গণপ্রজাতন্ত্রী বাংলাদেশ সরকার
স্বাস্থ্য অধিদপ্তর
মহাখালী, ঢাকা-১২১২।

স্মারক নং-স্বাঃ অধিঃ/হাসঃ/প্রাঃ ও ক্লিনিক সমূহ/করোনা চাহিদাপত্র/নড়াইল/ ৫৮২ তারিখঃ ০৬/০৫/2020

বরাবর
সচিব
স্বাস্থ্য সেবা বিভাগ
স্বাস্থ্য ও পরিবার কল্যাণ মন্ত্রণালয়
বাংলাদেশ সচিবালয়, ঢাকা।

দৃঃ আঃ অতিরিক্ত সচিব (হাসপাতাল)।

বিষয়ঃ "Convalescent Plasma therapy in severely & Critically ill COVID-19 Patients: a randomized clinical trial to observe the efficacy and safety" শীর্ষক প্রটোকল অনুমোদন ও আর্থিক বরাদ্দ প্রসংগে।

উপরোক্ত বিষয়ের প্রেক্ষিতে জানানো যাচ্ছে যে, কোভিড-১৯ রোগের সঠিক চিকিৎসা পদ্ধতি এখনও আবিষ্কৃত না হওয়ায় এবং বিভিন্ন দেশের ক্লিনিক্যাল ট্রায়াল এর আলোকে উৎসাহিত হয়ে বাংলাদেশে কোভিড-১৯ রোগীদের চিকিৎসার জন্য Convalescent Plasma'র ব্যবহারের জন্য ক্লিনিক্যাল ট্রায়াল প্রয়োজন। সে জন্য ইতপূর্বে একটি টেকনিক্যাল কমিটি গঠন করা হয়েছিল (কপি সংযুক্ত)। উক্ত টেকনিক্যাল কমিটি অধ্যাপক ডাঃ মোঃ মাজহারুল হক তপনকে Principal Investigator করে তাঁদের মাধ্যমে" "Convalescent Plasma therapy in severely & Critically ill COVID-19 Patients: a randomized clinical trial to observe the efficacy and safety" শীর্ষক একটি প্রটোকল দাখিল করেছেন।

করোনা মহামারী জনিত মারাত্বক খারাপ কোভিড-১৯ রোগীদের চিকিৎসার জন্য পৃথিবীর বিভিন্ন দেশে ইতপূর্বে কোভিড-১৯ এর আক্রান্ত হয়ে সেরে ওঠা রোগীদের রক্ত রস নিয়ে পরিসঞ্চালন করা হয়েছে। উক্ত প্রটোকলে চীনের কয়েকটি হাসপাতালে সীমিত আকারে সি.পি থেরাপীতে ভাল ফল পাওয়ার কথা উল্লেখ করা আছে।

মারাত্বক খারাপ কোভিড-১৯ রোগীদের চিকিৎসার জন্য উক্ত প্রস্তাবটি চিকিৎসার ক্ষেত্রে সুফল বয়ে আনতে পারে বলে প্রতীয়মান হয়। উক্ত ক্লিনিক্যাল ট্রায়ালটি ৬ মাস মেয়াদী এবং Sample Size 45 প্রস্তাব করা হয়েছে। উক্ত প্রটোকলটি বাস্তবায়নের অনুমোদনের প্রয়োজনীয় ব্যবস্থা গ্রহণের জন্য অনুরোধ করা হলো।

ইহাতে মহাপরিচালক মহোদয়ের অনুমোদন আছে।

০৬/০৫/2020
(ডাঃ মোঃ আমিনুল হাসান)
পরিচালক(হাসপাতাল ও ক্লিনিক সমূহ)
স্বাস্থ্য অধিদপ্তর, মহাখালী, ঢাকা-১২১২।
ফোন নং-০২-৫৫০৬৭১৫০ ,ফ্যাক্সঃ ০২-৫৫০৬৭১৫১
Email: directorhospital@ld.dghs.gov.bd

স্মারক নং-স্বাঃ অধিঃ/হাসঃ/প্রাঃ ও ক্লিনিক সমূহ/করোনা চাহিদাপত্র/নড়াইল/ তারিখঃ
অনুলিপি অবগতির জন্য প্রেরন করা হলো।
১। মহাপরিচালক, স্বাস্থ্য অধিদপ্তর, মহাখালী, ঢাকা। দৃঃ আঃ সহকারী পরিচালক(সমন্বয়)।

(ডাঃ মোঃ আমিনুল হাসান)
পরিচালক(হাসপাতাল ও ক্লিনিক সমূহ)
স্বাস্থ্য অধিদপ্তর, মহাখালী, ঢাকা-১২১২।

গণপ্রজাতন্ত্রী বাংলাদেশ সরকার
হাসপাতাল ও ক্লিনিক শাখা
স্বাস্থ্য অধিদপ্তর
মহাখালী, ঢাকা-১২১২।

