MINUTES OF THE 35TH MEETING OF THE CLINICAL STUDY COMMITTEE (CSC) HELD ON 13TH OCTOBER, 2022.

Table of Contents:

10.	**ITEM X:** APPLICATION TO REGISTER **THE AGA KHAN HOSPITAL FOR WOMEN & CHILDREN**, KHARADAR, KARACHI AS **CLINICAL TRIAL SITES** FOR A **PHASE-II** CLINICAL TRIAL TITLED, "CAN ESOMEPRAZOLE IMPROVE OUTCOMES IN WOMEN AT HIGH RISK OF PRE-ECLAMPSIA? A PHASE-II, PLACEBO-CONTROLLED RANDOMIZED MULTICENTER CLINICAL TRIAL (THE ESPRESSO STUDY)". **F. No.15-16/2022 DD (PS)**	**39**
11.	**ITEM XI:** APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "CAN ESOMEPRAZOLE IMPROVE OUTCOMES IN WOMEN AT HIGH RISK OF PRE-ECLAMPSIA? A PHASE II, PLACEBO-CONTROLLED RANDOMIZED MULTICENTER CLINICAL TRIAL **(THE ESPRESSO STUDY)**", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. **F.No.03-13/2022 DD (PS)**	**41**
12.	**ITEM XII:** APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "EFFECTIVENESS OF NOVEL APPROACHES TO RADICAL CURE WITH TAFENOQUINE AND PRIMAQUINE **(EFFORT)**- A RANDOMIZED CONTROLLED TRIAL IN P. VIVAX PATIENTS". FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. **F. No.03-10/2022-DD (PS)**	**45**
13.	**ITEM XIII:** APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "RANDOMIZED CONTROLLED TRIAL TO ASSESS THE IMMUNOGENICITY AND SAFETY OF FULL VERSUS FRACTIONAL DOSE OF PFIZER/BIONTECH, ASTRAZENECA, AND SINOVAC COVID-19 VACCINES GIVEN AS A BOOSTER DOSE AT LEAST 6 MONTHS AFTER PRIMARY VACCINATION SERIES OR PCR-CONFIRMED INFECTION WITH SARS-COY-2 IN HEALTHY ADULTS", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. **(FraCTCoV)**. **F. No.03-08/2022-DD (PS)**	**50**
14.	**ITEM XIV:** APPLICATION FOR REGISTRATION AND APPROVAL OF CLINICAL TRIAL TITLED "IMMUNOGEENICITY OF NOVEL **ORAL POLIOMYELITIS VACCINE TYPE 2 (nOPV2)** IN HEALTHV CHILDREN AGED 1- 15 YEARS IN SETTINGS AT HISH RISK OF cVDPV2 OUTBREAKS", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. **F. No.03-19/2022-DD (PS)**	**57**
15.	**ITEM XV:** APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "A PHASE-III, RANDOMIZED, OBSERVER-BLIND, MULTICENTER STUDY TO EVALUATE THE EFFICACY, IMMUNOGENICITY AND SAFETY OF **SEQIRUS**-CELL-BASED QUADRIVALENT SUBUNIT INFLUENZA VIRUS VACCINE (QIVc) COMPARED TO A NON-INFLUENZA VACCINE WHEN ADMINISTERED IN HEALTHY SUBJECTS AGED 6 MONTHS THROUGH 47 MONTHS", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. **F. No.03-11/2022-DD (PS)**	**66**
16.	**ITEM XVI:** APPLICATION FOR LICENSE TO ACT AS BIO ANALYTICAL LAB AT INSTITUTE OF BIOLOGICAL BIOCHEMICAL & PHARMACEUTICAL SCIENCES (IBBPS), AT DOW UNIVERSITY OF HEALTH SCIENCES, KARACHI. **F. No.15-15/2019-DD (PS)**	**69**
17.	**ITEM XVII:** REQUEST FOR ISSUANCE OF LICENCE TO ACT AS CRO AT M/S TRUST FOR VACCINE & IMMUNIZATION, KARACHI. **F. No.15-05/2022 DD (PS)**	**71**
18.	**ITEM XVIII:** APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "FINDING TREATMENTS FOR COVID-19: A PHASE-II, MULTI-CENTRE, ADAPTIVE PLATFORM TRIAL TO ASSESS ANTIVIRAL PHARMACODYNAMICS IN EARLY SYMPTOMATIC COVID-19 **(PLATCOV)**", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-18/2022-PS (CT)	**73**
19.	**ITEM XIX:** REQUEST FOR APPROVAL OF CLINICAL TRIAL UNIT (CTU) AT ZIAUDDIN UNIVERSITV. CLIFTON CAMPUS, KARACHI. TO CONDUCT CLINICAL RESEARCH AT DR. ZIAUDDIN HOSPITAL. CLIFTON CAMPUS. KARACHI". F. No.15-13/2022-DD (PS)	**82**
20.	**ITEM XX:** APPLICATION FOR LICENSE OF CLINICAL RESEARCH ORGANIZATION (CRO) FOR PROMEDIX (PRIVATE) LIMITED, MULTAN.	**84**

	(ADENOVIRUS TYPE 5 VECTOR) IN ADULTS 18 YEARS OF AGE AND OLDER" **(F.No.03-69/2021 DD (PS)).**	
35	**ITEM XXXV:** PROTECT TRIAL APPLICATION FOR THE REGISTRATION OF PROTECTS CLINICAL TRIAL ENTITLED HYDROXYCHLOROQUINE, OSELTAMIVIR AND AZITHROMYCIN FOR THE TRAETMENT OF COVID-19 **F.NO.3-21/2020-DD (PS)**	**133**
36	**ITEM XXXVI:** 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 PLUS TRIAL.	**134**
37	**ITEM XXXVII:** A PHASE-II, GLOBAL MULTI-CENTER, RANDOMIZED, DOUBLE BLIND, PARALLEL, -CONTROLLED, CLINICAL STUDY TO EVALUATE THE IMMUNOGENICITY & SAFETY OF DIFFERENT PRODUTION SCALE & BATCHES OF RECOMBINANT SARS-COV-2 FUSION PROTIEN VACCINE (V-01) IN ADULTS AGED 18-59 YEARS. **F. No.03-05/2022 DD (PS)**	**138**

35th meeting of the CSC was held in Committee Room of the Drug Regulatory Authority of Pakistan on 13th October, 2022.

The meeting was started with the recitation of the Holy Quean and salutation upon the Prophet (P.B.U.H.).

The meeting was attended by the following members: -

Sr. No.	Name	Designation
01	**Dr. Noor Muhammad Shah**	Chairman CSC / Director, Division of Pharmacy Services-DRAP.
02	**Malik Muhammad Asad.**	Secretary CSC/ Additional Director, Division of Pharmacy Services-DRAP.
03	**Dr. Nighat Murad**	Health Research Institute, National Institute of Health, Park Road, Chak Shahzad, Islamabad.
04	**Prof. Munawar Alam Ansari.**	Professor of Pharmacology, Dean Faculty of Pharmacy, Liaquat University of Medical Sciences, Jamshoro. ***(Sindh)***
05	**Dr. Mirza Tasawer Baig.**	Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi & Clinical Pharmacist at Dr. Ziauddin Hospital, Karachi. **(Sindh)**

3. The following members attended, the meeting online through; Zoom:

01	**Prof. Dr. Fazel e Subhan.**	Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar, **(Khyber Pakhtunkhwa)**.
02	**Mr. Waqas Latif**	Data Analyst/Biostatistician in Quality Enhancement Cell (QEC) at University of Health Sciences, Lahore. **(Punjab)**

AGENDA ITEM No. I:

WELCOME NOTE BY THE CHAIRMAN CSC.

The Chairman of the Committee warmly welcomed the honorable members on joining the meeting of the Committee after their nomination as the expert members by the Federal Government. He informed the respectable members regarding the importance of the job assigned to the Committee for safe guarding the public health through provision of safe and effective drugs to the patients. He elaborated that this is the assignment (clinical trials and bio equivalence study) through which we can obtain the safe and effective medicines. He further elaborated that the members have been nominated on the basis of their qualification, expertise and devotion for the said prestigious work and hoped that the members will fully use their capabilities for the sacred cause of public safety.

BRIEF REGARDING THE WORKING OF COMMITTEE BY THE SECRETARY

The Secretary of the Committee briefed the honorable members regarding the working of the Division of Pharmacy Services & the procedures to be undertaken by the Committee in the subject matter under the Bio-Study Rules, 2017.

AGENDA ITEM II:

REQUEST FOR APPROVAL OF M/S AGA KHAN MATERNAL & CHILD CARE CENTER (AKMCCC), HYDERABAD TO ACT AS A PHASE-IV CLINICAL TRIAL SITE TO CONDUCT CLINICAL STUDY TITLED "A MULTICOUNTRY, MULTI-CENTER, THREE-ARM, PARALLEL GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL OF TWO DOSES OF ANTENATAL CORTICOSTEROIDS FOR WOMEN WITH A HIGH PROBABILITY OF BIRTH IN THE LATE PRETERM PERIOD IN HOSPITAL IN LOW-RESOURCE COUNTRIES TO IMPROVE NEW-BORN OUTCOMES". F.No.15-52/2021 DD (PS)

Application from Dr. Sayed Mairajuddin Shah (CNIC-42201-3587009-7), Chief Operating Officer (COO) Secondary Hospitals, Aga Khan University Hospital Karachi, for approval of M/s Aga Khan Maternal & Child Care Center (AKMCCC), situated at PLOT #4/2, Main Jamshoro Rd, Hyderabad-Sindh, to act as Clinical Trial Site for Phase-IV Clinical Trial titled, "*A Multicounty, Multi-Center, Three-Arm, Parallel Group, Double-Blind, Placebo-Controlled, Randomized Trial of Two Doses of Antenatal Corticosteroids for Women with A High Probability of Birth in the Late Preterm Period In Hospital In Low-Resource Countries To Improve New-Born Outcomes*" received on 09th December 2021. Application is on prescribed Form-I along with a prescribed fee of Rs.100000/- paid vide challan number 64042981, dated 08th November 2021.

2. After initial scrutiny summary of the application & attached documents is as follows:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached.
2	Prescribed processing fee	Rs.100000/- paid vide challan number 64042981, dated 08th November 2021.
3	Particulars regarding the legal status of the applicant i.e. in the case of proprietorship the names of proprietors and their addresses, in the case of a 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.	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.	Attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling, etc.	Attached.
8	Undertaking on stamp paper	Attached.

3. The case was placed before 34th CSC meeting held on 13th January, 2022 & the CSC decided as follows:

Decision:

The CSC after detailed discussion and deliberation decided to delegate the power to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference. The CSC further decided that panel members shall be informed at least five (05) days before inspection of the proposed site.

4. Nominated Experts panel inspected the subject site on 10th February, 2022 & submitted inspection report with following remarks:

I have checked the observations given at time of inspection. There is evidence that, they have been addressed.

- **Recommendation for approval**

5. It is pertinent to mention here that, following expert members were nominated for inspection but report has been signed by the then Director Pharmacy Services:

i. Dr. Masud Ur Rehman (The then Chairman CSC/Director Pharmacy Services)
ii. Prof. Dr. Aamir Jaffary (The then Co-Opted CSC member)
iii. Dr. Ahson Siddiqui (The then Co-Opted CSC member)

6. It is submitted that, when inspection report received, the then Director of Pharmacy Services Division (i.e. Dr. Masud Ur Rehman) was retired from his post, so, the inspection report scanned & original report sent to Ex-Director for signatures. But in spite of many telephonic reminders report has not been signed by Ex-Director.

7. In view of above the case was placed before CSC for consideration & decision:

8. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and in light of expert inspection panel recommendations decided to approve "M/s Aga Khan Maternal & Child Care Center (AKMCCC), situated at PLOT #4/2, Main Jamshoro Rd, Hyderabad-Sindh, to act as Clinical Trial Site for Phase-IV Clinical Trial titled, "A Multicounty, Multi-Center, Three-Arm, Parallel Group, Double-Blind, Placebo-Controlled, Randomized Trial of Two Doses of Antenatal Corticosteroids for Women with A High Probability of Birth in the Late Preterm Period In Hospital In Low-Resource Countries To Improve New-Born Outcomes", under the Bio-Study Rules, 2017. It was deliberated that as the applicant has all the requisite facilities and has fulfilled all the other requirements he may not be harmed due to procedural changes on the part of department and as the case has already been delayed.

Further, the Committee delegated the power to the Chairman CSC, as was practiced previously, for constitution of the inspection panel to visit the site and reconfirm the requirements. The nominated expert panel report may be placed before CSC for information.

AGENDA ITEM III:

REQUEST FOR APPROVAL OF M/S AGA KHAN HOSPITAL FOR WOMEN & CHILDREN, KHARADAR, KARACHI TO ACT AS A PHASE-IV CLINICAL TRIAL SITE TO CONDUCT CLINICAL STUDY TITLED "A MULTICOUNTRY, MULTI-CENTER, THREE-ARM, PARALLEL GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL OF TWO DOSES OF ANTENATAL CORTICOSTEROIDS FOR WOMEN WITH A HIGH PROBABILITY OF BIRTH IN THE LATE PRETERM PERIOD IN HOSPITAL IN LOW-RESOURCE COUNTRIES TO IMPROVE NEW-BORN OUTCOMES". F. No.15-53/2021-DD (PS)

Application from Dr. Sayed Mairajuddin Shah (CNIC-42201-3587009-7), Chief Operating Officer (COO) Secondary Hospitals, Aga Khan University Hospital Karachi, for approval of M/s Aga Khan Hospital for Women & Children, Kharadar, situated at Atmaram Pritamdas Rd, Lyari, Karachi, Sindh, to act as Clinical Trial Site for Phase-IV Clinical Trial titled, "*A Multicounty, Multi-Center, Three-Arm, Parallel Group, Double-Blind, Placebo-Controlled, Randomized Trial of Two Doses of Antenatal Corticosteroids for Women with A High Probability of Birth in the Late Preterm Period In Hospital In Low-Resource Countries To Improve New-Born Outcomes*" received on 09th December 2021. Application is on prescribed Form-I along with a prescribed fee of Rs.100000/- paid vide challan number 10557869, dated 08th November 2021.

2. After initial scrutiny summary of the application & attached documents is as follows:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached.
2	Prescribed processing fee	Rs.100000/- paid vide challan number 10557869, dated 08th November 2021.
3	Particulars regarding the legal status of the applicant i.e. in the case of proprietorship the names of proprietors and their addresses, in the case of a 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.	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.	Attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling, etc.	Attached.
8	Undertaking on stamp paper	Attached.

3. The case was placed before 34th CSC meeting held on 13th January, 2022 & the CSC decided as follows:

Decision:

The CSC after detailed discussion and deliberation decided to delegate the power to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference. The CSC further decided that panel members shall be informed at least five (05) days before inspection of the proposed site.

4. Nominated Experts panel inspected the subject site on 10th February, 2022 & submitted inspection report with following remarks:

I have checked the observations given at time of inspection. There is evidence that, they have been addressed.

- **Recommendation for approval**

5. It is pertinent to mention here that, following expert members were nominated for inspection but report has been signed by the then Director Pharmacy Services:

iv. Dr. Masud Ur Rehman (The then Chairman CSC/Director Pharmacy Services)
v. Prof. Dr. Aamir Jaffary (The then Co-Opted CSC member)
vi. Dr. Ahson Siddiqui (The then Co-Opted CSC member)

6. It is submitted that, when inspection report received, the then Director of Pharmacy Services Division (i.e. Dr. Masud Ur Rehman) was retired from his post, so, the inspection report scanned & original report sent to Ex-Director for signatures. But in-spite of many telephonic reminders report has not been signed by Ex-Director.

7. In view of above the case was placed before CSC for consideration & decision:

8. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and in light of expert inspection panel recommendations decided to approve "M/s Aga Khan Hospital for Women & Children, Kharadar, situated at Atmaram Pritamdas Rd, Lyari, Karachi, Sindh, to act as Clinical Trial Site for Phase-IV Clinical Trial titled, "A Multicounty, Multi-Center, Three-Arm, Parallel Group, Double-Blind, Placebo-Controlled, Randomized Trial of Two Doses of Antenatal Corticosteroids for Women with A High Probability of Birth in the Late Preterm Period In Hospital In Low-Resource Countries To Improve New-Born Outcomes", under the Bio-Study Rules, 2017. It was deliberated that as the applicant has all the requisite facilities and has fulfilled all the other requirements he may not be harmed due to procedural changes on the part of department and as the case has already been delayed.

Further, the Committee delegated the power to the Chairman CSC, as was practiced previously, for constitution of the inspection panel to visit the site and reconfirm the requirements. The nominated expert panel report may be placed before CSC for information.

AGENDA ITEM IV:

REQUEST FOR APPROVAL & REGISTRATION OF PHASE-IV CLINICAL TRIAL TITLED "A MULTICOUNTRY, MULTI-CENTER, THREE-ARM, PARALLEL GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL OF TWO DOSES OF ANTENATAL CORTICOSTEROIDS FOR WOMEN WITH A HIGH PROBABILITY OF BIRTH IN THE LATE PRETERM PERIOD IN HOSPITAL IN LOW-RESOURCE COUNTRIES TO IMPROVE NEW-BORN OUTCOMES". F. No.03-84/2021-DD (PS)

Application from Dr. Shabina Ariff, (CNIC-42301-3976716-8), Associate Professor & Consultant Pediatrician & Neonatologist, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi, for approval & registration of subject Clinical Trial/Study, received on 13th December 2021. Application is on prescribed Form-I along with a prescribed fee of Rs.200000/- paid vide challan number 9886981532, dated 07th December 2021.

02. The details regarding trial, sponsor & responsible party is as under:

i. **Name of Investigational product, including all available names; trade, generic or INN name etc.:**
   a. Dexamethasone 4mg/ml (Active) (amber ampoules)
   b. Dexamethasone placebo (normal saline) 1ml (amber ampoules)
   c. Betamethasone 4mg/ml (Active) (clear ampoules)
   d. Betamethasone placebo (normal saline) 1 ml (clear ampoules).

ii. **Sponsor:** WHO, Geneva Switzerland.

iii. **Purpose of trial defining the indication along with the anticipated cost of the project and sources of fund:**

The aim of this multicenter trial is to assess the benefits and possible harms of two regimens of antenatal corticosteroids, dexamethasone phosphate 6mg IM and betamethasone phosphate 2mg IM compared to placebo administered q 12 hourly (total 4 doses) to pregnant women in the late preterm period (gestation age of 34^{+0} to 36^{+5} weeks) when they are at possible risk of preterm birth.

iv. **Primary Objective of the study:**

To compare the effect of an ACS regimen of dexamethasone phosphate 6mg q12h for 4 doses or until birth, whichever is earlier (Dexa-4x6mg) to placebo on a composite outcome of stillbirth, neonatal death or use of respiratory support within 72 hours of life, when given to pregnant women with a high probability birth in the late preterm period (34^{+0} to 36^{+5} weeks' gestation) in hospitals in low resource settings.

2. To compare the effect of an ACS regimen of betamethasone phosphate 2mg q12h for 4 doses or until birth, whichever is earlier (Beta-4x2mg) to placebo on a composite outcome of stillbirth, neonatal death or use of respiratory support within 72 hours of life, when given to pregnant women with a high probability birth in the late preterm period (34^{+0} to 36^{+5} weeks' gestation) in hospitals in low resource settings.

