MINUTES OF 13TH MEETING OF CSC HELD ON 11th AUGUST 2020.

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1. The 13th CSC Meeting was held on 11th August 2020 through Zoom under the chairmanship of Dr. Abdur Rashid, Director Pharmacy Services Division / Chairman (CSC). At 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	Muhammad Arif Chaudhry.	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	Prof. Brig. (R), Muzammil Hassan Najmi.	Professor of Pharmacology, Foundation University, Islamabad.
06	Prof. Dr. Sheikh Riaz-ud-Din	Director of Center for Excellence in Molecular Biology (CEMB) in Lahore. Co-opted Member.
07	Dr. Naseem Salahuddin.	Director Infectious Diseases Indus Hospital, Karachi Co-opted CSC Member.
08	Prof. Dr. Rizwana Chaudhri	HOD Gynecologist Holy Family Hospital, Rawalpindi Co-opted Member.
09	Dr. Aamir Jaffary	Sindh Institute of Urology & Transplantation (SIUT), Karachi Co-opted Member.
10	Prof: Dr. Mushtaq Ahmed	Professor of Cardiology, Bach Khan Medical College, Mardan, KPK Co-opted Member.

3. 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.

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

AGENDA ITEM - I: **CONFIRMATION OF THE MINUTES OF THE 12TH CLINICAL STUDIES COMMITTEE MEETING.**

1.1 Minutes of 12th CSC meeting are placed for confirmation of CSC members.

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

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

All the members confirmed the minutes of 12th CSC which was held on 22nd June 2020.

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

2.1) CHLOROQUINE/ HYDROXYCHLOROQUINE PREVENTION OF CORONA VIRUS DISEASE (COVID-19) IN THE HEALTHCARE SETTING (COPCOV) F.No.15-43/2020 DD (PS)

2.1.1. Application is from Dr. Muhammad Asim Beg, Professor & Consultant Parasitologist, Aga Khan University, dated 22nd July 2020, wherein request has been made for registration & approval of subject clinical trial, which will be carried out at Aga Khan University Hospital. It is a Randomized, Placebo-Controlled clinical trial, Application is submitted on prescribed Form-II without prescribed fee.

2.1.2. The study carried out under the supervision of Prof. Dr. Muhammad Asim Beg (PI). The primary objective of the trial is to evaluate Number of symptomatic COVID-19 infections will be compared between the Chloroquine or Hydroxychloroquine and placebo groups.

2.1.3. Application evaluated according to prerequisites of Form-II of the Bio-Study Rules 2017. The details of the submitted documents are as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Fee	Not provided.

3	Investigator Brochure (s)	Attached only for Chloroquine and also not as per ICH-GCP guidelines.
4	Final protocol	Attached.
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Applicant claimed that the study will be conducted in following countries: **Africa:** Benin, Botswana, Burkina Faso, Cameron, Cote d Ivore, Democratic Republic of Congo, Egypt, Ethiopia, Gambia, Ghana, Guinea, Kenya, Mali, Mozambique, Niger, Nigeria, Senegal, Sierra Leone, South Africa, Sudan, Tanzania, Tunisia, Uganda, Zambia, Zimbabwe, **Europe:** Croatia, France, Italy, Netherland, Russian Federation, Switzerland, Ukraine, United Kingdom. **North/South America:** Argentina, Brazil, Canada, Chile, Columbia, Cuba, Dominican Republic, Guatemala, Jamaica, Peru, Puerto Rico. **Asia:** Bangladesh, India, Indonesia, Malaysia, Maldives, Nepal, Pakistan, Saudi Arabia, Vietnam.
7	Phase of trial.	Not described.
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.	100 Tablets (Chloroquine / Hydroxychloroquine / Placebo) for each participant. * Described on cover letter.
9	Site of the trial	M/s Aga Khan University Hospital Karachi.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names	Attached.

	and designation of members.	
11	Approval of National Bio-ethics Committee (NBC)	Certificate Ref:No.4-87/NBC-COVID19-28/20/, Dated 17th July 2020 is attached.
12	CV's of the Investigators	Attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate of M/s Utopian Co., Ltd attached. COPP / Free Sale Certificate of Nitaquin Tablet is provided.
14	Pre-clinical/clinical safety studies	Not provided.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Not provided.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	400
19	Name of Monitors & Clinical Research Associate	N/A.
20	Evidence of registration in country of origin.	Attached.
21	Copy of registration letter (if registered in Pakistan)	N/A.
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	12 Months
23	Undertaking on Stamp paper	Not provided.

2.1.4. In the view of above following shortcomings are recorded:

i) Prescribed processing fee of Rs.200000/- is not provided.

ii) Patient Information leaflet of Nitaquin (Chloroquine Phosphate) 250mg Tablet is attached, Investigator brochure for Chloroquine & Hydroxychloroquine need to be provided as per ICH-GCP guidelines.

iii) Phase of trial need to be described.

iv) Pre-clinical/clinical safety studies need to be provided.

v) Summary of Investigator Brochure need to be provided.

vi) Undertaking on stamp paper is not provided.

2.1.5. Applicant informed regarding shortcomings vide letter even number dated 24th July 2020, but still response is awaited.

2.1.6. Submitted for perusal discussion and decision of CSC.

2.1.7. Dr. Saeed Hamid joined the meeting& briefed the committee regarding their COPCOV clinical study, and answered the question raised by the members.

2.1.8. ***Decision of 13th 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 titled "CHLOROQUINE/ HYDROXYCHLOROQUINE PREVENTION OF CORONA VIRUS DISEASE (COVID-19) IN THE HEALTHCARE SETTING (COPCOV)" By Aga Khan University Hospital, Karachi, subject to submission of prerequisites as per the Bio-Study Rules 2017 as soon as possible.

2.2) APPLICATION FOR APPROVAL OF CLINICAL STUDY TITLED "CLINCAL EVALUATION OF THE PANBIO™ COVID-19 AG ANTIGEN TEST IN SYMPTOMATIC SUBJECTS (CATSS)". F.No.03-40/2020 DD (PS)

2.2.1. Application is from Dr. Erum Khan, Professor and Chair Institutional Biosafety Committee, Department of Pathology & Laboratory Medicine, The Aga Khan University, Karachi dated 01st July 2020, wherein request has been made for registration & approval of subject clinical studies, which will be carried out at Aga Khan University Hospital, Karachi. Application is on prescribed Form-II, without prescribed fee.

2.2.2. The trial comprises of following primary objective;

i. The primary objective of this study is to estimate sensitivity & specificity of the Panbio™ COVID-19 Ag Rapid test based on the results obtained from the reference method used by the Central lab in symptomatic patients using nasal swab.

2.2.3. The details of the submitted documents are as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Fee	Not provided.
3	Investigator Brochure (s)	PIL attached, not as per ICH-GCP guidelines.
4	Final protocol	Attached

5	Informed consent and participant information sheet (Urdu to English)	Attached.
6	List of participating countries	US, India, South Africa & Pakistan.
7	Phase of trial.	Phase – II / III
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.	Attached.
9	Site of the trial	M/s Aga Khan University Hospital, Karachi.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached.
12	CV's of the Investigators	Attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided, as it an investigational device.
14	Pre-clinical/clinical safety studies	Not provided.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Not provided.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	150 subjects.
19	Name of Monitors & Clinical Research Associate	N/A
20	Evidence of registration in country of origin.	Not provided, authorized to laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

		Evidence of authorization for Abbott Rapid Diagnosis Jena GmbH is required.
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	Approximately 04 months, starting from June/July 2020.
23	Undertaking.	Attached.

