MINUTES OF THE 12TH CSC MEETING HELD ON 22ND JUNE 2020.

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1. The 12th CSC Meeting was held on 22nd June 2020 through Zoom under the chairmanship of Dr. Abdur Rashid, Director Pharmacy Services Division / Chairman (CSC). The meeting was held online through Zoom from the Committee Room, 4th Floor, Drug Regulatory Authority of Pakistan, Islamabad.

2. The meeting was attended by the following members:-

Sr. No.	Name	Designation
01	Dr. Abdur Rashid.	Chairman CSC / Director Pharmacy Services.
02	Dr. Masud Ur Rehman.	Secretary CSC / Additional Director, Pharmacy Services.

3. Following members attended the meeting online through Zoom:

01	Prof. Dr. Javed Akram.	Professor of Medicine, Physician, Vice Chancellor, University of Health Sciences, Lahore.
02	Dr. Faiza Bashir.	Chairman, Pakistan Health Research Council or his nominee, Islamabad.
03	Ms. Salwa Ahsan.	Chief of Pharmacy, Shifa International Hospital, Islamabad. Member CSC.
04	Dr. Farhana Badar.	Biostatistician & Epidemiologist, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore. Member CSC.
05	Dr. Tayab Husnain.	Head of CEMB / CAMB, Lahore. Co-opted CSC Member.
06	Prof. Brig. (R), Muzammil Hassan Najmi.	Professor of Pharmacology, Foundation University, Islamabad.
07	Prof. Dr. Sheikh Riaz-ud-Din	Director of Center for Excellence in Molecular Biology (CEMB) in Lahore. Co-opted Member.
08	Dr. Naseem Salahuddin.	Director Infectious Diseases Indus Hospital, Karachi Co-opted CSC Member.
09	Prof. Dr. Rizwana Chaudhri	HOD Gynecologist Holy Family Hospital, Rawalpindi Co-opted Member.
10	Dr. Aamir Jaffary	Sindh Institute of Urology & Transplantation (SIUT), Karachi Co-opted Member.
11	Prof: Dr. Mushtaq Ahmed	Professor of Cardiology, Bach Khan Medical College, Mardan, KPK Co-opted Member.

3. The Meeting started with the Holy Verses. Subsequently Chairman, CSC welcomed all the members. He briefed all members of meeting about the necessity of conducting this meeting in the era

of COVID-19 pandemic. Chairman, CSC also thanked members for their active participation online through Zoom & sparing their valuable time.

4. All the members emphasized for submission of complete cases before the Committee. Incomplete cases should not be submitted. Secondly agenda may be sent well head of meeting.

4. Secretary CSC, accordingly presented the agenda, serial wise.

AGENDA ITEM - I: **CONFIRMATION OF THE MINUTES OF THE 11TH CLINICAL STUDIES COMMITTEE MEETING.**

1.1 Minutes of 11th CSC meeting were placed for confirmation.

1.2. Submitted for perusal, discussion and decision of CSC.

1.3. ***Decision of 12th CSC meeting:***

All the members confirmed the minutes of 11th CSC which was held on 20th May 2020, by raising their hands.

AGENDA ITEM - II: **LICENSING & REGISTRATION OF CLINICAL TRIAL SITE & CLINICAL TRIALS / STUDIES IN RESPECT OF COVID-19.**

2.1) LICENCE TO ACT AS CRO/ CLINICAL TRIAL SITE/ LABORATORY AT FATIMA JINNAH MEDICAL UNIVERSITY, LAHORE.

2.1.1. Application is from Vice Prof. Dr. Aamer Zaman, Vice Chancellor, Fatima Jinnah Medical University (FJMU), Lahore, dated 30th April, 2020. Wherein the request has been made to license their University with DRAP to act as CRO/ Clinical Trial Site/ laboratory.

2.1.2. It is submitted that application evaluated according pre-requisites as mentioned in Form-I of the Bio-Study Rules 2017, and following shortcoming observed:

i. Prescribed fee is not provided.
ii. Applied for CRO, Clinical Trial Site & Laboratory on one application.

2.1.3. The Fatima Jinnah Medical University, Lahore is PMDC and HEC approved Medical University with three affiliated tertiary care hospitals

i. Sir Ganga Ram Hospital----------908 bedded Hospital.
ii. Shahdra Teaching Hospital---------263 bedded Hospital.
iii. Mozang Teaching Hospital---------30 bedded Hospital

2.1.4. Applicant has not clarified that for which hospital he want license as CRO/ Clinical Trial Site/ laboratory. In the view of above evaluation it is proposed that applicant may asked to specify the trial site and to submit information regarding that trial site. Further, he may be asked to submit the fee for trial site along with other necessary information as per the Bio-Study Rules 2017. Furthermore DRAP may also provide the copy of Bio-Study Rules 2017 to the applicant for their convenience

2.1.5. Submitted for perusal discussion and decision of CSC.

2.1.6. **Discussion:**

Case discussed by CSC members and after discussion it is decided to direct applicant for clarification

2.1.7. ***Decision of 12th CSC meeting:***

The CSC after detailed deliberation decided to defer the case till clarification regarding trial sites, CRO & Lab & shortcomings in application shall be forwarded to applicant. It was also decided that the applicant meanwhile submit prerequisites as per the Bio-Study Rules 2017 and apply separately for different trial sites.

2.2) APPLICATION FOR APPROVAL OF CLINICAL STUDIES TITLED "CORONA VIRUS RESPONSE - ACTIVE SUPPORT FOR HOSPITALISED COVID-19 PATIENTS" (CRASH-19) TRIAL.

2.2.1. Application is from Prof. Dr. Rizwana Chaudhry (National P.I.), Principal Scientist, Global Institute of Human Development, Shifa Tameer-e-Millat University, Gujar Khan Campus, near Rural Health Center, Mandra, Rawalpindi, dated 2nd June 2019, wherein request has been made for registration & approval of subject clinical trial, application is on prescribed Form-II, along with a fee of Rs.200,000/- deposited vide challan no.2039096. Proposed clinical trial sites are as follows:

i. Allied Hospital Faisalabad Unit-III.
ii. Benazir Bhutto Hospital Unit-II.
iii. Jinnah Post Graduate Medical Center.
iv. Services Hospital Lahore, Medical Unit-3.
v. Pakistan Institute of Medical Sciences Islamabad.
vi. Hayatabad Medical Complex, Peshawar

2.2.2. The CRASH-19 trial is a multinational, open-label, factorial, randomized **Phase-III** trial in adults hospitalized with suspected or confirmed acute COVID-19 infection. The design is pragmatic and efficient to allow rapid recruitment while minimizing the burden on front-line health workers. Eligibility criteria and consent procedures are practical in the emergency setting. The open-label design avoids the need for trial specific drug manufacture and shipping to participating hospitals. Recruiting clinicians can access the randomization service on-line that will provide the allocated treatment which is then prescribed and administered. Only essential data are collected with follow-

up data based on medical records. It is informed that the trial record is available on U.S National Trial Registry with identification number NCT03971500.

2.2.3. **OUTCOMES**: The primary outcome is in-hospital death (cause of death will be recorded). Secondary outcomes are myocardial infarction, cardiac failure, severe cardiac arrhythmia, myocarditis, respiratory failure including ARDS, viral pneumonitis, acute renal failure, sepsis, stroke, gastrointestinal bleeding, receipt of non-invasive or mechanical ventilation requiring endotracheal intubation, ability to self-care at hospital discharge and time to hospital discharge.

