MINUTES OF 9TH MEETING OF CSC HELD ON 8TH APRIL 2020.

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1. The 9th Meeting of CSC was held on 8th April, 2020 through Zoom under the chairmanship of Dr. Abdur Rashid, of Clinical Study Committee (CSC). The meeting was held online through zoom from the Committee Room, 4th Floor, Pakistan Engineering Council (PEC), Islamabad.

2. Following members attend the meeting at committee room of Pakistan Engineering Council (PEC), Islamabad.

Sr. No.	**Name**	**Designation**
1	Dr. Abdur Rashid.	Chairman CSC / Director Pharmacy Services.
2	Dr. Masud Ur Rehman.	Secretary CSC / Additional Director, Pharmacy Services.
3	Dr. Faiza Bashir	nominee of Executive Director, Pakistan Health Research Council (PHRC)

3. Following members attended the meeting online through Zoom:

Sr. No.	**Name**	**Designation**
3	Prof. Dr. Javed Akram	Professor of Medicine, Physician, Vice Chancellor, University of Health Sciences, Lahore. Member CSC.
4	Ms. Salwa Ahsan.	Chief of Pharmacy, Shifa International Hospital, Islamabad. Member CSC.
5	Prof. Nadeem Irfan Bukhari.	Professor of Bio-Pharmaceutics & Pharmacokinetics, University of Punjab, Lahore. Member CSC.
6	Dr. Faiza Bashir	Nominee of Executive Director, Pakistan Health Research Council (PHRC) Member CSC
7	Dr. Farhana Badar.	Biostatistician & Epidemiologist, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore. Member CSC.
8	Prof. Dr. Rizwana Chaudhri	HOD Gynecologist Holy Family Hospital, Rawalpindi. Co-opted CSC Member.
9	Dr. Aamir Jaffary	Sindh Institute of Urology & Transplantation (SIUT), Karachi, Sindh Co-opted CSC Member.
10	Prof. Dr. Mushtaq Ahmed	Professor of Cardiology, Bacha Khan Medical College Mardan, Khyber Pukhtoonkhwa. Co-opted CSC Member.

3. The Meeting started with the Holy Verses. Subsequently, Chairman, CSC welcomed the participants and accordingly briefed them about the necessity of holding this meeting in the era of COVID-19 pandemic. He added that thousands of patient are dying due COVD-19 across the world, therefore, there is a dire need to protect Pakistani population from this pandemic. Chairman, CSC also thanked members for their participation online through zoom.

4. Secretary CSC, accordingly presented the agenda to the members.

AGENDA ITEM - I: NEW CASES OF CLINICAL STUDIES.

1.1) APPLICATION FOR REGISTRATION OF PROTECTS CLINICAL TRIAL ENTITLE "HYDROXYCHLOROQUINE, OSELTAMIVIR AND AZITHROMYCIN FOR THE TREATMENT OF COVID-19. (F. No. 3-21/2020-DD (PS)

1.1.1 Application is from Professor Jawed Akram, Vice Chancellor, University of Health Sciences, Lahore dated 1st April, 2020, wherein reference has been made to 8th meeting of Clinical Studies Committee (CSC) on the subject case and accordingly the application is submitted for approval of CSC. It was stated that this will be a comprehensive cohort study in four different centres across Pakistan, where University of Health Sciences Lahore shall be Research Organization in Collaboration with Postgraduate Medical Institute Lahore/Ameeruddin Medical College and other supportive partners including Medical City UK and Indus Hospital Lahore. An independent Data Safety and Monitoring Board will be established for confidential interim data analyses to advise the Trial Steering Committee about the viability of continuing with the interventions at each planned stage of the adaptive design.

1.1.2. The principle investigator of the trail is Professor Javed Akram, whereas Prof. Dr. Muhammad Shahzad, Associate Prof. Dr. Allah Rakha and Assistant Prof. Dr. Shehnoor Azher will be Co Principle investigators in the trial.

