcome in between two group survival analysis by Kaplan-Meier curve will be done for the duration of recovery. Odds ratio will be formulated from linear logistic regression for early and late clinical recovery. Hazard ratio will be formulated from the cox regression analysis for severity conversion and persistence of the positivity. Crude odds ratio will be adjusted in cox proportional hazard ratio model. Each Ivermectin-Doxycycline plus standard of care group will be compared with the placebo plus standard care group using the log-rank test, hazard ratio and 95% CI. Participants who were lost to follow up, died, discontinue drugs due to adverse effect will censored on the last study day. All P values will be two-sided and will be shown without

adjustment for multiple testing. All analyses will be performed according to the intention to treat principle.

Dropout management: Intention to treat measure will be taken

Observation and Results:

Result of the study and statistical analysis will be presented by tables, figures, graphs, diagrams, charts and photographs. All these would have own legends (i.e. title) and will be serially numbered.

Discussion:

Discussion will be done on the basis of result obtained from the study and comparing with similar studies done at home and abroad.

Summary:

Summarization will be drawn after discussion.

Conclusion:

Conclusion would be drawn depending upon the results and discussion

Conflict of interest:

Popular pharmaceutical will only provide drugs and the placebo.
None of the investigators will receive remuneration from the pharmaceutical company.
They will not get any access to data profile.

Operational definition:

(According to WHO guideline)

Confirmed Covid-19:

Cases with positive RT-PCR for Covid 19 irrespective of symptoms**.**

Uncomplicated (mild) Illness

These patients usually present with symptoms of an upper respiratory tract viral infection, including mild fever, cough (dry), sore throat, nasal congestion, malaise, headache, muscle pain, or malaise. Signs and symptoms of a more serious disease, such as dyspnea, are not present.

Moderate Pneumonia

Respiratory symptoms such as cough and shortness of breath (or tachypnea in children) are present without signs of severe pneumonia.

Severe Pneumonia

Fever is associated with severe dyspnea, respiratory distress, tachypnea (> 30 breaths/min), and hypoxia (SpO2 < 90% on room air). However, the fever symptom must be interpreted carefully as even in severe forms of the disease, it can be moderate or even absent. Cyanosis can occur in children. In this definition, the diagnosis is clinical, and radiologic imaging is used for excluding complications.

Acute Respiratory Distress Syndrome (ARDS)

The diagnosis requires clinical and ventilatory criteria. This syndrome is suggestive of a serious new-onset respiratory failure or for worsening of an already identified respiratory picture. Different forms of ARDS are distinguished based on the degree of hypoxia. The reference parameter is the PaO2/FiO2:

- Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg. In not-ventilated patients or in those managed through non-invasive ventilation (NIV) by using positive end-expiratorypressure (PEEP) or a continuous positive airway pressure (CPAP) ≥ 5 cmH2O.
- Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg.
- Severe ARDS: PaO2/FiO2 ≤ 100 mmHg.

When PaO2 is not available, a ratio SpO2/FiO2 ≤ 315 is suggestive of ARDS.

Chest imaging utilized includes chest radiograph, CT scan, or lung ultrasound demonstrating bilateral opacities (lung infiltrates > 50%), not fully explained by effusions, lobar, or lung collapse.

Clinical improvement Criteria

1. Body temperature remains normal for at least 3 days (ear temperature is lower than 37.5 °C).

2. Respiratory symptoms are significantly improved.

3. Lung imaging shows obvious improvement in lesions.

4. There is no co-morbidities or complications which require hospitalization.

5. SpO2, >93% without assisted oxygen inhalation.

8. FLOW CHART of Study workup:

Sl No	Activities	1st	2nd	3rd	4th	5th, 6 th, 7 th	8th
1	**Recruitment and training of the field staff**						
2	**Pretesting and finalization of the questionnaire**						
3	**Consultative meeting**						
4	**Data collection**						
5	**Data entry and editing**						
6	**Data analysis and draft report writing**						
7	**Dissemination of Results**						

9. ETHICAL IMPLICATIONS

The following points will be considered during the study:

1. Patients (subjects) and key relatives were clearly informed about the scope and limitation of the study.

2. Written consent will be obtained from the patients (subjects) or from parents if patient (subject) is unable to give reliable information.

3. Confidentiality of the patients (subjects) about personal information was strictly maintained.

4. The study will not be causing any environmental hazard.

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Patient Information Sheet

(For the patients/respondents)

(Please read the handout in front of patient/respondent and explain in local language and understandable way).

The objective of this handout is to give you necessary information that will help you to take decision whether you will participate in this research work or not.