2.2.4. It is submitted that application evaluated according pre-requisites as mentioned in Form-II of the Bio-Study Rules 2017, and following shortcoming observed:

2.2.5. In the view of above following shortcomings were recorded.

i. Investigators Brochure & its summary are not provided.
ii. Proposed trial sites are not yet approved by CSC for subject clinical study.
iii. GMP certificate along with COPP & free sale certificate of the investigational products are not provided.
iv. Institutional Review Board (IRB) approval of national clinical trial sites need to be provided.
v. Undertaking on Stamp paper need to be provided.

2.2.6. Submitted for perusal, discussion and decision of CSC.

2.2.7. **Discussion:**

Dr. Aasia Kiyani presented the case before CSC & members asked many questions regarding ethical aspects and use of Losartan, Aspirin & Statins and their rationale in COVID-19 patients and showed their concerns based on scientific rationale. The PI answered the quarries of CSC members.

2.2.8. ***Decision of 12th CSC meeting:***

The CSC after detailed deliberation decided to defer the case till next CSC meeting & constituted a three membered committee of following experts, to evaluate the trial protocols.

i. ***Prof. Brig. (R), Muzammil Hassan Najmi, Professor of Pharmacology, Foundation University, Islamabad.***
ii. ***Dr. Faiza Bashir, Nominee of Chairman, Pakistan Health Research Council.***
iii. ***Dr. Mushtaq Ahmed, Professor of Cardiology, Bach Khan Medical College, Mardan, KPK, Co-opted Member of CSC.***

The above sub-committee shall evaluate the case in depth, after evaluation of the study protocol & ethical aspects submit their report to DRAP, and it will be presented before CSC in its meeting.

2.3) REQUEST FOR APPROVAL OF POSTGRADUATE MEDICAL INSTITUTE, LAHORE, AMEER-UD-DIN MEDICAL COLLEGE LAHORE & LAHORE GENERAL HOSPITAL, LAHORE, TO CONDUCT ALREDY APPROVED CLINICAL TRIAL TITLED "EXPERIMENTAL USE OF COVID IG CONVALESCENT PLASAMA FOR THE PURPOSE OF PASSIVE IMMUNIZATION IN CURRENT COVID.I9 PANDEMIC IN PAKISTAN IN 2020". F. No.15-46/2020 DD (PS)

2.3.1. Application from Prof. Sardar Alfareed Zafar (PI), Principal, Postgraduate Medical Institute, Lahore, Ameer-Ud-Din Medical College Lahore & Lahore General Hospital, Lahore, dated 08th June 2020, wherein the application is for approval of subject Clinical Trial site to conduct Clinical Trial titled "EXPERIMENTAL USE OF COVID-19 CONVALESCENT PLASAMA FOR THE PURPOSE OF PASSIVE IMMUNIZATION IN CURRENT COVID-19 PANDEMIC IN PAKISTAN IN 2020.", which was approved in 9th CSC meeting to be conducted at following trial sites:

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.

2.3.2. Later in the 11th CSC meeting following additional trial sites approved for the subject trial:

i. Hayatabad Medical Complex, Peshawar.
ii. Rawalpindi Medical University, Rawalpindi,

2.3.3. It is submitted that application evaluated according pre-requisites as mentioned in Form-I of the Bio-Study Rules 2017, and following shortcoming observed:

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

i. Application for three different trial sites applied on one application form.
ii. Prescribed fee for approval is not provided.
iii. Undertaking not provided.

2.3.5. Memorandum of understanding for above mentioned trial sites with Dr. Tahir Shamsi, National Institute of Blood Diseases, Karachi is attached.

2.3.6. Submitted for perusal discussion and decision of CSC.

2.3.7. Discussion:

The Case was discussed in respect of "EXPERIMENTAL USE OF COVID-19 CONVALESCENT PLASAMA FOR THE PURPOSE OF PASSIVE IMMUNIZATION IN CURRENT COVID-19 PANDEMIC IN PAKISTAN IN 2020." Study carried out under supervision of Dr. Tahir Shamsi. Dr. Tahir Shamsi joined the meeting and briefed & discussed the matter and as enrolment allowed by NBC-PHRC is completed and for further enrolment of subjects application for ethical clearance is under process at NBC-PHRC.

2.3.8. ***Decision of 12th CSC meeting:***

As the National Bio-ethics Committee (NBC) is reviewing the resubmitted protocols of Dr. Tahir Shamsi, CSC after detailed deliberation decided to defer the case till clarification regarding trial sites, fulfilment of shortcomings in application & ethical clearance from NBC-PHRC for further enrolment. It was also decided that the applicant meanwhile submit prerequisites as per the Bio-Study Rules 2017 and apply separately for different trial sites.

2.4) APPLICATION FOR APPROVAL OF "EXTENSION OF ALREADY APPROVED PASSIVE IMMUNIZATION CLINICAL TRIAL AS EXPENDED ACCESS TO OTHER CITIES & HOSPITALS IN THE COUNTRY, BY NATIONAL INSTITUTE OF BLOOD DISEASES & BONE MARROW TRANSPLANTATION, KARACHI.

2.4.1. Application is from Prof. Dr. Tahir S. Shamsi, Dean & Chairman, Professor of Internal Medicine, Clinical Hematology & BMT, National Institute of Blood Diseases & Bone Marrow Transplantation, Karachi. Wherein the request has been made for approval of "extension of already approved passive immunization clinical trial as expended access to other cities & hospitals in the country.

2.4.2. Applicant also informed that safety data of passive immunization trial over 150 patients showed that it is a safe adjunct treatment in COVID-19 patients. Over 78% patients who are not on ventilators yet are saved from invasive respiratory support. Further applicant informed that they have started receiving plasma requests from across the country treating physicians & family members directly approaching their helpline.

2.4.3. Applicant requested that allow them expanded access of Convalescent Plasma to all treating hospitals across the country and they will continue to supervise data collection across the country.

2.4.4. Clinical studies titled "Experimental Use of COVID-19 Convalescent Plasma for the Purpose of Passive Immunization in Current Covid-19 Pandemic in Pakistan In 2020", was approved by CSC in its 9th Meeting for following trial sites:

i. National Institute of Blood Disease and Bone Marrow, Transplantation (NIBD), Karachi (NIBD)
ii. University of Health Sciences, Lahore
iii. Liaquat University of Medical and Health Sciences, Jamshoro.

2.4.5 Later in the 11th CSC meeting following additional trial sites approved for the subject trial:

i. Hayatabad Medical Complex, Peshawar.
ii. Rawalpindi Medical University, Rawalpindi,

2.4.6 Submitted for perusal discussion and decision of CSC.

2.4.7. Discussion:

The Case was discussed in respect of "EXPERIMENTAL USE OF COVID-19 CONVALESCENT PLASAMA FOR THE PURPOSE OF PASSIVE IMMUNIZATION IN CURRENT COVID-19 PANDEMIC IN PAKISTAN IN 2020." Study was carried out under

supervision of Dr. Tahir Shamsi. Dr. Tahir Shamsi joined the meeting and briefed & discussed the matter. Enrolment allowed by NBC-PHRC has been completed in approved trial. The trial with new protocol for further enrolment of subject's application is under process at NBC-PHRC.