স্মারক নং-স্বাঃঅধিঃ/হাসঃ/Technical Comittee/২০২০/৫১০ তারিখঃ ১৮-০৪-২০২০খ্রিঃ।

বিষয়ঃ COVID-19 ব্যবস্থাপনায় জন্য Convalescent প্লাজমা অথবা Hyperimmune সিরাম প্রয়োগের ব্যাপারে Technical Comittee গঠন বিষয়ক।

COVID-19 রোগীর ব্যবস্থাপনার জন্য Convalescent সিরাম প্রয়োগের কাযকারীতা নিয়ে ল্যান্সসেটসহ বেশ কিছু Scientific জার্নালে Article প্রকাশিত হয়েছে। এ ব্যাপারে গত ১২-০৪-২০২০ ইং তারিখে অনুষ্ঠিত জাতীয় Technical Comittee এর সভায় উক্ত বিষয়ে প্রটোকল প্রস্তুতির জন্য একটি সাব কমিটি গঠনের সিদ্ধান্ত গৃহীত হয়। নিম্নে সাব কমিটি গঠন এবং কমিটির কর্মপরিধি প্রদান/উল্লেখ করা হলোঃ

(১) অধ্যাপক ডাঃ এম.এ.খান অধ্যাপক, হেমাটোলজি বিভাগ, ডিএমসিএইচ	সভাপতি
(২) অধ্যাপক ডাঃ সাইফুল্লাহ মুন্সী অধ্যাপক ও বিভাগীয় প্রধান, ভাইরোলজি বিভাগ, বিএসএমএমইউ	সদস্য
(৩) অধ্যাপক ডাঃ আহমেদুল কবির অধ্যাপক, মেডিসিন বিভাগ, ডিএমসিএইচ	সদস্য
(৪) অধ্যাপক ডাঃ মাজহারুল হক তপন অধ্যাপক ও বিভাগীয় প্রধান, ট্রান্সফিউশন মেডিসিন বিভাগ, ডিএমসিএইচ	সদস্য সচিব

(খ) সাব কমিটির কর্ম পরিধিঃ

(১) কমিটি আগামী ০৫ দিনের মধ্যে পরীক্ষামূলকভাবে Convalescent সিরাম প্রয়োগের জন্য প্রটোকল প্রস্তুত করবেন।
(২) প্রয়োজনে উক্ত কমিটি একাধিক সদস্য কো-অপ্ট করতে পারবে।

১৮/৪/২০২০
(ডাঃ মোঃ আমিনুল হাসান)
পরিচালক (হাসপাতাল ও ক্লিনিক সমূহ)
স্বাস্থ্য অধিদপ্তর, মহাখালী, ঢাকা-১২১২
Email:directorhospital@ld.dghs.gov.bd
ফোন: ০২-৫৫০৬৭১৫০ ফ্যাক্স নং: ৫৫০৬৭১৫১

বিতরণঃ

১. অধ্যাপক ডাঃ এম.এ.খান, অধ্যাপক, হেমাটোলজি বিভাগ, ঢাকা মেডিকেল কলেজ হাসপাতাল, ঢাকা
২. অধ্যাপক ডাঃ সাইফুল্লাহ মুন্সী, অধ্যাপক ও বিভাগীয় প্রধান, ভাইরোলজি বিভাগ, বিএসএমএমইউ, শাহবাগ, ঢাকা
৩. অধ্যাপক ডাঃ আহমেদুল কবির, অধ্যাপক, মেডিসিন বিভাগ, ঢাকা মেডিকেল কলেজ হাসপাতাল, ঢাকা
৪. অধ্যাপক ডাঃ মাজহারুল হক তপন, অধ্যাপক ও বিভাগীয় প্রধান, ট্রান্সফিউশন মেডিসিন বিভাগ, ডিএমসিএইচ

অনুলিপিঃ সদয় অবগতির জন্যঃ(জ্যেষ্ঠতার ক্রমানুসারে নয়)
১। সচিব, স্বাস্থ্য সেবা বিভাগ, স্বাস্থ্য ও পরিবার কল্যাণ মন্ত্রণালয় (দৃঃআঃ সচিব মহোদয়ের একান্ত সচিব)
২। মহাপরিচালক, স্বাস্থ্য অধিদপ্তর, মহাখালী, ঢাকা (দৃঃআঃ উপ-পরিচালক, সমন্বয়)
৩। উপাচায, বঙ্গবন্ধু শেখ মুজিব মেডিকেল বিশ্ববিদ্যালয়, শাহবাগ, ঢাকা।
৪। অতিরিক্ত সচিব (হাসপাতাল), স্বাস্থ্য সেবা বিভাগ, স্বাস্থ্য ও পরিবার কল্যাণ মন্ত্রণালয়, বাংলাদেশ সচিবালয়, ঢাকা
৫। অধ্যক্ষ/পরিচালক ঢাকা মেডিকেল কলেজ, ঢাকা।