2.2.4. After initial scrutiny following shortcomings were recorded:

i) Prescribed fee for approval of Clinical Studies is not provided.

ii) Patient Information Leaflet / Device Usage Guidance Document is attached besides of Investigator brochure, Investigator brochure as per ICH-GCP Guidelines need to be provided.

iii) Phase of trial is not clearly mentioned, Study is claimed as both Phase – II / III study.

iv) GMP certificate along with COPP & free sale not provided.

v) Summary of Investigator Brochure is need to be provided.

vi) Evidence of registration in country of origin need to be provided, authorized to laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Evidence of authorization for Abbott Rapid Diagnosis Jena GmbH is required.

vii) Sample of label of the investigational product / drug need to be provided.

2.2.5. Applicant informed regarding shortcomings vide letter even number dated 24th July 2020, but still response is awaited.

2.2.6. Submitted for perusal discussion and decision of CSC.

2.1.7. *Decision of 13th 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 titled "CLINCAL EVALUATION OF THE PANBIO™ COVID-19 AG ANTIGEN TEST IN SYMPTOMATIC SUBJECTS (CATSS)" By Aga Khan University Hospital, Karachi, subject to submission of prerequisites as per the Bio-Study Rules 2017 as soon as possible.

2.3) APPLICATION FOR APPROVAL AND REGISTRATION OF CLINICAL TRIAL TITLED "PHASE-III, DOUBLE BLIND, PLACEBO-CONTROLLED, RANDOMIZED CLINICAL TRIAL OF RECOMBINENT NOVEL CORONA VIRUS VACCINE (ADENOVIRUS TYPE 5 VECTOR)" F.No. 03-44/2020 DD (PS)

2.3.1 Application is from Major General Prof. Dr. Aamer Ikram, Executive Director National Institute of Health, Islamabad, dated 27th July 2020, wherein request has been made for registration & approval of subject Clinical Trial, which will be carried out at following clinical trial sites:

i. Aga Khan University Hospital, Karachi.
ii. The Indus Hospital, Karachi.
iii. Shaukat Khanum Memorial Cancer & Research Hospital, Lahore.
iv. Shifa International Hospital, Islamabad.
v. Dow University of Health Sciences, Karachi.
vi. Sindh Institute of Urology & Transplantation, Karachi.

2.3.2. Application is on prescribed Form-II, along with prescribed fee of Rs.200000/-, deposited vide challan number 2035237, dated 27th July 2020.

2.3.3. The study carried out under the supervision of Prof. Dr. Muhammad Raza Shah (PI) and the primary objective of the trial is to investigate/evaluate the safety of Inactivated SARS-CoV-2 Vaccine.

2.3.4. The details of the submitted documents are as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Fee	Prescribed fee of Rs.200000/-, deposited vide challan number 2035237, dated 27th July 2020
3	Investigator Brochure (s)	Attached.
4	Final protocol	Attached.
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Canada, Russia, Chile, Argentina & Pakistan
7	Phase of trial.	Phase – III
8	Quantity of drug / trial material to be imported on	25000 doses of Vaccine (approx.).

	Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	
9	Site of the trial	i. Aga Khan University Hospital, Karachi. ii. The Indus Hospital, Karachi. iii. Shaukat Khanum Memorial Cancer & Research Hospital, Lahore. iv. Shifa International Hospital, Islamabad. v. Dow University of Health Sciences, Karachi. vi. Sindh Institute of Urology & Transplantation, Karachi.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB / ERC approval from NIH is attached. Whereas IRB approval from Clinical Trial Site need to be provided.
11	Approval of National Bio-ethics Committee (NBC)	Certificate Ref:No.4-87/NBC521-COVID-35/20/ is attached.
12	CV's of the Investigators	CVs of Major General Prof. Dr. Aamer Ikram M. Khurram Zaki Khan. Attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate of M/s CanSino Biologics Inc is attached, whereas COPP/Free Sale is not available as the product is under clinical investigation process.
14	Pre-clinical/clinical safety studies	Attached.
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.	40000 Subjects
19	Name of Monitors & Clinical Research Associate	M/s Dimension Research CRO.
20	Evidence of registration in country of origin.	N/A The product is under investigation.
21	Copy of registration letter (if registered in Pakistan)	N/A The product is under investigation.
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	04 Months.
23	Undertaking	Attached.

2.3.5. In the view of above following shortcomings are recorded:

i. Sindh Institute of Urology & Transplantation, Karachi & Dow University of Health Sciences, Karachi are not approved clinical trial sites.

2.3.6. Submitted for perusal discussion and decision of CSC

2.3.7. Major General Prof. Dr. Aamer Ikram with his N.I.H. team and briefed the committee regarding the study. CSC members appreciated the efforts & conduct of vaccine clinical trial first time in Pakistan.

2.3.8. ***Decision of 13th 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 titled "PHASE-III, DOUBLE BLIND, PLACEBO-CONTROLLED, RANDOMIZED CLINICAL TRIAL OF RECOMBINENT NOVEL CORONA VIRUS VACCINE (ADENOVIRUS TYPE 5 VECTOR)" to be conducted at already approved clinical trial site only with following conditions:

i. National Data Safety Monitoring Committee look after & closely monitor the safety of the patients.

ii. ADRs / AEFI will submitted on monthly basis to PNPC, Pharmacy Services Division-DRAP.

2.4) APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "RANDOMIZED, DOUBLE BLINDED, PARALLEL, PLACEBO CONTROLLED, PHASE-I CLINICAL TRIAL TO EVALUATE THE SAFETY & IMMUNOGENICITY OF INACTIVATED SARS-CoV-2 VACCINE IN HEALTHY POPULATION AGED 18 & ABOVE" F.No. 03-41/2020 DD (PS)

2.4.1. Application is from Prof. Dr. Muhammad Raza Shah, Director, International Center for Chemical & Biological Sciences, University of Karachi, dated 01st July 2020, wherein request has been made for registration & approval of subject Clinical Trial, which will be carried out at CBSCR, International Center for Chemical & Biological Sciences, Karachi. Application is on prescribed Form-II, along with prescribed fee of Rs.200000/-, deposited vide challan number 0813999, dated 02nd July 2020.

2.4.2. The study carried out under the supervision of Prof. Dr. Muhammad Raza Shah (PI) and the primary objective of the trial is to investigate/evaluate the safety of Inactivated SARS-CoV-2 Vaccine.

2.4.3. The details of the submitted documents are as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Fee	Prescribed fee of Rs.200000/-, deposited vide challan number 0813999, dated 02nd July 2020.
3	Investigator Brochure (s)	Attached.
4	Final protocol	Attached.
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	UAE, China and Pakistan
7	Phase of trial.	Phase – I
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	CBSCR, International Center for Chemical & Biological Sciences, Karachi.

		Not approved yet.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref:No.4-87/NBC-COVID19-26/20/20 Dated 10th July 2020.
12	CV's of the Investigators	CVs of Prof. Dr. M. Iqbal Chodhary Prof. Dr. Ghazna Khalid Prof. Dr. Khalid Saeed Khan Attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	N/A Investigational Product not yet approved.
14	Pre-clinical/clinical safety studies	Attached.
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.	80
19	Name of Monitors & Clinical Research Associate	N/A
20	Evidence of registration in country of origin.	N/A Investigational Product not yet approved.
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	56 Days.
23	Undertaking on Stamp paper	Attached.