2.4.8. ***Decision of 12th CSC meeting:***

The CSC after detailed deliberation decided to defer the case till ethical clearance from NBC-PHRC for further enrolment & redesigning of protocol. Principal Investigator was asked for detailed report on previously approved trial protocol, and its statistical analysis and end results.

2.5.) LICENCE TO ACT AS CLINICAL TRIAL SITE UNIVERSITY OF LAHORE.

2.5.1. Application is from Dr. Zahid Pervaiz, University of Lahore, dated 12th June 2020. Wherein the request has been made to license their University with DRAP to act as Clinical Trial Site

2.5.2. It is submitted that application evaluated according pre-requisites as mentioned in Form-I of the Bio-Study Rules 2017, and following shortcoming observed:

i. Prescribed fee is not provided.
ii. Particulars regarding the legal status of the applicant need to be described.
iii. Details of premises including layout plan need to be provided.
iv. Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies need to be provided.
v. Names and qualifications of the above sections along with their staff, need to be provided.
vi. Details of the allied facilities associated with the trial center including ambulatory services, emergency handling need to be provided.
vii. Undertaking (on stamp paper) need to be provided.

2.5.3. Applied site is teaching hospital and **Clinical studies titled "Isolation, Purification and Enrichment of Immunoglobulin G and Immunoglobulin M from Human Plasma of Recovered Individuals from COVID-19 Destined for Passive Immunization" applied to be conducted at the site.**

2.5.4. Submitted for perusal discussion and decision of CSC.

2.5.5. ***Decision of 12th CSC meeting:***

The CSC after detailed deliberation decided to defer the case till fulfilment of all prerequisites as per the Bio-Study Rules 2017, the decision shall be communicated to applicant.

2.6) APPLICATION FOR APPROVAL OF CLINICAL STUDIES TITLED "ISOLATION, PURIFICATION AND ENRICHMENT OF IMMUNOGLOBULIN G AND IMMUNOGLOBULIN M FROM HUMAN PLASMA OF RECOVERED INDIVIDUALS FROM COVID-19 DESTINED FOR PASSIVE IMMUNIZATION" BY UNIVERSITY OF LAHORE, LAHORE.

2.6.1. Application from Dr. Zahid Pervaiz, University of Lahore, Lahore, dated 12th June 2020, wherein the application is in reference to approval of Clinical Studies titled "ISOLATION, PURIFICATION AND ENRICHMENT OF IMMUNOGLOBULIN G AND IMMUNOGLOBULIN M FROM HUMAN PLASMA OF RECOVERED INDIVIDUALS FROM COVID-19 DESTINED FOR PASSIVE IMMUNIZATION". The study will be conducted in collaboration & support of M/s AMSON Vaccines & Pharma (Pvt) Ltd.

2.6.2. It is submitted that application evaluated according pre-requisites as mentioned in Form-II of the Bio-Study Rules 2017, and following shortcoming observed:

i. Prescribed fee for approval of Clinical Trial is not provided.
ii. Ethical clearance from National Bioethics Committee is needed to be provided.
iii. Investigators Brochure is need to be provided.
iv. Study protocol is attached but not as per ICH-GCP guidelines.
v. Phase of trial need to be described.
vi. Proposed trial site is not yet approved by CSC.
vii. Summary of study Protocol & Investigator Brochure are need to be provided.
viii. Adverse Event Reporting Form need to be provided.
ix. Number of patients to be enrolled need to be described.
x. Name of Monitors & Clinical Research Associate need to be described.
xi. Sample of label of the investigational product / drug need to be provided.
xii. Duration of trial need to be described.
xiii. Undertaking on Stamp paper need to be provided.

2.6.3. Submitted for perusal, discussion and decision of CSC.

2.6.4. ***Decision of 12th CSC meeting:***

The CSC after detailed deliberation decided to defer the case till fulfilment of all prerequisites as per the Bio-Study Rules 2017.

2.7) APPLICATION FOR REGISTRATION OF PROTECT CLINICAL TRIAL AT FATIMA JINNAH MEDICAL UNIVERSITY, LAHORE, LAHORE. F. No.03-38/2020 DD (PS)

2.7.1. Application from Prof. Dr. Aamer Zaman, Vice Chancellor, Fatima Jinnah Medical University (FJMU), Lahore, No. 3507 Dated 11th May 2020, forwarded by Assistant Director (Admin), Lahore. Wherein the request has been made for registration of already discussed & conditionally approved clinical trial titled “Hydroxychloroquine, Oseltamivir and Azithromycin for the treatment of COVID-19 **(PROTECT)**"to be conducted at Fatima Jinnah Medical University, Lahore, Lahore.

2.7.2. It is submitted that application evaluated according pre-requisites as mentioned in Form-II of the Bio-Study Rules 2017, and following shortcoming observed:

i) Prescribed processing fee is not provided.
ii) Approval of National Bio-ethics Committee (NBC) is not provided.
iii) Investigator's Brochure & its summary, need to be provided.
iv) Summary of Protocol is need to be provided.
v) Informed consent is provided only in Urdu.
vi) Proposed trial site is not approved yet by CSC.
vii) Details regarding number of patients to be enrolled in each center is not provided.
viii) Sample of label of the investigational product / drug is not provided.
ix) Duration of trial is not described.
x) Undertaking on stamp paper is not provided.

2.7.3. Submitted for perusal discussion and decision of CSC.

2.7.4. ***Decision of 12th CSC meeting:***

The CSC after detailed deliberation decided to defer the case till fulfilment of all prerequisites as per the Bio-Study Rules 2017.

2.8) APPLICATION FOR APPROVAL OF CLINICAL RESEARCH DEPARTMENT OF CHILDERN'S HOSPITAL KARACHI TO ACT AS CLINICAL TRIAL SITE FOR CONVALESCENT PLASMA TRIAL.

2.8.1. Application is from Dr. Saqib Hussain Ansari, Children's Hospital Karachi and Research Institute for Blood, Genetic & Bone Marrow Transplant, Karachi, dated 9th June 2020. Wherein the request has been made to license their hospital with DRAP to act as Clinical Trial Site.

2.8.2. It is submitted that application evaluated according pre-requisites as mentioned in Form-I of the Bio-Study Rules 2017, and following shortcoming observed:

i) Particulars regarding the legal status of the applicant are need to be submitted.
ii) Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies, need to be provided.
iii) Names and qualifications of the above sections along with their staff, need to be provided.
iv) Undertaking on stamp paper, need to be provided.

2.8.3. Submitted for perusal discussion and decision of CSC.

2.8.4. ***Decision of 12th CSC meeting:***

The CSC after detailed deliberation decided to defer the case till fulfilment of all prerequisites as per the Bio-Study Rules 2017.

2.9) DECESION OF THE MEMBERS OF THE EXPERT COMMITTEE ON THE CLINICAL STUDIES OF COVID.19 PATIENTS IN PAKISTAN.