1.1.3. The Primary objective of the study is to evaluate the effectiveness of Azithromycin (500 mg PO x I dose on Day l, followed by 250 mg PO qDay on Days 2-5) alone, hydroxychloroquine (200 mg PO 8hr tds for 5 days) alone and Oseltamivir (75 mg PO ql2hr for 5 days) alone and combinations of hydroxychloroquine with Oseltamivir, Hydroxychloroquine with azithromycin, oseltamivir with azithromycin and a combination of all three drugs in clearing the coronavirus nucleic acid from throat and nasal swab.

1.1.4. The details of the submitted documents are as under:

S. No.	Document	Remarks

1	Application on prescribed Form-II	Application is not on prescribed Form-II.
2	Fee	. Rs. 200,030 (two hundreds thousands and thirty rupees only) submitted in ABL on 31-03-2020 for clinical trial.
3	Investigator Brochure (s)	Not Attached
4	Final protocol	Attached
5	Informed consent and participant information sheet (Urdu to English)	Attached in English and in local language (Urdu).
6	List of participating countries.	Participant country will be Pakistan as per Protocol.
7	Phase of trial.	No detail provided
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Not described.
9	Site of the trial	It was informed that trial would be in four different centres across Pakistan, where University of Health Sciences Lahore shall be Research Organization in Collaboration with Postgraduate Medical Institute Lahore/Ameeruddin Medical College and other supportive partners including Medical City UK and Indus Hospital Lahore. No comprehensive details about the trial sites have been provided.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Consideration letter from Prof. Dr. Nadeem Afzal, Convener, Ethical Review Committee, and University of Health Sciences Lahore has been attached. No composition of Ethical Review Committee provided.
11	Approval of National Bio-ethics Committee (NBC)	No approval from NBC is attached.
12	CV's of the Investigators	No CVs of Investigators are attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided.

14	Pre-clinical/clinical safety studies	Not Provided
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Not proved.
17	Adverse Event Reporting Form	Not attached.
18	No of patients to be enrolled in each centre.	1560 patient that will be equally split among three treatment and one observation group.
19	Name of Monitors & Clinical Research Associate	Only detail about Principal Investigator and Co-Principal Investigators is provided. No detail about Monitors and Clinical Research Associate is provided.
20	Evidence of registration in country of origin.	Not provided.
21	Copy of registration letter (if registered in Pakistan)	Not provided
22	Sample of label of the investigational product / drug.	Not provided.
22	Duration of trial	Not Provided
23	Undertaking on Stamp paper	Not provided.

1.1.5. In the view of above following shortcomings were recorded:

I) Application is not on prescribed form-II of the Bio-Study Rules 2017.
ii) Quantity of drug / trial material to be imported or used in the trial is not described.
iii) Investigator Brochure is not provided.
iv) None of the described clinical trial sites is approved from DRAP; neither the applicant has submitted application for their licensing. The applicant should be asked to submit separate application for all the four trial sites.
v) Institutional Review Board (IRB) approval of sites with complete composition of committee is not provided, only consideration letter from Dr. Nadeem Afzal, Convener, Ethical Review Committee, and University of Health Sciences Lahore has been attached.
vi) Approval from NBC is not attached.
vii) GMP certificate along with COPP & free sale certificate are not provided.
viii) Pre-clinical/clinical safety studies are not provided.
ix) Summary of Investigator Brochure is not provided.
x) Evidence of registration in country of origin is not provided.
xi) Sample of label of the investigational product / drug is not provided.
xii) Undertaking on stamp paper is not provided.

DISCUSSION:

A brief of case was presented by Secretary CSC, who also made reference to the 8th meeting of CSC held online through Zoom, wherein Prof. Javed Akram was advised to submit the pre-requisite documents to the Division of Pharmacy Services, DRAP as early as possible.

Subsequently, Prof Javed Akram, applicant of the trial briefed the members about the Protects trial. He added that the primary aim of the trial is to protect the population of Pakistan from the pandemic effects of COVID-19. He also said that, at present, all the documents were not submitted as they have to start the trial on urgent grounds due to the pandemic. However, he assured that the entire shortcoming will be removed soon.