2.4.4. Following shortcomings in the application were forwarded vide letter number F.No. 03-41/2020 DD (PS) dated 17th July 2020.

i) Proposed Clinical Trial Site (i.e. CBSCR, International Center for Chemical & Biological Sciences, Karachi) is not yet approved.

ii) Quantity of drug / trial material need to be imported is not described.

2.4.5. Applicant provided Interim summary of Safety & Immunogenicity for Phase I/II Clinical Study of Inactivated SARS-CoV Vaccine, attached for experts review. (**Annex-I**)

2.4.5. Submitted for perusal discussion and decision of CSC.

2.4.7. Prof. Dr. Muhammad Raza Shah, Director, International Center for Chemical & Biological Sciences, University of Karachi joined the meeting and briefed the committee regarding the study. As ICCBS is not approved as a Clinical Trial Site, so it was discussed upon request of applicant, that ICCBS may act as a CRO to conduct this study at the Indus Hospital Karachi. CSC members appreciated the efforts & conduct of vaccine clinical trial first time in Pakistan.

2.4.8. ***Decision of 13th 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 titled "RANDOMIZED, DOUBLE BLINDED, PARALLEL, PLACEBO CONTROLLED, PHASE-I CLINICAL TRIAL TO EVALUATE THE SAFETY & IMMUNOGENICITY OF INACTIVATED SARS-CoV-2 VACCINE IN HEALTHY POPULATION AGED 18 & ABOVE" to be conducted at the INDUS Hospital, Karachi with following conditions:

i. ***National Data Safety Monitoring Committee look after & closely monitor the safety of the patients.***
ii. ***ADRs / AEFI will submitted on monthly basis to PNPC, Pharmacy Services Division-DRAP.***

2.5) "A MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, PHASE-II CLINICAL TRIAL ON THE EFFECTIVENESS & SAFETY OF JINHUA QINGGAN GRANULES (JHQG) FOR THE TREATMENT OF COVID-19 PATIENTS", F.No. 03-33/2020 DD (PS).

2.5.1. Application is from Dr. Muhammad Raza Shah, General Manager, CBSCR, Dr. Panjwani Center for Molecular Medicine & Drug Research, International Center for Chemical & Biological Sciences, University of Karachi, dated 12th May 2020, wherein request has been made for registration & approval of subject Clinical Trial, which will be carried out at DOW University Hospital, Karachi, Civil Hospital Karachi & other collaborative Hospitals. It is a Randomized, Double Blind, Placebo Controlled, Phase-II Clinical Trial, Application is on prescribed Form-II, without prescribed fee.

2.5.2. Study will be carried out under the supervision of Prof. Dr. Muhammad Raza Shah, by investigating CRO "Center for Bioequivalence & Clinical Research, International Center for Chemical & Biological Sciences, University of Karachi

2.5.3. The primary objective of the trial is to evaluate the efficacy and safety of Jinhua Qinggan Granules (JHQG) for the treatment of COVID-19 Patients.

2.5.4. Application was discussed in the 11th CSC meeting and the CSC decided as follows:

Decision of 11th CSC meeting:

The CSC discussed the trial protocol of TCM formulation i.e. Jinhua Qinggan Granules, submitted by ICCBS and asked the applicant for National Bioethics Committee (NBC) approval.

2.5.5. Dr. Muhammad Raza Shah, General Manager, CBSCR, International Center for Chemical & Biological Sciences, University of Karachi, submitted reply on 29th July 2020, wherein reply following documents submitted through email:

i. Business License of M/s Juxiechang (Beijing) Pharmaceutical Company Limited, China
ii. Investigational Medicine Label.
iii. Pharmaceutical Production License of M/s Juxiechang (Beijing) Pharmaceutical Company Limited, China
iv. Consent letter form M/s Indus Hospital to act as Clinical Trial Site for Subject Trial.

2.5.6. After scrutiny / evaluation of reply according to pre-requisites as mentioned in Form-II of the Bio-Study Rules 2017, following shortcomings observed:

i) Institutional Review Board (IRB) approval of sites (i.e. M/s The Indus Hospital, Karachi) with complete composition of committee i.e. names and designation of members, is not provided.

ii) COPP & Free Sale Certificate for the Investigational Medicinal Product (IMP) are not provided.

2.5.7. IRB approval from CBSCR-ICCBS is provided,

2.5.8. Submitted for perusal discussion and decision of CSC.

2.5.7. Prof. Dr. Muhammad Raza Shah, Director, International Center for Chemical & Biological Sciences, University of Karachi, joined the meeting & briefed the committee regarding their clinical study, and answered the question raised by the members.

2.5.8. ***Decision of 13th 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 titled "A MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, PHASE-II CLINICAL TRIAL ON THE EFFECTIVENESS & SAFETY OF JINHUA QINGGAN GRANULES (JHQG) FOR THE TREATMENT OF COVID-19 PATIENTS" to be conducted at the INDUS Hospital, Karachi subject to submission of prerequisites as per the Bio-Study Rules 2017 as soon as possible & with following conditions:

i. Steroid testing of trial drug will be part of the protocol.

2.6) HAYAT ABAD MEDICAL COMPLEX NEW TRIAL SITE FOR SOLIDARITY TRIAL. F. No.15-41/2020 DD (PS)

2.6.1. Application is from Mariam Hassan, National Lead Coordinator, Shaukat Khanum Memorial trust dated 14th July 2020, wherein the application is in reference to approval of Clinical Trial titled "AN INTERNATIONAL RANDOMIZED TRIAL OF ADDITIONAL TREATMENTS FOR COVID-19 IN HOSPITALIZED PATIENTS WHO ARE ALL RECEIVING THE LOCAL STANDARD OF CARE. TRIAL SHORT TITLE: SOLIDARITY PUBLIC HEALTH EMERGENCY CLINICAL TRIAL.", which was approved in 11th CSC meeting held on dated 20th May 2020 to be conducted at following trial sites:

i. Shaukat Khanum Memorial Cancer Hospital & Research Center Lahore.
ii. Pakistan Institute of Medical Sciences (PIMS) Islamabad.
iii. Shifa International Hospital, Islamabad,
iv. Agha Khan University Hospital AKUH, Karachi,
v. Indus Hospital, Karachi.

2.6.2. Applicant has requested for new site that is Hayat Abad Medical Complex, Peshawar, and applicant has informed that Hayat Abad Medical Complex, Peshawar is a tertiary care hospital. Institutional Review & Ethical Board approval & CV of principal investigator is provided.

2.6.3. It is submitted that application is not on prescribed Form-I as per the Bio-Study Rules 2017, and without prerequisites.

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

2.6.5. ***Decision of 13th 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 application for conduct of clinical trial titled "AN INTERNATIONAL RANDOMIZED TRIAL OF ADDITIONAL TREATMENTS FOR COVID-19 IN HOSPITALIZED PATIENTS WHO ARE ALL RECEIVING THE LOCAL STANDARD OF CARE. TRIAL SHORT TITLE: SOLIDARITY PUBLIC HEALTH EMERGENCY CLINICAL TRIAL" at already approved HAYAT ABAD MEDICAL COMPLEX, Peshawar.