3. To compare the effect of an ACS regimen of dexamethasone phosphate 4x6mg q12h to a regimen of betamethasone phosphate 4x2mg IM q12h, on a composite outcome of stillbirth, neonatal death or use of respiratory support within 72 hours of life, when given to pregnant women with a high probability birth in the late preterm period (34^{+0} to 36^{+5} weeks' gestation) in hospitals in low resource settings.

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

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

2	Prescribed processing fee	Fee of Rs.200000/- paid vide challan number 9886981532, dated 07th December 2021
3	Investigator Brochure (s)	Attached.
4	Final protocol	Protocol Version 1.1 attached. *Details regarding financing & insurance as per ICH-GCP guidelines are not described/included in the protocol.
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Pakistan, Bangladesh, Kenya, Nigeria & India.
7	Phase of trial.	Phase-IV
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.	Assuming * 2000-2500 patients will be recruited at your site over the life of the trial. the import quantities for your site over the life of the trial will be: i. 5714 amps of active dexamethasone 4mg/ml (amber amps) ii. 11429 amps of dexamethasone placebo (normal saline) 1ml (amber) iii. 2857 amps of active betamethasone 4mg/ml (clear) iv. 5714 amps of betamethasone placebo (normal saline) 1 ml (clear). These ampules will come packed in trays - one tray per participant. Each tray will contain 12 ampules. The identity of the ampules in the tray not be possible to decipher on visual inspection.
9	Site of the trial	i. Clinical Trial Unit, Aga Khan University Hospital Main Campus, Stadium Road, Karachi. (CTS-0003) ii. Aga Khan Hospital for Women, Garden, Karachi (CTS-0062) iii. The Aga Khan Hospital for Women & Children, Kharadar, Karachi (Application for approval received) iv. The Aga Khan maternal & Child Care Center (AKMCCC), Hyderabad (Application for approval received)
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Copy of AKUH-IRB/ERC approval dated 11th March 2021 is attached. * Original copy of Ethical approval from IRB/ERC also need to be provided to Division of Pharmacy Services-DRAP.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref:No.4-87/NBC-616/21/, dated 21st May 2021.
12	CV's of the Investigators	CVs of following (P.I/Co-PI) are attached: i. Dr. Shabina Ariff (PI), Associate Professor & Consultant Pediatrician & Neonatologist, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi.

		ii. Dr. Sajid Soofi (Co-PI), Professor & Associate Director, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi. iii. Dr. Lumaan Sheikh (Co-PI), Professor & Associate Director, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi. * PI & Co-PIs are from AKUH, Karachi, nominated PIs/Co-PIs from proposed sites are not described or included in the study.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Copy of GMP Certificates of following are attached: i. M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany. ii. Labesfal- Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal. Certificate of analysis of following IMPs are attached: iii. Betamethasone 4mg/ml Ampoules manufactured by M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany. iv. Betamethasone (Placebo) 4mg/ml Ampoules manufactured by M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany. v. Dexamethasone 4mg/ml, 1ml Injection manufactured by Labesfal- Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal. vi. Sodium Chloride0.9%, 1ml Injection manufactured by Labesfal- Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal. CoPP of following IMPs are not provided: i. Betamethasone 4mg/ml Ampoules manufactured by M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany. ii. Dexamethasone 4mg/ml, 1ml Injection manufactured by Labesfal- Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal.
14	Pre-clinical/clinical safety studies	Multiple research artless are 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.	Altogether 2000 to 2500 (70-100 Subjects/Month) will be enrolled from all study sites.
19	Name of Monitors & Clinical Research Associate	i. Dr. Atif Habib MBBS, MPH, PHD Director Projects and Assistant Professor Centre of Excellence women and child health Aga Khan University Hospital. ii. Dr. Khalil Ahmed FCPS (Pediatrics) Assistant Professor Department of Pediatrics and Child Health Aga Khan University Hospital.

		ii. Dr. Shah Mohammed MBBS, MPH, Senior Manager Centre of Excellence in Women and Child Health Aga Khan University Hospital. v. Dr. Adnan Mirza MBBS, MRCPCH, FRCP Assistant Professor Department of Pediatrics and Child Health Aga Khan University Hospital. * Monitors are from proposed trial sites instead of Co-PIs
20	Evidence of registration in country of origin.	Not provided & claimed as "Not Applicable".
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	30 Months
23	Undertaking on Stamp paper	Attached.

4. After initial scrutiny following shortcomings observed:

i. Details regarding financing/source of funding of the trial & insurance of trial participants as required by ICH-GCP guidelines are not described/included in the protocol. Applicant need to revise/amend study protocol & incorporate required details.
ii. Evidence for registration/approval of IMPs in country of origin is not provided.
iii. CoPP of following IMPs are not provided:
    a. Betamethasone 4mg/ml Ampoules (Active & Placebo) manufactured by M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany.
    b. Dexamethasone 4mg/ml, 1ml Injection (Active & Placebo) manufactured by Labesfal- Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal.
iv. Original copy of Ethical approval from IRB/ERC also need to be provided to Division of Pharmacy Services-DRAP.
v. Nominated PI & Co-PIs are only from AKUH, Karachi, Co-PIs should also from other proposed sites.
vi. Nominated monitors & Clinical Research Associates should be Co-PIs of the study from proposed Clinical Trial Sites.

5. Shortcomings communicated to applicant vide letter bearing number F. No.03-84/2021-DD (PS) dated 16th December 2021 yet response is awaited.

6. Application was placed before 34th CSC meeting & the CSC decided as follows:

Decision:

*The CSC after detailed discussion and deliberation, **deferred** the case for submission of soft copies of the protocol & investigator's brochure so as to share the same with expert members for their review and fulfillment of following shortcomings already communicated to the applicant:*

i. Details regarding financing/source of funding of the trial & insurance of trial participants as required by ICH-GCP guidelines are not described/included in the protocol. Applicant need to revise/amend study protocol & incorporate required details.
ii. Evidence for registration/approval of IMPs in country of origin is not provided.
iii. CoPP of following IMPs are not provided:
a. Betamethasone 4mg/ml Ampoules (Active & Placebo) manufactured by M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany.

b. Dexamethasone 4mg/ml, 1ml Injection (Active & Placebo) manufactured by Labesfal- Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal.

iv. Original copy of Ethical approval from IRB/ERC of each Clinical Trial Site, also need to be provided to Division of Pharmacy Services-DRAP.

v. Nominated PI & Co-PIs are only from AKUH, Karachi, Co-PIs should also from other proposed sites.

vi. Nominated monitors & Clinical Research Associates should be Co-PIs of the study from proposed Clinical Trial Sites.

2. Further, the Committee also asked the applicant to submit the reference studies of this nature/type that have been conducted in developed countries etc. and publication of such studies if any.

7. Accordingly, decision of the CSC communicated to the applicant vide letter bearing even number dated 14th January, 2022.

8. Applicant / PI, Dr. Shabina Ariff, Associate Professor & Consultant Pediatrician & Neonatologist, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi, submitted reply in reference to this Division's letter bearing even number dated 24th February 2022. Applicant reply is as under:

With reference to your letter No. Nil dated February 24th, 2022. Following are our responses to the observations raised in the letter.

Observation 1:
Instead of evidence of registration in country of origin, change of owner ship document for Betnesol (Betamethasone) 4mg/ml Injection is attached in favor of M/S RPH Pharmaceutical AB, Lagervagen 7, Jordbro, Sweden. In the certificate M/S Wasserburger Arzneimittelwerk GmbH HerderstaBe 1,2 and Molkerei-Bauer-StraBe 18, Germany, is not mentioned as previously informed.
Reply:
Thank you for raising this point, the drug will be manufactured in Germany (GMP license attached); however, authorization for marketing and product license pertains to Sweden as mentioned in appended COPP for your review (see Annexure 1)
Observation 2:
Change of ownership/marketing authorization certificate is attached for Betnesol (Betamethasone) 4mg/ml injection. Whereas previously generic drugs were mentioned as IMPS. Applicant needed to clarify regarding brands & manufacturers of IMPS to be procured for subject clinical trial.
Reply:
Thank you for your query, a certificate of generic IMP is attached for your review (See annexure 2)
Observation 3:
Kindly provide English translation for attached CoPP certificate for Dexamethasone
Reply:
COPP of Dexamethasone in English is attached for your review (see Annexure 3)

Observation 4:
CoPP certificate submitted through email are for Mozambique & Syria. Whereas both countries are not participating in the trial.
Reply:
Thank you for pointing this out, these CoPPs are for reference only. CoPP for Pakistan is attached for your review (see Annexure 3)
Observation 5:
Authorization letter for manufacture of placebo, to be used as IMP, issued by regulatory of country of origin need to be provided.
Reply:
A Normal saline solution of sodium chloride will be used as placebo; however, CoPP of both placebos (Betamethasone & Dexamethasone) are attached for review (see Annexure 4).

9. As applicant submitted reply for all shortcoming, so, it is placed before CSC for consideration & decision, please.

10. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and deliberation decided to approve the Clinical Trial titled, "A Multi-country, Multi-Center, Three-Arm, Parallel Group, Double-Blind, Placebo-Controlled, Randomized Trial of Two Doses of Antenatal Corticosteroids for Women with a High Probability of Birth in the Late Preterm Period in Hospital in Low-Resource Countries to Improve New-Born Outcomes", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Sites:

i. *M/s Aga Khan Maternal & Child Care Center (AKMCCC), situated at PLOT #4/2, Main Jamshoro Rd, Hyderabad-Sindh*
ii. *M/s Aga Khan Hospital for Women & Children, Kharadar, situated at Atmaram Pritamdas Rd, Lyari, Karachi, Sindh.*

AGENDA ITEM V:

APPLICATION FOR APPROVAL OF M/S DEFENSE SCIENCE & TECHNOLOGY ORGANIZATION (DESTO), BIOLOGICAL RESEARCH CENTER (BRC), KARACHI TO ACT AS BIOANALYTICAL LABORATORY. F. No.15-51/2021 DD (PS)

Application is from Dr. Saifullah Khan, (CNIC:42205-2782657-5), Deputy Director General, Defense Science & Technology Organization (DESTO), Biological Research Center (BRC), Karachi. Wherein the request has been made to license the subject site with DRAP to act as Bioanalytical Laboratory, the application is on prescribed Form-I of the Bio-Study Rules along with a prescribed fee of Rs.300000/- submitted vide challan No. 5526958410, dated 04th November, 2021.

2. It is submitted that application evaluated according pre-requisites as mentioned in Form-I of the Bio-Study Rules, summary of submitted documents is as follows:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules.	Attached
2	Prescribed Fee	Fee of Rs.300000/- submitted vide challan No. 5526958410, dated 04th November, 2021 * It is submitted that the fee challan is not verified due to some system error, the matter is informed to MIS Division.
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).	The organization is a part of NECOM, SPD.
4	Details of premises including layout plan of the site.	Only layout 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.	Attached. * CVs of the staff also attached
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Attached. * Not applicable as the site is applied for Bioanalytical Laboratory.
8	Undertaking on stamp paper.	Attached.

3. In view of above, it is proposed that inspection panel may be constituted by CSC, for verification of facilities available at the proposed Bio-analytical laboratory as per requirements under the Bio-Study Rules 2017 & GCP guidelines.

4. The case was placed before 34th CSC meeting held on 13th January, 2022 & the CSC decided as follows:

Decision:

The CSC after detailed discussion and deliberation decided to delegate the power to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference. CSC further decided that, panel members shall be informed at least five (05) days before inspection of the proposed site.

5. Accordingly, Chairman CSC nominated the following panel for inspection.

i. **Dr. Masud Ur Rehman (Coordinator),** Chairman CSC / Director, Division of Pharmacy Services-DRAP.
i. **Dr. Saif Ur Rehman Khattak,** Additional Director, In charge CDL- Karachi.
ii. **Dr. Najam Us Saquib,** Additional Director, In charge DRAP-Karachi.

6. Experts panel inspected the subject site on 11th February 2022 & submitted inspection report with following remarks:

DESTO Biological Research Center is a public sector institution involved in research since 1963. The infrastructure facilities, equipment, personnel, protecting and safety arrangements and environmental conditions related to test and analysis are according to the standards. The procedures are properly defined and control measures are in place. The institute has proper IRB to look into the ethical consideration regarding the biological research. The overall function of the institute is overseen on the national level through proper quality management system.

Concluding status of inspection / application

- **Recommended for approval**

8. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and in light of expert inspection panel recommendations decided to approve M/s Defense Science & Technology Organization (DESTO), Biological Research Center (BRC), Karachi, to act as Bio-Analytical Laboratory for CSC approved Clinical Trial(s), under the Bio-Study Rules, 2017.

AGENDA ITEM VI:

REQUEST FOR APPROVAL TO PROCURE STUDY VACCINE FOR CLINICAL TRIAL TITLED "IMMUNOLOGY & SAFETY OF HETEROLOGOUS COMBINATIONS OF COVID-19 VACCINES AVAILABLE UNDER EMERGENCY USE AUTHORIZATION IN PAKISTAN: A RANDOMIZED PHASE-II TRIAL" (COMBAT-COVID). F. No.03-85/2021-DD (PS)

Application is from Dr. Farah Naz Qamar, (CNIC-42201-8579891-2), Associate Professor, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi, for approval & registration of subject Clinical Trial/Study, received on 14th December 2021. Application is on prescribed Form-II along with a prescribed fee of Rs.200000/- paid vide challan number 070962990744, dated 07th December 2021.

2. The details regarding trial, sponsor & responsible party is as under:

i. Name of Investigational product, including all available names; trade, generic or INN name etc.:

S.No.	Investigational Product	Trade Name	Generic Name	INN Name
01	Sinopharm	Sinopharm	Inactivated SARS-COV-2	
02	CanSinoBIO	Convidecia™	Ad5-nCoV	
03	AstraZeneca	Covishield and Vaxzevria	Viral Vector Vaccine	COVID-19 Vaccine (ChAdOx)

ii. Sponsor:
This study is funded by Coalition for Epidemic Preparedness Innovations (CEPI). In collaboration with University of Oxford, International Vaccine Institute (Korea), Ragon Institute (USA), Harvard School of Medicine, (USA), CEPI central laboratories (VisMederi, Italy) and National Institute of Health (Islamabad).

iii. Estimated Cost of Project: 11,707,911 USD

iv. Sources of fund:
This study is funded by Coalition for Epidemic Preparedness Innovations (CEPI) which is an innovative global partnership between public, private, philanthropic, and civil society organizations. It was launched in Davos in 2017 to develop vaccines to stop future epidemics. CEPI has a mission to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for people during outbreaks.

v. Study design & arms:
The study will enroll participants after obtaining informed consent and after enrollment the participants will be randomized in 9 study arms:

Group / Arm	First Dose	Second Dose	Booster Dose	SS*
1	BIBP (CNBG, SinoPharm) WIV	CanSino BIO		1680 (160 in each heterologous group and 240 in each homologous group)
2	BIBP (CNBG, SinoPharm) WIV	AstraZeneca ChAdOx		
3	CanSino BIO	BIBP (CNBG, SinoPharm) WIV		
4	CanSino BIO	AstraZeneca ChAdOx		
5	AstraZeneca ChAdOx	BIBP (CNBG, SinoPharm) WIV		
6	AstraZeneca ChAdOx	CanSino BIO		

7(ref)**	BIBP (CNBG, SinoPharm) WIV	BIBP (CNBG, SinoPharm) WIV	Six-month post second dose	
8(ref)**	CanSino BIO	CanSino BIO		
9(ref)**	AstraZeneca ChAdOx	AstraZeneca ChAdOx		

vi. Purpose of trial defining the indication along with the anticipated cost of the project and sources of fund:

The purpose of this study is to evaluate the safety and immunogenicity of combinations of vaccines approved for use in Pakistan. This exploration meets emergency needs and may assist in the formulation of public health policies.

vii. **Primary Objective of the study:**

a. To determine whether the serum anti-spike IgG concentration against SARS-COV-2 four weeks post boost in COVID seronegative participants immunized with HPB COVID-19 vaccines regimens is non-inferior to that observed following homologous immunization (second dose at Day 70).

viii. **Secondary Objectives**:

a. To assess the safety and reactogenicity of different combinations of heterologous and homologous COVID-19 vaccines.
b. To characterize the neutralizing antibody response (pseudo-virus neutralization assay) against SARS-CoV-2 (as per schedule of events) in COVID seronegative participants immunized with HPB and homologous COVID-19 vaccines regimens.
c. To assess trend in immunogenicity (anti-spike IgG, anti-nucleocapsid) against SARS-COV-2 as per schedule events in COVID seronegative participants immunized with HPB and homologous CVODI-19 vaccines regimens.
d. To assess safety and immunogenicity of homologous full dose versus fractional dose homologous booster as compared to no booster at 6 months following the second dose of primary series among the participants in homologous arms.

ix. Details of Investigators & Roles:

Role	**Name**	**Affiliated Organization**	**Responsibilities**
Principal Investigator (PI)	Farah Naz Qamar	Aga Khan University Hospital, Pakistan (AKU)	Project design, protocol development, site visits and project supervision, data monitoring and analysis, report writing. Dissemination of results (reports, manuscripts). Overall project coordination.
(Co-I)	M. Tahir Yousafzai	AKUH	Project design, protocol development, field supervision and monitoring, guided data analysis, site supervision, report, and manuscript writing.
(Co-I)	Zahra Hassan	AKUH	Project design, protocol development, standardizing lab protocols, guided data analysis, supervision of lab analysis, report, and manuscript writing.
(Co-I)	Junaid Iqbal	AKUH	Project design, protocol development, standardizing lab protocols, guided data analysis, supervision of lab analysis, report, and manuscript writing
(Co-I)	Kiran Iqbal	AKUH	Standardizing lab protocols, guided data analysis, supervision of lab analysis, report, and manuscript writing.
(Co-I)	Sonia Qureshi	AKUH	Project design, protocol development, field supervision and monitoring, guided data analysis, report, and manuscript writing.
(Co-I)	Maria Fletcher	AKUH	Project design, protocol development, standardizing lab protocols, guided data

			analysis, supervision of lab analysis, report, and manuscript writing.
(Co-I)	Najeeha Iqbal	AKUH	Standardizing lab protocols, guided data analysis, supervision of lab assays, report, and manuscript writing.
(Co-I)	Momin Kazi	AKUH	Field supervision and monitoring, and eCRFs designing.
(Co-I)	Shazia Sultana	AKUH	Field supervision and monitoring, site supervision, and CRFs development.
National and International Collaborators			
(Co-I)	i. Andrew Pollard ii. Matthew Snape iii. Teresa Lambe iv. Xinxue Liu	University of Oxford	Scientific, technical, and clinical support, Biostatistics and data management support, and clinical samples testing support.
(Co-I)	i. Anh Wartel ii. Jean-Louis Excler iii. Deok-Ryun Kim	International Vaccine Institute (IVI), Korea	Scientific, technical, and clinical support. Biostatistics and data management support.
(Co-I)	Galit Alter	Ragon Institute, Harvard School of Medicine, USA	Support in system serology assays.
(Co-I)	i. Maj. Gen. Aamir Ikram. ii. Ghazala Parveen iii. Firdous Nawaz Khan iv. Omera Naseer	National Institute of Health (NIH) Pakistan	Central Vaccine storage and management. Technical, advisory, and laboratory support. Support in obtaining regulatory approvals.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Prescribed processing fee	Fee of Rs.200000/- paid vide challan number 070962990744, dated 07th December 2021.
3	Investigator Brochure (s)	i. COVID-19 Vaccine (Vero Cells) Inactivated manufactured by Beijing Institute of Biological Products. Version 3.1 dated 19th April 2021. ii. AZD1222 - A recombinant chimpanzee adenovirus expressing the severe respiratory syndrome-coronavirus-2 Spike (S) surface (SARS-CoV-2) glycoprotein. Version 3.1 dated 05th July 2021. iii. Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector). Version 1.2 dated 07th April 2021.
4	Final protocol	Protocol Version 1.1 attached.
5	Informed consent and participant information sheet (Urdu to English)	Attached