Chairman, CSC, Dr. Faiza Bashir and Dr. Aamir Jaffary also stated that National Bio-Ethics Committee (NBC) has not given approval to the said trial, neither does Prof. Javed Akram has applied for it. Prof. Javed Akram replied that owing to the situation in the country due COVID-19, they were not able to submit the document to National Bio-Ethics Committee (NBC). He was advised by Chairman, CSC, Dr. Faiza Bashir and Dr. Aamir Jaffary to submit the document online for ethical clearance.

Chairman, CSC informed the applicant that he has submitted the fee for the registration of "Protect" clinical trial, but has neither submitted fee for trial sites nor submitted separate applications for the licensing of each clinical trial site. Prof Javed Akram replied that he would remove the short-coming as soon as possible; but, at present the trial should be approved.

Decision of 9th CSC meeting:

It was the same case as was presented in 8th meeting of CSC held online. The CSC after detailed deliberation and owing to situation of COVID-19 pandemic in Pakistan, decided to approve the Protects clinical trial entitle "Hydroxychloroquine, Oseltamivir and Azithromycin for the treatment of COVID-19". However, the CSC also directed the applicant to fulfil the shortcomings within one week; otherwise the study would stand deferred.

1.2) APPLICATION FOR APPROVAL FOR CENTRE AND CLINICAL TRIAL, EXPERIMENTAL USE OF COVID-19 CONVALESCENT PLASAMA FOR THE PURPOSE OF PASSIVE IMMUNIZATION IN CURRENT COVID-19 PANDEMIC IN PAKISTAN IN 2020. (F. No.03-23/2020-DD (PS)

1.2.1. Application is Dr Tahir Shamsi, Principal Investigator, Professor and Chairman, National Institute of Blood Disease and Bone Marrow Transplantation, Karachi, dated 31st March, 2020, wherein request has been made for approval of subject Centres and Clinical Trial, which will be carried out at following three Clinical Trial Sites in Pakistan:

i. National Institute of Blood Disease and Bone Marrow Transplantation (NIBD), Karachi (Principal Investigator, Dr Tahir Shamsi);

ii. Liaquat University of Medical and Health Sciences, Jamshoro (Co-Investigator, Dr. Bekha Ram);

iii. University of Health Sciences, Lahore (Co-investigator, Prof Jawed Akram).

1.2.2 The details of the submitted documents are as under:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Not on prescribed format.
2	Fee	2. Rs. 200,000 (two Lakhs) for the clinical trial submitted on 31-03-2020 at ABL, 1-9 Markaz Branch. 3. Rs. 100,000 (one Lakh) submitted for the trial site of National Institute of Blood Disease and Bone Marrow Transplantation (NIBD), Karachi on 31-03-2020 at ABL, 1-9 Markaz Branch. 4. Rs 100,000 (one Lakh) submitted for the trial site of Liaquat University of Medical and Health Sciences, Jamshoro on 31-03-2020 at ABL, 1-9 Markaz Branch. 5. Rs. 100,000 (one Lakh) submitted for the trial site of University of Health Sciences, Lahore on 31-03-2020 at ABL, 1-9 Markaz Branch.
3	Investigator Brochure (s)	Attached
4	Final protocol	Attached
5	Informed consent and participant information sheet (Urdu to English)	Attached in English and in local language (Urdu).
6	List of participating countries	All sites are in Pakistan
7	Phase of trial.	-
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Not described.

9	Site of the trial	i. National Institute of Blood Disease and Bone Marrow Transplantation (NIBD), Karachi. ii. Liaquat University of Medical and Health Sciences, Jamshoro. iii. University of Health Sciences, Lahore.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Approval only from Dr. Shabnum Dildar, Chairperson, Institutional Review Board/ Ethic Committee, NIBD & BMT on 26th March, 2020. No composition of committee is given.
11	Approval of National Bio-ethics Committee (NBC)	Approval from NBC is attached.
12	CV's of the Investigators	1. Dr Tahir Shamsi 2. Professor Jawed Akram 3. Prof. Bekha Ram
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided.
14	Pre-clinical/clinical safety studies	Provided
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Attached
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	2000
19	Name of Monitors & Clinical Research Associate	1. Dr. Arshi Niaz, National Institute of Blood Disease and Bone Marrow Transplantation (NIBD), Karachi. 2. Dr. Neeta Maheshwary
20	Evidence of registration in country of origin.	Not provided.
21	Copy of registration letter (if registered in Pakistan)	N/A

22	Sample of label of the investigational product / drug.	Not provided.
22	Duration of trial	Not Provided
23	Undertaking on Stamp paper	Not provided.