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 MATIARI RESEARCH CENTER APPROVAL AS A CLINICAL TRIAL SITE TO CONDUCT CLINICAL TRIAL TITLED "PROSPECTIVE, CLUSTER RANDOMIZED EVALUATION OF THE EFFECTIVENESS OF SUPPLIMENTATION WITH MULTIPLE MICRONUTRIENTS AND LIFE SKILLS DEVELOPMENT EDUCATION PROVIDED FROM PRECONCEPTION ON HEALTH AND BIRTH OUTCOMES AMONG YOUNG, REPRODUCTIVE-AGE [PAKISTANI WOMEN (15-24 YEARS)." F.No. 15-35/2020 DD (PS)

3.1.1. Application is from Dr. Zulfiqar A. Bhutta, founding Director, Centre of Excellence in Women and Child Health, the Aga Khan University Hospital, Stadium Road, Karachi, dated 20th January 2020, wherein F.R. is an application for approval of Matiari Research & Training Center as a Clinical Trial Site for conduct of "Cluster Randomized Evaluation of the Effectiveness of Supplementation with Multiple Micronutrients and Life Skills Development Education provided from Preconception on Health and Birth outcomes among young, reproductive-age {[Pakistani Women (15-24 Years)". The application is accompanied with fee challan of Rs.100000/- deposited vide fee deposit slip number 0741122, dated 08th January 2020.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached,
2	Prescribed fee	Only Rs.200000/- submitted vide challan number 0741122, dated 08th January, 2020.
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Charter of the Aga Khan University, attached and described that Matiari Research & Training Center is AKU's own center.
4	Details of premises including layout plan of the site.	Attached.

5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Attached.
6	Names and qualifications of the above sections along with their staff.	CVs Attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Center had facility of emergency transportation to any sick patients (enrolled in study) to nearby rural health center or District Headquarter Hospital or even to Hyderabad Civil Hospital.
8	Undertaking on stamp paper	Attached.

3.1.3. Application was discussed in the 7th CSC meeting & CSC decided as follows:

Decision of 7th CSC Meeting:-

The CSC after deliberations decided to conduct the inspection of Matiari Research and Training Center Matiari, Sindh. The team, comprising of the following experts will inspect. In case any member is not available the committee authorized its chairman to add another suitable member of the relevant expertise from the pool of experts. The applicant shall be informed for the proposed date of inspection accordingly.-

i.	Dr. Abdur Rashid (Coordinator).
ii.	Dr. Ali Jawa.
iii.	Waqas Latif.
Iv	Salwa Ahsan.
v	Dr. Najam Us Saquib.

3.1.4. Following expert panel members conducted inspection of the site on 16th July 2020 and panel coordinator submitted report today on 20th July 2020.

i.	Dr. Abdur Rashid (Coordinator).
ii.	Dr. Ali Jawa.
iii.	Dr. Najam Us Saquib.

3.1.5. Expert panel members recommended the site for approval with following remarks on inspection report:

"The facility is geared towards Community Based Clinical Trial Site. It meets &exceeds the standards. The CTS is well equipped, well-staffed and has good corporate governance system. The CTS has conducted seven high profile clinical trials under its belt. The principal investigators are well experienced and highly respected researchers."

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

3.1.7. ***Decision of 13th CSC meeting:***

Based on the recommendations of inspection panel, CSC after detailed deliberation decided to approve Matiari Research & Training Center, Matiari *to act as a clinical trial site to conduct* ***the clinical studies titled "PROSPECTIVE, CLUSTER RANDOMIZED EVALUATION OF THE EFFECTIVENESS OF SUPPLIMENTATION WITH MULTIPLE MICRONUTRIENTS AND LIFE SKILLS DEVELOPMENT EDUCATION PROVIDED FROM PRECONCEPTION ON HEALTH AND BIRTH OUTCOMES AMONG YOUNG, REPRODUCTIVE-AGE [PAKISTANI WOMEN (15-24 YEARS)".***

3.2) APPROVAL FOR PROCUREMENT OF MICRONUTRIENT TABLETS FOR PROSPECTIVE, CLUSTER RANDOMIZED EVALUATION OF THE EFFECTIVENESS OF SUPPLIMENTATION WITH MULTIPLE MICRONUTRIENTS AND LIFE SKILLS DEVELOPMENT EDUCATION PROVIDED FROM PRECONCEPTION ON HEALTH AND BIRTH OUTCOMES AMONG YOUNG, REPRODUCTIVE-AGE [PAKISTANI WOMEN (15-24 YEARS). F. No.03-14/2019-DD (PS)

3.2.1. Application is from Dr. Zulfiqar A. Bhutta, MBBS, FRCPCH, FAAP, Ph.D., The Noordin Noormahomed Sheriff Professor & Founding Director, Centre of Excellence in Women and Child Health, Aga Khan University Hospital, Karachi, dated 14th October, 2019, wherein FR is in reply of letter no. F.No. 1-2(NA)/2019-Dir (Nut)-NHSRC, wherein FR request has been made for procurement of trial drug and registration of trial.

3.2.2. Brief summary of the trial is as follows:

"The primary aims of this study is to evaluate the impact of supplementation with multiple micronutrients (MMN) from preconception and life skills education among women 15-18.9 years of age at enrolment on the prevalence of anemia in a population setting; and 2) To evaluate the impact of supplementation with MMN from preconception and life skills education among young women 15-24 years of age on the rate of low birth weight (LBW) in a population setting. Infants born to mothers enrolled in the study will be followed for 1 year. This study aims to enroll 25,400 non-pregnant young women in Matiari district. This sample size is anticipated to equate to 1456 births. Participants will be randomized by cluster to receive either MMN supplements and life skills education or the standard of care at enrolment. Clusters have been defined based on health facility catchment areas. MMN supplements will be provided twice weekly during the preconception period,

once daily during the pregnancy period, and once daily until 6 months after giving birth during the postpartum period; and a package of life skills education materials will be provided bi-monthly during the preconception period. In addition to the primary outcomes, measurements will include micronutrient status, anthropometrics, birth outcomes, dietary intake and feeding practices, adherence, and indices of empowerment."

3.2.3. The trial is registered on U.S. National Trial Registry with reference number **NCT03287882**, as per available details on the registry (last update posted on 19th September, 2017), the study location is Matiari Research and Training Centre, Matiari, Sindh, Pakistan and trial is on recruiting stage, trial timelines are as follows:

- Actual Study Start Date: **June 30, 2017.**
- Estimated Primary Completion Date **April 30, 2020.**
- Estimated Study Completion Date **April 30, 2021.**

3.2.4. The study is under sponsorship of Aga Khan University, with collaboration of The Hospital for Sick Children, National Program for Family Planning and Primary Health Care and Bill and Melinda Gates Foundation, and responsible person is Dr. Zulfiqar Ahmed Bhutta (PI), Aga Khan University.

3.2.5. It is pertinent to mention here that the application is for approval of ongoing trial, which was started from 30th June, 2017 without intimation and approval from DRAP and NBC-PHRC.

3.2.6. Objectives of the study are as follows:

i) **Primary Study Objective:**

To evaluate the impact of life skill based education (LSBE) materials and supplementation with multiple micronutrients (MMN) among adolescent girls (15-19 years of age at enrolment) on the prevalence of anemia in a population setting.

To evaluate the impact of LSBE materials and supplementation with MMN among young women (15-24 year of age) on the rate of low birth weight (LBW) in a population setting.

ii) **Secondary Study Objective:**

Secondary objective are aimed to evaluate the impact of interventions on micronutrient status (iron, vitamin A, and D), participants' BMI, pregnancy outcomes, infant growth and mortality and empowerment, menstrual hygiene management, early marriages and continued education.

3.2.7. After re-evaluation of application, the description & details of the submitted documents is as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Fee	Copy Attached.