2.9.1. Dr. M. Zeeshan Danish, Member, coordinator, National Safety Data Monitoring Committee, DRAP, submitted a report on meeting of Sub-Committee on National safety Data Monitoring, details are as follows:

2.9.2. BACKGROUND:

Upon the recommendations of higher authorities, an emergent meeting of the authorized member of the committee of the National safety Data Monitoring committee, Drug Regulatory Authority, Pakistan was held on 04-1G06-2020 to review and discuss the following:

2.9.3. AGENDA ITEMS:

i. W.H.O INTERNATIONAL RANDOMIZED TRIALS ON HOSPITALIZED COVID.1g PATIENTS: SOLIDARITY PUBLIC HEALTH EMERGENCY CLINICAL TRTALS submitted by Dr. Aun Raza (Consultant Physician infectious Diseases) Shaukat Khanum Cancer Hospital, Pakistan.

ii. PROTECT CLINICAL TRIALS submitted by Prof. Dr. Javed Akram, (VC, UHS, Lahore).

iii. CLINICAL TRIALS submitted by Dr. Ammar Sarwar, (Director, Harvard Medical School, USA).

2.9.4. MINUTES OF THE MEETING:

i. Meeting was held at University of the Punjab, Secretariat of the National Safety Data Monitoring Committee to review the studies on the use of Hydroxychloroquine and Chloroquine.

ii. Meeting was started with the recitation of Holy Quran by Dr. M. Zeeshan Danish.
Prof. Dr. Aziz-ur-Rehman and Dr. Muhammad Zeeshan Danish experts of the committee concluded that after publication of the Lancet Articles, several concerns were raised worldwide due to which clinical trials on COVID-19 patients using HCQ and CQ were stopped for the time being.

iii. It was discussed that the honorable minister of health Pakistan also announced the suspension of all related clinical trials in Pakistan following the announcement from WHO. Since the above concerned raised, emergency meeting of the national safety data management committee was held all related studies were stopped for the time being and the time of 72 hours was given to the investigators to present their data and report to the experts of the committee.

iv. Reports and data were presented to the committee of experts and perpetual meetings were held to review the data and mortalities occurred during the period of study. Experts of the committee concluded that the collaboration in good faith and at a time of great need during the COVID-19 pandemic.

2.9.5. DECESION OF THE COMMTTTEE:

i. The PEACE and PRECISE and PROTEC7, Clinical Trials are being run in Pakistan through the Institutional researchers of the Government of the Punjab. Data of the PEACE and PRECISE trials presented data of 261 enrolled patients using the same dose of hydroxychloroquine as the recently published NEJM (2016) trial data. The entire data submitted of all patients (261) of the said trials were shared with us and after evaluation we concluded that, NO DEATHS BEEN AND NO SEVER ADVERSE EVENTS been reported so far after 14 days of therapy.

ii. W.H.O international randomized SOLIDARITY public health emergency Clinical trials submitted by Dr. Aun Raza (Consultant Physician Infectious Diseases) Shaukat Khanum Cancer Hospital, can be started on COVID-19 patients and in case of any adverse events, committee must be immediately reported based on the decisions of WHO and their investigators.

iii. Therefore, new patients are allowed to be recruited for the studies conducted under the supervision of Dr. Ammar Sarwar (Harvard Medical School) and prof. Dr. Javed Akram (VC, UHS Lahore) using HCQ and CQ for COVTD-19 patients.

iv. Committee synonymously concluded that all studies of drugs and devices on COVID-19 patients should be allowed to proceed if there is no harmful effect appeared in future. All investigators using HCQ or CQ must be directed to submit and present their data results before the committee after the completion of their clinical trials.

v. If any adverse event appears on any treated patients the Clinical Trials would be automatically stopped to avoid any loss of life and all lead investigators are responsible for reporting any adverse event or risks appeared during the study. Data results of all the other approved trials of Drugs and Devices should be submitted perpetually to the coordinator of the committee so as safety of the therapies should be ensured accordingly by the members of national safety monitoring board, drug Regulatory Authority, Pakistan (DRAP).

2.9.6. Submitted for perusal discussion and decision of CSC.

2.9.7. **Discussion:**

Chairman CSC briefed the members regarding meeting of Sub-Committee on National Data Safety Monitoring & informed that during these studies no deaths and serious adverse events reported yet.

2.9.8. ***Decision of 12th CSC meeting:***

Based on the recommendations of Sub-Committee on National Data Safety Monitoring, CSC after detailed deliberation decided to allow for continuation of following clinical studies:

i. W.H.O INTERNATIONAL RANDOMIZED TRIALS ON HOSPITALIZED COVID.1g PATIENTS: SOLIDARITY PUBLIC HEALTH EMERGENCY CL|N|CAL TRTALS submitted

by Dr. Aun Raza (Consultant Physician infectious Diseases) Shaukat Khanum Cancer Hospital, Pakistan.

ii. PROTECT CLINICAL TRIALS submitted by Prof. Dr. Javed Akram, (VC, UHS, Lahore).

iii. CLINICAL TRIALS submitted by Dr. Ammar Sarwar, (Director, Harvard Medical School, USA).

2. Data & reports regarding trial will be asked from all Principal investigators of above mentioned trial/studies.

2.10) <u>DIAGNOSTIC KITS FOR SARS COV-2 (COVID-19), SYBER GREEN BASED, DEVELOPED BY DR ANEELA JAVED AND DR. ALI ZOHAIB OF ASAB LABS, NATIONAL UNIVERSITY OF SCIENCE AND TECHNOLOGY (NUST).</u>

2.10.1. This is the same case which was already discussed in 1st and 2nd meeting of Expert Committee on COVID-19 Diagnostic Kits and 9th Meeting of CSC. In the 1st meeting of Expert Committee on Diagnostic Kits, minimum requirements for the evaluation of any diagnostic kit which is produced/ prepared by the local research group were outlined, and the NUST team was advised to submit their documents in light of minimum requirements outlined in the 1st meeting.

2.10.2. The team of NUST was invited to 2nd meeting of Expert Committee on Diagnostic Kits to present their reply, based on the required outlined in the 1st meeting of Expert Committee on COVID-l9 Diagnostic kits. The NUST team presented their reply through power point presentation. Dr Tahir Aziz presented his comments on the revised reply of the NUST team, which were accordingly asked by Gen Suhaib Ahmed in the question/ answers session in the 2nd meeting. The NUST accordingly answered the questions asked by Gen Suhaib. Subsequently, the expert committee on diagnostic kits recommended the NUST diagnostic kit for lab trial. The decision of 2nd meeting of Expert Committee on Diagnostic Kits is reproduced as under:

I. The team of NUST must complete the documentation (in a comprehensive format) as required and desired by Experts Committee on Diagnostic Kits.

II. The Committee recommended the COVID-19 diagnostic kits of ASAB, NUST for lab trials testing subject to the following condition:

a. A laboratory will be established by the NUST research group at either AFIP or NIH with the facilitation of Chairman, Expert Committee on Diagnostic kits for comparative testing of COVID-19 kits;

b. For oversight/supervision, DRAP will deploy officers from Biological Drugs Division who will be present on site (not necessarily in the laboratory where tests are being performed) to certify the performance of the kits and their results.

c. The tests will be carried out on the given samples (RNA extracts of clinical specimens). These RNA extracts would be provided by the tertiary care laboratory after they have set up their own tests with appropriate labelling.

The results of these tests will not be shared with the NUST research group. Results from the tertiary care laboratory and results from NUST research group laboratory (duly certified by the DRAP appointed scientific officer) will be provided to DRAP for subsequent analysis by the Expert Committee.

d. Samples size of tests should be over three hundreds.

e. After completion of lab trial, the report will be submitted to expert committee on diagnostic kits for further assessment.

f. After completion of lab trial, the NUST team may submit application to Clinical Study Committee, DRAP for registration of clinical trial as per the relevant provisions of Bio-Study Rules, 2017, if recommended by expert committee based on the results of lab trial.