April 20, 2020

To

Director

Director General of Health Services, Dhaka, Bangladesh

Subject: Permission for conducting clinical trial of Favipiravir tablet (Brand – Favipira),

Manufactured by –Beacon for COVID-19

Dear Sir,

The outbreak of Corona virus has badly effected whole World as well as Bangladesh. There is no definite treatment in treating the disease caused by COVID 19. Beacon Pharmaceuticals Limited- a local Pharma company of Bangladesh, has produced the generic version of Avigan- a Favipiravir preparation produced by Fuji Toyama Chemical Co. Limited, Japan. Favipiravir is introduced in 2014 in Japan and used mainly for flu. But during Corona epidemic in China, this drug is used against COVID-19 and received good results. Different countries including Japan, USA are also conducting the clinical trial of this product.

Under such circumstance, Bangladesh Society of Medicine would like to conduct a clinical trial Study on Safety and Efficacy of Favipiravir (Favipira) on COVID-19 positive patient in selected hospitals of Bangladesh. The protocol of the clinical trial is attached herewith.

Selected hospitals for clinical trial will be at **Kurmitola General Hospital and Kuwait Bangladesh Maitry Govt. Hospital**

Considering the outbreak of Corona virus and need of an authentic medicine for treating Corona, we are requesting you to give ethical permission to conduct the trail on above two mentioned hospital.

With best regards

PROF. AHMEDUL KABIR
Principle Investigator
Favipiravir Clinical Trial
&
PROFESSOR, DEPARTMENT OF MEDICINE
DHAKA MEDICAL COLLEGE AND HOSPITAL

BMRC

Prof. Dr. Syed Modasser Ali
FRCS, FRCOphth (London)
Chairman
Bangladesh Medical Research Council (BMRC)
Former Adviser to Hon'ble Prime Minister of Bangladesh
Health & Family Welfare and Social Welfare Affairs (Status of a Cabinet Minister)

Ref:

April 20, 2020

Prof. Dr. Ahmedul Kabir
Principle Investigator
Favipiravir Clinical Trial
&
Professor, Department of Medicine
Dhaka Medical College & Hospital

Subject : Ethical Permission for conducting clinical trial of Favipiravir tablet (Brand – Favipira), Manufactured by –Beacon for COVID-19

Dear Dr. Kabir,

Thanks for taking such a good initiative to conduct the clinical trial of Tablet Favipiravir. Considering the countrywide lock down situation, we can't organize a formal meeting to review the trial protocol. I have gone through the protocol of the trail and discussed about it with the ethical committee of the clinical trial review committee.

Considering the national crisis of medicine for treating COVID-19, as a Chairman of BMRC, I am giving ethical permission to conduct the clinical trial of Favipiravir tablet (Brand – Favipira), Manufactured by –Beacon for COVID-19.

We look forward to hear the outcome of the trial at your earliest possible.

With best regards

Professor Dr. Syed Modasser Ali
Chairman,
Bangladesh Medical Research Council (BMRC)
Dhaka, Bangladesh

BANGLADESH MEDICAL RESEARCH COUNCIL

MOHAKHALI, DHAKA-1212, BANGLADESH

Tel: 8819311, 8828396, Fax: 880-2-8828820

Email: info@bmrcbd.org; Web: www.bmrcbd.org

DOCUMENTS TO BE SUBMITTED FOR ETHICAL APPROVAL

01. **Cover Letter to Director for Ethical Clearance by Principal Investigator.**

02. **Filled-up Ethical Clearance Application Form. (*Annexure - A*)**

03. **Signature of Principal Investigator (s) & Co-investigator (s) with details address. (*Annexure - A*)**

04. **Abstract for National Research Ethics Committee (NREC) (*Annexure - B*)**

05. **BMRC format for Submission of the Proposal for Ethical Approval (*Annexure - C*)**

06. **Informed consent form (Both Bangla and English) from participant's or from the Parent / legal guardian. (*Annexure - D*)**

07. **Questionnaire or interview schedule (Both Bangla and English).**

08. **Procedure for maintaining confidentiality.**

09. **Budget (*Annexure - E*)**

10. **Copy of approval from valid scientific review committee (If any).**

11. **Four (4) copies of all documents to be submitted to Bangladesh Medical Research Council (BMRC).**

12. **A Soft Copy in CD to be submitted.**

13. **All Documents should be Submitted in a A-4 Size Data Bank File / Folder.**

14. **Review and Processing Fee (RPF) for ethical approval:**

I. Review and Processing Fee will be determined based on 2% of the total cost of the approved Research Project, but it will not exceed Tk 5,00,000 (5 lacs).

II. At the time of initial submission of proposal, Principal Investigator will have to pay Tk 20000 (Twenty Thousand) to BMRC.

III. In case of Clinical Trial/Drug Research, Principal Investigator will have to pay Tk 50000 (Fifty Thousand) to BMRC at the time of initial submission.