6	List of participating countries	Pakistan, UK, Korea & USA.
7	Phase of trial.	Phase-II
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.	4500 Doses There are three different Vaccines, applicant has not provided justifications & quantities of different IMPs doses
9	Site(s) of the trial	i. Clinical Trial Unit, Aga Khan University Hospital Main Campus, Stadium Road, Karachi. (CTS-0003) ii. National Institute of Health, Park Road, Chak Shahzad, Islamabad. (CTS-0042) iii. Central Park Teaching Hospital, Lahore) (CTS-0049) * Applicant has not provided evidence for approval/ copy of trial site(s) approval. Further as per DRAP record, it is pertinent to mention here that, NIH, Islamabad is a phase-III trial specific approved site, Central Park Teaching Hospital, Lahore is approved for Phase-III & Phase IV Clinical Trials only & AKUH, Karachi has no facilities for Pharmacokinetic & Pharmacodynamic Studies facilities required in a Phase-II Clinical Trial. ** Following are mentioned as field sites for sample collection & as a laboratory: i. Aga Khan Hospital for Women, Karimabad, Karachi. ii. Aga Khan Hospital for Women, Garden, Karachi. iii. Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad. iv. Chughtai Lab & affiliated clinics Lahore. v. NIH Lab Islamabad. It is submitted that, under the Bio-Study Rules 2017 except Chughtai Lab Lahore, other mentioned sample collection/field sites & Laboratories are not approved by DRAP for Phase-II Clinical Trials. Applicant need to provide complete details regarding sites & laboratories involved or will be part of the trial and provide evidence of approval from DRAP.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Copy of AKUH-IRB/ERC approval dated 28th October 2021 is attached. Whereas, IRB/ERC approval from other proposed sites along with IRB/ERC composition need to be provided.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref:No.4-87/COVID-98/21/838 dated 26th November 2021.
12	CV's of the Investigators	CVs of following (P.I/Co-PI) are attached: i. Dr. Farah Naz Qamar (PI), Associate Professor, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi. ii. Mohammad Tahir Yousafzai iii. Prof. Zahra Hassan iv. Junaid Iqbal v. Kiran Iqbal Masood

		vi. Dr. Sonia Qureshi vii. Noshi Maria Fletcher viii. Iqbal, Najia Talat ix. Abdul Momin Kazi x. Andrew John Pollard xi. N.T. Anh Wartel xii. Jean Louis Excler, MD xiii. Deok Ryun Kim xiv. Mathew Snape xv. Teresa Lambe xvi. Xinxue Liu
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided.
14	Pre-clinical/clinical safety studies	Attached, further preclinical studies data also attached in relevant IB of the IMPs.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Provided in IB of each IMPs.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	160 participants per heterologous group 240 per homologous group Total Subjects=1680
19	Name of Monitors & Clinical Research Associate	It is informed that, Sponsor/Applicant still looking for Monitors & Clinical Research Associate for the trial
20	Evidence of registration in country of origin.	Not provided.
21	Copy of registration letter (if registered in Pakistan)	Not provided.
22	Sample of label of the investigational product / drug.	It is claimed that, labels are attached as annexure-XIII, but actually not provided/attached in the file.
22	Duration of trial	30 Months (2.5 Year)
23	Undertaking on Stamp paper	Attached.

04. After initial scrutiny following shortcomings observed:

i. Evidence of approval/ copy of trial site(s) license(s) of proposed sites need to be provided.
ii. It is informed that, as per DRAP record, M/s NIH, Islamabad is a phase-III trial specific approved site, Central Park Teaching Hospital, Lahore is approved for Phase-III & Phase IV Clinical Trials only & AKUH, Karachi has no facilities for Pharmacokinetic & Pharmacodynamic Studies facilities as required in a Phase-II Clinical Trial, applicant need to submit clarification.
iii. Following are mentioned as field sites for sample collection & as a laboratory but as per DRAP record not approved for a phase-II clinical trial. Further, affiliated clinics of Chughtai Lab are not approved:
    a. Aga Khan Hospital for Women, Karimabad, Karachi.
    b. Aga Khan Hospital for Women, Garden, Karachi.
    c. Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad.
    d. Chughtai Lab affiliated clinics Lahore.
iv. It is submitted that, under the Bio-Study Rules 2017 except Chughtai Lab Lahore, other mentioned sample collection laboratories are not approved by DRAP for Phase-II Clinical Trials. Applicant need to provide complete details regarding sites, field sites & laboratories involved or will be part of the trial and provide evidence of approval from DRAP.
v. There are three different Vaccines to be used as IMPs, applicant need to provide justifications & quantities of each vaccine need to be imported or procured.
vi. Evidence of registration/ EUA of IMPs in country of origin is not provided.

vii. CoPP/EUA of Investigational Medicinal Products (IMPs) are not provided.
viii. GMP Certificate(s) of manufacturer of each IMPs are not provided.
ix. Ethical approval from each trial site's IRB/ERC along with complete composition of committee need to be provided.
x. It is claimed in the protocol that, volunteers for the trial will be identified by social mobilization, advertisement & communication. Whereas, material used for advertisement for trial recruitment is not provided with the application.
xi. It is claimed that, labels are attached as annexure-XIII, but actually labels of IMPs are not provided/attached in the file.

5. Shortcomings communicated to applicant vide letter bearing number F. No.03-85/2021-DD (PS) dated 17th December 2021.

6. Applicant/PI, Dr. Farah Naz Qamar, (CNIC-42201-8579891-2), Associate Professor, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi, for approval & registration of subject Clinical Trial/Study, submitted reply, received on 11th January 2022.

7. It is informed by the applicant that; the study site of Lahore is changed from Chughtai laboratories and clinics to Central Park Teaching Hospital for the study tilted "Immunogenicity and safety of heterologous combinations of COVID-19 vaccines available under Emergency Use Authorization in Pakistan: A randomized phase II trial."

8. Reply regarding shortcoming is as follows:

Shortcomings	**Reply**	**Remarks**
1. Only copy of licence of M/s AKUH, Karachi is provided. Evidence of approval/ copy of trial site(s) license(s) of proposed site(s) need to be provided.	We will not be performing any tests at these sites" These sites will be used for participant recruitment For recruitment and vaccination participants will come to the DRAP approved site of AKU which is the Clinical Trial Unit of AKU for enrollment. NIH DRAP phase-II trial license is attached. Central Park Teaching Hospital, Lahore is applying for phase-II trial approval in DRAP.	Any site involved in the trial for any of trial operation should be approved for that trial or trial phase by DRAP.
2. As per DRAP record, M/s NIH, Islamabad is a phase-III trial specific approved site, M/s Central Park Teaching Hospital, Lahore is approved for Phase-III & Phase IV Clinical Trials only & M/s AKUH, Karachi has no facilities for Pharmacokinetic & Pharmacodynamic Studies facilities as required in a Phase-II Clinical Trial, applicant need to submit clarification.	The trial being conducted is a Phase-II vaccine trial, There is no requirement for pharmacokinetic or pharmacodynamic studies to be done for this vaccine trial. Hence, we will not be conducting any pharmacokinetic or pharmacodynamic tests.	Even pharmacokinetic or pharmacodynamic studies are not required in the trial, following proposed trial sites are not approved for Phase-II Clinical Trial by the DRAP: i. M/s NIH, Islamabad. ii. M/s Central Park Teaching Hospital, Lahore. ii. Aga Khan Hospital for Women, Karimabad, Karachi. v. Aga Khan Hospital for Women, Garden, Karachi. v. Isolation Hospitals & Infection Treatment

		Centre (IHITC), Islamabad.
3. Following are mentioned as field sites for sample collection & as a laboratory but as per DRAP record not approved for a phase-II clinical trial. Further, affiliated clinics of Chughtai Lab are not approved: a. Aga Khan Hospital for Women, Karimabad, Karachi. b. Aga Khan Hospital for Women, Garden, Karachi. 4. Following are mentioned as field sites for sample collection & as a laboratory but as per DRAP record not approved as Clinical Trial Site: a. Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad. b. Chughtai Lab affiliated clinics Lahore. 5. It is informed that, as per DRAP record except M/s Chughtai Lab Lahore, other mentioned sample collection laboratories are not approved by DRAP to act as laboratories for Clinical Trials under the Bio-Study Rues 2017. Kindly provide complete details regarding sites, field sites & laboratories involved or will be part of the trial and provide evidence of approval to act as Clinical Trial Site/Laboratory under the Bio-Study Rules 2017.	There will be no lab tests performed at any of these sites. Only participant identification for recruitment will be done at these sites.	-do-
6. There are three different Vaccines to be used as IMPs, applicant need to provide justifications & quantities of each vaccine need to be imported or procured.	The protocol was developed in the first quarter of 2021, at that time only these 3 vaccines were available in Pakistan for mass vaccination so only these were included in the study. Regarding quantities of vaccines, they have been calculated according to the sample size and the cohort distribution as mentioned on page no 28-29 of the protocol.	---
7. Evidence of registration/ EUA of Investigational Medicinal Products (IMPs) in country of origin is not provided. 8. CoPP/EUA of Investigational Medicinal Products (IMPs) are not provided. 9. GMP Certificate(s) of manufacturer of each IMPs are not provided.	The EUAs of these IMPs are already in DRAP Pakistan. This trial is funded by Coalition for Epidemic Preparedness Innovations (CEPI)and is based on commercially available vaccines, the manufacturers of vaccines are not part of this trial, so the GMP is not required as they are needed in only manufacture's-initiated trials.	Applicant need to provide EUAs of Vaccines utilized in the trial & GMP Certificates of manufacturer as required under Form-II of the Bio-Study Rules 2017.
10. Copy of AKUH IRB/ERC is provided. Whereas ethical approval from each trial site's IRB/ERC along with complete composition of committee need to be provided & IRB/ERC approval(s) should be in original.	AKU and NIH ERC approvals have been provided while application for approval has been submitted to IRBs of Lahore, IVI, and Oxford which will be shared soon once received.	IRB/ERC approval from all proposed / participating sites need to be provided.
11. It is mentioned in the protocol that, volunteers for the trial shall be identified by social mobilization, advertisement &		

communication. Whereas, material used for advertisement for trial recruitment is not provided with the application.		
12. It is claimed that, labels are attached as annexure-XIII, but actually labels of IMPs are not provided/attached in the file.	Labels are required for the IMPs which are in development phase however these are the commercially available vaccines and are also available in Government of Pakistan's vaccination program.	For labelling & masking of IMPs ICH-GCP guidelines need to be followed & sample label need to be provided. Further Vaccines (IMPs) should be labelled as "For trial purpose only"

9. After initial scrutiny of submitted reply following shortcomings were observed;

i. As claimed even if pharmacokinetic or pharmacodynamic studies are not required in the trial, following proposed trial sites are not approved for Phase-II Clinical Trials by the DRAP:
   a) M/s National Institute of Health, Islamabad. (The site is approved for specific Phase-III Trial) CTS-0042
   b) M/s Central Park Teaching Hospital, Lahore. (The site is approved for Phase-III & IV Clinical Trials only) CTS-0049
   c) Aga Khan Hospital for Women, Karimabad, Karachi. (The site is approved for Phase-IV Clinical Trials only) CTS-0061
   d) Aga Khan Hospital for Women, Garden, Karachi. (The site is approved for Phase-IV Clinical Trials only) CTS-0062
   e) Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad. (Application for the site not received yet)

ii. Any site involved in the trial for any of trial operation should be approved for that trial or trial phase by DRAP.

iii. Ethical approvals from IRB/ERC of all proposed / participating sites need to be provided.

iv. Evidence of registration/ EUA of Investigational Medicinal Products (IMPs) in country of origin is not provided.

v. CoPP/EUA of Investigational Medicinal Products (IMPs) are not provided.

vi. GMP Certificate(s) of manufacturer of each IMPs are not provided.

vii. For labelling & masking of IMPs ICH-GCP guidelines need to be followed & sample label need to be provided. Further Vaccines (IMPs) should be labelled as "For trial purpose only"

10. In view of above, the applicant/PI was advised to fulfill all prerequisites as per Form-II of the Bio-Study Rules 2017. Accordingly, DFA was prepared & attached. Further the case was placed before CSC for its consideration & decision.

11. Application was placed before the CSC in its 34th Meeting held on 13th January, 2022 & the CSC decided the case as follows:

Decision:

*The CSC after detailed discussion and deliberation, **deferred** the case for submission of soft copies of the protocol & investigator's brochure so as to share the same with expert members of the Committee for their review and fulfillment of following shortcomings already communicated to the applicant:*

i. As claimed even if pharmacokinetic or pharmacodynamics studies are not required in the trial, following proposed trial sites are not approved for Phase-II Clinical Trials by the DRAP:
   a) M/s National Institute of Health, Islamabad. (The site is approved for specific Phase-III Trial) CTS-0042
   b) M/s Central Park Teaching Hospital, Lahore. (The site is approved for Phase-III & IV Clinical Trials only) CTS-0049
   c) Aga Khan Hospital for Women, Karim Abad, Karachi. (The site is approved for Phase-IV Clinical Trials only) CTS-0061

d) *Aga Khan Hospital for Women, Garden, Karachi. (The site is approved for Phase-IV Clinical Trials only) CTS-0062*
e) *Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad. (Application for the site not received yet)*

ii. *Any site involved in the trial for any of trial operation should be approved for that trial or trial phase by DRAP.*
iii. *Ethical approvals from IRB/ERC of all proposed / participating sites need to be provided.*
iv. *Evidence of registration/ EUA of Investigational Medicinal Products (IMPs) in country of origin is not provided.*
v. *CoPP/EUA of Investigational Medicinal Products (IMPs) are not provided.*
vi. *GMP Certificate(s) of manufacturer of each IMPs are not provided.*
vii. *For labelling & masking of IMPs ICH-GCP guidelines need to be followed & sample label need to be provided. Further Vaccines (IMPs) should be labelled as "For trial purpose only".*

12. It is submitted that, applicant/PI of the trial shared a letter dated 24th May, 2022 which was a notice with following subject shared by the Sponsor:

"**Notice to Terminate Funding Agreement between Coalition for Epidemic Preparedness Innovations (CEPI) and the Aga Khan University for the project titled 'Immunogenicity and Safety of Heterologous Prime Boost Combinations of the Available COVID-19 Vaccines in Pakistan: A Randomized Single Blind Trial**"

13. It is submitted that in the light of above the trial application no longer exists as per information provided by the applicant

14. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC rejected the application, being withdrawn by the applicant.

AGENDA ITEM VII:

REQEST FOR APPROVAL OF THE ELIKIDS STUDY TITLED, "OPEN LABEL, TWO COHORT (WITH & WITHOUT IMIGLUCERASE), MULTICENTER STUDY TO EVALUATE PHARMACOKINETICS, SAFETY & EFFICACY OF ELIGLUSTAT IN PEDIATRIC PATIENT WITH GAUCHER DISEASE TYPE 1 AND TYPE 3 (ELIKIDS). F.NO.03-83/2021 DD (PS).

Application is from Dr. Saba Abbasi, CNIC 42201-0571036-8, for M/s Sanofi Aventis, Medical Lead, M/s Sanofi Aventis, Karachi, dated 01st October 2021, on prescribed Form-II along with a fee of Rs.200000/- deposited vide challan No. 05834487331, dated 31st August 2021. Wherein request has been made for registration & approval of subject clinical trial, which will be carried out at M/s National Hospital & Medical Center, Lahore.

02. The details regarding trial design & sponsor is as under:

a. Study Arms & design:

Arms	Intervention/treatment
Experimental: Cohort 1: Eliglustat monotherapy Eliglustat for at least two years. Cohort 1 patients that experience significant clinical decline will receive rescue treatment. Rescue Treatment Step 1: Switch from eliglustat to imiglucerase monotherapy.	Drug: Eliglustat GZ385660 Pharmaceutical form: Capsule, Liquid Route of administration: Oral Other Name: Cerdelga

Rescue Treatment Step 2: Patients who after 6 months of rescue therapy with imiglucerase monotherapy do not show improvement in the parameter(s) that led to the switch from eliglustat to imiglucerase, will then receive combination therapy with eliglustat + imiglucerase.	
Experimental: Cohort 2: Eliglustat plus imiglucerase Eliglustat plus imiglucerase for two years, at the dose of enzyme replacement therapy received before enrollment. After Week 52, Cohort 2 patients will switch to eliglustat monotherapy for the remainder of the study if the desired clinical response has been achieved.	Drug: Eliglustat GZ385660 Pharmaceutical form: Capsule, Liquid Route of administration: Oral Other Name: Cerdelga Drug: Imiglucerase GZ437843 Pharmaceutical form: Powder for solution for infusion Route of administration: Intravenous Other Name: Cerezyme

i. **Sponsor:** M/s Sanofi Genzyme Corporation, 50 Binney Street, Cambridge, MA 02142, USA.

ii. Primary Objective of the study:

a. Assessment of pharmacokinetic (PK) parameter of eliglustat: Cmax [Time Frame: Weeks 2, 13, 26 and 52]
Maximum concentration (Cmax) of eliglustat in plasma

b. Assessment of PK parameter of eliglustat: AUC [Time Frame: Weeks 2 and 52]
Area under the plasma eliglustat concentration-time curve (AUC)

c. Adverse Events [Time Frame: Up to Week 364]
Number of adverse events in pediatric patients

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Prescribed processing fee	Rs.200000/- deposited vide challan no.05834487331, dated 31st August 2021
3	Investigator Brochure (s)	Attached. Number: GENZ-112638(GZ385660)-eliglustat Edition Number-16 Brochure for Cerezyme (imiglucerase) is not as per ICH-GCP guidelines.
4	Final protocol	Version 3.0 Protocol no. VV-CLIN-0225720 (Cerdelga®/ eliglustat/ GZ385660)
5	Informed consent and participant information sheet (Urdu to English)	Core Study Information & Informed Consent Form is attached. Whereas, compensation & insurance statement should be mentioned in the all ICF & all assent Form for children & adolescents which will be signed by Subject, Witness & Sponsor. Further, in the assent Form for children parents/ subject's legally acceptable representative signature should be added.