		Prescribed fee of Rs.200000/- submitted vide challan number 0801281, dated October 2019.
3	Investigator Brochure (s)	Attached. Not as per ICH-GCP Guidelines.
4	Final protocol	Attached.(Version-4)
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Pakistan.
7	Phase of trial.	Phase – III (Effectiveness Trial) Proposed timeline 2016-2020
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.	1500 MMN Jars required for remaining trial. (Each jar contains 1000 tablets).
9	Site of the trial	Matiari Research and Training Centre, Matiari, Sindh, Pakistan **of** M/s Aga Khan University Hospital Karachi. **(**Not yet licensed by DRAP**).**
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Certificate Ref: No. 4-87/NBC-377/19/1870, Dated 29th March 2019
12	CV's of the Investigators	**CVs of following investigators & concerned employees are attached:** **1-Dr. Zulfiqar A. Bhutta**, MBBS, FRCPCH, FAAP, Ph.D.

		Founding Director, Center of Excellence in Women & Child Health, Pediatrics & Child Health, The Aga Khan University, South Central Asia, East Africa & United Kingdom, Karachi, 74800 Pakistan. (P.I) **2-Dr. Sajid b. Soofi**, Associate professor, Pediatrics & Child Health & Associate Director, Center of Excellence in Women & Child Health, Pediatrics & Child Health-MC The Aga Khan University Karachi, 74800, Pakistan. (Co-P.I) **3-Dr. Jo-Anna Baxter, (**PhD candidate) Canadian Institute for Health Research, Government of Canada. **4-Mr. Yaqub Wasan** (Manager Research), Department of Pediatrics & Child Health, Aga Khan University Karachi
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP certificate of Lomapharm GmbH, Langes Feld 5, 31860 Emmerthal, Germany & COPP for "Pregnancy & Lactation Micronutrient tablets" is attached.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Not provided and claimed that as drugs used in the trial is not an investigational product.
16	Summary of Investigator Brochure	Not provided.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	25400 Subjects (Approx.). As per National Trial Registry record
19	Name of Monitors & Clinical Research Associate	Attached.
20	Evidence of registration in country of origin.	Attached.
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	48 Months
23	Undertaking	Attached.

3.2.8. After re-evaluation following shortcomings were observed & will communicated to the applicant:

i. Evidence of registration in country of origin is not provided.
ii. Summary of Investigator Brochure is not provided.
iv. Provided investigator's brochure is not as per ICH-GCP Guidelines.
iv. Summary of protocol is not provided and claimed that as drugs used in the trial is not an investigational product.

3.2.9. Mr. Yaqub Wasan (Manager Research), from Department of Pediatrics & Child Health, Aga Khan University Karachi, participated in the 7th CSC meeting & briefed CSC members regarding subject trial.

3.2.10. CSC members after getting background of the study questioned and discussed that as this study is an ongoing study, which was started in June 2017 after getting ethical approval from Aga Khan University ERC & NBC-PHRC, but Clinical Trial Site is not yet approved, so the members of CSC decided as follows:

3.2.11. **Decision of 7thCSC Meeting:** -

"The CSC after deliberations decided to defer the case till fulfilment of all prerequisites as per Form-II of the Bio-Study Rules 2017 & inspection of Matiari Research and Training Center Matiari, Sindh & recommendations of inspection panel.

3.2.12. Applicant referring to shortcoming letter even number dated 25th February 2020, submitted reply as follows:

i. Summary of protocol is not provided and claimed that as drugs used in the trial is not an investigational product.

Reply:

- We would note that concerned study United Nations Multiple Micronutrient Preparation (UNIMMAP) tablets are not an investigational drug, but a well-recognized nutritional supplement widely used and procured in the UN system. UNIMMAP tablets have been previously used and evaluated in many low and middle income countries (LMICs) including Pakistan (Annexure 1). (Page 530-533/corr.)
  Collectively, WHO guidelines & UNICEF documents (Annexure 2 & 3) (Page 534-560/corr.) Coupled with findings from various trials, reviews and meta-analysis (Annexure 1) (Page 530-533/corr.) suggest that policy makers in populations with a high prevalence of nutritional deficiencies may choose to give UNIMMAP supplements to mothers, particularly supplements including iron and folic acid. Our recent national guidelines on adolescent nutrition (2019) released by Nutrition Wing, Ministry of National Health Services Regulations & Coordination & WHO (Annexure 4) (Page 561-

615/corr.) recommend the provision of Multi-Micronutrient tablets to underweight non-pregnant married women, at the dose of one tablet per day for three months.

- Further the evidence described below demonstrate why this supplement is not an investigational drug and that the amounts in the study supplements are safe for consumption in the trial population.
- Summary points from the WHO, UNICEF and United Nation University (UNU) technical workshop document where UNIMMAP composition was first conceived3. (Annexure 3) (Page 539-560/corr.)
- Given widespread micro nutritional deficiencies in LMICs and known to have a negative impact on pregnancy outcomes (i-e in the 1990's). Supplement with other micronutrients, and combining different micronutrients into one supplement was considered to be efficient from a programme point of view. Such a multi-supplement specifically designed for women from developing countries did not exist. The selection of nutrients was based on available evidence around deficiencies, possible consequences of deficiencies for mother and child, weighing of risks versus advantages, and on interaction between nutrients. It was decided to include 15 micronutrients (Vit A, D, E,8182,86, Bi 2, C, Niacin, Folic Acid, Fe ,Zn, Cu, l, Se). The amount of folic acid was set at 400 µg. However, the other micronutrients are provided at the level of the recommended dietary allowance (RDA), which are reference ranges for micronutrients set by the Institute of Medicine (USA and Canada), RDA values are set to meet the needs of the vast majority (97 to 98 percent) of the target healthy population, The actual nutrient needs of a given individual will be different than the RDA. However, since we know that 97 to 98 percent of the population's needs are met by the RDA, we can assume that if a person is consuming the RDA of a given nutrient, they are most likely meeting their nutritional need for that nutrient. The important thing to remember is that the RDA is meant as a recommendation and meeting the RDA means it is very likely that you are meeting your actual requirement for that nutrient. Each micronutrient also has an upper limit (UL). The UL was established to help distinguish healthful and harmful nutrient intakes. Developed
  in part as a response to the growing usage of dietary supplements, ULs indicate the highest level of continuous intake of a particular nutrient that may be taken without causing health problems. For safety, the UL is set far above the RDA.
- Finally it was proposed that pregnant women should take the tablet on a daily basis for as much of the pregnancy as possible, and should continue until 3 months post-partum.
  Technical group agreed that other target group could include, adolescent girls, in order to improve their micronutrient status in advance of pregnancy. For the sake of realistic programming it was recommended that the effectiveness of delivering supplements to adolescent girls once or twice a week be further explored.
- Holistically, this WHO, UNICEF and UNU document serve the basis of UNIMMAP composition which is quite safe and well within the ranges RDAs. This also pledged to conduct effectiveness trials to explore risks and benefits of using UNIMMAP programmatically We also provide the evaluation of these UNIMMAPP tablets in Pakistan previously (2002-2004) with successful impact on maternal anemia and birth weight4 (Annexure 5) (Page 616-625/corr.)
- The table below shows the RDA for women (pre-pregnancy and pregnancy), the UNIMMAP formulation, the standard of care, and the upper limit (UL). It's extremely unlikely that the amounts of vitamins and minerals given to participants who receive the UNIMMAP supplements within the trial would cause harm, because the UL is far above the RDA. Furthermore, because the dietary intake of the vitamins and minerals included in the UNIMMAP supplement is low among adolescent and young women in Pakistan, we do not believe participants will exceed the UL in taking the supplement and consuming their usual diet.