IV. Undergraduate students will have to pay total Tk 2000 (Two Thousand) at the time of the submission of the proposal.

V. Total Fee will be paid by the Principal Investigator after ethical approval (at the time of receiving approval letter) by an Account Payee Cheque in favor of Bangladesh Medical Research Council.

VI. For amendment and renewal 50% of the first approval fee will be charged.

ANNEXURE - A

BANGLADESH MEDICAL RESEARCH COUNCIL

MOHAKHALI, DHAKA-1212, BANGLADESH
Tel: 8819311, 8828396, Fax: 880-2-8828820
Email: info@bmrcbd.org; Web: www.bmrcbd.org

Application for Ethical Clearance

1. **Principal Investigator(s):**

Name: Prof. Ahmedul Kabir
Qualification: MBBS, FCPS(Medicine), FACP, FRCP

Detail Address: Professor, Department of Medicine

Dhaka Medical College & Hospital

Mobile: 01720910541 Telephone (Off./Res)

e-mail: ahmedul_986@yahoo.com

2. **Co-Investigator(s):**

Name: Prof. Md. Billal Alam

Qualification: MBBS, FCPS(Medicine), MD, MACP, FACP

Detail Address: Professor & Head, Department of Medicine

Sir Salimullah Medical College & Hospital

Mobile: 01716210121 Telephone (Off. /Res)

e-mail: profbillal66@gmail.com

3. **Place of the Study/Institution(s):** Kurmitola General Hospital and Kuwait Bangladesh Maitry Govt. Hospital

4. **Title of Study:** Study on safety and efficacy of Favipiravir (Favipira) for COVID-19 patient in selected hospitals of Bangladesh

5. **Type of Study:** Randomized control study

6. **Duration of Study:** 2 months (April 23, 2020 to June 23, 2020)

7. **Total Cost:** BD Tk. 90.0 Lac (approx.)

8. **Funding Agency:** Beacon Pharmaceuticals Limited

Circle the appropriate answer to each of the following
(If not Applicable write NA)

1. Source of Population:

(a) ILL Participant — Yes — No

(b) NonILL Participant — Yes — No

(c) Minors or persons under guardianship — Yes — No

2. Does the study involve?

(a) Physical risks To the subjects — Yes — No

(b) Social Risks — Yes — No

(c) Psychological Risks to subjects — Yes — No

(d) Discomfort to Subjects — Yes — No

(e) Invasion of the body — Yes — No

(f) Invasion of Privacy — Yes — No

(g) Disclosure of Information damaging to Subject or others — Yes — No

3. Does the study involve?

(a) Use of records, (Hospital, medical, Death, birth or other) — Yes — No

(b) Use of fetal tissue Or abortus — Yes — No

(c) Use of organs or Body fluids — Yes — No

4. Are subjects clearly informed about?

(a) Nature and purposes of study — Yes — No

(b) Procedures to be followed including alternatives used — Yes — No

(c) Physical risks — Yes — No

(d) Private questions — Yes — No

(e) Invasion of the Body — Yes — No

(f) Benefits to be Derived — Yes — No

(g) Right to refuse to participate or to withdraw from study — Yes — No

(h) Confidential handling of data — Yes — No

(i) Compensation where there are risks or loss of working time or privacy is involved in any particular procedure — Yes — No

5. Will signed consent form/verbal consent be required?

(a) From Subjects — Yes — No

(b) From parent or guardian (if subjects are minors) — Yes — No

6. Will precautions be taken to protect anonymity of subjects — Yes — No

Note: If the final instrument / questionnaire is not completed prior to review, the following information should be included in the abstract.

1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific question to be asked in the sensitive areas.
3. An indication as to whom the questionnaire will be presented to the committee for review.

We agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects or any changes of the Methodology before making any such changes.

Signature

Name of the Principal Investigator/Leader/Coordinator

Date: 16/04/2020

Name of Co-investigator(S) **Signature:**

1. Prof. Dr. Md. Billal Alam

2.

3.

4.

5.

** Include all the Investigator, Co –Investigators.*

ANNEXURE - B

PREPARATION OF AN ABSTRACT
FOR
NATIONAL RESEARCH ETHICS COMMITTEE (NREC)

A recent outbreak of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan, China, at the end of 2019. The clinical characteristics of COVID-19 include respiratory symptoms, fever, cough, dyspnea, and pneumonia. 80% patients were moderate, without acute respiratory distress syndrome (ARDS). Without effective treatment, moderate patients could convert into severe patients and develop ARDS and multi-organ failure. Because most, if not all, death cases arise from severe patients, it is of great significance to carry out effective antiviral treatment in the 80% moderate patients with COVID-19, which can reduce the risk for moderate patients converting into severe cases.