DISCUSSION.

The brief of trial was presented by Secretary CSC to the members. Accordingly, Dr. Tahir Shamsi, applicant of the trial was allowed to present his case before the participants. He said that convalescent plasma for the purpose of passive immunization is being used for different disease since ages. He added that plasma would be collected from COVID-19 recovered patients, who are tested negative since past four week and would be injected into moderate and severe COVID-19 patients. Recipients of the plasma would be voluntary, upon their consent and we would save our patient from going onto ventilators.

Dr. Javed Akram also stated that this procedure is used since ages and is well established. Answering the question of Chairman CSC about testing and treatment facility at the trial sites, Prof Javed Akram replied that the procedures would take place in those hospital where all the facility are available such as plasmapheresis, and Independent Data Safety and Monitoring Board/Team will also be established for safety monitoring.

Professor Rizwana Chaudhry asked whether the plasma would be injected one time or in multiple injections, and about the outcome of the study. Professor Javed Akram and Dr. Tahir Shamsi replied that one time plasma of 400-600mL would be injected to moderate and severe COVID-19 patient. The endpoint of the study will be a negative COVID-19 test and saving the patient from going on to ventilators.

Faiza Bashir raised question whether the facility of testing the IGE/ IGM titration is available in Pakistan. Javed Akram replied that we have kits imported from Austria which are FDA approved, that would be used for IGE/IGM detection. Faiza Bashir also asked to submit revised protocol of the study to the Division.

Dr. Farhana Badar asked the question about the sample size to which Dr. Tahir Shamsi replied that a total of 357 moderate and sever COVID-19 patients would be selected across all three clinical trial sites in Pakistan.

Dr. Salwa Ahsan said, she has gone through such type of studies of China, and there are not control groups in such studies. Dr. Javed Akram and Dr. Tahir Shamsi replied that placebo cannot be given to moderate and sever patients of COVID-19; therefore, there is not a need of control group.

Dr. Aamir Jaffary stated that donors of convalescent plasma should not be the part of your study and therefore should be not consented.

Secretary, Clinical Study Committee said that there should be a team of Physicians for the supervision of safety of the patients. Javed Akram replied that an Independent Data Safety Monitoring Board, headed must be established.

Chairman, Clinical Study Committee apprised the applicant that has submitted the fees for all three clinical trial sites, but, have not submitted separated application for their licensing. Dr. Javed Akram replied that due COVID-19 pandemic; we were not able to submit separate application. Some of the trial sites are already approved and in current situation the inspection of the new trial sites could not be accomplished. The fee of all the trails sites is submitted.

Decision of 9th CSC meeting:

The CSC after detailed deliberation and owing to situation of COVID-19 pandemic in Pakistan in order to protect the patients, decided to approve the clinical trial with title "Experimental use of COVID-19 convalescent plasma for the purpose of passive immunization in current COVID-19 pandemic in Pakistan in 2020". Three trial sites namely: National Institute of Blood Disease and Bone Marrow Transplantation (NIBD), Karachi; Liaquat University of Medical and Health Sciences, Jamshoro; and University of Health Sciences, Lahore were also allowed to conduct this trial. It was also decided that the applicant would submit revised protocol to the CSC and establish independent safety monitoring board.

1.3) APPLICATION FOR CLINICAL TRIAL/ TEST OF BASIC VENTILATORS.