Table 1. RDA, UNIMMAP composition, standard of care, and UL for vitamins and minerals in UNIMMAP

Nutrient	RDA for Women	RDA for Pregnancy	UNIMMAP formulation	Standard of care during pregnancy	Upper limit
Vitamin A (µg RE)	700	**750**	**800**	**-**	**3000**
Vitamin D (µg)	5	**5**	**5**	**-**	**100**
Vitamin E (mg)	15	**15**	**10**	**-**	**1000**
Folic acid (µg)	400	**600**	**400**	**400**	**1000**
Vitamin B1 (mg; thiamine)	1.1	**1.4**	**1.4**	**-**	**Not determined.**
Vitamin B2 (mg; riboflavin)	1.1	**1.4**	**1.4**	**-**	**Not determined.**
Niacin (mg)	14	**18**	**18**	**-**	**35**
Vitamin B12 (µg)	2.4	**2.6**	**2.6**	**-**	**Not determined.**
Vitamin B6 (mg)	1.3	**1.9**	**1.9**	**-**	**100**
Vitamin C (mg)	75	**80**	**70**	**-**	**2000**
Iron (mg)	18	**27**	**30**	**60**	**45**
Zinc (mg)	8	**12**	**15**	**-**	**40**
Iodine (µg)	150	**220**	**150**	**-**	**1000**
Copper (µg)	900	**1000**	**2000**	**-**	**10000**
Selenium (µg)	55	**60**	**65**	**-**	**400**

- WHO recommendations on antenatal care for a positive pregnancy experience (2015)s
  Remarks: There is some evidence of additional benefit of UNIMMAP supplements containing 13-15 different micronutrients (including iron and folic acid) over iron and folic acid supplements alone, but there is also some evidence of risk, and some important gaps in the evidence. Although the Guideline Development Group (GDG) agreed that overall there was insufficient evidence to warrant a recommendation, the group agreed that policymakers in populations with a high prevalence of nutritional deficiencies might consider the benefits of UNIMMAP supplements on maternal health to outweigh the disadvantages, and may choose to give UNIMMAP supplements that include iron and folic acid. More research is needed to determine which micronutrients improve maternal and perinatal outcomes, and how these can be optimally combined into a single supplement. (Annexure 2) (Page 534-538/corr.)

- A recent situational analysis (2018)of the market, manufacturing and policy factors that driving the production of multiple micronutrient supplements in 12 lower and upper middle income countries

found that most countries have the capacity to produce locally multiple micronutrient supplements but not one country had a formulation that matched the globally recommended formulation of the UNIMMAP. The major barriers observed for sustainable and affordable production include (a) poor technical capacity and policies for ensuring quality along the value chain and (b) lack of policy coherence to incentivize local production and lower the manufacture and retail price of supplements.(Annexure 5) (Page 616-625/corr.)

- UNIMMAP is available at UNICEF supply division page. While UNICEF products are aligned with normative standards and guidelines and designed to facilitate rational use to the lowest level of health care service delivery. WHO Model of Essential medicines List (EML) and disease specific treatment guidelines inform UNICEF product selection. WHO technical guidance informs specifications and requirements for procured products, including non-standard items. Further details on UNICEF's technical requirement for nutritional products are detailed in appended document.

ii. Evidence of registration in country of origin not provided.

Reply:

- We have requested UNICEF to kindly arrange the said certificate. In the absence of this, we believe certificate of origin of dispatch, certificate of analysis, certificate of GMP and certificate of a pharmaceuticals product would be sufficient to consider UNIMMAP a reliable product. For UNICEF nutritional products WHO technical guidance informs specifications and requirements for procured products, including non-standard items.

iv. Summary of investigator's brochure is not provided.

Reply:

- In query first we described this at length that this is not an investigational drug. Short description on content is appended which is taken from UNICEF supply division.

v. Provided investigator's brochure is not as per ICH-GCP guidelines.

Reply:

- Given our details above which shows that UNIMMAP is a nutritional supplement. Therefore we shared you a one pager brief details of supplement. The supplement is not investigational so the brochure is not available.

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

3.2.14. ***Decision of 13th CSC meeting:***

CSC after detailed deliberation decided to approve the clinical studies titled "PROSPECTIVE, CLUSTER RANDOMIZED EVALUATION OF THE EFFECTIVENESS OF SUPPLIMENTATION WITH MULTIPLE MICRONUTRIENTS AND LIFE SKILLS DEVELOPMENT EDUCATION PROVIDED FROM PRECONCEPTION ON HEALTH

AND BIRTH OUTCOMES AMONG YOUNG, REPRODUCTIVE-AGE [PAKISTANI WOMEN (15-24 YEARS).", to be conducted at Matiari Research & Training Center, Matiari.

3.3) <u>APPLICATION FOR APPROVAL OF INSTITUTE OF CHEST DISEASES, KOTRI (IDCK) TO ACT AS CLINICAL TRIAL SITE FOR endTB & endTB-Q CLINCAL TRIAL. F. No.15-50/2020 DD (PS)</u>

2.3.1. Application is from Prof. Dr. Abdul Bari Khan, CEO, The Indus Hospital, Karachi, dated 13th July 2020, wherein the request has been made to license of Institute of Chest Diseases, Jamshoro from DRAP, the application is on prescribed Form-I of the Bio-Study Rules 2017.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Attached
3	Details of premises including layout plan of the site.	Only Layout is attached no details provided. Whereas site is a specialized care government hospital.
4	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Attached
5	Names and qualifications of the above sections along with their staff.	Attached
6	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Applied site is a specialized care hospital.
7	Affidavit on Stamp paper	Attached
8	Prescribed Fee	Photocopy of challan is attached.

2.3.3. In the view of above, it is proposed that the case may include in next CSC meeting agenda, to present the case before CSC for further perusal.

2.3.4. Submitted for perusal discussion and decision of CSC.

2.3.5. The case was discussed in the meeting and as applied site is Government Hospital so inspection is exempted.

2.3.6. ***Decision of 13th CSC meeting:***

CSC after detailed deliberation decided to as approve "INSTITUTE OF CHEST DISEASES, KOTRI (IDCK)", to act as a clinical trial site to conduct already approved endTB & endTB-Q clinical trials.

3.4) APPLICATION FOR APPROVAL FOR THE PROJECT TITLED "TRANSNASAL CAPSULE ENDOMICROSCOPY FOR VISUALIZATION OF THE SMALL INTESTINE IN ENVIRONMENTAL ENTERIC DYSFUNCTION (EED) POPULATION IN PAKISTAN. F. No.03-18/2020-DD (PS).

3.4.1. Application is from Dr. Sayed Asad Ali, Professor, Department of Pediatrics & Child Health, Associate Dean, Research, Medical College, Aga Khan University, Karachi, dated 3rd January 2020, wherein request has been made for approval of subject studies / trial on prescribed Form-II of the Bio-Study Rules 2017, and fee of Rs.200000/- submitted vide challan No 0801290, dated 03 January 2020.

3.4.2. The study is sponsored by **Bill and Melinda Gates Foundation,** The aim of the study is as follows:

Primary Outcome:

The primary outcome of this research is the translation and dissemination of these minimally-invasive medical devices (TNIT and a compatible image guided brush biopsy, cryobiopsy and IPD) that will enable the detailed evaluation of the small intestine of infants for the development of effective environmental enteric dysfunction (EED) interventions. This result will be achieved upon demonstration of the use of these devices in infants in setting where EED is endemic (e.g. Matiari district in Pakistan) and the capability of these technologies to differentiate the EED intestine.