At the moment, there is no specific treatment for COVID-19, so healthcare providers treat the clinical symptoms (e.g. fever, difficulty breathing) of patients. According to world health organization (WHO), COVID-19 updates on 10th April, 2020, globally confirmed cases were 16,17,204, confirmed deaths were 97,039, recovered 364686 peoples. In Bangladesh confirmed cases were 424, confirmed deaths were 27, recovered 33 peoples. On March 11, 2020, the WHO declared COVID-19 a global pandemic

In Japan, the new Phase III trial will assess Avigan's(Favipiravir) safety and efficacy as a potential Covid-19 treatment. Last month, China's Science and Technology Ministry official Zhang Xinmin said that favipiravir helped patients recover in an 80-day participant trial conducted in Shenzhen city. According to the study data, the drug was able to shorten the recovery time from 11 days to four days for mild and moderate cases. Favipiravir secured Chinese approval for manufacturing and holds approval in China as an investigational treatment for Covid-19.

A few studies have been published in international journals regarding the efficacy and safety of Favipiravir. However, this type of study on Favipiravir (Favipira) has not yet been done in our country. So, we want to conduct an open label randomized control study in Isolation word of Kurmitola General Hospital and Kuwait Bangladesh Maitry Govt. Hospital to evaluate the Efficacy and safety of Favipiravir for COVID-19 a global pandemic.

**** a 'new' drug means one which is not registered for free and open sale in Bangladesh.***

ANNEXURE - C

FORMAT FOR SUBMISSION OF A RESEARCH PROPOSAL FOR ETHICAL APPROVAL

Project Title: Study on safety and efficacy of Favipiravir (Favipira) for COVID-19 patient in selected hospitals of Bangladesh

- **Summary:**

A recent outbreak of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan, China, at the end of 2019. The clinical characteristics of COVID-19 include respiratory symptoms, fever, cough, dyspnea, and pneumonia. As of 25 February 2020, at least 77 785 cases and 2666 deaths had been identified across China and in other countries; in particular, 977 and 861 cases were identified in South Korea and Japan, respectively. The outbreak has already caused global alarm. On 30 January 2020, the World Health Organization (WHO) declared that the outbreak of SARS-CoV-2 constituted a Public Health Emergency of International Concern (PHEIC), and issued advice in the form of temporary recommendations under the International Health Regulations (IHR).It has been revealed that SARS-CoV-2 has a genome sequence that is 75%–80% identical to that of SARS-CoV, and has more similarities to several bat coronaviruses. SARS-CoV-2 is the seventh reported human-infecting member of the family Coronaviridae, which also includes SARS-CoV and the Middle East respiratory syndrome (MERS)-CoV. It has been identified as the causative agent of COVID-19. Both the clinical and the epidemiological features of COVID-19 patients demonstrate that SARS-CoV-2 infection can lead to intensive care unit (ICU) admission and high mortality. About 16%–21% of people with the virus in China have become severely ill, with a 2%–3% mortality rate. However, there is no specific treatment against the new virus. Therefore, it is urgently necessary to identify effective antiviral agents to combat the disease and explore the clinical effect of antiviral drugs. One efficient approach to discover effective drugs is to test whether the existing antiviral drugs are effective in treating other related viral infections. Several drugs, such as ribavirin, interferon (IFN), Favipiravir (FPV), and Lopinavir (LPV)/ritonavir (RTV), have been used in patients with SARS or MERS, although the efficacy of some drugs remains controversial. It has recently been demonstrated that, as a prodrug, Favipiravir (half maximal effective concentration (EC50) = 61.88 μmol·L−1, half-maximal cytotoxic concentration (CC50) > 400 μmol·L−1, selectivity index (SI) > 6.46) effectively inhibits the SARS-CoV-2 infection in Vero E6 cells (ATCC-1586). Furthermore, other reports show that FPV is effective in protecting mice against Ebola virus challenge, although its EC50 value in Vero E6 cells was as high as 67 μmol·L−1. Therefore, clinical studies are urgently needed to evaluate the efficacy and safety of this antiviral nucleoside for COVID-19 treatment.

- **Objectives:**
- **General Objectives:**

To evaluate the efficacy and safety of Favipiravir (Favipira) for the treatment of COVID-19 in a group of Bangladeshi patients

Specific objectives:

Primary end point:

- To assess the treatment efficacy: Negative for the virus at 4-10 days of therapy.

- To assess the treatment efficacy: X-ray findings of lung condition improvement at Day-4, Day-7 and Day-10 of therapy.

Secondary end point:

- Clinical recovery rate at 7-10 days of therapy and reduced duration of fever, cough, relief time auxiliary oxygen therapy or noninvasive mechanical ventilation rate.

- To assess the adverse effects of drug.

- ICU admission rate

- Mortality rate

Hypothesis

Favipiravir might be an effective drug for the treatment of COVID-19.