6	List of participating countries	Canada, Turkey, Argentina, Russia, Japan, United Kingdom, France, Italy, Spain, Sweden & Pakistan
7	Phase of trial.	Phase – 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.	• **Imiglucerase:** 228 vials per year & per patient, during 2 years. A minimum of 1824 vials of imiglucerase would be used in the trial, but considering a rate of 15% for kits damage, we anticipate a total number of approximately **2100** vials to be used in the trial • **Eliglustat:** 16 bottles of 60 capsules per year & per patient, during 4 years. So, a minimum of 256 bottles of eliglustat would be used in the trial but considering a rate of 15% for kits damage, we anticipate a total number of approximately **300** bottles to be used in the trial. * There are three different strengths (84mg, 42mg & 21mg) of Eliglustat Capsules, it is not described that which strength will be utilized in the trial & what quantities of each strength will be imported.
9	Site of the trial	Evidence (Licence issued by DRAP) of sites approval is not provided. Applied site (M/s National Hospital & Medical Center, Lahore) is approved as trial specific site. The site is not approved for Phase-III Clinical Trials.
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-659/21/237 dated 17th August 2021.
12	CV's of the Investigators	CVs of following (P.Is) are attached: iv. Dr. Huma Arshad Cheema, Professor / Consultant Pediatric Gastroenterology-Hepatology, Children Hospital & Institute of Child Health Lahore.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	• Un-signed GMP Certificate of following are attached: i. M/s Genzyme, Ireland Limited, Ireland. ii. M/s Sanofi-Aventis Recherche & Developpement, France. • Un-signed Manufacturer Authorization of following is attached; M/s Sanofi-Aventis Recherche & Developpement, France. • COA of following also attached;

		i. Eliglustat 21 mg Capsule (CAP B DRF 1 Clinical) ii. Eliglustat 50 mg Capsule (Pearlescent active clinical capsules) iii. Eliglustat 100 mg Capsule (Pearlescent active clinical capsules)
14	Pre-clinical/clinical safety studies	Eliglustat Clinical Trials & Registry publication links are provided. Whereas, data regarding Imiglucerase is not provided.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Summary for Eliglustat is attached. Whereas summary of Investigator's Brochure for Cerezyme (imiglucerase) is not provided.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Globally 60 Subjects For Pakistan: 04Subjects
19	Name of Monitors & Clinical Research Associate	Wajahat Imran. CV of CRA need to be submitted.
20	Evidence of registration in country of origin.	NDA Certificate No. 205494, issued by US-FDA is attached. European Commission is attached. No certificate is provided for Cerezyme (Imiglucerase) Solution for infusion from country of origin.
21	Copy of registration letter (if registered in Pakistan)	Copy of registration letter number 107918 in the name of M/s Sanofi-Aventis (Importer) for Cerezyme (Imiglucerase) Solution for infusion.
22	Sample of label of the investigational product / drug.	Sample of label of following IMPs are attached: i. Eliglustat 84 mg Capsule ii. Eliglustat 42 mg Capsule iii. Eliglustat 21 mg Capsule iv. Imiglucerase 400 IU (Powder for concentrate for solution for infusion)
22	Duration of trial	04 Years * The enrollment period will last on 30th March 2022 & the study duration for individual will be at least 2 years.
23	Undertaking on Stamp paper	Not provided.

4. Following additional trail related documents were also provided:

i. ELIKIDS Study Patient Diary, Version 1 (English & Urdu).
ii. ELIKIDS Study Patient Diary, Unscheduled for Dose Adjustment, Version 1. (English & Urdu).
iii. Dose Worksheet Version 1 (English & Urdu).
iv. Visual Demonstration Card Version 1
v. Electronic Case Report Form (eCRF)
vi. Matrix Blank CRF (Folders 7 Forms)

5. After initial scrutiny following shortcomings were observed:

i. Provided Investigator's Brochure for Cerezyme (Imiglucerase) is not as per ICH-GCP guidelines & Summary of Investigator's Brochure for Cerezyme (imiglucerase) is not provided.
ii. Statement regarding compensation & insurance should be mentioned in all ICF & all assent forms for children & adolescents which will be signed by Subject, Subject's legally acceptable representative, Witness & PI/Sponsor.
iii. Further, Subject's legally acceptable representative signature should be added in the ICF/assent Form for children.
iv. There are three different strengths (84mg, 42mg & 21mg) of Eliglustat Capsules, it is not described that which strength will be utilized in the trial & what quantities of each strength will be imported.
v. Pre-clinical/clinical safety studies data regarding Cerezyme (Imiglucerase) is not provided.
vi. Applied site (M/s National Hospital & Medical Center, Lahore) was approved for Phase-IV Clinical Trial titled, "*Observational Study Program Assessing Effectiveness and Tolerability of Gliclazide 60 Mg Modified Release Tablet in patients with Type-II diabetes, fasting during Ramadan (Dia-Ramadan)*".
vii. Un-signed GMP Certificate of following are attached:
    a. M/s Genzyme, Ireland Limited, Ireland.
    b. M/s Sanofi-Aventis Recherche & Developpement, France.
viii. Un-signed Manufacturer Authorization of following is attached;
    a. M/s Sanofi-Aventis Recherche & Developpement, France.
ix. CoPP of following IMPs are not provided.
    a. Cerezyme (Imiglucerase) Capsule.
    b. Cerdelga (Eliglustat GZ385660), Powder for solution for infusion.
x. Details & CV of Clinical Research Associate need to be provided.
xi. It is mentioned in the application that, both IMPs will be imported but certificate is for Cerezyme (Imiglucerase) Solution for infusion from country of origin is not provided.
xii. Undertaking on Stamp paper is not provided.

6. Above mentioned shortcomings were communicated to applicant vide letter even number dated 28th October 2021.

7. Applicant Dr. Saba Abbasi, Medical Manager, M/s Sanofi Aventis, Karachi, submitted following reply on 10th November 2021.

S.No.	Shortcomings	Reply	Remarks
01	Provided Investigator's Brochure for Cerezyme (Imiglucerase) is not as per ICH-GCP guidelines & Summary of Investigator's Brochure for Cerezyme (imiglucerase) is not provided.	Cerezyme (Imiglucerase) is a commercialized product approved in Pakistan by DRAP. Therefore, we will use SmPC & IMPD. Both documents are enclosed again for convenience. (Page 1969-1996/Corr.)	---
02	Statement regarding compensation & insurance should be mentioned in all ICF & all assent forms for children & adolescents which will be signed by Subject, Subject's legally acceptable representative, Witness & PI/Sponsor.	Core Study Information and Informed Consent Form - Written subject information for patients that turn 18 years of age, version No. 4 dated 10-October-2019, on page 24 and 25 and Core Study Information and Informed Consent Form - Written Subject Information for parents and	---

		Legally Accepted Representatives, Version No.4 dated 10-October-2019 on page no.25 and 26 it is described that they will be able to claim for study visit travel expenses and reasonable costs as meals, hotels. If due to the study treatment or procedures subjects are ill or need any treatment, the costs of that treatment will be covered by the study insurance and on "Core Pediatric Information and Assent Form statement for children (13 to 17 years), Version 4 dated 10- October'2019 the same statement as parents appears in section "compensation and expenses" from page 13.	
03	Further, Subject's legally acceptable representative signature should be added in the ICF/assent Form for children.	There is a specific ICF for parents or LAR (legally accepted Representative) "Core Study Information and Informed Consent Form - Written Subject Information for Parents and Legally Accepted Representatives, Version No.4 dated 1O-October-2019". There is also consent page (ln assent Form: Core Pediatric Information and Assent Form statement for children (13 to 17 years), Version 4 dated 10-October-2019;13-17 years old) on Page no. 12 and Written Subject Information (according to ICH/GCP 4.8 and Data Protection Requirements - Assent statement for children (6 to 12 years), Version 4 dated 10-October-2019 on Page No. 6 of each age there is another field so the LAR / Parents / witness must sign as well)	---
04	There are three different strengths (84mg, 42mg & 21mg) of Eliglustat Capsules, it is not described that which strength will be utilized in the trial & what quantities of each strength will be imported.	In protocol amendment 3, section 8.2, it is described the different doses that will be administered depending on subject age, weight and metabolization profile. Hence the three strengths of eliglustat capsules will be imported as we can't anticipate the type of subject who will participate.	---
05	Pre-clinical/clinical safety studies data regarding Cerezyme (Imiglucerase) is not provided.	Imiglucerase (Cerezyme) is already approved by DRAP in Pakistan and approval letter is submitted. Preclinical and clinical studies data were previously submitted during product approval. Although imiglucerase is an	---

		investigational Medicinal Product in the ELIKIDS study, this will be used in combination with eliglustat as per protocol.	
06	Applied site (M/s National Hospital & Medical Center, Lahore) was approved for Phase-IV Clinical Trial titled, "*Observational Study Program Assessing Effectiveness and Tolerability of Gliclazide 60 Mg Modified Release Tablet in patients with Type-II diabetes, fasting during Ramadan (Dia-Ramadan)*".	This site "National Hospital and Medical Center, Lahore is already approved for phase II-III-IV Clinical Trials and letter Dated 21 August 2019 is attached.	It was informed to applicant that, applied site is approved for a specific Clinical Trial, but applicant again submitted the same letter claiming that the site is approved.
07	Un-signed GMP Certificate of following are attached: M/s Genzyme, Ireland Limited, Ireland. M/s Sanofi-Aventis Recherche & Developpement, France.	Certified GMP Certificates are attached. (Page 2000-2010/Corr.)	---
08	Un-signed Manufacturer Authorization of following is attached; M/s Sanofi-Aventis Recherche & Developpement, France.	Certified Manufacturer's Authorization is attached. (Page 2011-2024/Corr.)	---
09	CoPP of following IMPs are not provided. Cerezyme (Imiglucerase) Capsule. Cerdelga (Eliglustat GZ385660), Powder for solution for infusion.	**a.** Eliglustat Certificates of Analysis from clinical batch were provided in the submission package. Find them enclosed again for your convenience. **b.** Find the Certificate of analysis of imiglucerase for bulk and vials. (Page 2029-2034/Corr.)	Applicant was asked to submit CoPP of following IMPs: a. Cerezyme (Imiglucerase) Capsule. b. Cerdelga (Eliglustat GZ385660), Powder for solution for infusion. But applicant provided again COA for the IMPs instead of CoPP Certificates.
10	Details & CV of Clinical Research Associate need to be provided.	CV of Clinical Research Associate is attached. (Page 2035-2037/Corr.)	---
11	It is mentioned in the application that, both IMPs will be imported but certificate is for Cerezyme (Imiglucerase) Solution for infusion from country of origin is not provided.	Marketed authorization granted by FDA for imiglucerase is provided. (Page 2039/Corr.).	It is submitted that, attached document is an NDA approval & its not a marketing authorization.
	Undertaking on Stamp paper is not provided.	Undertaking on Stamp Paper is attached (Page 2042/Corr.)	---

08. After review following shortcomings were recorded:

i. Applied site (M/s National Hospital & Medical Center, Lahore) was approved only for a Phase-IV Clinical Trial titled, "*Observational Study Program Assessing Effectiveness and Tolerability of Gliclazide 60 Mg Modified Release Tablet in patients with Type-II diabetes, fasting during Ramadan (Dia-Ramadan)*". See licence number CTS-0020, issued on 14th February 2020

ii. It was claimed that both IMPs used in the trial are approved & Marketing Authorization for Cerezyme (Imiglucerase) Solution for infusion issued by US FDA is attached, but attached document is NDA issued by US FDA.

iii. CoPP of following IMPs need to be submitted:
   a. Cerezyme (Imiglucerase) Capsule.
   b. Cerdelga (Eliglustat GZ385660), Powder for solution for infusion.

9. Above mentioned shortcomings were communicated to applicant vide letter even number dated 25th November 2021.

10. Applicant Dr. Saba Abbasi, Medical Manager, M/s Sanofi Aventis, Karachi, submitted following reply on 06th December 2021.

S.No.	Shortcomings	Reply	Remarks
01	Applied site (M/s National Hospital & Medical Center, Lahore) was approved only for a Phase-IV Clinical Trial titled, "*Observational Study Program Assessing Effectiveness and Tolerability of Gliclazide 60 Mg Modified Release Tablet in patients with Type-II diabetes, fasting during Ramadan (Dia-Ramadan)*". See licence number CTS-0020, issued on 14th February 2020	The Letter Previously provided dated: 21 August 2012, "Approval of National Hospital & Medical Center", Lahore clearly mentioned that, "The CSC unanimously approved the National Hospital and Medical Centre, Lahore as Clinical Trial site for Phase II, III, IV for both outdoor and indoor Patients". The letter Dated 21st August 2019 is attached again. In addition to that, site is currently approved for Two - phase 3 trials, as mentioned below: The Site is currently approved for the two Phase 3 Trials: *1. A Phase III Randomized, Double Blind, Placebo Controlled Clinical Trial in 18 Years of Age and Above to Determine the Safety and Efficacy of ZF-2001, A Recombinant Novel Corona Vaccine (CHO Cell) For Prevention of COVID-19. F.No. 03-5212020 DD (PS)- Registration Number CT: 0023. Approved, Dated 19th March 2021.* *2. Phase III Study: A randomized double-blind controlled clinical trial ff DWJ1248 in prevention of COVID-19 infection after exposure of SARS COV-2 F. No.03-73/2021 DD (PS)*	Applicant has not provided the copy of CTS licence issued for the proposed site. National Hospital & Medical Center, Lahore was approved for a Phase-IV clinical trial. During COVID-19 pandemic CSC approved the site for two clinical trials related to COVID-19 owing to situation of COVID-I9 pandemic in Pakistan in order to protect the patients. Applicant needs to provide copy of licence issued by the DRAP for the proposed trial site to support their claim regarding site approval or submit a new application for approval of proposed trial site.
02	It was claimed that both IMPs used in the trial are approved & Marketing Authorization for Cerezyme (Imiglucerase) Solution for infusion issued by US FDA is attached, but attached document is NDA issued by US FDA.	The NDA (New Drug Authorization) letters which were previously provided are the approved letter from FDA authorizing marketing / commercializing of the product, it is all published publicly on the FDA website. There are no other letter FDA issues. Please find attached the "FDA website screenshot for the reference, IMIGLUCERACE FDA approval Letter and original	---

		approval of IMIGLUCERASE support for Pediatrics use.	
03	CoPP of following IMPs need to be submitted: a. Cerezyme (Imiglucerase) Powder for solution for infusion. b. Cerdelga (Eliglustat GZ385660) Capsule.	Cerezyme is a powder for solution for infusion (COA attached) and Eliglustat is a capsule (we provided all COA from the 3 strengths as part of the initial submission package). Attached again, 1. Certificate of Analysis - G2385660 EFC13738 OPEN LABEL SERIALIZED IMIGLUCERASE 2. Certificate of Analysis - IMIGLUCERASE (CEREZYME) 424 UNIT VIAL (400UN/10M1) POWDER FOR SOLUTION FOR INFUSION 4A1 3. Certificate of Analysis - Eliglustat 25 mg Cap. 4. Certificate of Analysis - Eliglustat 50 mg Cap. 5. Certificate of Analysis - Eliglustat 100 mg Cap.	Applicant submitting COA of the IMPs again & again. CoPP of following IMPs need to provided: a. Cerezyme (Imiglucerase) Powder for solution for infusion. b. Cerdelga (Eliglustat GZ385660) Capsule.

11. In view of above reply following shortcomings were recorded:

i. Applicant needs to provide copy of licence issued by the DRAP for the proposed trial site to support their claim regarding site approval or submit a new application for approval of proposed trial site.
ii. Applicant need to provide CoPP of following IMPs:
    a. Cerezyme (Imiglucerase) Powder for solution for infusion.
    b. Cerdelga (Eliglustat GZ385660) Capsule.

12. Shortcomings communicated to applicant vide letter bearing number F. No.03-85/2021-DD (PS) dated 28th October 2021& a reminder letter issued on 10th December 2021 & 11th January 2022, yet response is awaited.

13. Application was placed before CSC in its 34th meeting held on 13th January, 2022 & the CSC decided as follow:

Decision:

*The CSC after detailed discussion and deliberation, **deferred** the case for submission of soft copies of the protocol & investigator's brochure so as to share the same with expert members of the CSC for their review and fulfillment of following shortcomings already communicated to the applicant:*

i. Applicant needs to provide copy of license issued by the DRAP for the proposed trial site to support their claim regarding site approval or submit a new application for approval of proposed trial site.
ii. Applicant need to provide CoPP of following IMPs:
    c. Cerezyme (Imiglucerase) Powder for solution for infusion.
    d. Cerdelga (Eliglustat GZ385660) Capsule.

14. Afterwards, the applicant submitted application for termination of the subject trial/study initiation process in Pakistan on 10th June, 2022, due to very tight timeline & Sanofi Aventis decided to terminate the initiation process in Pakistan.

15. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC rejected the application, being withdrawn by the applicant.

AGENDA ITEM-VIII:

REQUEST FOR APPROVAL AND REGISTRATION OF BIOEQUIVALENCE STUDY OF RAHMACIN (CLARITHROMYCIN) 250 MG / 5 ML SUSPENSION MANUFACTURED BY M/S MEDISURE LABORATORIES (PVT) LIMITED, KARACHI. F. No. 14-12/2021 DD (PS)

Application is from Dr. Sadia Asim, Director, Institute of Biological & Pharmaceutical Sciences (IBBPS), Dow University of Health Sciences, Ojha Campus Karachi, for approval of subject Bioequivalence Study, under the Bio-Study Rules, 2017, S.R.O.697/(I) 2018 along with prescribed processing fee of Rs.200000/- deposited vide challan number 1932889, dated 08th April 2021.

2. The summary of the proposed study is as under;

i. **Study title:** A Single-dose, Randomize, Open-Label, two-period, two-sequence, two-treatment, 2 x 2, crossover bioequivalence study Rahmacin® 250mg/5ml suspension compared with Klaricid® 250mg/5ml suspension in 26 healthy adult human subjects, under fasting condition.
ii. **Purpose of study:** To determine the Bioequivalence of Clarithromycin test product (Rahmacin 250mg/5ml Suspension) manufactured by M/s Medisure Laboratories Pakistan (Pvt) Ltd, compared with reference product (Klaricid 250mg/5ml Suspension) manufactured by Abbott Laboratories in healthy adult human subjects under the fasting condition.
iii. **Investigational Product:** Rahmacin® (Clarithromycin) 250mg/5ml Suspension of M/s Medisure Laboratories Pakistan (Pvt.) Ltd., Karachi.
iv. **Reference Product:** Klaricid® (Clarithromycin) 250mg/5ml Suspension of M/s Medisure Laboratories Pakistan (Pvt.) Ltd., Karachi.
v. **Sponsor:** M/s Medisure Laboratories Pakistan (Pvt.) Ltd., Karachi.
vi. **Principal Investigator:** Dr. Aftab A. Ali Mukhi (PI)
vii. **Co-Principal Investigator:** Dr. Javaria Choudhry & Dr. Sadia Asim.
viii. **Funding Source**: M/s Medisure Laboratories Pakistan (Pvt.) Ltd., Karachi.
ix. **Cost of the Project**: Provided.
x. **Subjects enrolment**: 26 Subjects will be enrolled in the study.

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

S. No.	Document	Remarks
1	Application on prescribed form-IIA.	Application on Form – IIA is provided.
2	Prescribed processing fee	Processing fee of Rs.200000/- deposited vide challan number 1932889, dated 08th April 2021.
3	Name of Investigational Product (including all available names; trade,	Attached

	generic or INN name, chemical code, etc.,)	
4	Dosage Form of Investigational Product	Attached
5	Formulation of Investigational Product	COA of the Product attached.
6	Pharmacodynamics and Pharmacokinetics of Investigational Product	Attached. *Need to be reviewed by CSC experts.
7	Purpose of study defining the indication along with the anticipated cost of the project and sources of fund	To determine the Bioequivalence of Clarithromycin test product (Rahmacin 250mg/5ml Suspension) manufactured by M/s Medisure Laboratories Pakistan (Pvt) Ltd, compared with reference product (Klaricid 250mg/5ml Suspension) manufactured by Abbott Laboratories in healthy adult human subjects under the fasting condition.
8	Proposed center for the study	BA/BE Studies Center at Institute of Biological & Pharmaceutical Sciences (IBBPS), Dow University of Health Sciences, Ojha Campus Karachi,
9	Investigational design and study plan	A Single-dose, Randomize, Open-Label, two-period, two-sequence, two-treatment, 2 x 2, crossover bioequivalence study Rahmacin® 250mg/5ml suspension compared with Klaricid® 250mg/5ml suspension in **26 healthy adult human subjects**, under fasting condition.
10	Pre-clinical or clinical data or safety studies	Attached. *Need to be reviewed by CSC experts.
11	Final protocol	Protocol Number: IBBPS-012-CLA-2021/Protocol/1.0 Attached.
12	Detail of the investigator (Principal investigator, analysts, and others along with CV)	CVs of the following are attached: Dr. Aftab A. Ali Mukhi (PI) Dr. Javaria Choudhry (Co-PI) Dr. Sadia Asim (Co-PI)
13	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Copy of IRB approval, Ref:IRB-198/DUHS/Approval/2021, dated 27th March 2021 is attached. * IRB approval is for one year.
14	Approval of National Bio-ethics Committee (NBC)	Copy of NBC approval, Ref. No.4-87/NBC-617/21/61 dated 15th July 2021 is attached
15	Site approval by the Ethics committee	Attached.
16	Informed consent (English and Urdu)	Attached.