2.10.3. Subsequently, the NUST team carried out comparative testing of 330 blinded samples (collected from NIH) in ASAB Labs, NUST under the supervision of nominated officers of DRAP. Statistics of the tests carried out are as under:

NUST * NIH Crosstabulation

			NIH		
			Negative	Positive	Total
NUST	Negative	Count	125	30	155
		% within NUST	80.6%	19.4%	100.0%
		% within NIH	64.8%	21.9%	47.0%
	Positive	Count	45	94	139
		% within NUST	32.4%	67.6%	100.0%
		% within NIH	23.3%	68.6%	42.1%
	Suspected	Count	23	13	36
		% within NUST	63.9%	36.1%	100.0%
		% within NIH	11.9%	9.5%	10.9%
Total		Count	193	137	330
		% within NUST	58.5%	41.5%	100.0%
		% within NIH	100.0%	100.0%	100.0%

NUST_Binary * NIH Crosstabulation

			NIH		
			Negative	Positive	Total
NUST_Binary	Negative	Count	125	30	155
		% within NUST_Binary	80.6%	19.4%	100.0%
		% within NIH	64.8%	21.9%	47.0%
	Positive	Count	68	107	175
		% within NUST_Binary	38.9%	61.1%	100.0%
		% within NIH	35.2%	78.1%	53.0%
Total		Count	193	137	330
		% within NUST_Binary	58.5%	41.5%	100.0%
		% within NIH	100.0%	100.0%	100.0%

Treated NUST suspected cases as a NUST positive

i. Sensitivity: 78%
ii. Specificity: 65%
iii. PPV: 61%
iv. NPV: 80%

Summary of Results

Summary of NIH Results:

Total Samples =	330
Total Positive =	123
Total Negative =	207

Summary of DRAP Results:

Total Samples =	330
Total Positive =	187
Total Suspected Positive =	24
Total Negative =	119

Summary of NUST Results:

Total Samples =	330
Total Positive =	134
Total Suspected =	36
Total Negative =	160

2.10.4. The case of ASAB Labs, NUST was discussed in 3rd Meeting of Expert Committee on Diagnostic Kits, held on 9th of June, 2020. The Committee after detailed deliberation and owing to the situation of COVID-19 pandemic in the country decided as follows*:*
"The Committee recommended the use of the NUST COVID-19 testing kits for epidemiology study (seroprevalence) at the national level under the supervision of NIH, under emergency need testing authorization. The emergency need testing authorization shall stand withdrawn if COVID-19 pandemic is resolved. The Expert Committee recommended the NUST COVID-19 testing kits to be placed before Clinical Study Committee (CSC) for the approval of clinical trial for the testing of the kit, which the NUST team will conduct under the supervision of NIH. NUST team was advised to submit application to Clinical Study Committee for registration of clinical trial for the testing of the kit as per the relevant provisions of Bio-Study Rules, 2017"

2.10.5. Submitted for deliberation and consideration of CSC.

2.10.6. **Discussion:**

Secretary CSC briefed the case as he is also coordinator & secretary of the Expert Committee for Assessment/Evaluation of locally manufactured "COVID-19 testing kits constituted by honorable Minister National Health Services Regulation & Coordination. Dr Faiza Bashir informed the committee that NBC-PHRC approval for the subject application is under process

2.10.7. ***Decision of 12th CSC meeting:***

The CSC after detailed deliberation accepted the recommendations of Expert Committee on Diagnostic Kits, and decided to defer the case till submission of formal application along with ethical approval from National Bio-Ethics Committee-PHRC. Islamabad.

2.11) APPLICATION FOR APPROVAL OF LOCAL MANUFACTURING OF SARS-COV-2 RAPID DIAGNOSTIC KITS BY DR. NASIR JALAL OF PSIMEGA (PHARMACEUTICAL SALT FORMULATION AND PESTICIDES IMPORT COMPANY).

2.11.1. Application is from Dr. Nasir Jalal, Proprietor, PsiMega (Pharmaceutical Salt Formulation and Pesticides Import Company), where he has submitted application for local manufacturing of SARS-COV-2 rapid diagnostic testing kits. The SARS-COV-2 serological antibody based testing kits will be manufactured locally under the authorization of the United States based company namely Boston molecules and special permission has been granted from the applicant ex-colleague and inventor of this patented technology. Boston molecules have achieved the declaration of conformity for CE and USFDA manufacturing approval. The applicant said that tests have already been tested on human patients and their clinical lab data demonstrated 96.3% sensitivity and 100% specificity (compared to PCR) for detection of antibodies against SARS-COV-2.

2.11.2. The applicant has submitted critical comparison of RT-qPCR V/S Rapid antibody testing of SARS-CoV-2 which is reproduced as under:

	RT-qPCR	Rapid diagnostic test (RDT) kits
1	**Expensive** (approx. PKR 8,000-10,000) and time consuming (2-5 days)	**Low cost** (approx. PKR 1000-2000) point of care test.
2	**Cannot** be used for seroprevalence or disease surveillance or to give immediate immunity passport to passengers or travelers at airports, railway stations or bus stations.	**Can** be used for seroprevalence and immune surveillance or contact tracing of patient in recovery or for clinical evaluation of any anti-SARS-CoV-2 drug or vaccine.
3	**Very high running cost** and high cost of materials.	**No running cost**, cheaper to manufacture
4	**Time-consuming** (at least 5-10 hours per run), requires testing to be run in batches.	**Time efficient** (only 10-15 minutes per test), individual tests can be run anytime, anyplace.
5	Requires **highly trained lab personnel** and expensive lab equipment to run.	**No trained personnel**, lab or expensive equipment required, thus can be used as a **Point-of care** medical device anywhere.
6	Requires a valid DNA sample of patient and **DNA extraction** for SARS-CoV-2 detection	**One-step process**, uses only a drop of blood or serum to detect IgM or IgG.
7	**More accurate (compared to RDT) but still has a high false negative rate.**	**Relatively less sensitive** and specific compared to RT-qPCR test.
8	Used to **rule-out cases**	Used to **rule-in cases**
9	**Cannot be used to detect virus after infection** or when the virus is not shedding.	IgM detectable after 4 days of infection while **IgG can be detected weeks after the infection** is over. Note: Our RDT uses a combo of antibodies for both IgM and IgG, thus has more precision than other products and uses Chicken IgY (control) to minimize false positives
10	N/A	Gold nano-colloid conjugated antibodies dramatically improve the sensitivity for IgM and IgG

2.11.3. The applicant submitted the following evidence (already shared with members through WhatsApp) in support of his claims:

A. NIH can consider rapid testing if the diagnostic kit has a CE mark or FDA approved or FDA notified as per its notification issued on April 2, 2020.
B. All major public health bodies and scientists now believe that SARS-CoV-2 infections will remain with us for a long time, thus we must prepare accordingly and follow contact tracing to flatten the infection curve. PCR based contact-tracing is very expensive, laborious & time-consuming.
C. SARS-CoV-2 Virus likely to return in waves each year.
D. International travelers held from boarding planes due to lack of testing facilities at airports.
E. Rapid testing at airports to provide on-site immunity passports, a new International Air Transport Administration (IATA) policy to be implemented soon.
F. CDC recommends that effective contact-tracing is vital to control spread of virus. Rapid testing on-site could be the key for immediate, fast and effective contact-tracing.
G. Several European Countries now adopting rapid testing as a routine strategy to understand the scope of epidemiology of this disease.