- **Rationale:** Coronavirus disease 2019 (COVID-19) is defined as illness caused by a novel coronavirus now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV), which was first identified amid an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China.[15] It was initially reported to the World Health Organization (WHO) on December 31, 2019. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency.[16,17] On March 11, 2020, the WHO declared COVID-19 a global pandemic, its first such designation since declaring H1N1 influenza a pandemic in 2009.[18]No drugs or biologics have been proven to be effective for the prevention or treatment of COVID-19. Numerous antiviral agents, immunotherapies, and vaccines are being investigated and developed as potential therapies [19] Fujifilm Toyama Chemical has started a Phase III clinical trial of its antiviral influenza drug Avigan (favipiravir) for the treatment of Covid-19 patients in Japan. Avigan specifically blocks RNA polymerase associated with influenza viral replication. The mechanism is expected to have an antiviral effect on SARS-CoV-2, the novel coronavirus that causes Covid-19.[2]In Japan, the new Phase III trial will assess Avigan's safety and efficacy as a potential Covid-19 treatment. Last month,

China's Science and Technology Ministry official Zhang Xinmin said that favipiravir helped patients recover in an 80-day participant trial conducted in Shenzhen city.[20]

According to the study data, the drug was able to shorten the recovery time from 11 days to four days for mild and moderate cases. Favipiravir secured Chinese approval for manufacturing by Zhejiang Hisun Pharmaceutical to treat adults with new or recurring influenza. It also holds approval in China as an investigational treatment for Covid-19.[20] A drug developed by Fujifilm Toyama Chemical in Japan is showing promising outcomes in treating at least mild to moderate cases of COVID-19, Live Science previously reported. The antiviral drug, called Favipiravir or Avigan, has been used in Japan to treat influenza, and last month, the drug was approved as an experimental treatment for COVID-19 infection. The drug, which works by preventing certain viruses from replicating, seemed to shorten the duration of the virus as well as improve lung conditions (as seen in X-rays) in tested patients.

A few studies have been published in international journals regarding the efficacy and safety of Favipiravir. However, this type of study on Favipiravir (Favipira) has not yet been done in our country. This is the rationale why we have designed this clinical trial in Bangladesh to fight against COVID-19 a global pandemic.

Methodology:

Study design: An open label randomized control study.
Randomization will be done by computerized randomization table.

Place of study: Isolation word of Kurmitola General Hospital and Kuwait Bangladesh Maitry Govt. Hospital.

Duration of study: 2 months (April 23, 2020 to June 23, 2020)

Study population: Clinically and Laboratory-confirmed patients with COVID-19

Sample Size: 50

The sample size has been calculated using the following formula;

$n = z2\ pq/d2$

$= [(1.96)\ 2 \times 0.5 \times 0.5]/0.22 = 24.$

Here n=desired sample size

z= standard normal deviate 1.96 at 95% confidence interval,

p= anticipated prevalence of COVID-19, as there is no epidemiological study on prevalence of COVID-19 in Bangladesh has been documented considering the risk of COVID-19 as 50% (0.5)

q=(1-p) and d= acceptable level of error = .20

So, the total sample size is = 24

We will take total sample = 50

Randomization will be done by computerized randomization table

Group A Patient (25) = Favipiravir + Standard Treatment

Group B Patient (25) = Only Standard Treatment

For better result sample size may be multiply on the basis of availability of COVID-19 patient in the study hospital.

Diagnostic Criteria

All patients diagnosed as COVID-19 positive on the basis of clinical and Laboratory findings.

Selection Criteria:

Inclusion Criteria:

1.Age: Male or female patients 18 -65 years old

2.Respiratory samples tested positive for the novel coronavirus.

3. Coronavirus positive at hospitalization

4. Nonpregnant women (confirmed by urine HCG test prior to enrollment)

Exclusion Criteria:

- Severe clinical condition (meeting one of the following criteria: a resting respiratory rate greater than 30 per minute, oxygen saturation below 93%, oxygenation index (OI) < 300 mmHg (1 mmHg = 133.3 Pa), respiratory failure, shock, and/or combined failure of other organs that required ICU monitoring and treatment).
- Chronic liver and kidney disease and reaching end stage.
- ICU patient
- Previous history of allergic reactions to Favipiravir.
- Pregnant or lactating women
- Women of a childbearing age with a positive pregnancy test.
- Miscarriage, or within 2 weeks after delivery

Data Collection Procedure:

Patient admitted in Isolation ward with COVID-19 positive will be used. Study population again will be confirmed by laboratory findings. Patients will be selected for the study following inclusion and exclusion criteria. Written consent will be taken from the patient for treatment with Favipiravir. After data collection, data will be analyzed for result. Finally, Summary and conclusion will be published.

Background of Data Collectors:

Data will be collected by Co-investigators of the study who are employed as physicians in the Isolation word for COVID-19 positive patients in the designated hospitals. Co-investigators are familiar about the data collection procedure as per clinical trial protocol.

Precaution for the Data Collectors:

Data Collectors should fill up data collection sheet properly. Proper monitoring of the patient should be carefully done.

Treatment:

Favipiravir 200 mg (Favipira) tablet will be given orally.