1. About the study:

To assess the differences in clinical and microbiologic outcome difference between the patients receiving ivermectin and doxycycline and the patient not having these. This research work will be conducted by the Department of Medicine, Dhaka Medical College, Dhaka. We want to include you as a study participant after receiving a written consent from you. I will explain you in a moment what are the components and your role in the study.

2. Purpose of the study:

Find out the differences in clinical and microbiologic outcome difference between the patients receiving ivermectin and doxycycline and the patient not having these.

3. Confidentiality:

The information that we will collect from this research project will be kept confidential unless permitted by you. Information that will be collected from this study will only be used for research purpose. Your personal information will not be disclosed to anyone other than the investigators.

4. Right to refuse or withdraw:

You have all the right to refuse to participate in this study if you do not wish to do so. Refusing to participate will not affect your treatment in any way. You may stop participating in this study at any time you wish.

5. Incentives:

You will not be provided any incentives to take part in this research. You will be given honorium and conveyance expenditure if you are to come for this research work.

6. Risks and discomforts:

There is a slight risk that you may share some personal and confidential information by chance or that you may feel uncomfortable about some of the topics. However, we do not wish this to happen. You may refuse to give answer to any question or any portion of it if you need to do so.

7. Benefits:

You might not get direct benefit from this study. You will get appropriate treatment in this hospital after the diagnosis of your disease. Your participation is likely to help us to acquire more knowledge about this disease which may be of benefit to other patients of our country.

8. Procedure of research:

If you agree, we will enroll you as a study participant and will adopt the following procedures for your participation-

i. We will take signature/thumb impression in the attached consent form in duplicate and a copy will be returned to you.
ii. We will ask you some questions to fill in a printed Case Record Form.
iii. You will be examined physically for the sake of this study.

If you agree to participate in this study, please sign the attached consent form.

INFORMED CONSENT FORM

I, Mr/Mrs/Miss ……., hereby giving informed consent willingly to participate in the study to be done by Dr. Reaz Mahmud. I agree to participate in the study voluntarily without any prejudice. I am fully convinced that during study I will not suffer from any serious physical or psychological problems. I am also informed that this study was carried out in the developed countries safely and my participation will bring fruitful result that will be beneficial for most patients in our country. I have right to withdraw myself from this study at any time. I shall not receive any financial benefit. I have understood that my personal information, medical records & laboratory tests will be kept strictly confidential & will be used for research purpose only.

Signature/Thumb impression of participant/Guardian:…….

Date: ……

Name: ……

Address: ……

…….

…….

Signature of witness

Date:

Name of witness:

Signature of Researcher

Date:

Project Title: A Randomized, Double-Blind Placebo Controlled Clinical Trial of Ivermectin plus doxycycline for the Treatment of Confirmed Covid -19 Infection

Case Record Form

Patient ID: ……

Demography

1. Name: 2. Age: 3. Sex: M / F
4. Address:
5. **Epidemiological link**: Y / N
5. Mobile No:
6. Residency: Urban / Rural
7. Smoker: Y / N
8. Marital Status: Married / Single
9. Education: Literate / Illiterate

Date of starting symptoms

Date of becoming Covid positive

Hospital Admission Date

Clinical Feature

Trait		Follow-up Yes-1, No-2												
	On Enrollment	D 2	D3	D4	D-5	D-6	D-7	D-8	D-9	D-10	D-11	D-12	D-13	D-14
Fever	☐Yes ☐ No													
Cough	☐Yes ☐ No													
Running nose	☐Yes ☐ No													
Sputum	☐Yes ☐ No													
Respiratory distress	☐Yes ☐ No													
Sore throat	☐Yes ☐ No													
Hoarseness of voice	☐Yes ☐ No													
Chest pain	☐Yes ☐ No													
Diarrhoea	☐Yes ☐ No													
Vomiting	☐Yes ☐ No													
Anosmia	☐Yes ☐ No													
Anorexia	☐Yes ☐ No													
Headache	☐Yes ☐ No													
Confusion	☐Yes ☐ No													

Obsrvation

Trait		Follow-up Yes-1, No-2												
	On Enrollment	D 2	D3	D4	D-5	D-6	D-7	D-8	D-9	D-10	D-11	D-12	D-13	D-14
Temperature														
Pulse rate														
BP														
Respiratory Rate														
Oxygen saturation														
Co- Morbidity	DM/HTN/ IHD/ HF/ CKD/CLD/Asthma/COPD/Malignancy/ CTD													

Investigations Profile

Trait	**Value**					
	Admission	**D-3**	**D-5**	**D-7**	**D-10**	**D-14**
Hb						
WBC						
Neutrophil						
Lymphocyte						
Platelet						
ESR						
CRP						
RBS						
Creatinine						
SGPT						
D-Dimer						
Na						
K						
ECG						
Covid-19 RT-PCR						

Radio-Imaging

Trait	**Findings**
Chest X-Ray CT Chest	Normal/ Consolidation (unilateral or bilateral) / Patchy opacity Consolidation/ Ground Glass Opacity/nodule/ multifocal

Principal Investigators: …….. Date:

Annexure-1

Popular Pharmaceuticals Ltd.