Sustainability will be addressed by developing infrastructure/partnerships to fabricate and support these devices so that they can be widely deployed and utilized for EED studies.

3.4.3. Study will be conducted only in Pakistan & 30 subjects / Children of 06 to 59 months residing in Matiari district will be recruited.

3.4.4. Application scrutinized & evaluated as per prerequisites of the Bio-Study Rules 2017, details of the submitted documents is as under;

S. No.	Document	Remarks
1	Application on prescribed form	Attached
2	Fee	Rs.200000/- submitted vide challan No 0801290, dated 03 January 2020.
3	Investigator Brochure (s)	Attached but not as per ICH-GCP guidelines.
4	Final protocol	Version 1.0
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Pakistan.
7	Phase of trial.	Not described.
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.	In subject study medical devices is utilized, description & quantity is as follows: 1- Fifty (50) Trans-nasal Endomicroscopy devices will be imported for the total duration of study at different time points. 2. Accessories includes: i-Compact Imaging System (02pcs) ii-Rotary Junction (02pcs)
9	Site of the trial	Aga Khan University, Matiari Research Center, Matiari.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB approval from ERC of Aga Khan Hospital is attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Certificate Ref: no. 4-87/NBC-429/19/1111, dated 17th October 2019.
12	CV's of the Investigators	i- Dr. Sayed Asad Ali (PI), Aga Khan University Hospital, Karachi.

		ii- Dr. Guillermo J. Tearney (PI), Professor of Harvard Medical School. iii- Dr. Kamran Sadiq (Co-PI), Aga khan University, Karachi. iv- Dr. Sheraz Ahmed, (Manager Research), Aga khan University, Karachi. iv- Dr. Fayaz Ahmed (Research Specialist), Aga khan University, Karachi. **(CVs Attached)**
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided. It is informed & claimed that the Transdermal Endomicroscopy, Compact Imaging System, Rotary Junction and its accessory device are developed and assembled in a not for profit, academic research lab at the Massachusetts General Hospital in Boston, MA, USA. The devices are not intended to be commercialized and are intended to be research purpose only. The devices are not registered in the country of origin (USA), hence GMP, CoPP or Free Sale Certificates are not provided.
14	Pre-clinical/clinical safety studies	Irrelevant documents attached.
15	Summary of Protocol	Version 1.0
16	Summary of Investigator Brochure	Attached but not as per ICH-GCP guidelines.
17	Adverse Event Reporting Form	Attached
18	No of patients to be enrolled in each center.	Children of 06 to 59 months residing in Matiari district. Study total sample size (30 subjects): i- 15 Well-nourished. ii- 15 Malnourished.
19	Name of Monitors & Clinical Research Associate	i- Dr. Sayed Asad Ali (PI), Aga Khan University Hospital, Karachi.

		ii- Dr. Guillermo J. Tearney (PI), Professor of Harvard Medical School.
20	Evidence of registration in country of origin.	Not provided. It is informed & claimed that the Transdermal Endomicroscopy, Compact Imaging System, Rotary Junction and its accessory device are developed and assembled in a not for profit, academic research lab at the Massachusetts General Hospital in Boston, MA, USA. The devices are not intended to be commercialized and are intended to be research purpose only. The devices are not registered in the country of origin (USA)
21	Copy of registration letter (if registered in Pakistan)	N/A.
22	Sample of label of the investigational product / drug.	N/A In subject study medical devices is utilized by experts.
23	Duration of trial	Subject participation duration is 3-6 months. Total study duration is from December 2019 to May 2022. (29 Months)
24	Undertaking on stamp paper	Attached.

3.4.5. After evaluation following shortcomings are recorded:

i. Attached investigator brochure is not as per ICH-GCP guidelines.
ii. Phase of trial / study is not described.
iii. GMP certificate along with COPP & free sale certificate of the investigational product are not provided and informed & claimed that the Transdermal Endomicroscopy, Compact Imaging System, Rotary Junction and its accessory device are developed and assembled in a not for profit, academic research lab at the Massachusetts General Hospital in Boston, MA, USA. The devices are not intended to be commercialized and are intended to be research purpose only.
iv. Pre-clinical/clinical safety studies are not provided.
v. Evidence of registration in country of origin is not provided & informed that the devices are not registered in the country of origin (USA)

3.4.6. Application was discussed in the 7th CSC meeting and the CSC decided as follows:

Decision of 7thCSC Meeting: -

"The CSC after deliberations decided to defer the case till fulfilment of all prerequisites as per Form-II of the Bio-Study Rules 2017 & recommendations of same inspection panel. Which will inspect Matiari Research and Training Center, Matiari, Sindh.

3.4.7. Shortcomings of application was forwarded vide letter no. F.No. 03-18/2020 DD (PS), dated 24th July 2020, response is yet awaited.

3.4.8. Submitted for perusal discussion and decision of CSC.

3.4.9. *Decision of 13th CSC meeting:*

CSC after detailed deliberation decided to approve the clinical studies titled "TRANSNASAL CAPSULE ENDOMICROSCOPY FOR VISUALIZATION OF THE SMALL INTESTINE IN ENVIRONMENTAL ENTERIC DYSFUNCTION (EED) POPULATION IN PAKISTAN", to be conducted at Matiari Research & Training Center, Matiari.

3.5) APPLICATION FOR LICENSE TO ACT AS BA/BE STUDIES LAB, AT M/S OLIVE WORLDWIDE (SMC-PVT) LTD. F.No. 15-32/2019 DD (PS)

Application from Mohsin Ali Jawa CEO, M/s Olive Worldwide (SMC-PVT) Ltd, 3-4-5 M, Model Town Extension, Lahore, wherein the request has been made to license their company with DRAP to work as BA/BE studies lab at M/s Olive Worldwide (SMC-PVT) Ltd, the application is on prescribed Form-I of the Bio-Study Rules 2017 along with fee of Rs.300000/- deposited vide challan no.0846242, dated 29th August 2019.

3.5.2. It is submitted that application evaluated according pre- requisites as mentioned in Form-I of the Bio-Study Rules 2017, and status of application is as follows:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Fee	Attached
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Attached
4	Details of premises including layout plan of the site.	Only layout Attached, details not provided.

5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	List attached, but equipment required for BA/BE Studies Center are not in the list.
6	Names and qualifications of the above sections along with their staff.	Attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	List of available services at Wilcare Hospital is attached.
8	Undertaking on stamp paper	Not provided.

3.5.3. Application was discussed in the 6th meeting of CSC & CSC decided as follows:

3.5.4. Decision of 6th CSC Meeting:-

The CSC after deliberations decided to conduct the inspection of BA/BE Studies Center from team, comprising of the following experts. In case any member is not available the committee authorized its chairman to add another suitable member of the relevant expertise from the pool of experts. The applicant shall be informed for the proposed date of inspection accordingly.-

i.	Dr. Abdur Rashid
ii.	Prof. Dr. Javaid Akram
iii.	Dr. Masud ur Rehman
iv.	Dr. Nadeem Irfan
v.	Dr. Farhana Badar

3.5.5. Due to unavailability of pool members Chairman CSC, exercising the power delegated by the CSC in its 3rd meeting, replaced the inspection pool members for the inspection, and following expert's panel inspected the facility on02nd July, 2019:

i.	Dr. Abdur Rashid (Coordinator)
ii.	Prof. Dr. Nadeem Irfan
iii.	Dr. Farhana Badar
iv.	Associate Prof. Dr. Uzma Malik

3.5.6. Remarks of inspection team:

Keeping in view the human resources, equipment, technical experts, SOPs, documentation, PK solver for pharmacokinetic parameters, ambulance facility, data integrity, bio statistical expertise, and other facilities, **the site is recommended for approval.**

3.5.7. Request for the change of name:

Mohsin Ali Jawa, CEO, Olive Worldwide (Pvt) Ltd. Has requested dated 28th July 2020 for the name of BABE center be as follow in the license issued by the DRAP.