17	Summary of the protocol or synopsis (Investigational Product)	Attached.
18	Adverse Event Reporting Form	Attached.
19	Name of the monitor or clinical research associate	Muhammad Ibrar Ahmad Khan (CV attached)
20	Evidence of registration in the country of origin (GMP certificate along with CoPP or Free sale certificate)	Copy of GMP Certificate for M/s Medisure Laboratories Pakistan (Pvt) Ltd, Karachi is attached. Whereas, GMP Certificate for M/s PT. ABBOTT Indonesia, Marketing Authorization holder (Imported & Distributed by): Abbot Laboratories, Philippines.is not provided.
21	Copy of registration letter if registered in Pakistan	Copy of registration letter for Rahmacin (Clarithromycin) 250mg/5ml Suspension M/s Medisure Laboratories Pakistan (Pvt) Ltd, Karachi is attached. Whereas, registration letter of Klaricid® (Clarithromycin) 250mg / 5ml Suspension of M/s Abbott Laboratories Pakistan is not provided.
22	The proposed label of investigational product	Attached.
23	Quantity of investigational product to be used in the study along with justification (Note: All the quantities of the each of investigational product should be procured from one single source)	Attached.
24	Undertaking on affidavit	Attached.

4. After initial scrutiny following shortcomings were communicated to the applicant again & again but applicant informed that they are unable to provide evidence of registration, CoPP & GMP Certificate for the reference product.

5. Applicant submitted reply as follows:

S.No.	Shortcomings	Reply
01	BA/BE Study Center approval letter copy is not attached.	Provided in attachment.
02	Registration letter & GMP Certificate of Klaricid® (Clarithromycin) 250mg / 5ml Suspension of M/s Abbott Laboratories Pakistan is not provided.	Please note that Bioequivalence study will be submitted to exporting countries regulatory authorities, currently sponsor has the intention to submit the Bioequivalence study Rahmacin suspension 250mg/5ml in FDA Philippines. As per FDA Philippines Reference product Klaricid (Clarithromycin) 250mg / 5ml Suspension should be registered and Marketed in Philippines, because of that product has been procured from the Philippines market. Therefore,

		it is difficult to obtain Registration letter & GMP certificate of M/s Abbott Laboratories Philippines.
03	Clarification regarding formulation is required, as formulation furnished is **Clarocin** Suspension 250mg/5ml (70ml), whereas investigational product to be tested is **Rahmacin** Dry Suspension 250mg/5ml.	Please note that both Clarocin Suspension Rahmacin 250mg/5ml dry 250mg/5ml has same formulation. Batch formulas are also attached Suspension for your reference. Also note that Clarocin Suspension 250mg/5ml is locally registered brand name whereas Rahmacin dry Suspension 250mg/5ml is an approved brand name for export.
04	Complete Registration letter need to be provided.	Provided in attachment.
05	Label of Reference product are not provided.	Provided in attachment.
06	Quantity of test & reference product according to dose(s) to be used in the study need to described.	Provided in attachment.
07	Cost of the project is not described	Provided in attachment.

6. In view of above, it is informed by the applicant that, they are unable to produce CoPP of reference product & GMP Certificate of reference product manufacturer, as required under the Bio-Study Rules 2017.

7. The application was placed before CSC in its 34th meeting held on 13th January, 2022 & the CSC decided as follows:

Decision:

"The CSC after detailed discussion and deliberation decided to defer the case for fulfillment of following prerequisites as per Form-IIA of the Bio-Study Rules:

i. CoPP of reference product (i.e. Klaricid® (Clarithromycin) 250mg/5ml Suspension of M/s PT. ABBOTT Indonesia).
ii. GMP Certificate of reference product manufacturer (i.e. M/s PT. ABBOTT Indonesia)".

8. Accordingly, decision of the Committee was communicated to applicant vide letter bearing number F.No.16-34/2022 DD (PS) & F.No.14-12/2022, dated 14th January 2022 & 01st February 2022 respectively.

9. Applicant reply is reproduced as under:

Reference to the letter received on 1't February 2022 (F. No.14-1212020 - DD (PS)), regarding the fulfillment of prerequisites i.e. CoPP and GMP certificate of reference product manufacturer on application for the Bioequivalence Study of Rahmacin (Clarithromycin) 250m9/5ml suspension, We M/s Institute of Biological Biochemical & Pharmaceutical Sciences hereby enlightens the Clinical Study Committee that we have intimate the sponsor regarding the requirement of CoPP and GMP certificate of reference product manufacturers but unfortunately sponsor did not found any way to arrange the required documents.

ln order to fulfill the requirement of CSC committee we explore the web portal of National Agency for Drug and Food Control of Indonesia or Badan POM or BPOM & FDA Philippines there we found that M/s PT . ABBOTT Indonesia is registered & marketing their products in said drug regulatory agencies, we also found the evidence of clarithromycin product registration in both said drug regulatory agencies links & screenshots are provided for you reference:

Evidence of Product Registration in NADFC Indonesia:

https://cekbpom.pom.go.id//home/produUb78hom8v2h651vi9iilvivali3/all/row/1O/page/2/order/4/DESC/search/S/clarithromycin

Evidence of PT. ABBOTT Indonesia Registration in NADFC Indonesia:
https://cekbpom.pom.go.id//home/sarana/b78hom8v2h651vi9iilvivali3/idi001.OBD-2794.05

Evidence of ABBOTT LABORATORIES Registration in FDA Philippines:
https://verification.fda.gov.ph/DRUG_TRADEReview.php?showdetail=&ACCOUNTCODE=CDRR-NCR-DT-35827

Evidence of Product Registration in FDA Philippines:
https://verification.fda.gov.ph/druq_productslist.php?cmd=search&t=drug_products&psearch=CLARITHROMYCIN&psearchtype=

Hoping that above clarification & evidences will suffice the requirement of CSC committee for the grant of Approval & Registration of Bioequivalence Study of Rahmacin (Clarithromycin) 250mg/5ml suspension.

10. It is submitted that, CoPP & GMP Certificates for test & reference IMPs is a legal requirement as per Form-II of the Bio-Study Rules 2017.

11. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of all prerequisites as per Form-IIA of the Bio-Study Rules, 2017. Further, applicant is directed to provide the said requisite documents within 30 days positively, failing which the application is liable to be rejected.

AGENDA ITEM IX:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED, "A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, NON-INFERIORITY PHASE-II CLINICAL TRIAL ON THE EFFICACY & SAFETY OF HOUTOU JIANWEILING TABLET IN THE TREATMENT OF CHRONIC NON-ATROPIC GASTRITIS. F.No.03-19/2020 DD (PS)

Application was from Prof. Dr. Muhammad Raza Shah, General Manager, CBSCR, International Center for Chemical & Biological Sciences, University of Karachi, dated 18th September 2021, wherein FR is in reply of this Division letter bearing even number dated 08th September 2021.

2. It is submitted that, the subject application was placed before CSC in its 34th meeting held on 13th January, 2022. The committee decided the case as follow:

Decision:

"The CSC after detailed discussion and deliberation decided to defer the case for submission of CoPP of reference product i.e. Omeprazole enteric coated Tablets, manufactured by M/s China National Pharmaceutical Industry Co, Ltd., Beijing, China, as the applicant provided re-registration certificate OF THE product instead of its CoPP".

3. Applicant provided following requisite document:

i. Copy of CoPP for Omeprazole enteric coated Tablets, manufactured by M/s China National Pharmaceutical Industry Co, Ltd., Beijing, China.

4. In view of above, the applicant submitted all prerequisite documents & placed again before CSC for consideration.

5. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to approve the Clinical Trial titled, "A Randomized, Double Blind, Placebo Controlled, Non-Inferiority Phase-II Clinical Trial on the Efficacy & Safety of Houtou Jianweiling Tablet in The Treatment of Chronic Non-Atropic Gastritis", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site:

M/s Center for Bioequivalence Studies and Clinical Research (CBSCR), International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, Sindh (CTS-0046)

AGENDA ITEM X:

APPLICATION TO REGISTER THE AGA KHAN HOSPITAL FOR WOMEN & CHILDREN, KHARADAR, KARACHI AS STUDY SITES FOR A PHASE-II CLINICAL TRIAL TITLED, "CAN ESOMEPRAZOLE IMPROVE OUTCOMES IN WOMEN AT HIGH RISK OF PRE-ECLAMPSIA? A PHASE-II, PLACEBO-CONTROLLED RANDOMIZED MULTICENTER CLINICAL TRIAL (THE ESPRESSO STUDY)". F. No.15-16/2022 DD (PS)

Application is from Dr. Syed Mairajuddin Shah, Chief Operating Officer (COO), Secondary Hospital, Aga Khan University Hospital, Stadium Road, Karachi, dated 15th August 2022. Wherein the request has been made to license the subject site for Phase-II Clinical Trial titled, "Can Esomeprazole Improve Outcomes in Women at High Risk of Pre-Eclampsia? a Phase-II, Placebo-Controlled Randomized Multicenter Clinical Trial (The Espresso Study), the application is on prescribed Form-I of the Bio-Study Rules, 2017 with prescribed processing fee of Rs.100000/- paid vide challan No. 23729484194, dated 03rd August, 2022.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Fee	Prescribed processing fee of Rs.100000/- is paid vide challan No. 23729484194, dated 03rd August, 2022.
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.	Attached.

5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Some details are provided but equipment & facilities are not fulfilling requirement of tests required in Phase-II Clinical trials & the list of minimum equipments required for a bioanalytical assay in Phase-I/II Clinical Trials. Further there is no approved Bioanalytical laboratory at proposed site.
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.	Some of details are provided but the facilities available at the proposed primary Health care Site are not enough to conduct a Phase-II Clinical Trial at the site.
8	Undertaking on stamp paper	Attached.

3. After initial scrutiny following shortcomings observed:

i. List of section wise equipment and machinery required for analytical or bio-analytical and clinical studies is not provided.
ii. Equipments mentioned in the list are not fulfilling requirement of tests/assay required in Phase-II Clinical Trials (i.e. Pharmacokinetic & Pharmacodynamics Studies).
iii. Further there is no approved Bioanalytical laboratory at proposed trial site, which is required for Phase-I/ Phase-II Clinical Trials.
iv. Allied facilities & emergency handling facilities available at the proposed Primary Health Care Site are not enough to conduct a Phase-II Clinical Trial at the site.
v. Approval from Health Care Commission of Sindh need to be provided.

4. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of following shortcomings as per Form-II of the Bio-Study Rules, 2017:

i. List of section wise equipment and machinery required for analytical or bio-analytical and clinical studies is not provided.
ii. Equipments mentioned in the list are not fulfilling requirement of tests/assay required in Phase-II Clinical Trials (i.e. Pharmacokinetic & Pharmacodynamics Studies).
iii. Further there is no approved Bioanalytical laboratory at proposed trial site, which is required for Phase-I/ Phase-II Clinical Trials.
iv. Allied facilities & emergency handling facilities available at the proposed Primary Health Care Site are not enough to conduct a Phase-II Clinical Trial at the site.
v. Approval from Health Care Commission of Sindh need to be provided.

Further, applicant is directed to provide requisite documents within 30 days positively, failing which the application is liable to be rejected.

AGENDA ITEM XI:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "CAN ESOMEPRAZOLE IMPROVE OUTCOMES IN WOMEN AT HIGH RISK OF PRE-ECLAMPSIA? A PHASE II, PLACEBO-CONTROLLED RANDOMIZED MULTICENTER CLINICAL TRIAL (THE ESPRESSO STUDY)", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F.No.03-13/2022 DD (PS)

Application is from Dr. Sidrah Nausheen, Assistant Professor, Department of Obstetrics & Gynecology, The Aga Khan Hospital for Women & Children Kharadar, Atmaram Pritamdas Rd, near well come, Dharamsala Hamara Lyari, Karachi, Sindh dated 04th August, 2022, received on 19th August, 2022, wherein request has been made for approval of subject Clinical Trial. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide challan no. 7090456982, dated 03rd August, 2022. The trial is enlisted on U.S National Trial Registry with identification number ACTRN12618001755224 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375343)

2. The details regarding trial, sponsor & responsible party is as under:

iii. **Sponsor:** The University of Sydney, Australia.

iv. **Funding Source**: National Health and Medical Research Council (NHMRC) Clinical Trials Centre, Australia

v. **Contact information:** Prof Jon Hyett, +61295158777, jon.hyett@sydney.edu.au

vi. **Brief Summary/Purpose of trial:** The purpose of this study is to evaluate The risk of pre-eclampsia (elevated blood pressure in pregnancy) can be predicted through a screening test at 11-13+6 weeks' gestation. Previous work has shown that 'high risk' women benefit from taking aspirin through their pregnancy - resulting in a 62% reduction in pre-eclampsia prevalence before 37 weeks. Current treatment does not alter the prevalence of term pre-eclampsia (i.e. after 37 weeks). This study will test whether adding another treatment (esomeprazole) will cause a further reduction in blood pressure at the end of pregnancy. Pregnant women will take one esomeprazole or placebo tablet each day from before 16 weeks until delivery, in addition to aspirin, and will have their blood pressure measured throughout the study.

vii. **Intervention/Exposure:**

Description of intervention(s) / exposure	Esomeprazole 40mg oral tablet at night commencing prior to 16 weeks gestation and continuing until delivery of pregnancy. Required background therapy is aspirin 150mg oral tablet at night commencing prior to 16 weeks gestation and continuing until 36 weeks gestation. Participants will be questioned on compliance at each visit, and a tablet count performed at 28 and 36 weeks
Comparator / control treatment	Placebo oral microcellulose tablet at night commencing prior to 16 weeks gestation and continuing until delivery of pregnancy. Required background therapy is aspirin 150mg oral tablet at night commencing prior to 16 weeks gestation and continuing until 36 weeks gestation.

viii. **Number of subjects to be recruited:** 200 Subjects will be enrolled on both sites of Pakistan.

ix. **Study design & details:**

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	500 participants (Globally)
Allocation:	Randomized Controlled Trial
Intervention Model:	Parallel Assignment
Masking:	Quadruple Blinded (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Prevention
Official Title:	Can esomeprazole improve outcomes in women at high risk of pre-eclampsia? A phase II placebo-controlled randomised multi-centre clinical trial. The ESPRESSO Study

3. The study carried out under the supervision of Dr. Sidrah Nausheen (PI). The trial comprises of following objective(s);

Primary Outcome: Mean arterial pressure, measured by 24-hour ambulatory blood pressure (Time point: 36 weeks gestation)

Secondary Outcome: MoM mean arterial pressure. The MoM (multiple of the median) of mean arterial pressure will be calculated by computing the ratio of observed mean arterial pressure to expected mean arterial pressure that would be anticipated for maternal characteristics at that specific gestational age. The measured mean arterial pressure will be calculated from a 24-hour ambulatory blood pressure record (see primary outcome measure). The expected mean arterial pressure will be derived from normative data reported in the literature (Time point: 36 weeks gestation)

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed processing fee	Rs. 200,000/- deposited vide challan no. 7090456982, dated 03rd August, 2022.
3	Investigator Brochure (s)	Investigational Product Handling Manual is attached & informed that, in the ESPRESSO Study the approved product information for **esomeprazole** & **aspirin** will be utilised in place of Investigator's brochures.
4	Final protocol	Trial Protocol No. CTC 0179 ESPRESSO, Version 2.0, dated 06th June, 2018 is attached. * Financing & insurance details are not provided
5	Informed consent and participant information sheet (Urdu to English)	Attached but following points need to be clarified * Study is not insured & subjects need to file petition for compensation it need to be clarified & study should be insured.
6	List of participating countries	Australia & Pakistan. * Details of Australia is not provided.
7	Phase of trial.	Phase – II

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.	The approximate required quantity of following IMPs will be as follows: i. Aspirin 300mg (Solprin®) Tablets (235 Packs 92s) ii. Esomeprazole/Placebo 40mg Tablets (35 Tablets/bottle) (410 Bottles)
9	Site of the trial	i. Aga Khan University Hospital, Karachi. ii. Aga Khan Hospital for Women & Children, Kharadar, Karachi. * It is noted that, AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	AKUH IRB/ERC approval, dated 27th January, 2022, for a period of **one year** is attached. **Note:** The composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval.
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No.4-87/NBC-760/22/1688, dated 15th March, 2022 (for a period of **one** months). **Note:** As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.
12	CV's of the Investigators	CVs of following experts are attached. **i.** Dr. Sidrah Nausheen (PI) (117-139/Corr.) **ii.** Dr. Sajid Sufi (Co-PI) (140-179/Corr.) **iii.** Dr. Shabina Ariff (Co-PI) (180-210/Corr.) **iv.** Dr. Lumaan Sheikh (Co-PI) (211-237/Corr.)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following are need to be provided: i. Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia. ii. Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India iii. Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia * GMP certificate of all manufacturer issued by respective country drugs regulatory body need to be provided. ** Further, connection & role of mentioned manufacturers need to be provided.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Summary of IB is attached only for esomeprazole manufactured by M/s Ranbaxy Australia
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	200 Subjects on both site in Pakistan. Details regarding Subjects to be enrolled in Australia need to be provided.
19	Name of Monitors & Clinical Research Associate	Attached
20	Evidence of registration in country of origin.	TGA public summary is attached

21	Copy of registration letter (if registered in Pakistan)	Not applicable.
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	Approximately 03 Years.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings were recorded:

i. As per provided documents, composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval.
ii. As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.
iii. AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials.
iv. GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided.

    a. Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.
    b. Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India
    c. Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia

v. Details regarding Subjects to be enrolled in Australia need to be provided.
vi. As per Informed Consent Form, the study is not insured & subjects need to file petition for compensation. It need to be clarified & study should be insured.
vii. Financing & insurance details is not incorporated in trial protocol.
viii. Anticipated cost of the project need to be informed.

06. In the view of above, shortcoming letter was issued on 11th October, 2022, but still reply is awaited.

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07. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of following shortcomings as per Form-II of the Bio-Study Rules, 2017:

i. As per provided documents, composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval.
ii. As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.
iii. AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials.
iv. GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided.

a. *Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.*
b. *Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India*
c. *Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia*

v. *Details regarding Subjects to be enrolled in Australia need to be provided.*
vi. *As per Informed Consent Form, the study is not insured & subjects need to file petition for compensation. It need to be clarified & study should be insured.*
vii. *Financing & insurance details is not incorporated in trial protocol.*
viii. *Anticipated cost of the project need to be informed.*

Further, applicant is directed to provide requisite documents within 30 days positively, failing which the application is liable to be rejected.