POPULAR

QUALITY ASSURANCE DEPARTMENT

Certificate of Analysis

Product Name: Placebo Tablet of Imec 6 Tablet

Batch No.: PB029 **Mfg. Date:** JUN 2020 **Exp. Date:** MAY 2022

Appearance: A pale yellow colored, round, standard bi-convex uncoated tablet with a break line on one side and other side plain

Composition:

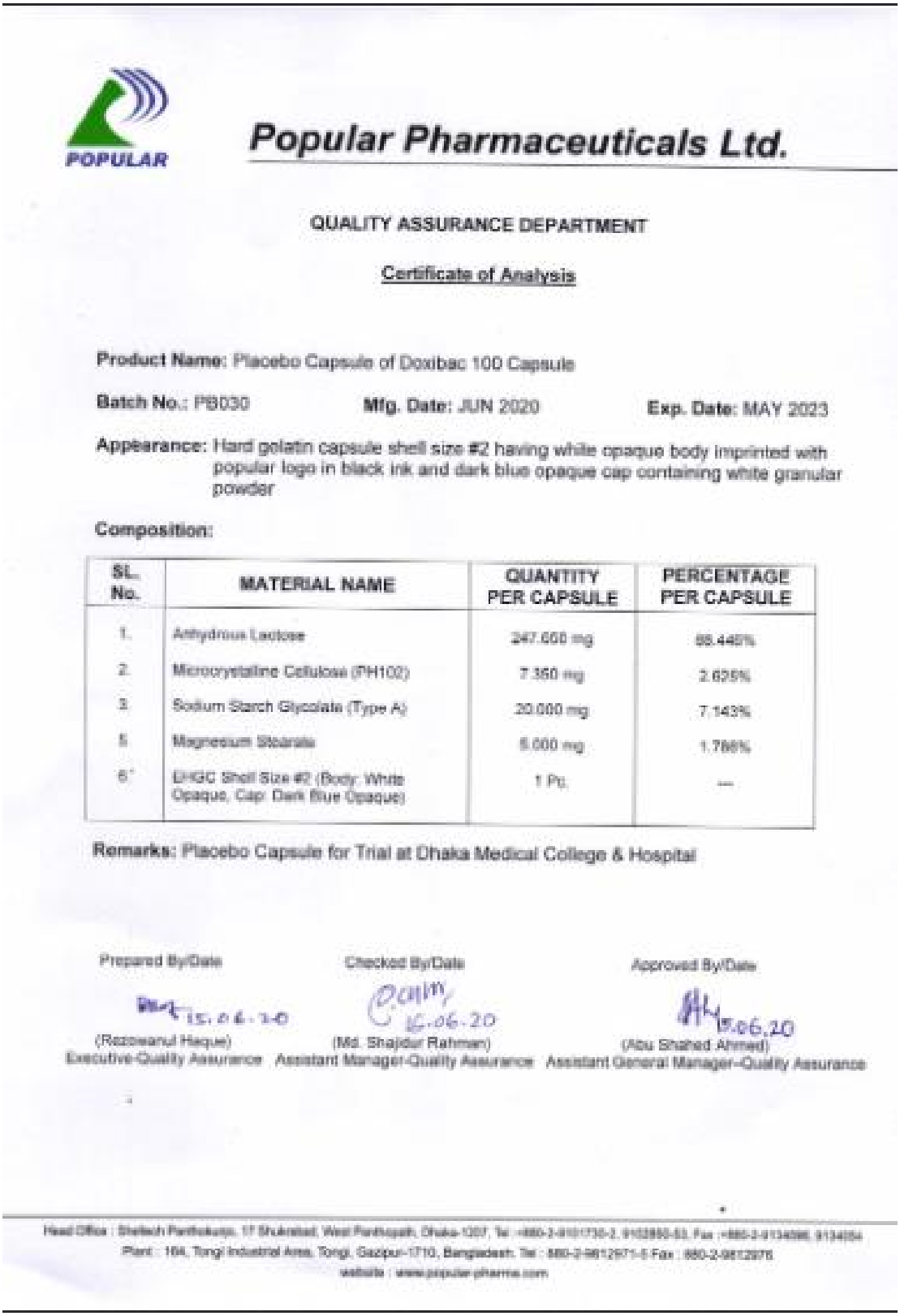
SL. No.	MATERIAL NAME	QUANTITY PER TABLET	PERCENTAGE PER TABLET
1.	Microcrystalline Cellulose (PH102)	93.325 mg	74.644 %
2.	Pregelatinised Starch (Starch 1500)	20.000 mg	16.000 %
3.	Sodium Starch Glycolate (Type A)	9.375 mg	7.500 %
4.	Anhydrous Citric Acid	0.013 mg	0.010 %
5.	Butylated Hydroxyanisol (BHA)	0.012 mg	0.010 %
6.	Pigment Blend Yellow PB3071	0.045 mg	0.036 %
7.	Colloidal Anhydrous Silica (Aerosil 200)	0.530 mg	0.400 %
8.	Magnesium Stearate	1.750 mg	1.400 %