H. Published and cited research articles to support the use of rapid testing. Sensitivity of RDT is reported to be better than RT-qPCR after day 8 of infection onset.
I. As the virus evolves, so should human beings affected by it and adopt faster, more rapid testing means to stay ahead of the disease spread.
J. Mutated SPIKE protein makes the virus more transmissible than before, hence the PCR primers designed against Canonical SPIKE will need modification following genome mapping of the new strains. RDTs on the other hand can continue to detect immune response to the virus efficiently.

2.11.4. The applicant has also submitted his response against the comments of Coordinator of Expert Committee on COVID-19 diagnostic kits which are summarized as under:

1. Are we considering this kit for its use in clinical settings?

Response: They can use it in clinical setting as well as non-clinical settings such as Airports, Railway stations, Bus stations and places of huge gatherings to give people a fast immunity passport. Emirates Airlines became the first international airline to adopt rapid testing at airports before passengers are allowed to board the plane. Most likely new IATA policies would soon require all airlines to adopt what Emirates has implemented.

2. We need the registration status in FDA and from other drug regulatory authorities with technical details about antigen and the antibodies being detected.

Response: Manufacturing operator # 10070123 and registration # 3016734013 (Annex A). Device EUA Status pending with FDA. Shared through WhatsApp with members.

3. The technical data as regards sensitivity is not given in comparison with sensitive methods to detect antibodies such as by ELISA or Chemiluminescence.

Response: PLEASE SEE FRESH ATTACHED DATA (Annex B). Shared through WhatsApp with members.

4. The cross reactivity data using sera from patients with RA is not valid to find out if antibodies detected by this system are SARS nCov-2 specific.

Response: They are currently in the process of doing that at their USA facility. As soon as results are available, they will share them with DRAP.

5. For manufacturing local company profile and its experience in manufacturing of similar products for human diagnostics is essential. GMP certifications are essential.

Response: Their Company PsiMega2 is registered in Pakistan while the US Company Boston Molecules Inc., is registered in the USA. As for GMP certification, he is a Pakistani scientist and an academician who does not have prior experience in manufacturing but can surely follow the procedures under these urgent situations.

2.11.5. The case of Rapid Diagnostic Kits of Dr. Nasir Jalal, PsiMega was discussed in 3rd meeting of Expert Committee on Diagnostic Kits for COVID-19, held on 9th of June, 2020.The committee

after detailed deliberation and owing to the situation of COVID-19 pandemic in the country decided as follows:

i. *Dr. Nasir Jalal**,** Proprietor, PsiMega (Pharmaceutical Salt Formulation and Pesticides Import Company) was allowed to import the original version of testing kit from Boston molecules, United States or any other standard kit from stringent regulatory authorities for comparative studies/ testing with locally manufactured kit of PsiMega. The company was also allowed to import the raw material for manufacturing of rapid diagnostic kits in Pakistan. This import of raw material and original version of the kit has been allowed under emergency need testing authorization and will stand withdrawn when COVID-19 pandemic is resolved.*

ii. *The PsiMega will inform the Expert Committee about the batch completion then the committee will discuss the way forward for these kits which may include comparison (in the same manner as done for NUST kit) of these kits with other standard testing kit of the same category which are in regular use in the market.*

2.11.6. Submitted for deliberation and consideration of CSC.

2.11.7. **Discussion:**

Secretary CSC briefed the case as he is also coordinator & secretary of the Expert Committee for Assessment/Evaluation of locally manufactured "COVID-19 testing kits constituted by honorable Minister National Health Services Regulation & Coordination.

2.11.7. ***Decision of 12th CSC meeting:***

The CSC after detailed deliberation decided to accept the recommendations of Expert Committee on Diagnostic Kits. Further the company was also allowed to import the raw material for manufacturing of rapid testing diagnostic kits in Pakistan. This import of raw material for manufacture allowed under emergency need testing authorization and will stand withdrawn when COVID-19 pandemic is resolved. The applicant may be advised to take NOC for material to be imported for manufacturing indigenous kits and import of reference kits. The copy of letter may be endorsed to concerned A.D. Import & Export DRAP office.

AGENDA ITEM - III: LICENSING & REGISTRATION OF CLINICAL TRIAL SITE & CLINICAL STUDIES AND BIO-ANALYTICAL LABS UNDER THE BIO STUDY RULES, 2017.

3.1) APPLICATION FOR APPROVAL OF CLINICAL STUDY TITLED "COLCHICINE FOR THE PREVENTION OF PERIOPERATIVE ATRIAL FIBRILLATION IN PATIENTS UNDERGOING THORACIC SURGERY" (COP-AF) Protocol No. 2017-001-COPAF, BY SHIFA INTERNATIONAL HOSPITAL ISLAMABAD. F. No.03-37/2020-DD (PS)

3.1.1. Application is from Prof. Dr. Muhammad Amir (P.I. & National leader COP-AF Trial), Dean Faculty of Health Sciences, Shifa Tameer-e-Millat University, Rawalpindi, dated 2nd June 2020,

wherein request has been made for registration & approval of subject clinical trial, application is on prescribed Form-II, along with a fee of Rs.200,000/- deposited vide challan no.2028951.

3.1.2. It's a **Phase-III**, Multi-center, blinded, randomized controlled trial with a sample size of **2800** subjects, primary objective of the trial is:

> ***"To determine whether the administration of colchicine compared with placebo reduces the occurrence of perioperative atrial fibrillation / atrial flutter (AF) within 14 days of randomization"***

3.1.3. Treatment regimen is oral colchicine at a dose of 0.5mg or matching placebo will be given within 4 hours before surgery. The second dose of 0.5mg will be given in the evening after surgery. Thereafter all patients will continue to receive oral colchicine 0.5 mg or matching placebo twice daily for a total of 10 days

3.1.4. It is submitted that application evaluated according pre-requisites as mentioned in Form-II of the Bio-Study Rules 2017, and following shortcoming observed:

i. Number of patients to be enrolled in each center & duration of trial is not described.
ii. Evidence of registration in country of origin is not provided.

3.1.5. Submitted for perusal, discussion and decision of CSC.

3.1.6. Discussion:

Dr. Summaeya Azam from Shifa International Hospital, Islamabad joined the meeting & presented the case before CSC, CSC members asked many questions regarding the trial, use of colchicine, number of subjects and duration of trial. Dr. Summaeya briefed and replied all questions and informed that the sample size will be 2800 subjects globally.

3.1.7. ***Decision of 12th CSC meeting:***

CSC after detailed deliberation decided to approve the clinical studies titled ""Colchicine for the Prevention of Perioperative Atrial Fibrillation in patients undergoing thoracic surgery" (COP-AF) protocol no. 2017-001-COPAF, to be conducted at Shifa International Hospital Islamabad.".

3.2) APPLICATION FOR THE USE OF GRANULOCYTE COLONY STIMULATING FACTOR (GCSF) FOR BILIARY ATRESIA AS PART OF A PHASE-II CLINICAL TRIAL. F. No.03-10/2019-DD (PS)

3.2.1. Application is from Dr. Saqib Hamid Qazi, Assistant Professor & Head – Section of Pediatric Surgery, Director Pediatric Sugary Residency Program, Co-Chief – Children Hospital Service Line (Pediatric Surgery), Aga Khan University Hospital, Karachi, dated 16th May, 2019,

wherein request has been made for registration & approval of subject clinical trial, which will be carried out at Aga Khan University Hospital, Stadium Road, Karachi.