AGENDA ITEM XII:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "EFFECTIVENESS OF NOVEL APPROACHES TO RADICAL CURE WITH TAFENOQUINE AND PRIMAQUINE (EFFORT)- A RANDOMIZED CONTROLLED TRIAL IN P. VIVAX PATIENTS". FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-10/2022-DD (PS)

Applicant is from Dr. M. Asim (42201-0543067-7), Professor and Consultant Parasitologist, institutional Lead for APMEN, Former Chair Hospital Ethics Committee, Department of Pathology & Microbiology, Aga Khan University, Stadium Road, Karachi, dated 28th July, 2022. Wherein request has been made for approval of subject Clinical Trial on prescribed Form-II of the Bio-Study Rules, 2017, along with a fee of Rs.200000/- deposited vide challan number: 30174303601, dated 15th July 2022. The trial is also enlisted on U.S National Trial Registry with identification number NCT04411836 *(https://clinicaltrials.gov/ct2/show/NCT04411836)* (Page 413-418/Corr.)

2. The details regarding trial, sponsor & responsible party is as under:

i. **Sponsor:** Menzies School of Health Research, Australia
ii. **Collaborators**:
   a. Aga Khan University Hospital, Karachi, Pakistan.
   b. University of Melbourne, Australia.
   c. National Centre for Parasitology, Entomology and Malaria Control, Cambodia.
   d. Mahidol Oxford Tropical Medicine Research Unit, UK.
   e. Ethiopian Public Health Institute, Ethiopia.
   f. Universitas Sumatera Utara, Indonesia.
   g. Arba Minch University, Ethiopia.

iii. **Contact information:** Kamala Thriemer, MD, MPH, PhD
0889468644
kamala.ley-thriemer@menzies.edu.au

iv. **Purpose of trial:** There have been three major advances in the tools available to tackle P. vivax relapses recently: single dose Tafenoquine (TQ), short course high dose Primaquine (PQ) and a novel quantitative point of care G6PD test. Whilst single dose radical cure with TQ represents a major advance, there are concerns that the pivotal Phase 3 clinical trials were designed for non-inferiority to the low dose PQ regimen. There is increased evidence that in many locations, low dose PQ is inferior to a high dose PQ regimen. Now that the G6PD diagnosis can be assured and short-course high-dose PQ can be administered safely, there is a dire need to compare the safety and efficacy of these alternative treatment strategies. We propose a multicenter

open label randomized controlled study to compare the effectiveness of these three key radical cure options, their safety, cost effectiveness and feasibility.

The study is designed as a prospective parallel group randomised controlled superiority effectiveness trial of patients with uncomplicated P. vivax malaria. For the purpose of study preparation, only patients with a G6PD activity > 70oA of the adjusted male median (AMM) as determined by the Biosensor™ (SD Bioline, ROK) will be eligible for enrolment into the trial. In order to determine l0O% G6PD activity in each site, a total of 30 non-related adult males attending the health facility will be sampled, who will only be included in the pre-study to calculate the local AMM if they are negative for malaria as confirmed by microscopy, no history of fever in the receding 48 hours, no history of malaria, major injury, surgery or blood transfusion within the last 6 months. Written informed consent will be requested along with a 10µl fingerpick sample and G6PD activity will be measured in duplicate using the Biosensor. No follow up of those patients will be required.

Eligible patients who have provided written informed consent will be enrolled into the following treatment arms in a ratio of 1 :1 :1.

a) ***The control arm:*** patients are treated with schizontocidal treatment plus low dose PQ (total dose 3.5mg/kg) unsupervised over 14 days (PQ14)
b) ***The first intervention arm:*** patients are treated with schizontocidal treatment plus high dose PQ (total dose 7 mg/kg) unsupervised over 7 days (PQ7)
c) ***The second intervention arm:*** patients are treated with schizontocidal treatment plus a single dose of Tafenoquine (TQ)

v. Detailed Description:

- To assess the effectiveness of a short-course of high dose primaquine (total dose 7mg/kg given unsupervised over 7 days) compared to the current standard low dose primaquine regimen (total dose 3.5mg/kg given unsupervised over 14 days).
- To assess the effectiveness of tafenoquine (single dose of 300mg) compared to the short-course high dose primaquine regimen.
- To assess the safety of tafenoquine compared to the high and low dose primaquine regimens.
- To assess the cost-effectiveness and feasibility of high dose primaquine and tafenoquine compared to the current low dose primaquine regimen

vi. Study design & details:

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	960 participants (Globally) as per US Trial Registry 720 participants (Globally) as per application & 240 participants in Pakistan.
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open label)
Primary Purpose:	Treatment
Official Title:	Effectiveness of Novel Approaches to Radical Cure with Tafenoquine and Primaquine - a Randomized Controlled Trial in P. Vivax Patients
Estimated Study Start Date :	25 April, 2021
Estimated Primary Completion Date :	01st June, 2022
Estimated Study Completion Date :	31st December, 2022

vii. Eligibility Criteria:

a. Inclusion Criteria

- P. vivax peripheral parasitemia (mono-infection) as determined by microscopy.
- G6PD normal status (G6PD activity ≥ 70% of the adjusted male median as determined by the Biosensor™ (SD Biosensor, ROK))
- Fever (temperature ≥37.5ºC) or history of fever in the preceding 48 hours
- Age ≥18 years

- Written informed consent
- Living in the study area and willing to be followed for six months

b. Exclusion Criteria:

- Danger signs or symptoms of severe malaria.
- Anaemia (defined as Hb <8g/dl)
- Pregnant or lactating females
- Known hypersensitivity to any of the study drugs
- Regular use of drugs with haemolytic potential

3. Details regarding Clinical Trial Sites, PI & Co-PI in Pakistan is as follows:

A. Khidmat-e-Alam Medicine centre, Karachi, Nazimabad, Pakistan (Not approved yet)
   - **i.** Principal Investigator: Asim Beg, MD.
   - **ii.** Sub-Investigator: Dr. Najia Ghanchi, MD.
   - **iii.** Sub-Investigator: Dr. Momin Kazi, MD.
   - **iv.** Sub-Investigator: Dr. Farah Qamar, MD.

B. Thatta Civil Hospital, Thatta, Sindh, Pakistan (Not approved yet)
   - **i.** Principal Investigator: Asim Beg, MD.
   - **ii.** Sub-Investigator: Najia Ghanchi, MD.
   - **iii.** Sub-Investigator: Momin Kazi, MD.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs.200000/- deposited vide challan number: 30174303601, dated 15th July 2022.
3	Investigator Brochure (s)	Attached **i.** Kodatef ® (Tafenoquine Succinate) 100mg Tablet (14-27/Corr.) **ii.** Primaquine 15mg Tablets (28-33/Corr.)
4	Final protocol	Attached Version 2.2, dated August, 2022 * In study objective Pakistan is not mentioned. ** Details of trial subject insurance & finance amount is not mentioned.
5	Informed consent and participant information sheet (Urdu to English)	ICF in English, Urdu & Sindhi are attached but following point need to be clarified * It is mentioned in the Informed Consent Form that, "*The study cannot compensate you or pay for life-long or long-term care for study related injuries or for any long-term ill effects to your health*".
6	List of participating countries	Ethiopia, Indonesia, Cambodia & Pakistan.
7	Phase of trial.	Phase – 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.	The approximate required quantity of IMPs are as follows: **i.** Kodatef (Tafenoquine) 100 mg Tablets 19 boxes (16 tablets per box) **Total 304 Tablets** **ii.** Primaquine 15mg Tablets 31 boxes/bottles (250 tablets per box/bottle) **Total 7750 Tablets.** * Justification for IMPs as per number of subject & dosing need to be provided.
9	Site of the trial	a. Khidmat-e-Alam Medical center, Nazimabad, Pakistan. b. Thatta Civil Hospital, Thatta, Sindh province, Pakistan.

10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	AKUH IRB/ERC approval, dated 05th August, 2022 for a period of one year is attached.
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter no.4-87/COVID-111/22/123, dated 10th August, 2022 (for a period of **Six** months).
12	CV's of the Investigators	CVs of following are attached. **v.** Dr. Muhammad Asim Beg, AKUH, Karachi (National-PI) (81-110/Corr.) **vi.** Dr. Farah Naz Qamar, AKUH, Karachi (Co-PI) (11-123/Corr.) **vii.** Dr. Abdul Momin Kazi, AKUH, Karachi (Co-PI) (124-149/Corr.) **viii.** Dr. Najia Ghanchi, MD., AKUH, Karachi (Co-PI) (150-164/Corr.) ***** All above PI/Co-PI are from AKUH, Karachi, none of PI/Co-PIs are nominated from proposed CTS(s).
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following IMPs manufacturer(s) are attached: iv. M/s The Government Pharmaceutical Organization, Thailand. v. M/s Piramal Pharma Limited, India. CoPP/Free Sale Certificate(s) of following IMPs are attached: i. Primaquine 15mg Tablets manufactured by M/s The Government Pharmaceutical Organization, Thailand. * CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.
14	Pre-clinical/clinical safety studies	Not applicable as both IMPs are registered & PIL are provided: **i.** Kodatef ® (Tafenoquine Succinate) 100mg Tablet (14-27/Corr.) **ii.** Primaquine 15mg Tablets (28-33/Corr.)
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Not applicable as both IMPs are registered & PIL are provided: **iii.** Kodatef ® (Tafenoquine Succinate) 100mg Tablet (14-27/Corr.) **iv.** Primaquine 15mg Tablets (28-33/Corr.)
17	Adverse Event Reporting Form	Not provided.
18	No of patients to be enrolled in each center.	960 participants (Globally) as per US Trial Registry 720 participants (Globally) as per application & 240 participants in Pakistan.
19	Name of Monitors & Clinical Research Associate	Not provided.
20	Evidence of registration in country of origin.	**Not provided.** GMP Certificate(s) of following IMPs manufacturer(s) are attached: vi. M/s The Government Pharmaceutical Organization, Thailand. vii. M/s Piramal Pharma Limited, India.

		CoPP/Free Sale Certificate(s) of following IMPs are attached: ii. Primaquine 15mg Tablets manufactured by M/s The Government Pharmaceutical Organization, Thailand. * CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.
21	Copy of registration letter (if registered in Pakistan)	**Not applicable.**
22	Sample of label of the investigational product / drug.	Attached but not as per ICH-GCP Guidelines, IMPs label should contain following statement: *For Investigational Use only.*
22	Duration of trial	Individual trial duration approximately 6 months Total trial duration is estimated to 24 months.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings were recorded:

i. In study objective in Pakistan are not described as mentioned for other countries in provided protocol.
ii. Details regarding trial subject(s) insurance in Pakistan is not provided.
iii. Anticipated cost of the project has not been informed.
iv. It is mentioned in the Informed Consent Form that, "*The study cannot compensate you or pay for life-long or long-term care for study related injuries or for any long-term ill effects to your health*". It needs to be clarified as ethically trial associated injuries/health issues should be covered in trial subject insurance.
v. As per U.S. trial registry there are 960 participants (Globally) for the trial. Whereas in the application 720 participants (Globally) & 240 participants will be enrolled in Pakistan. Clarification need to be provided for difference in trial subjects.
vi. Justification for IMPs quantity need to be imported for the CT as per number of subject(s), dosing & surplus quantity/retention sample, need to be provided.
vii. Following proposed CTS are not approved:
    a. Khidmat-e-Alam Medical center, Nazimabad, Pakistan.
    b. Thatta Civil Hospital, Thatta, Sindh province, Pakistan.
viii. None of PI/Co-PI are involved from proposed Clinical trial Site(s).
ix. CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia, need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.
x. Sample label is attached but not as per ICH-GCP Guidelines, IMPs label should contain following statement:

    a. *For Investigational Use only.*

06. In the view of above, shortcomings communicated to applicant/PI for fulfillments on 30th August, 2022 but still response is awaited.

07. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of following shortcomings as per Form-II of the Bio-Study Rules, 2017:

i. *As per provided documents, composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval.*
ii. *As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.*
iii. *AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials.*
iv. *GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided.*

    a. *Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.*
    b. *Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India*
    c. *Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia*

v. *Details regarding Subjects to be enrolled in Australia need to be provided.*
vi. *As per Informed Consent Form, the study is not insured & subjects need to file petition for compensation. It need to be clarified & study should be insured.*
vii. *Financing & insurance details is not incorporated in trial protocol.*
viii. *Anticipated cost of the project need to be informed.*

Further, applicant is directed to provide requisite documents within 30 days positively, failing which the application is liable to be rejected.

AGENDA ITEM XIII:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "RANDOMIZED CONTROLLED TRIAL TO ASSESS THE IMMUNOGENICITY AND SAFETY OF FULL VERSUS FRACTIONAL DOSE OF PFIZER/BIONTECH, ASTRAZENECA, AND SINOVAC COVID-19 VACCINES GIVEN AS A BOOSTER DOSE AT LEAST 6 MONTHS AFTER PRIMARY VACCINATION SERIES OR PCR-CONFIRMED INFECTION WITH SARS-COY-2 IN HEALTHY ADULTS", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. (FraCTCoV)F. No.03-08/2022-DD (PS)

Application is from Dr. Farah Naz Qamar, Associate Professor, Department of Pediatrics, Aga Khan University Hospital, Stadium Road, Karachi dated 18th July, 2022, wherein request has been made for approval of subject Clinical Trial, which will be carried out at Aga Khan University Hospital, Karachi. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide challan no. 136679529555, dated 13th July 2022. The trial is also enlisted on U.S National Trial Registry with identification number ***NCT05343871*** *(*https://clinicaltrials.gov/ct2/show/NCT05343871 *)*

2. The details regarding trial, sponsor & responsible party is as under:

i. **Sponsor:** Albert B. Sabin Vaccine Institute, USA.
ii. **Collaborators**:
    a. Aga Khan University Hospital, Karachi, Pakistan.
    b. Oswaldo Cruz Foundation, Brazil.
    c. Stanford University, USA.
iii. **Contact information:** Denise Garrett, MD +1 202 842 5025 sabin@sabin.org

iv. Purpose of trial: The purpose of this study is to evaluate the safety and immunogenicity of full versus fractional dose of Pfizer/BioNTech, AstraZeneca and Sinovac COVID-19 vaccines given as a booster dose at least 6 months after primary vaccination series or PCR-confirmed infection with SARS-CoV-2 in healthy adults in Pakistan. This exploration may help in determining if lower doses are effective and may be helpful in the formulation of public health policies for lower doses of these vaccines to overcome vaccine shortage issues.

v. Source of Investigational Medical Products (IMPs):

a. **Pakistan:-** Study vaccines will be purcha5cd from the MoH. The EPI department of MoH is responsible for ensuring the quality of vaccines. The MoH has a well- established monitoring and evaluation unit, which is responsible for monitoring vaccination sites/centers per vaccine protocol and documenting findings. For all vaccines that are purchased from local vendors, the National Control Laboratory for Biologicals of the Drug Regulatory Authority of Pakistan ensures the quality and issues a lot of release certificates. For all vaccines that are imported or received through UNICEF, the manufacturer at the country of origin ensures quality and provides a lot release certificate for its vaccines. The vaccines will be transported from the National Institute of Health of Pakistan to the study pharmacy as per recommended temperature, ensuring the maintenance of the cold chain, by using data loggers and/or vaccine vial monitor labeled vaccines, as appropriate.

b. **Brazil:-** Study vaccines will be donated by the Ministry of Health (MoH). The quality of the vaccine product itself is the responsibility of the industry, and the MoH is responsible for quality assurance in storage and transport to the vaccination sites. The transport is carried out by a specialized company with temperature monitoring. Vaccine monitoring is documented and delivered with the vaccine. If any vaccine quality control issues are identified, until arrival at the site, the principal investigator or someone delegated by him, must report it to the industry and to the National Health Regulatory Agency - ANVISA. The report can be on the website or by phone.

vi. Number of subjects to be recruited: 2880 Subjects

vii. Anticipated cost of the project: USD 2,102,1921/-

viii. Study design & details:

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	2880 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description:	The study will be observer-blind. Participants, data collectors (e.g., Investigator), and data evaluators (e.g., trial statisticians) are blinded. Only the staff involved in vaccine delivery will be unblinded and aware of which vaccine the participant is receiving (group allocation). Study staff who collect information on symptoms and adverse events, laboratory staff and statisticians conducting the analysis will all be blinded to the vaccine and dosage received.
Primary Purpose:	Prevention
Official Title:	Randomized Controlled Trial to Assess the Immunogenicity and Safety of Full Versus Fractional Dose of Pfizer/BioNTech, AstraZeneca, and Sinovac COVID-19 Vaccines Given as a Booster Dose at Least 6 Months After Primary Vaccination Series or PCR confirmed Infection With SARS-CoV-2 in Healthy Adults
Estimated Study Start Date :	July 2022
Estimated Primary Completion Date :	December 2022

Estimated Study Completion Date :	June 2023

3. The study carried out under the supervision of Dr. Farah Naz Qamar (PI). The trial comprises of following primary objective(s);

A. Sero-response rate by Spike IgG binding ELISA at 28 days post booster [Time Frame: Day 28]. Assess and compare humoral immune response from a fractional vs. full booster dose of BNT162b2 or AZD1222 in immunocompetent adults fully primed with BNT162b2, AZD1222, or Sinovac vaccines or natural infection, measured by anti-Spike IgG binding ELISA at 28 days post booster

B. Safety and reactogenicity profile of fractional and full dose of study vaccines at 28 days post-booster vaccination [Time Frame: Day 28]. Describe the safety and reactogenicity profile of fractional and full dose of study vaccines at 28 days post-booster vaccination through estimated incidence of solicited local and systemic adverse events, and incidence of unsolicited reported adverse events

i. Occurrence of solicited local and systemic reactions within 7 days of booster
ii. Occurrence of unsolicited AEs within 28 days of booster.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs.200000/- deposited vide challan number: 136679529555, dated 13th July 2022.
3	Investigator Brochure (s)	Attached **iii.** Pfizer/BioNTech (Comirnaty®) (08-64/Corr.) **iv.** Sinovac (65-102/Corr.) Not as per ICH-GCP Guidelines. **v.** AstraZeneca (103-143/Corr.)
4	Final protocol	Attached Protocol No. Sabin CoV 22 Version 1.1, dated 12th April, 2022 * Four (04) Co-Investigators from NIH are mentioned in protocol under the AKUH, whereas NIH is a Government organization & is not a proposed site for the trial. So, revision of protocol or clarification from PI is required regarding Co-Investigators role in the trial as their role is procurement & supply of the IMPs.
5	Informed consent and participant information sheet (Urdu to English)	Attached but following points need to be clarified * It is mentioned in the Informed Consent Form that vaccine(s) used in the trial are registered from DRAP , which is a misleading statement. Whereas it should be clarified that, the vaccine(s) utilized in the trial are EUA holder. (Page 721-722 & 727-728/Corr.) ** There is different arrangement of sentences in English & Urdu under the heading of *Discomfort, Risks and benefits* , which affecting the meaning. (Page 721-722 & 727-728/Corr.)
6	List of participating countries	USA, Brazil & Pakistan. * Details/role of USA in the trial is not provided.
7	Phase of trial.	Phase – IV

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.	The approximate required quantity of each vaccine will be as follows: iii. Pfizer/BioNTech (Comirnaty®) (201 vials) iv. AstraZeneca (205 vials) v. Sinovac (102 vials).
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.	AKUH IRB/ERC approval, dated 05th June 2022 for a period of one year is attached. **Note:** The composition of AKUH IRB/ERC is not as per the Bio-Study Rules 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial.
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter no.4-87/COVID-106/22/2435, dated 28th June, 2022 (<u>for a period of **Six** months</u>). **Note:** As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.
12	CV's of the Investigators	CVs of following experts are attached. **i.** Denise Ganett (GPI) (475-500/Corr.) **ii.** Farah Naz Qamar (PI) (AKUH)(501-508/Corr.) **iii.** Zahra Hassan (Role in CT is not mentioned in protocol) (509-511/Corr.) **iv.** M. Tahir Yousafzai (Co-PI) (512-516/Corr.) **v.** Junaid Iqbal (Co-PI) (517-519/Corr.) **vi.** Abdul Momin Kazi (Role in CT is not mentioned in protocol) (520-525/Corr.) **vii.** Kiran Iqbal Masood (Co-PI) (526-529/Corr.) **viii.** Maj. Gen. Dr. M. Aamer Ikram (Co-PI) (530-602/Corr.) **ix.** M. Firdous Khan (Co-PI) (NIH) (603-604/Corr.) **x.** Ghazala Parveen (Co-PI) (NIH) (605-610/Corr.) **xi.** Dr.Omera Naseer (Co-PI) (NIH)(611-619/Corr.) **xii.** Stephan P.Luby (Role in CT is not mentioned in protocol) (620-678/Corr.) **xiii.** Joelle Rosser (Co-Investigator) Stanford University (679-684/Corr.) **xiv.** Vivek Charu (Role in CT is not mentioned in protocol) (685-690/Corr.) **xv.** Victor Ritter (Role in CT is not mentioned in protocol) (691-693/Corr.) **xvi.** Haley K. Hedlin (Lead Statistician) Stanford University (694-705/Corr.) **xvii.** Amy Zhung (Role in CT is not mentioned in protocol) (706-708/Corr.) * **CVs of** Kiran Iqbal & Maria Fletcher are not provided
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following are attached: viii. AstraZeneca UK Limited. ix. Pfizer Limited, UK. As IMPs are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs, along with GMP Certificate of M/s Sinovac Biotech Ltd, China need to be provided.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached. As attached protocol is not finalized & signed so after its finalization & signature need to be submitted along with its summary.
16	Summary of Investigator Brochure	Summary of IB for following IMPs are not provided; **i.** Pfizer/BioNTech (Comirnaty®) (08-64/Corr.) **ii.** Sinovac (65-102/Corr.)