1.3.1 Application is from Engr. Tariq Javed (R), Advisor on Innovation, Pakistan Engineering Council in reference to prevailing pandemic environment for the approval of special permission for conducting clinical test/ analysis of Basic Ventilators designated by (Engr. Muneed and Engr. Muiz) for initial validation. Accordingly, Additional Director, Division of Pharmacy Services through a letter allowed the shifting of their equipment ventilators to the hospital where it will be used to treat COVID-19 patients to save the time.

1.3.2 Following Technical Committee was constituted by DRAP through a letter F.16-5/2020-MD, dated 4th April, 2020 for assessment/ evaluation of locally manufactured medical devices (Ventilators).

1. Maj. Gen. Aslam Khan (R): Prof. of Pulmonology and Critical Care, Bahria International Hospital, Rawalpindi.
2. Maj. Gen prof Dr. Shahabuddin: Prof. of Anesthesia and Critical Care, Rawal Institute of Health Sciences, Islamabad.
3. Dr. Rana Imran Sikandar: Prof. of Anesthesia and Critical Care, PIMS Islamabad.
4. Dr. Mushtaq Ahmad: Prof. of Cardiology, Bacha Khan Institute of Cardiology, Mardan.
5. Dr. Saqib Saeed, Pulmonologist, King Edward Medical University Lahore.
6. Dr. Madiha Hashmi: Prof. of Anesthesia and Critical Care, Ziauddin Hospital Karachi.
7. Dr Fazal Hameed Khan, Anesthetist, AKUH, Karachi
8. Dr. Saeeda Haider: Prof. of Anesthesia and Critical Care Indus Hospital Karachi
9. Dr. Arshad Tagi: Anesthetist and Critical Care specialist, Hameed Latif Hospital, Lahore.
10. Dr. Kamran Cheema, SIMS, Lahore.

1.3.3 The above committee has recommended the following protocol for testing the ventilators:

A. **Performance Qualification: (Clinical Study)**

A clinical study should be conducted under the supervision of Principal Investigator (PI) and his team comprising of Anesthetist(s), Critical Care Health specialist(s) and Biomedical Engineer(s) and Professional Engineer(s) etc. duly constituted by PEC/DRAP.

A.1 **Study Structure**: Clinical Study should be structured while observing standard guidelines given by DRAP and should include minimum parameters like, Title, Methodology, Duration, Location /Hospital, Number of Human Subjects, Diagnosis and Inclusion Criteria, exclusion criteria, Product & Planned Use, Reference Equipment, Statistical Methodology and Analysis.

A.2 **Minimum Number of Hours on Human Subjects**: 96 hours continuous operation (more than 1 human subject may be used).

A.3 **Clinical Study Report:** Signed by Clinical Study Team and OEM's Rep

A.4 **User Feedback & Acceptance**: Form Under development

C**. Recommendation for Regulatory Acceptance** should include:

C.1 Test Report of Physical & Functional Qualification with recommendations

C.2 Clinical Study Report with recommendations

C.3 User feedback and Recommendations

1.3.4 The applicant has not submitted the application for trial sites. However, the trial would be conducted at the following well-known, established hospitals as trail sites:

i. Combined Military Hospital, Rawalpindi;
ii. Indus Hospital, Karachi; and
iii. Mayo Hospital, Lahore.

1.3.5 Details of the composition of Technical Committee constituted by Pakistan Engineering Council (PEC) to prepare fast-track acceptance test procedures for locally developed mechanical ventilators for COVID-19 pandemic, along with guidance document to outline structures approach for the testing and acceptance of locally developed mechanical ventilators for COVID-19 is Annexed as "Annexure A"

DISCUSSION.

Chairman, CSC presented a brief of the case to the members of committee. He said that the project is a joint venture of Military and Civil side. There is shortage of ventilators across the world and in Pakistan. Therefore, there is a dire need of indigenous development of ventilators. He further added that Special Assistant to Prime Minister (SAPM) on National Health Services and Minister of Science and Technology met to discuss this project. On the advice of SAPM on National Health Services, two expert committees for evaluation of projects of locally manufactured medical devices (ventilators) and diagnostic kits for SARS-COV2 were constituted by DRAP. The ten-member team for assessment/ evaluation of locally manufactured medical devices (ventilators) was comprised of anesthetists, cardiologists, critical care specialists and pulmonologists. The said team has recommended the approval of these basic ventilators for testing on Simulators for testing ventilators.