Day 1: Tablet Favipiravir 1600 mg twice daily

Days 2–Days 10: Tablet Favipiravir 600 mg twice daily.

Group A Patient (25) = Favipiravir + Standard Treatment

Group B Patient (25) = Only Standard Treatment

Standard treatment included oxygen inhalation, oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, antibiotics and antiemetic drugs & the medication any patient is on due to any concomitant diseases.

Management of adverse events:

Monitoring and managing toxicities promptly and effectively as they arise during treatment with Favipiravir.

Follow-up System:

Baseline clinical symptoms and Laboratory findings will be monitored from first day and follow up will be continued at Day-4, Day-7 and Day-10. Viral clearance will be checked by RT-PCR at Day-4, Day-7 and Day-10. X-ray findings will be monitored from Day-1 followed by Day-4, Day-7 and Day-10 to see the lung condition. Any Side effects of drugs will be documented.

Statistical Analysis:

All data will be analyzed by using the statistical package for social science (SPSS) 22. All data were given as mean ± standard deviation (SD). Chi-square test was used to compare differences between the frequencies. Serum cytokines levels were analyzed using the normality test. The statistical significance was accepted as P value < 0.05.

- **Utilization of Results:**

  A recent outbreak of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan, China, at the end of 2019. The clinical characteristics of COVID-19 include respiratory symptoms, fever, cough, dyspnea, and pneumonia. According to world health organization (WHO), COVID-19 updates on 10th April, 2020, globally confirmed cases were 16,17,204, confirmed deaths were 97,039, recovered 364686 peoples. In Bangladesh confirmed cases were 424, confirmed deaths were 27, recovered 33 peoples.

  No drugs or biologics have been proven to be effective for the prevention or treatment of COVID-19. Numerous antiviral agents, immunotherapies, and vaccines are being investigated and developed as potential therapies. A drug developed by Fujifilm Toyama Chemical in Japan is showing promising outcomes in treating at least mild to moderate cases of COVID-19, Live Science previously reported. The antiviral drug, called Favipiravir or Avigan, has been used in Japan to treat influenza, and last month, the drug was approved as an experimental treatment for COVID-19 infection. The drug, which works by preventing certain viruses from replicating, seemed to shorten the duration of the virus as well as improve lung conditions (as seen in X-rays) in tested patients.In our study on Favipiravir (Favipira), if we will get promising result regarding efficacy and safety, then it saves thousands life of Bangladeshi people. We may also export the Medicine across the globe to fight against COVID-19 a global pandemic.

- **Facilities:** Kurmitola General Hospital and Kuwait Bangladesh Maitry Govt. Hospital, both Hospitals are Bangladesh Govt. approved hospital for COVID-19 treatment. So, almost all facilities will be available.

- **Flow Chart:** 2 months
  Data collection: April 23, 2020 to May 23,2020 (One month)
  Data analysis and result: May 24 ,2020 to June 07,2020 (15 days)
  Summary and conclusion: June 08,2020 to June 23,2020 (15 days)

- **Ethical Implications:**

  •Permission will be taken from Bangladesh Medical Research Council and The Directorate General of Drug Administration (DGDA) for conducting this study.

  •Before data collection objective of the study will be informed to the respondent.
  •Informed written consent will be obtained from the participants of the study
  •The privacy and confidentiality will strictly be maintained during data collection
  •Right to discontinue from the study at any time will be ensured
  •Any adverse or side effect will be managed immediately after occurrence following standard treatment procedure.

- **References:**

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. E pub 2020 Feb 7.

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.

3. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. Epub 2020 Jan 29.
4.Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13.

5.National Health Commission of the People's Republic of China. Daily briefing on novel coronavirus cases in China [Internet]. Beijing: National Health Commission of the People's Republic of China 2020 [updated 2020 Mar 12; cited 2020 Feb 25]. Available form: http://en.nhc.gov.cn/DailyBriefing.html.

6.Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395(10224):565–74.

7.Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019nCoV) in vitro. Cell Res 2020; 30:269–71.

8.Oestereich L, Lüdtke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. Antiviral Res 2014; 105:17–21

9.Coronavirus disease 2019 (COVID-19) Situation Report. World Health Organization. 2020.3.14. https://www.who.int/

10.Max Roser, Hannah Ritchie and Esteban Ortiz-Ospina. Coronavirus Disease (COVID-19)-Statistics and Research. https://ourworldindata.org/coronavirus

11.Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; published online Feb 07. doi: 10.1001/jama.2020.1585.

12.Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; published online Mar 11. doi: 10.1016/S0140-6736(20)30566-3.

13. Worldometers.info/coronavirus/country/Bangladesh/April 10,2020

14. Gordon, C.J.; Tchesnokov, E.P.; Feng, J.Y.; Porter, D.P.; Gotte, M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J. Biol. Chem. 2020, 295, 4773–4779

15. Novel coronavirus, wuhan, china, centers for disease control and prevention.http://www.cdc.gov/coronavirus/2019ncov/about/index.html.Accessed March 25,2020.