17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	1440 for Pakistan 1440 for Brazil Total 2880 Subjects.
19	Name of Monitors & Clinical Research Associate	M/s Metrics Research (CRO), Karachi, Pakistan.
20	Evidence of registration in country of origin.	**Not provided.** As IMPs are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs need to be provided. Further lot/batch wise COAs of IMPs need to be provided. Which will be utilized in the trial after its approval.
21	Copy of registration letter (if registered in Pakistan)	**Not provided.** As IMPs are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs need to be provided.
22	Sample of label of the investigational product / drug.	Attached but contains typographic errors & IMPs label should contains following statement: *For Investigational Use only.*
22	Duration of trial	Approximately 16 Months.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings are recorded:

i. Attached Investigator's Brochure for Sinovac is not as per ICH-GCP Guidelines.

ii. Summary of Investigator's Brochure for Pfizer/BioNTech (Comirnaty®) & Sinovac are not provided.

iii. Four Co-Investigators from NIH are mentioned in protocol & will work under/in collaboration with AKUH, whereas NIH is a Government organization & its role is only procurement, storage & transportation of the IMPs which are procured from EPI. Role in regulatory approvals need to be clarified as National Bioethics Committee operates under NIH, which is a regulatory function in Clinical research. So, it may be conflict of interest.

iv. It is mentioned in Informed Consent Form that, IMPs/Vaccine(s) used in the trial are registered from DRAP, which is a misleading statement. Whereas it should be clarified that, the vaccine(s) utilized in the trial are EUA holder issued by various Drug Regulatory Authorities.

v. There is different arrangement of sentences in English & Urdu ICF, under the heading of *Discomfort, Risks and benefits,* which affecting the meaning. Further, insurance details/statement should also be part of ICF.

vi. In the list of participating countries, USA, Brazil & Pakistan are mentioned but Clinical Trial Site(s) are situated in Brazil & Pakistan only. Details/role of USA in the trial is not provided.

vii. The composition of AKUH's IRB/ERC is not as per the Bio-Study Rules 2017 & the ICH-GCP Guidelines. So, its approval for the subject trial is not in compliance of the Bio-Study Rules 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial. PI is advised to got a fresh approval from re-notified IRB/ERC & then from NBC and submit both approval letter to the DRAP.

viii. As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017 and NBC approval is also issued on the basis of that IRB/ERC, so need to be reviewed & approved again.

ix. CVs of following experts are attached whom role is not defined in protocol or elsewhere :

a. Zahra Hassan.
b. Abdul Momin Kazi.
c. Stephan P.Luby.
d. Vivek Charu.
e. Victor Ritter.

f. Amy Zhung.

x. CV of following experts are need to be provided:
   a. Kiran lqbal.
   b. Maria Fletcher.

xi. As IMPs (Vaccines) utilized in the trial are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs (Vaccines), along with GMP Certificate of M/s Sinovac Biotech Ltd, China need to be provided. Further lot/batch wise COAs along with lot release & other related documents need to be provided after approval of trial & before utilization of IMPs.

xii. Sample label for IMPs is attached but contains typographic errors which need to be corrected. Further, IMPs label(s) should contain following statement:
   a. *For Investigational Use only.*

06. Accordingly, shortcomings communicated to Principal Investigator & nominated CRO for fulfillments on 10th August, 2022.

07. Applicant/PI, Dr. Farah Naz Qamar, Associate Professor, Department of Pediatrics, Aga Khan University Hospital, Stadium Road, Karachi, submitted reply, dated 28th August, 2022.

08. Summary of submitted reply along with attachments is as follows:

Sr.	Descriptions / Shortcomings	Reply	Remarks
01	Attached Investigator's Brochure for Sinovac is not as per ICH-GCP Guidelines.	The Investigator Brochure for Sinovac according to ICH-GCP guidelines is attached. (Page 921-1004/Corr.)	---
02	Summary of Investigator's Brochure for Pfizer/BioNTech (Comirnaty®) & Sinovac are not provided.	Summary of Investigators Brochure for Pfizer/ BioNTech (Comirnaty®) & Sinovac can be reviewed in detailed IB document. (Page 1005-1091/Corr.)	---
03	Four Co-Investigators from NIH are mentioned in protocol & will work under/in collaboration with AKUH, whereas NIH is a Government organization & its role is only procurement, storage & transportation of the IMPs which are procured from EPI. Role in regulatory approvals need to be clarified as National Bioethics Committee operates under NIH, which is a regulatory function in Clinical research. So, it may be conflict of interest.	Thank you for pointing this out, the roles of Co-investigators from NIH are revised in the protocol as suggested. The role of NIH in regulatory approvals is removed altogether. (Page 1092-1161/Corr.)	---
04	It is mentioned in Informed Consent Form that, IMPs/Vaccine(s) used in the trial are registered from DRAP, which is a misleading statement. Whereas it should be clarified that, the vaccine(s) utilized in the trial are EUA holder issued by various Drug Regulatory Authorities.	The statement 'registered by DRAP' is revised as 'DRAP has provided EUA for the IMPs / Vaccine(s). Additionally, other relevant statements have also been revised in the Discomforts, Risks & Benefits section. (Page 1162-1175/Corr.)	---
05	There is different arrangement of sentences in English & Urdu ICF, under the heading of *Discomfort, Risks and benefits,* which	Arrangement of sentences in English & Urdu ICF have been aligned now under specific headings. Insurance	---

	affecting the meaning. Further, insurance details/statement should also be part of ICF.	policy details have also been added in the ICFs. (Page 1162-1175/Corr.)	
06	In the list of participating countries, USA, Brazil & Pakistan are mentioned but Clinical Trial Site(s) are situated in Brazil & Pakistan only. Details/role of USA in the trial is not provided.	Clinical trial sites are situated in Pakistan & Brazil only. Sabin Vaccine Institute based in USA is the sponsor of the study & Stanford University supporting us for data software only.	---
07	The composition of AKUH's IRB/ERC is not as per the Bio-Study Rules 2017 & the ICH-GCP Guidelines. So, its approval for the subject trial is not in compliance of the Bio-Study Rules 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial. PI is advised to get a fresh approval from re-notified IRB/ERC & then from NBC and submit both approval letter to the DRAP.	As per your suggestion we have attached a fresh approval letter from AKU-ERC as per ICH-GCP Guidelines. The new letter of approval from the AKU-ERC and ERC members list is attached. (Page 1176-1182/Corr.)	AKUH-ERC revised approval letter dated 05th August, 2022 with new composition is attached.
08	As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017 and NBC approval is also issued on the basis of that IRB/ERC, so need to be reviewed & approved again.	Application for NBC approval has been submitted again on the basis of the revised AKU-ERC approval. Attached is the fresh NBC approval letter. (Page 1183/Corr.)	NBC- revised approval letter Ref:No.4-87/COVID-106/22/124 dated 10th August, 2022 with new composition is attached.
09	CVs of following experts are attached whom role is not defined in protocol or elsewhere: a. Zahra Hassan. b. Abdul Momin Kazi. c. Stephan P. Luby. d. Vivek Charu. e. Victor Ritter. f. Amy Zhung.	a. Zahra Hassan - expert in PCR and genetics, will support the lab component of the project b. Stephan P. Luby - role is mentioned in the protocol under Stanford team	---
10	CV of following experts are need to be provided: a. Kiran lqbal. b. Maria Fletcher.	We have attached the CV of Kiran lqbal. Maria Fletcher has resigned from the Department of Pediatrics recently, hence her role from specified study protocol has been removed. a. Kiran lqbal (CV attached) b. Maria Fletcher (removed from protocol) (Page 1184-1187/Corr.)	---
11	As IMPs (Vaccines) utilized in the trial are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs (Vaccines), along with GMP Certificate of M/s Sinovac	Emergency Use Authorization certificates of all used vaccines, Pfizer/ BioNTech, Sinovac are attached with this	

	Biotech Ltd, China need to be provided. Further lot/batch wise COAs along with lot release & other related documents need to be provided after approval of trial & before utilization of IMPs.	application. For Astra Zeneca vaccine, we are attaching EUAs (from WHO & other countries). GMP Certificate of the Sinovac Biotech Ltd is also attached. Further, we will provide all the relevant documents related to IMPs before utilization in the trial. (Page 1188-1200/Corr.)	
12	Sample label for IMPs is attached but contains typographic errors which need to be corrected. Further, IMPs label(s) should contain following statement: a. *For Investigational Use only.*	Typographic errors have been corrected and the Statement "Investigational Use Only" is added in the label. (Page 1201/Corr.)	

09. The applicant has rectified the shortcomings.

10. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to approve the Clinical Trial titled, "Randomized Controlled Trial to Assess the Immunogenicity and Safety of Full Versus Fractional Dose of Pfizer/BioNTech, AstraZeneca, and Sinovac Covid-19 Vaccines Given as a Booster Dose at Least 6 Months after Primary Vaccination Series or PCR-Confirmed Infection with Sars-COV-2 in Healthy Adults. (FraCTCoV)", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site:

- *M/s Aga Khan University Hospital, Karachi, Sindh (CTS-0003)*

AGENDA ITEM XIV:

APPLICATION FOR REGISTRATION AND APPROVAL OF CLINICAL TRIAL TITLED "IMMUNOGEENICITY OF NOVEL ORAL POLIOMYELITIS VACCINE TYPE 2 (nOPV2) IN HEALTHY CHILDREN AGED 1- 15 YEARS IN SETTINGS AT HISH RISK OF cVDPV2 OUTBREAKS", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-19/2022-DD (PS)

Application is from Dr. Ali Faisal Saleem (CNIC 42201-0534184-9), Associate Professor, Vice Chair - Clinical Services, Department of Pediatrics & Child Health – MC, Director. Infectious Diseases Research Laboratory, Aga Khan University Hospital, Stadium Road, Karachi dated 29th August, 2022, wherein request has been made for approval of subject Clinical Trial, which will be carried out at Aga Khan University Hospital, Karachi. Application is on prescribed Form-II, along with a fee of Rs.200000/- deposited vide challan number: 9650965016, dated 12th August, 2022.

2. The details regarding trial, sponsor & responsible party is as under:

i. **Sponsor:** Global Polio Eradication Initiative (GPEI)
ii. Collaborators;
    a. National Emergency Operations Center, Pakistan.

b. National Institute of Health, Pakistan.
c. Centers for Disease Control and Prevention, USA

iii. Purpose/background of trial: The Global Commission for the Certification of Poliomyelitis Eradication (GCC) declared worldwide eradication of wild type 2 poliovirus (WPV2) in2015. However, continued used of trivalent oral polio vaccine (tOPV) posed an on-going risk of circulating vaccine-derived poliovirus 2 (cVDPV2) and vaccine-associated paralytic poliomyelitis (VAPP), due to the small chance of neurovirulence. Therefore, all countries using oral polio vaccine switched to bivalent oral polio vaccine (bOPV2) without type 2 strain in 2016. This has resulted in waning immunity for polio type 2 over the years. Current outbreak control measures include the use of monovalent sabin oral poliovirus vaccine type 2 (mOPV2). However, the use sabin moPV2 for cVDPV2 outbreak control has led to further seeding of cVDPV2 outbreaks, with approximately 1048 cases of cVDPV2 reported in2020 from 33 countries.

The novel OPV2 (nOPV2) was developed with the intention of having an OPV with increased genetic stability, thereby reducing the possibility of seeding VDPV. The nOPV2 has been clinically tested in randomized control trials among adults in Belgium and among infants and children in Panama and found to be safe and immunogenic. The nOPV2 received recommendation under the WHO Emergency Use Listing (EUL) procedure in November 2020, for use in vaccination campaigns as part of response to cVDPV2 outbreaks.

Mass polio vaccination campaigns traditionally target children under 5 years of age, the primary age group that reports poliomyelitis and is responsible for highest proportion of transmission. However, as intestinal immunity to poliovirus wanes over time, individuals previously vaccinated with oral poliovirus vaccine (OPV) can become re-infected and shed poliovirus. Whilst cases of poliomyelitis among older children and adults are rare, infection in this group can contribute to sustained transmission. There is clinical data demonstrating the ability of OPV and IPV to boost mucosal and humoral immunity in older children that have previously been vaccinated or exposed to circulating virus. The strategy of expanding the age range of outbreak response vaccination campaigns with Sabin OPV has been implemented in some circumstances, such as in Tajikistan and Namibia.

The new GPEI strategic plan proposes expanding the age range of mass vaccination campaigns in high-risk areas. Therefore, it is necessary to evaluate the ability of nOPV2 to boost mucosal and humoral immunity in older children in high-risk areas. This study aims generate data on the immunogenicity of one and two doses of nOPV2 in high-risk polio settings such as Pakistan in children in an expanded age range. The secondary objective will assess nOPV2's ability to induce mucosal immunity expressed by the reduction in shedding of the vaccine virus after the 2nd nOPV2 dose. ln addition, baseline blood sample and shedding after the 1st nOVP2 dose will provide an insight into the current humoral and mucosal immunity in older children in high-risk areas.

iv. Role of Partners

- **WHO** will provide funding for the successful implementation of the study, provide technical support and oversight, conduct analyses of the study results, support the development of conference abstract(s) and manuscript(s).

- **Aga Khan University** will provide scientific leadership, recruit study team members (e.g., data collectors, data entry and analyst, nurses and/or lab technicians etc.) develop the sampling frame, conduct training workshop, conduct field activities, support the development of conference abstract(s) and manuscript(s), generate and submit final report and disseminate reports to the Liberian MoH and partners, etc.

- **NIH Pakistan** will conduct the laboratory analyses of blood and stool samples.

v. Source of Investigational Medical Products (IMPs):

a. NOVEL ORAL POLIOMYELITIS VACCINE TYPE 2 (NOPV2); Drops; Box, 10 vials @ 5 ml (50 doses) manufactured by M/s PT. BIO FARMA, Jl. Pasteur No. 28 Bandung 40161 – Indonesia.

vi. Number of subjects to be recruited: 525 Subjects (Children's) in Pakistan.

vii. Anticipated cost of the project: USD 151,556/-

viii. Study design & details:

a. Cross-Sectional Survey

3. The study carried out under the supervision of Dr. Ali Faisal Saleem (PI). The trial comprises of following objective(s);

A. Primary Objective: To determine the immunogenicity of one and two doses of nOPV2 in healthy children aged 1- 15 years in settings at high risk of cVDPV2 outbreaks.

B. Secondary Objectives: To assess nOPV2's ability to induce mucosal immunity in children aged 1- 15 years, expressed by the reduction in shedding of the vaccine virus after the 2nd nOPV2 dose.

C. Endpoints: Seroconversion will be defined as a change from seronegative (reciprocal titer <8) to seropositive (reciprocal titer >= 8) for subjects with no detectable antibody titers at baseline OR a four-fold rise in antibody titres over the expected decline of maternal antibodies.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs.200000/- deposited vide challan number: 9650965016, dated 12th August, 2022. * Original challan (DRAP's Copy) need to be provided.
3	Investigator Brochure (s)	Patient Information Leaflet is attached, as IMP is registered.
4	Final protocol	Attached Protocol No. nOPV2Pak2022v4 Version V4_31032022. * Protocol is not as per ICH-GCP Guidelines. ** There is no detail regarding insurance of study subjects. *** As per mentioned role of NIH, Islamabad, no evident document is attached for NIH approval as a Bio-Analytical Laboratory for Clinical Trials from DRAP.
5	Informed consent and participant information sheet (Urdu to English)	Attached I English only. * There is no detail regarding insurance of study subjects.
6	List of participating countries	Pakistan only.
7	Phase of trial.	Phase – IV
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.	Total 525 Children's will be enrolled in the study & each child will be given two doses of nOPV2. Therefore 30 vials of 50 doses each (1500 doses) will be required.
9	Site of the trial	Clinical Trial Unit, Aga Khan University Hospital, Karachi. • Bin-Qasim town (Cattle colony) • Ali Akbar Shah • Rehri Goth and extension area • Ibrahim Hyderi and extension area Mentioned Study sites/areas are not approved from DRAP.