Remarks: Placebo Tablet for Trial at Dhaka Medical College & Hospital

Prepared By/Date	Checked By/Date	Approved By/Date
15.06.20	16.06.20	17.06.20
(Razwanul Haque)	(Md. Shajidur Rahman)	(Abu Shahed Ahmed)
Executive-Quality Assurance	Assistant Manager-Quality Assurance	Assistant General Manager-Quality Assurance

Head Office : Shelltech Panthokunjo, 17 Shukrabad, West Panthapath, Dhaka-1207, Tel: +880-2-9101730-2, 9102890-93, Fax: +880-2-9134096, 9134094
Plant : 184, Tongi Industrial Area, Tongi, Gazipur-1710, Bangladesh. Tel : 880-2-9812971-5 Fax : 880-2-9812976

Annexure II:



POPULAR

Popular Pharmaceuticals Ltd.

QUALITY ASSURANCE DEPARTMENT

Certificate of Analysis

Product Name: Placebo Capsule of Doxibac 100 Capsule

Batch No.: PB030 **Mfg. Date:** JUN 2020 **Exp. Date:** MAY 2023

Appearance: Hard gelatin capsule shell size #2 having white opaque body imprinted with popular logo in black ink and dark blue opaque cap containing white granular powder

Composition:

SL. No.	MATERIAL NAME	QUANTITY PER CAPSULE	PERCENTAGE PER CAPSULE
1.	Anhydrous Lactose	247.600 mg	88.446%
2.	Microcrystalline Cellulose (PH102)	7.350 mg	2.625%
3.	Sodium Starch Glycolate (Type A)	20.000 mg	7.143%
5.	Magnesium Stearate	5.000 mg	1.786%
6.	EHGC Shell Size #2 (Body: White Opaque, Cap: Dark Blue Opaque)	1 Pc.	---

Remarks: Placebo Capsule for Trial at Dhaka Medical College & Hospital

Prepared By/Date	Checked By/Date	Approved By/Date
15.06.20	16.06.20	15.06.20
(Razowanul Haque)	(Md. Shajidur Rahman)	(Abu Shahed Ahmed)
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website : www.popular-pharma.com

DSM Board Minutes

Office of the Ethical Review Committee

Dhaka Medical College Hospital

Dhaka, Bangladesh

Minutes of the Data Safety Monitoring Board Meeting.

In response to ApplicantDr. Reaz Mahmud ,principal investigator, of an ongoing Randomized controlled trial naming"**A Randomized, Double-Blind Placebo Controlled Clinical Trial of Ivermectin plus Doxycycline for the Treatment of Confirmed Covid -19 Infection**" Trial No 117, a Data Safety Monitoring (DSM) board was formed. Its Meeting was held on 25.08.20 at 9.30 AM at Principal's Conference room, Dhaka Medical College. The meeting presided by the Chairman of the Ethical Review committee Professor Dr. SM Shamsuzzamaz, Head of the department of microbiology. The following board members were also present in the meeting:

1. Professor Dr. Khan AbulKalam Azad, Principal Dhaka Medical College.
2. Professor MD ShafiqulAlam Chowdhury, vice Principal Dhaka Medical College.
3. Professor DrAdhirKumer Das, Head of the department,pharmacology,Dhaka Medical College
4. ProfessorDr Md. Hafizur Rahman, Head of the department, Biochemistry,Dhaka Medical College

On behalf of the trial team Dr. Reaz Mahmud, Assistant professor Neurology, Presented before the board about the tolerability and adverse outcome of the Trial drug Ivermectin and Doxycycline. Professor Dr. Mujibur Rahman, Head of the department, Medicine,Dhaka Medical College, was also present on behalf of the trial team.

Dr. Reaz Mahmud presented the trial tolerability and adverse effect report by a nice power point presentation. All of the boardmembers agreedthat the drug has good tolerability and minimum side effect profiles. They all agreed that the trial might becontinued.

26/08/2020

Professor Dr. SM Shamsuzzaman

Head, Department of Microbiology and

Chairman, Ethical review committee and Data safety monitoring Board,

Dhaka Medical College

Dhaka, Bangladesh