16.Gallegos A.WHO declares public health emergency for Novel coronavirus. Medscape Medical news. http://www.medscape.com/viewarticle/924596. Accessed March 25,2020

17.Ramzy A, MC Neil DG.WHO declares global emergency as wuhan coronavirus spreads. The New York times. http://nytims/2 RER70 M. Accessed March 25,2020

18.The New York times. Corona virus live updates WHO declares pandemic as number of infected countries00000000 grows. http://www.nytimes.com/2020/03/11/world/coronavirus-news.html#link-6282e5606. Accessed March 24,2020

19.David J Cennimo , Michael Stuart Bronze, et al. Coronavirus Disease 2019 (COVID-19) Treatment & Management: Mar 27, 2020

20. Fujifilm commences Phase III trial of Avigan for Covid-19. https://www.clinicaltrialsarena.com/news/fujifilm-avigan-covid-19-trial-japan/

ANNEXURE - D

INFORMED CONSENT FORM SHOULD BE WRITTEN IN BENGALI & ENGLISH

সম্মতিপত্র

গবেষণার শিরনাম: Efficacy and safety of Favipiravir (Favipira) for COVID-19: An open label randomized control study.

মুখ্য গবেষকের নাম: Prof. Ahmedul Kabir, Professor, Department of Medicine, Dhaka Medical College & Hospital, Bangladesh

আমি নিম্ন স্বাক্ষরকারী **ডাঃ** ----------**এর নিকট থেকে জানতে পারলাম যে** ---------- ---------- **হাসপাতালে করোনা রোগীর** উপর একটি গবেষণা করা চলছে। তিনি আমাকে গবেষণা কাজটির উদ্দেশ্য, পদ্ধতি এবং সময়কাল, অংশগ্রহণের ফলে আমার সুবিধা,আমার তথ্য সমূহের প্রয়োজনীয় গোপনীয়তা রক্ষার উপায় সম্পর্কে অবহিত করেছেন। তিনি আমাকে আশ্বস্ত করেছেন এই গবেষনার অংশগ্রহন আমার ইচ্ছাধীন, অংশগ্রহনে আপত্তি জানালে আমার চিকিৎসা সেবা ব্যাহত হবেনা।

উলেখিত বিষয়াদি সম্পর্কে অবহিত হয়ে আমি স্বজ্ঞানে এবং স্বেচ্ছায় এই গবেষণা কাজে অংশগ্রহনে সম্মতি প্রদান করলাম। ইহাতে কোন প্রকার অনাকাঙ্খিত দূর্ঘটনা ঘটলে ডাক্তার বা হাসপাতাল কর্তৃপক্ষ দায়ী থাকবে না।

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অংশগ্রহকারীর স্বাক্ষর/বৃদ্ধাঙ্গুলীর ছাপ

নামঃ

ঠিকানাঃ

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সাক্ষীর স্বাক্ষর

নামঃ

ঠিকানাঃ

ANNEXURE - D

INFORMED CONSENT FORM SHOULD BE WRITTEN IN ENGLISH

CONSENT FORM

Title: Efficacy and safety of Favipiravir (Favipira) for COVID-19: An open label randomized control study.

Principal Investigator: Prof. Ahmedul Kabir, Professor, Department of Medicine, Dhaka Medical College & Hospital, Bangladesh

I am informed from Dr.----------that ---------- ---------- Hospital involve in clinical trial on Corona virus affected patient. He informed me about the clinical trial objectives, procedure and time frame. He also informing me regarding my benefit of trial and hide my personal information. He gave me assurance that my participation in this clinical trial is independent and if I will disagree to participate in the trial, my treatment will be no hamper.

I am fully informed about the above information and I myself give consent to participate in the clinical trial. If there will any kind of unwanted accidental incidence occurs, Doctors or Hospital Management will not take any responsibility.

Signature of Participant/ Finger Print

Name:
Address:

Signature of Witness

Name:
Address:

ANNEXURE - E

- Total Budget: Taka 90 Lac.
- Detailed Budget:

1. Personnel Cost: (Professional Scientific Staff, Technical & Other Staff. Please mention percentage of time to be devoted by each personnel to this Project): Tk. 20.0 lac
2. Field Expenses/Laboratory Cost: Tk. 35.0 lac
3. Supplies and Materials (Items & quantity to be specified): Tk.2.5 lac
4. Patient Cost (If applicable): Tk. 0.5 lac
5. Travel Cost (Internal travel cost only): Tk. 0.25 lac
6. Transportation of Goods: Nil
7. Office Stationery (Items & quantity to be specified): Tk. 0.25 lac
8. Data Processing/Computer Charges (If applicable): Tk 0.25 lac
9. Printing and Reproduction: Tk. 0.25 lac
10. Contractual Services (Other than manpower): Tk. 1.0 lac
11. Miscellaneous: Medicine – Tk. 30 lac