Olive Worldwide (SMC-PVT) Ltd. BABE center doing business as EON BioCenter

EON BioCenter is shorter and easier for our customers, hence the change request.

3.5.8. Submitted for perusal discussion and decision of CSC.

3.5.9. *Decision of 13th CSC meeting:*

Based on the recommendations of inspection panel, CSC after detailed deliberation decided to approve M/s Olive Worldwide (SMC-PVT) Ltd., Lahore to act as a BA/BE Studies Center. Further request for use of business name of "EON BioCenter" is deferred.

ITEM IV: MISCELLANEOUS AGENDA ITEMS

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

4.1.1. Application was 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

4.1.2. 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.

4.1.3. **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.

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

4.1.5. 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.

4.1.6. Application was presented before CSC I its 12th meeting, 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.

4.1.8. ***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.

4.1.9. As per CSC decision, soft copies of Trial protocol, Investigators Brochure & presentation forwarded through email, opinion/comments of experts are attached as **Annex-II**.

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

4.1.11. ***Decision of 13th CSC meeting:***

Based on the recommendations of experts and after detailed deliberation decided to not recommend the trial.

4.2) APPLICATION FOR AMENDMENT IN APPROVED PRPOTOCOL OF CLINICAL TRIAL TITLED "EVALUATING NEWLY APPROVED DRUGS IN COMBINATION REGIMENS FOR MULTI DRUG- RESISTANT TB WITH FLOUROQUINOLONE RESISTANCE (Q) (endTB-Q) PHASE-III CLINICAL TRIAL".

4.2.1 Application is from Dr. Naseem Salahuddin, Principal Investigator of endTB-Q Clinical Trial, The Indus Hospital Karachi, dated 06th July 2020, for minor administrative amendments made to the Protocol version 2.2 resulting in a new Protocol version 3.0. for endTB-Q Clinical Trial.

4.2.2. Ethical approval from NBC is attached, Reference number 4-87/NBC-410-Amendments/20/2071, dated 19th May 2020 along with prescribed fee for amendment is deposited vide challan no. 2018805 dated 16th June 2020.

4.2.3. **CHANGES TO THE PROTOCOL**

A redlined soft copy of Protocol Amendment 3.0 was forwarded with agenda & summary of protocol is attached as **Annex-III.**

4.2.4. Submitted for perusal discussion and decision of CSC.

4.2.5. ***Decision of 13th CSC meeting:***

The CSC after detailed deliberation decided to approve the amendments in already approved protocol titled "EVALUATING NEWLY APPROVED DRUGS IN COMBINATION REGIMENS FOR MULTI DRUG- RESISTANT TB WITH FLOUROQUINOLONE RESISTANCE (Q) (endTB-Q) PHASE-III CLINICAL TRIAL", by the CSC in its 6th meeting held on 20th January 2020.

4.3) APPLICATION FOR NOTIFICATION OF INFORMED CONSENT FORMS AND PATIENT MATERIAL (EVALUATING NEWLY APPROVED DRUGS FOR MULTI-DRUG RESISTANT TB) PHASE-III CLINICAL TRIAL.

4.3.1 Application is from Meherunissa Hamid, Site Study Coordinator, , The Indus Hospital Karachi, dated 06th July 2020, for amendments in informed consent form, patient material and

removed Delhi Medical Center and Red Crescent Hospital & added Institute of Chest Disease, Kotri (after site approval).

4.3.2. Applicant requested for notification for above described changes, summary of changes attached as additional **annex-I**.

4.3.3. Applicant has not been provided prescribed fee for changes.

4.3.4. Submitted for perusal discussion and decision of CSC.

4.3.5. ***Decision of 13th CSC meeting:***

The CSC after detailed deliberation decided to approve the amendments in already approved protocol titled "EVALUATING NEWLY APPROVED DRUGS IN COMBINATION REGIMENS FOR MULTI DRUG- RESISTANT TB (endTB)", by the CSC in its 6th meeting held on 20th January 2020, subject to submission of prescribed fee for amendment.

4.4) EXPLANATION

4.4.1 It was observed that there was a reliable information from different sources, electronic & print media that Dr. Javed Akram has started clinical trial on vaccine, as per record University of Health Sciences, Lahore neither applied for approval of Clinical Trial for vaccine nor any Clinical Trial has been approved by the Clinical Studies Committee.

4.4.2. To conduct a clinical trial on vaccine / biological / Drugs without prior permission / approval from the CSC is violation and against the Bio-Study Rules 2017. In this regard Dr. Javed Akram was directed to stop clinical study immediately and directed to stop recruitment of human subject for the study.

4.4.3. Dr. Javed Akram, asked to explain his position that why he has started clinical trial without approval from CSC. And on violation of Bio-Study Rules 2017, why not an action may be taken against him and other personnel involved in the conduct of clinical trial on vaccine without permission / approval.

4.4.4. In reference to this division explanation letter number 1-1/2020 (DIR-DS), issued on 8th August 2020, Professor Javed Akram, Vice Chancellor, University of Health Sciences Lahore, submitted his reply to Director Pharmacy Services Division, dated 8th August 2020, as under:

"*This is with reference to your letter No. 1-1/2020 (DIR. DS), dated August 08, 2020, on subject cited above.*

Let me make it abundantly clear at the very onset that your information about the start of clinical trial on vaccines by the University of Health Sciences (UHS), Lahore, is not correct.

The fact of the matter is that the University is in negotiations with Flinders University, Adelaide, Australia, where a team of scientists led by Professor Nikolai Petrovsky, has developed a vaccine, COVAX-19, for coronavirus. The phase 2 trial of this vaccine is underway in different countries including Australia, Korea, Azerbaijan and USA. Once we reach a consensus on the terms

and conditions, and protocols of research, an MoU will be signed between the institutions and after that formal approval will be taken to start the trial from relevant bodies and authorities including Institutional Ethical Review Board, National Bioethics Committee and Clinical Study Committee of Drug Regulatory Authority of Pakistan. Till that time, this is just a proposal and we are not proceeding an inch forward with the study. This thing was made clear to the media and that is why it has been duly reflected in news report (Copy enclosed).

This is further to be noted that UHS is a law-abiding institution and we are fully aware of the protocols of such studies. You have our track record and it should be appreciated that we have always been complied with the protocols of research.

With regards to recruitment of volunteers/subjects for trial, it is clarified that no such enrollment or induction has been started so far.

I assure you that there is absolutely no violation of Bio-safety Rules 2017, or for that matter, any other law or regulation concerning start of a clinical trial. We wouldn't take a single step ahead unless we got all the approvals from concerned authorities including DRAP."

4.4.5. Submitted for perusal discussion and decision of CSC.

4.4.6. Chairman CSC briefed the committee regarding background of explanation & reply submitted by Prof. Dr. Javaid Akram.

4.4.7. ***Decision of 13th CSC meeting:***

The CSC has accepted reply of Prof. Dr. Javed Akram. He further informed that they are under negotiation with Flinders University, Adelaide, Australia, UHS, Lahore will apply for approval of trial with all codal formalities as per the Bio-Study Rules 2017, when it required.