Engr. Tariq Javed, briefed the members about the project. He informed that at present there are approximately 5000 ventilators in Pakistan and other countries are reluctant to provide ventilators to Pakistan. There is a dire need to develop locally manufactured ventilators in order to avert the pandemic effects of COVID-19. He further added that on 26th March, 2020, Medical and Health Product Regulatory Authority of United Kingdom issued guidance document of Rapid Manufactured Ventilators System, and the same was picked up by Pakistan Engineering Council (PEC) to develop locally manufactured ventilators in Pakistan. Accordingly, two team namely, team of medical and critical care experts and team of biomedical and professional engineering deliberated upon the ventilators and prepared the guidance document for testing/ evaluation of locally manufactured ventilators, which has now been approved by Special Assistant to Prime Minister. The submitted application is in line with the said document and its specification would be of that of advance countries. The study would be done for the use of ventilators not for the trail.

Prof. Nadeem Irfan Bukhari said that whether the critical points are well established and whether there were doctors in team of Pakistan Engineering Council (PEC) for this project. Engr. Tariq Javed replied that critical points are well established and the team of PEC consisted of clinicians such as anaesthetists. Thereafter, Prof. Dr. Rizwana Chaudhry stated that as the team of ten-

member committee for its evaluation consisted of well-known anesthetists, pulmonologists and critical care experts, therefore, this must be approved for testing.

Ms. Salwa Ahsan asked about the safety of patients, and about the infection control as the ventilators would be used between multiple patients. She further asked about the training of hospital staff and their dealing with trouble shooting once it is used in patient. Engr. Tariq Javed replied that this designed prototype ventilators and would be operated in the presence of anaesthetists and engineers and they are well trained in its handling. Dr. Farhana Badar asked about the number of patient it can be used to which Engr. Tariq Javed replied that it can be operated for 96 hours continuously and more than one human subject may be used

Prof. Dr. Mushtaq Ahmed agreed with the proposal of PEC and said that he was one of medical expert of Technical Committee, which has prepared the guidance document for acceptance test procedure (APT) for locally developed mechanical ventilators. He suggested that the said document should be used as a benchmark for evaluation of locally manufactured ventilators and if any ventilators does not met this benchmark, then it should be evaluated as per the guidance document of MHRA for Rapid Manufactured Ventilators System.

Decision of 9th CSC meeting:

The CSC after detailed deliberation and owing to situation of COVID-19 pandemic in Pakistan, decided to approve the testing of Ventilators on simulators for testing ventilators, based on the recommendation of ten-member technical committee which was constituted by DRAP for assessment/ evaluation of locally manufactured ventilators.
In addition, the CSC also approved the guidance document prepared by Technical Committee constituted by DRAP as a benchmark for testing/ evaluation of locally manufactured ventilators.

Item II: ADDITIONAL AGENDA ADDED IN THE MEETING

2.1 APPRISING CSC ABOUT MEETING OF THE TECHNICAL COMMITTEE DIAGNOSTIC KITS.

Secretary, CSC also apprised the CSC about the proceeding of second expert committee/group which was notified for evaluation of locally manufactured diagnostic kits for SARS-COV-2 by DRAP under the direction of SAPM. The expert committee/group for evaluation of diagnostic kits comprised of immunologists, hematologists and lab-specialists. The said committee was constituted by DRAP in response to evaluation of project of diagnostic kits for SARS-COV-2 by team of scientists of National University of Science and Technology (NUST). The committee outlined minimum requirements for evaluation of any diagnostic kit which is produced/ prepared by local group. The expert committee advised the team of scientist of NUST to fulfill the minimum requirements and submit the required document in booklet/ folder form for its evaluation. The Secretary, CSC apprised the members that the minutes of the said committee have been approved and will be shared with you in due course of time. He further added that case of diagnostic kits of SARS-COV-2 developed by team of scientists of NUST will be presented before the CSC once it is evaluated by expert committee on diagnostic kit.