3.2.2. The study carried out under the supervision of Dr. Saqib Qazi (P.I) and Dr. Abeer Aziz (Co-P.I), The primary objective is aim to assess the hypothesis that GCSF therapy improves the short term clinical outcome of biliary atresia in a multi institutional trial and to prospectively evaluate, using the parameters mentioned within the study endpoints, the safety and efficacy of GCSF in each of two groups of newly diagnosed patients.

3.2.3. Application presented & briefed by Dr. Jai K. Das, Assistant Professor, Aga Khan University Hospital, Karachi, in the 6th CSC meeting.

3.2.4. **Decision of 6thCSC Meeting:** -

"The CSC after deliberations deferred the case & decided to get experts opinion, because investigational drug is a chemotherapeutic drug and utilized & tested in the trial for it's off label use.

Applicant will be asked for trial data to be sent to the following experts for their opinion regarding the trail:

i) Maj. Gen. Dr. Salman, Fazaia Medical College, Rawalpindi.

ii) Dr. Yasir, Oncologist, Shifa International Hospital, Islamabad.

iii) Dr. Samiya, ex-Head of Paediatrics Department, PIMS Hospital, Islamabad.

Expert's opinion & recommendations will be presented before CSC in its next meeting."

3.2.5. Experts nominated by the CSC requested for their opinion on the trial through letter number F.No.03-10/2019, dated 27th February 2020, and a reminder also sent to Dr. Samiya & Dr. Yasir on 20th April 2020, but yet response is awaited.

3.2.6. After reevaluation following shortcomings were recorded & communicated to applicant vide letter number F.No.03-10/2019, dated 27th February 2020, but response is yet awaited:

i. Original verified challan for deposited slip number 0801287 is not provided.
ii. As per your submitted reply, if GCSF (Filgen) is an equivalent & similar product, so provide its BA/BE / Bio similarity studies & details regarding other IMPs used in the study at all trial sites.
iii. Investigators Brochure is attached for Neupogen®, whereas Filgen or use of alternate brands of "**Filgrastim**" is not described in the brochure.

3.2.7. **Maj. General Salman Ali** HI (M) (R), Principal & Professor of pediatrics, Fazaia Medical College, Air University, Islamabad, dated 12th April 2020, informed that, he had received & gone through the details of the trial and had opinion that the DRAP may allow the subject trial to be carried out under the international protocol & the stipulated terms & conditions.

3.2.8. Expert opinion from following experts is yet awaited:
Dr. Samiya, ex-Head of Pediatrics Department, PIMS Hospital, Islamabad.
Dr. Yasir, Oncologist, Shifa International Hospital, Islamabad.

3.2.9. Reminder also forwarded to above mentioned experts for their opinion vide letter number F.No.03-10/2019, dated 20th April 2020.

3.2.10. Application placed before CSC in its 11th meeting held on 20th May 2020 & CSC decided as follows:

Decision of 11th CSC meeting:

The CSC after detailed deliberation decided to defer the case and also decided that as Dr. Samiya, ex-Head of Pediatrics Department, PIMS Hospital, Islamabad didn't replied & not submitted her opinion, so CSC replaced her with Prof Dr. Munir Malik, Shifa Tameer-e-Millat University, Shifa International Hospital, Islamabad, to get expert opinion on the subject clinical studies.

3.2.11. Prof. Dr. Munir Malik, Shifa Tameer-e-Millat University, Shifa International Hospital, Islamabad, dated 17th June 2020, informed that, he had received & gone through the details of the trial and had opinion that trial will be beneficial for scientific knowledge and for patients & study should be approved.

3.2.12. Submitted for perusal discussion and decision of CSC.

3.2.13. ***Decision of 12th CSC meeting:***

Based on the recommendations of experts, CSC after detailed deliberation decided to as approve in principle the clinical studies titled "Use of Granulocyte Colony Stimulating Factor (GCSF) Adjunct Therapy for Biliary Atresia, as part of a Phase-II Clinical Trial", subject to fulfilment of following shortcomings:

i. Original verified challan for deposited slip number 0801287 is not provided.
ii. As per your submitted reply, if GCSF (Filgen) is an equivalent & similar product, so provide its BA/BE / Bio similarity studies & details regarding other IMPs used in the study at all trial sites.
iii. Investigators Brochure is attached for Neupogen®, whereas Filgen or use of alternate brands of "Filgrastim" is not described in the brochure.

ITEM IV: MISCELLANEOUS AGENDA ITEMS

4.1) AMENDMENTS IN ALREADY APPROVED CLINICAL TRIAL TITLED "A PHASE 3, MATRIX DESIGN, PARTIALLY DOUBLE BLIND, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF 50 MG LONAFARNIB/ 100 MG RITONAVIR BID WITH AND WITHOUT 180 MCG PEG IFN-ALFA-2A FOR 48 WEEKS COMPARED WITH PEG IFN ALFA-2A MONOTHERAPY AND PLACEBO TREATMENT IN PATIENTS CHRONICALLY INFECTED WITH HEPATITIS DELTA VIRUS BEING MAINTAINED ON ANTI-HBV NUCLEOS (T) IDE THERAPY"DLIVR. Protocol EIG-LNF-011 Amendment 02

4.1.1. Application is from Dr. Saeed Hamid, Director Clinical Trial Unit, Professor & Consultant Gastroenterologist, Aga Khan University, Karachi, wherein FR is in reference to amendments in already approved protocol.

4.1.2. Summary of Changes in previously approved protocol is as follows:

4.1.3. OVERVIEW

The primary reasons for this protocol amendment were to incorporate feedback received from various clinical site and regulatory health authority reviews; refer to Table 1 for a summary of the changes and Section 2 for a redline representation of the changes.

Table 1: Summary of Protocol Amendment 02 Changes

Sections	Change
Title page; 1.1.	The Sponsor representative was changed to Colin Hislop, MD, Senior Vice President Clinical & Development Operations
2.; 6.2.; 6.3.; 13.2.2.1.	To align with the statistical analysis plan, secondary and exploratory virologic, biochemical, and histological objectives were modified to include comparison to PEG IFN-alfa-2a. Analysis of HDV RNA samples < LLOQ, target not detected, was added.
2.; 5.4.2.2.; 8.1.; 9.1.; 9.1.4.; 9.3.; 11.3.; 11.3.9.	The allowable anti-HBV nucleos(t)ide therapies were expanded to include tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF). This change was incorporated throughout the protocol.
2.; 11.2.; 11.2.6.; 12.	Assessment for possible farnesyl transferase polymorphism was added, including text regarding the timing of sample collection and sample management.
2.; 8.1.	Entry requirements for confirmation of HDV infection were clarified. The entry criterion for serum ALT was revised to > 1.0 x upper limit of the ULN and < 10 x ULN. Entry criteria were updated to clarify the ability to read and understand study materials.

2.; 8.1.; 12.5.	Allowable contraception procedures were revised to include progestin-based therapies.
2.; 8.2.; 11.1.	Rescreening procedures were revised and specify ECGs or clinical laboratory tests.
2.; 8.2.; 12.4.	The list of concomitant medications was updated based on current clinical pharmacology data.
Table 1, Table 2, Table 3	Refer to Section 2 of this document to see the scope of changes in the schedule of events tables, updated based on the revisions incorporated throughout the protocol. Additionally, descriptions used for Pre-screening and Screening were clarified; a footnote was inserted to indicate the total duration of screening is intended to be 6 months and that review of entry criteria will begin during Pre-screening, continue throughout Screening, and will be verified prior to randomization; a new column was added for an Early Termination visit, including separate footnote for the Early Termination liver biopsy procedure; for continued study drug administration (as applicable) leading up to the final liver biopsy, a footnote was added to clarify study drug dispensation at Week 48, and a row was added for posttreatment Week 4 for continued study drug administration and accountability; a row was added for IWRS (interactive web response system).
5.2.4.	The section was revised to clarify entry criteria for EIG-LNF-012.
8.3.2.	Language regarding study drug adjustment was moved to Section 10.1.1. Cross-reference was added for information regarding dose interruption or withdrawal. The section was updated to clarify that patients who discontinue study medication and are unable to return for the remaining study visits should return for an Early Termination visit. Withdrawal procedures were revised to clarify the timing of the second (paired) biopsy for patients who have taken study drug for a duration of ≥ 12 weeks and to clarify no further PK

	samples will be collected for patients that discontinue study drug prior to Week 48. Study procedures were clarified to specify unblinding will occur after the last patient completes the Week 48 visit.
9.1.4.	The descriptive text for the anti-HBV nucleoside analog entecavir was pared down.
9.3.	Storage conditions for LNF, RTV, and LNF and RTV placebo, plus tenofovir alafenamide fumarate (TAF) were added.
10.1.	The dosing schedule on Day 1 was clarified and a dosing window (12 hours ± 2 hours) was added. Language indicating procedures for a missed dose was incorporated.
10.1.1.	The dose adjustment sections were clarified, and a new section on procedures for increasing or restarting dosing was inserted.
11.1.	Text in this section was removed and a cross-reference to Table 1 (Schedule of Events) was inserted in its place to specify screening assessments.
11.2.	The timing of efficacy assessments was revised to instead cross-reference to the Schedule of Events tables (Table 1, Table 2, and Table 3).
11.2.1.	The definition of a virologic failure was revised to exclude detectable HDV RNA at EOT.

11.2.3.	The timing of the liver biopsies was clarified and cross-references to Table 1 and Table 2 (Schedule of Events) were added.
11.3.4.; 12.	Ophthalmological examinations were updated to indicate assessment of normal dilated retina will be conducted at each scheduled examination.
11.3.6.	The section describing electrocardiograms was revised to indicate study-provided machines should be used and to allow additional examinations based on symptomology.
11.4.; 11.4.1.	The language describing the collections for the subset of patients for serial collections was clarified, and a note was inserted to indicate no further PK samples will be collected if study drug administration is interrupted or discontinued prior to Week 48.
Table 12	For the terminal elimination collections, text was added to allow patients to take the final dose of oral study drug the evening prior to the Week 48 visit. As a result, the previously identified study day of planned collection was removed from the table to avoid confusion.
12.	Introductory text in Section 12.1 was clarified to indicate the intent of each pre-treatment
	period (ie, pre-screening for patients who need to initiate anti-HBV therapy and screening for
	patients who will have taken an approved anti-HBV therapy for ≥ 12 weeks prior to initiation
	of study treatment).
	Pre-screening activities were clarified to indicate inclusion/exclusion criteria will initiate at

	Pre-screening and will be verified prior to randomization.
	The criterion for blood alcohol concentration was clarified to occur either at Pre-screening or
	Screening, per the Schedule of Events.
	The language regarding dispensing of anti-HBV nucleos(t)ide therapy for use on study was
	revised.
	IWRS (interactive web response system) was added for study procedures as outlined in
	Tables 1, 2, and 3.
	The monitoring of depression was updated per Table 2.
	Text was added to clarify ECGs, as applicable, should be conducted up to 30 minutes prior to
	scheduled PK collections.
	Dispensation of study drugs was added to Week 48 (EOT) per Table 2.
	An Early Termination visit was added, with the list of assessments to be conducted per
	Table 2.
13.	Text was added to clarify unblinding will occur after the last patient completes the Week 48
	visit.
13.2.5.	The language regarding the Cochran-Mantel-Haenszel test was revised to indicate an exact test
	will be conducted and information will be recorded in the IRT.
14.6.1.	The section was updated to clarify procedures for reporting SAEs that occur during the study,
	including the use of the electronic data capture or if not available, by email, fax, or telephone.

14.8.	The Regional Medical Advisors were added to the section, and text now indicates they should
	be contacted (as applicable), in addition to the Medical Monitor and Sponsor, for medical emergency.
17.	References were updated, as applicable, based on in-text revisions.
Appendix A	The Ishak-modified histology activity index score was added.

4.1.4. **CHANGES TO THE PROTOCOL**

A redlined copy of Protocol Amendment 02 is attached in this section to show changes since Protocol Amendment 01, dated 13 December 2018, was issued. Minor formatting changes are not shown and hyperlinks are not active. Soft copy as Annex-I is attached with agenda.

4.1.5 It is submitted that ***CSC has approved the trial in its 4th meeting held on 17th July 2019.***

4.1.6. Submitted for perusal, discussion and decision of CSC.

4.1.7. **Discussion:**

Dr. Saeed Hamid form Aga Khan University Hospital, Karachi joined the meeting and briefed regarding amendments in the previously approved protocol, CSC members asked questions regarding amendments and applicant answered all questions.

4.1.8. ***Decision of 12th CSC meeting:***

The CSC after detailed deliberation decided to approve the amendments in already approved protocol titled "A PHASE 3, MATRIX DESIGN, PARTIALLY DOUBLE BLIND, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF 50 MG LONAFARNIB/ 100 MG RITONAVIR BID WITH AND WITHOUT 180 MCG PEG IFN-ALFA-2A FOR 48 WEEKS COMPARED WITH PEG IFN ALFA-2A MONOTHERAPY AND PLACEBO TREATMENT IN PATIENTS CHRONICALLY INFECTED WITH HEPATITIS DELTA VIRUS BEING MAINTAINED ON ANTI-HBV NUCLEOS (T) IDE THERAPY", by the CSC in its 4th meeting held on 17th July 2019, subject to submission of prescribed fee for the amendment.

4.2) SUBMISSION OF REPORTS OF ALL CSC APPROVED CLINICAL TRIALS.

4.2.1. Dr. Masud Ur Rehman, Secretary CSC proposed that all Principal Investigators of Clinical Trial approved under the Bio-Study Rules 2017 need to be directed to send report & data regarding their trial, so the division of Pharmacy Services update status of their trial.

4.2.2. Principal Investigator also directed to submit SAEs to Pakistan National Pharmacovigilance Center.

4.2.3. Submitted for perusal, discussion and decision of CSC.

4.2.4. Discussion:

Secretary CSC briefed members regarding need & importance of reports to be submitted by all principal investigators of all CSC approved Clinical Studies.

4.2.5. ***Decision of 12th CSC meeting***

The CSC after detailed deliberation decided to direct all principal investigators of CSC approved Clinical Studies to submitted updated status of their studies along with detailed reports of their trials.