10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Approval reference letter No. Nil, dated 22nd October, 2021 is attached (for a period of **one** year). * As IRB approval is near to its expiry, fresh IRB approval need to be provided.
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No. 4-87/NBC-693/21/724, dated 05th November, 2021 & 4-87/NBC-693/22/1636, dated 08th March, 2022 (for a period of **One** year) (Amendment) is attached.
12	CV's of the Investigators	CVs of following experts are attached. **ix.** Dr. Ali Faisal Saleem (PI) (59-66/Corr.) **x.** Dr. Zaubina Umar Kazi (Co-PI) (67-69/Corr.)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Certificate of Pharmaceutical Product of following is attached: x. NOVEL ORAL POLIOMYELITIS VACCINE TYPE 2 (NOPV2); Drops; Box, 10 vials @ 5 mL (50 doses) GMP Certificate of the manufacturer is not provided: i. M/s PT. BIO FARMA, Jl. Pasteur No. 28 Bandung 40161 – Indonesia.
14	Pre-clinical/clinical safety studies	Not provided. Available Preclinical & Clinical Data need to be provided.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	As product is registered in the country of origin so not applicable.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	525 Subjects (Children's) in Pakistan.
19	Name of Monitors & Clinical Research Associate	--
20	Evidence of registration in country of origin.	Certificate of Pharmaceutical Product of following is attached: i. NOVEL ORAL POLIOMYELITIS VACCINE TYPE 2 (NOPV2); Drops; Box, 10 vials @ 5 mL (50 doses)
21	Copy of registration letter (if registered in Pakistan)	**Not applicable.**
22	Sample of label of the investigational product / drug.	Attached. But IMPs label should contains following statement: *For Investigational Use only.*
22	Duration of trial	12 Months. This includes 6 months for data collection and the remaining 6 months for data entry, cleaning, analysis, and dissemination.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings are recorded:

i. Original fee challan (DRAP's Copy) is not provided.
ii. Following study sites/areas mentioned in the application are not approved from DRAP
    a. Bin-Qasim town (Cattle colony)
    b. Ali Akbar Shah
    c. Rehri Goth and extension area
    d. Ibrahim Hyderi and extension area
iii. Attached protocol is not as per ICH-GCP Guidelines.
iv. There is no detail regarding insurance of study subjects in Protocol and in the Informed Consent Form.

v. As per mentioned role of NIH, Islamabad, no evident document is attached for NIH approval as a Bio-Analytical Laboratory for Clinical Trials from DRAP.
vi. In attached protocol (Annex-1, Consent Form) it is mentioned that, blood samples will be stored at -800°C at AKUH-Infectious Diseases Research Laboratory (IDRL)but there is no freezer available with this range.
vii. Approval reference letter No. Nil, dated 22nd October, 2021 is attached (for a period of **one** year). As IRB approval is near to its expiry, fresh IRB approval need to be provided.
viii. GMP Certificate of the manufacturer M/s PT. BIO FARMA, Jl. Pasteur No. 28 Bandung 40161 – Indonesia, is not provided.
ix. Pre-Clinical/Clinical data is not provided. Available Preclinical & Clinical Data need to be provided.
x. Sample label for IMPs is attached. Further, IMPs label(s) should contain following statement:
   a. *For Investigational Use only.*

06. Accordingly, shortcomings have been communicated vide letter bearing even number dated 29th September, 2022 but still response is awaited.

07. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of following shortcomings as per Form-II of the Bio-Study Rules, 2017:

i. Original fee challan (DRAP's Copy) is not provided.
ii. Following study sites/areas mentioned in the application are not approved from DRAP
   a. Bin-Qasim town (Cattle colony)
   b. Ali Akbar Shah
   c. Rehri Goth and extension area
   d. Ibrahim Hyderi and extension area
iii. Attached protocol is not as per ICH-GCP Guidelines.
iv. There is no detail regarding insurance of study subjects in Protocol and in the Informed Consent Form.
v. As per mentioned role of NIH, Islamabad, no evident document is attached for NIH approval as a Bio-Analytical Laboratory for Clinical Trials from DRAP.
vi. In attached protocol (Annex-1, Consent Form) it is mentioned that, blood samples will be stored at -800°C at AKUH-Infectious Diseases Research Laboratory (IDRL)but there is no freezer available with this range.
vii. Approval reference letter No. Nil, dated 22nd October, 2021 is attached (for a period of **one** year). As IRB approval is near to its expiry, fresh IRB approval need to be provided.
viii. GMP Certificate of the manufacturer M/s PT. BIO FARMA, Jl. Pasteur No. 28 Bandung 40161 – Indonesia, is not provided.
ix. Pre-Clinical/Clinical data is not provided. Available Preclinical & Clinical Data need to be provided.
x. Sample label for IMPs is attached. Further, IMPs label(s) should contain following statement:
   b. *For Investigational Use only.*

Further, applicant is directed to provide requisite documents within 30 days positively, failing which the application is liable to be rejected.

AGENDA ITEM XV:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "A PHASE-III, RANDOMIZED, OBSERVER-BLIND, MULTICENTER STUDY TO EVALUATE THE EFFICACY, IMMUNOGENICITY AND SAFETY OF SEQIRUS-CELL-BASED QUADRIVALENT SUBUNIT INFLUENZA VIRUS VACCINE (QIVc) COMPARED TO A NON-INFLUENZA VACCINE WHEN ADMINISTERED IN HEALTHY SUBJECTS AGED 6 MONTHS THROUGH 47 MONTHS", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-11/2022-DD (PS)

Application is from Dr. Fatima Mir, CNIC number: 17301-7749502-0, PI of applied trial & Associate Professor, Department of Pediatrics and Child Health, The Aga Khan University Hospital, Karachi, Pakistan, Stadium Road, Karachi dated 10th August, 2022, wherein request has been made for approval of subject Clinical Trial. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide challan no. 20970065, dated 10th August, 2022. The trial is also enlisted on U.S National Trial Registry with identification number ***NCT03932682*** *(*https://clinicaltrials.gov/ct2/show/NCT03932682*)*

2. The study is sponsored by Seqirus a CSL company, Ltd., The study is scheduled to be carried out during the upcoming influenza season (September 2022-September 2023) in Bangladesh, Philippines, South Africa, Sri Lanka, Sweden and in various sites within Pakistan (Al-Shifa Eye trust hospital, Rawalpindi, Shifa International Hospital, Islamabad, Avicenna Medical College and Hospital & The Central Park Teaching Hospital, Lahore. National Hospital and Medical Center, Lahore and Akram Medical Complex Lahore are additional CTS subject to DRAP approval to act as Phase-III Clinical Trials & AKUH will be the main leading site.

3. Further, Applicant/PI requested for accelerated review & approval, request is reproduced below:

This study is part of a pediatric investigation plan (PIP) agreed by the European Medicines Agency's (EMA) Pediatric Committee (PDCO) to support the authorization of QIVc in children 2 6 months of age. Given the significant reduction of influenza circulation during the COVID-19 global pandemic, in addition to the three completed seasons, two new seasons are being included in this study.
As described in the protocol, the enrollment period takes place just before the influenza season starts in each hemisphere. For the Northern Hemisphere 2022 (NH2022) season, the recruitment is expected to begin on 12 September 2022, allowing the required time for up to two vaccine doses to be administered to participants prior to the influenza season. The recruitment period ends on the 30 November 2022.

Given the seasonality of the study and the requirement to have participants vaccinated by November 2022, (enrolment will start in Sep 2022 and will be closed on 30 Nov 2022) I kindly request an accelerate review of our submission, which will allow us to quickly progress with import license application by October 2022.We aim to allow sites to have sufficient time to receive all supplies, Investigational Product, & for sites to be activated and to recruit the required number of subjects. Knowing the sequential order of submissions/review/approvals in Pakistan, we understand it could have impact on the duration of the enrolment period in the country - and therefore we believe that expedited review will help us to activate sites for enrolment as early as possible.

The inclusion of Pakistan in the NH2022 season will bring an important geographical diversity to the study's data set and will be key in supporting the endpoints of this trial.

4. The details regarding trial, sponsor & responsible party is as under:

x. **Sponsor:** Seqirus, UK.
xi. **Collaborators**: Seqirus, UK.
xii. Purpose of trial: The aim of this multicentre phase-III clinical study is to evaluate the efficacy, safety, and immunogenicity of a cell-based quadrivalent subunit influenza virus-vaccine (QIVc) compared to non-influenza vaccine in subjects between 6 months through 47 months of age. The study features an observer blind design, parallel groups and 1:1 randomization between QIVc and the non-influenza vaccine. Based on previous influenza vaccination history, subjects will receive either one or two doses of either QIVc or comparator (non-

influenza vaccine/placebo). The non-influenza vaccine is a conjugate vaccine for prevention of invasive disease caused by Neisseria meningitidis serogroup C (MenC vaccine). ln subjects who require two doses, MenC and placebo (saline for injection) will be administered separated by 28 days. ln this study placebo will be used as masking dose. All subjects aged 6 through 11 months at enrolment, regardless of treatment assignment, will receive a dose of the MenC vaccine at the end of the study.

Influenza is an infectious disease caused by the influenza virus, an orthomyxovirus with two clinically relevant types (Type A and B). Influenza Type A/H1N1, A/H3N2, and Type B/Victoria and B/Yamagata strains have circulated and caused disease in humans on a global basis since 1977 (Fiore, 2010), with a high susceptibility to severe influenza in children (Izurieta, 2000) (Bourgeois, 2006). Children aged < 5 years, and particularly those < 2 years of age, are at high risk of infection and are a priority for annual seasonal influenza vaccination throughout the world (WHO, 2012) (AAP, 2016). With vaccination as the recommended method to prevent influenza, both childhood influenza disease burden and community viral transmission could be reduced (Mertz,2016). Seqirus' quadrivalent (QIVc) Flucelvax Quadrivalent/Flucelvax Tetra, r's a cell based quadrivalent inactivated subunit influenza vaccine prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cells and approved by the FDA. for use in children aged 6 months and older. As a quadrivalent vaccine, QIVc is formulated to contain two influenza A strains and two influenza B strains updated annually as recommended by the World Health Organization (WHO) for a specific influenza season. A shift from eggs to cell culture has several advantages, for example it avoids the risk of egg-adoptive mutations in the HA protein (Lambert,20I0).

The aim of this study is to evaluate the efficacy of QIVc in the prevention of RT-PCR confirmed influenza A or B disease in children 6 through 47 months of age, compared to a non-influenza vaccine. Efficacy data from all planned influenza seasons will be combined. By successfully demonstrating that QIVc decreases influenza disease in this age group, it will have the potential to play an important role in the prevention of influenza worldwide.

xiii. Quantity of IMPs required along with justification:

IMPs	Molecule	Strength	Pack Size	Manufacturer	No. of Patients	Per Patient Does	Frequency	TOTAL
Active – Flucelvax Quadrivalent (QIVc)	Cell-derived season Quadrivalent influenza vaccine	Total of 60 µg hemagglutinin (HA) per 0.5m1 does in the recommended ration of 15 µg HA of each of the four (4) influenza strains recommended by WHO for inclusion in the quadrivalent vaccine formulation for the influenza season corresponding to the season of conduct of the study	1 Pre-filled Syringe (PFS) 0.5ml per kit.	Seqirus Inc., 475 Green Oaks Parkway, Holly Springs, NC 27540, United States.	199	2	1	100x2=398
Placebo - Saline	Isotonic Sodium Chloride Solution	Isotonic Sodium Chloride Solution 0.9% 0.5m1 single dose be administered	1 ampoule 10ml per kit (one single dose of 0.5ml to be administered -ampoule to be discarded after the single dose is withdrawn)	B. Braun Melgungen AG Mistelweg 2, 12357 Berlin, Germany.	199	1 Dose of Saline at Visit 2	28 Days	199x1=199 199x1=199 (Each of NeisVac-C and Saline)
Comparator - NeisVac-C		10 µg of meningococcal group C polysaccharide conjugated with 10 to 20 µg of tetanus toxoid protein, absorbed to aluminum hydroxide (1.4 µg equivalent to 0.5 µg aluminum), plus the following ingredients: sodium chloride and water	1 Pre-filled Syringe (PFS) 0.5ml per kit	Pfizer Manufacturing Belgium NV, Rijksweg 12, BE-2870 Purus, Belgium	199	1 Dose of NeisVac at Visit 1	28 Days	199x1=199 199x1=199 (Each of NeisVac-C and Saline)

		(4.1 µg for injection, Qs to 0.5ml)						

Wastage and Damage %will be 25%:
Active: 398 x 25% = 100; Total Import Quantity: 398 + 100 = 498
Placebo: 199 x 25% = 50; Total Import Quantity: 199 + 50 = 249
Comparator: 199 x 25% = 50; Total Import Quantity: 199 + 50 = 249

xiv. Source of Investigational Medical Products (IMPs):

- **Generic Name:** *Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc)*
- **Trade Name:** *Flucelvax Quadrivalent/Flucelvax Tetra ® Mfd: by:* Seqirus Inc., 475 Green Oaks Parkway, Holly Springs, NC 27540, United States.
- **Generic Name:** *non-influenza vaccine is s a conjugate vaccine (MenC vaccine)*
- **Trade Name:** *NeisVac-C ®, Pfizer ® Mfd by:* Pfizer Manufacturing Belgium NV, Rijksweg 12, BE-2870 Purus, Belgium

xv. Number of subjects to be recruited: 3830 Subjects

xvi. Anticipated cost of the project: USD 381,349/-

xvii. Study design & details:

	Interventional (Clinical Trial)
Estimated Enrollment :	3830 participants (Globally)
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description:	The trial is designed as an observer-blind study. During the treatment period of the study designated and trained unblinded personnel will be responsible for administering the study vaccines to the subjects
Primary Purpose:	Prevention
Official Title:	A Phase 3, Randomized, Observer-blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus' Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine When Administrated in Healthy Subjects Aged 6 Months Through 47 Months
Estimated Study Start Date :	13 May, 2019
Estimated Primary Completion Date :	27th September, 2023
Estimated Study Completion Date :	27th September, 2023

5. The study will be carried out at mentioned sites comprising of following primary objective(s);

Site(s)	PI
Aga Khan University Hospital, Karachi	Dr Fatima Mir (National-PI)
Shifa International Hospital, Islamabad.	Dr. Ejaz A. Khan, Site-PI
Avicenna Medical college and Hospital, Lahore.	Dr. Aneela Zareen, Site-PI
Central Park Teaching Hospital, Lahore.	Dr. Muhammad Fakharul Zaman, Site-PI
Al-Shifa Trust Eye Hospital, Islamabad.	Dr. Ume Sughra, Site-PI
Akram Medical Complex, Lahore. (Additional site subject to DRAP approval.)	Dr. Javed Akram, Site-PI
National Hospital & Medical Centre Lahore - (Additional site subject to DRAP approval.)	Dr. Nadia Majeed, Site-PI

i. Efficacy Endpoint: First occurrence of RT-PCR confirmed influenza, due to any influenza Type A and/or B virus regardless of antigenic match [Time Frame: Day 14 to Day 180]

First occurrence of RT-PCR confirmed influenza, due to any influenza Type A and/or B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined influenza-like illness (ILI) symptoms

ii. Efficacy Endpoint: First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the strains selected for the seasonal influenza vaccine [Time Frame: Day 14 to Day 180]

First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs.200000/- deposited vide challan number: 20970065, dated 10th August, 2022. * Original DRAP's copy of fee challan need to be provided.
3	Investigator Brochure (s)	Edition: # 2, Dated: 29th January 2015 is attached * IB of NeisVac-C is not provided.
4	Final protocol	Attached Protocol No. V130_14 Version 4.0, dated 12th April, 2022 * Financing & Insurance details should be part of protocol as per ICH-GCP guidelines.
5	Informed consent and participant information sheet (Urdu to English)	Attached.
6	List of participating countries	NH22/23 Bulgaria, Poland, Estonia, Romania and Pakistan. SH23 Bangladesh, South Africa and Philippines.
7	Phase of trial.	Phase – 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.	Wastage and Damage %will be 25%: Active: 398 x 25% = 100; Total Import Quantity: 398 + 100 = 498 Placebo: 199 x 25% = 50; Total Import Quantity: 199 + 50 = 249 Comparator: 199 x 25% = 50; Total Import Quantity: 199 + 50 = 249
9	Site of the trial	Site(s) / PI/Co-PI Aga Khan University Hospital, Karachi / Dr Fatima Mir (National-PI) Shifa International Hospital, Islamabad. / Dr. Ejaz A. Khan, Site-PI Avicenna Medical college and Hospital, Lahore. / Dr. Aneela Zareen, Site-PI Central Park Teaching Hospital, Lahore. / Dr. Muhammad Fakharul Zaman, Site-PI Al-Shifa Trust Eye Hospital, Islamabad. / Dr. Ume Sughra, Site-PI

		Akram Medical Complex, Lahore. (Additional site subject to DRAP approval.) — Dr. Javed Akram, Site-PI National Hospital & Medical Centre Lahore - (Additional site subject to DRAP approval.) — Dr. Nadia Majeed, Site-PI
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB approval of following CTS are attached: i. IRB/ERC approval of AKUH, Karachi, dated 02nd August, 2022 for a period of one year is attached. (495-497/Corr.) ii. IRB/ERC approval of Al-Shifa Trust Eye Hospital, Rawalpindi, for a period of one year is attached. (503-512/Corr.) iii. IRB/ERC approval of Avicenna Medical College & Hospital, Lahore, for a period of one year is attached. (513-517/Corr.) iv. IRB/ERC approval of Central Park Hospital, Lahore, for a period of one year is attached. (518-521/Corr.) v. IRB/ERC approval of Shifa International Hospital Limited, Rawalpindi, for a period of one year is attached. (526-529/Corr.) vi. IRB/ERC approval of Akram Medical Complex, Lahore is attached. (498-502/Corr.) vii. IRB/ERC approval of National Hospital & Medical Center, Lahore, for a period of one year is attached. (522-525/Corr.)
11	Approval of National Bio-ethics Committee (NBC)	Provisional approval reference letter No.4-87/NBC-844/22/112, dated 04th August, 2022. * Final NBC approval need to be provided. (NBC approval reference letter No.4-87/NBC-844/22/, dated 25th August, 2022 is provided.)
12	CV's of the Investigators	CVs of following (PI & Co-PI) experts are attached. **xi.** Dr Fatima Mir (National-PI) AKUH, Karachi (391-418/Corr.) **xii.** Dr. Ejaz A. Khan (Shifa Int. Hospital) (421-441/Corr.) **xiii.** Dr. M. Fakharul Zaman (PI) (Central Park Teaching Hospital, Lahore) (442-444/Corr.) **xiv.** Prof. Dr. Ume Sughra (PI) (Al-Shifa Eye Trust Hospital, Rawalpindi) (445-459/Corr.) **xv.** Dr. Aneela Zareen (PI) (489-494/Corr.) **xvi.** Prof. Dr. Javed Akram (PI) Akram Medical Complex, Lahore (461-488/Corr.) (Additional site subject to DRAP approval.) **xvii.** Dr. Nadia Majeed (PI) (NH&MC, Lahore)(419-420/Corr.) (Additional site subject to DRAP approval.)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following manufacturer(s) are attached: xi. Seqirus Inc., 475 Green Oaks Parkway, Holly Springs, NC 27540, United States. xii. Seqirus Inc., Gaskill Road, Speke, Liverpool, L24 9GR, United Kingdom. xiii. Seqirus Netherlands B.V., Pasheuvelweg 28, Amsterdam, 1105BJ, Netherlands. xiv. Catalent Germany Schorndorf GmbH, Steinbeisstr, 1- 2, Schorndorf, Baden-Wuerttentberg,73614, Germany. xv. Catalent Pharma Solutions Inc., 10381 Decatur Road, Philadelphia, 19114, United States. xvi. CSL Behring GmbH, Emil-von-Behring-Straße 76, 35041, Marburg, Germany. CoPP of any product has net been provided.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Summary of IB for following IMPs are not provided; **iii.** Flucelvax Quadrivalent (QIVc) (Active). **iv.** IB of NeisVac-C (Comparator).

17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Number of patients enrolled at each site in Pakistan: **i.** Dr Fatima Mir (National-PI) AKUH, Karachi (86 Subjects) **ii.** Dr. Ejaz A. Khan (Shifa Int. Hospital) (57 Subjects) **iii.** Dr. M. Fakharul Zaman (PI) (Central Park Teaching Hospital, Lahore) (46 Subjects) **iv.** Prof. Dr. Ume Sughra (PI) (Al-Shifa Eye Trust Hospital, Rawalpindi) (57 Subjects) **v.** Dr. Anila Zareen (PI) (86 Subjects) **vi.** Prof. Dr. Javed Akram (PI) Akram Medical Complex, Lahore (26 Subjects.) (Additional site subject to DRAP approval.) **vii.** Dr. Nadia Majeed (PI) (NH&MC, Lahore) (40 Subjects.) Total 398 for Pakistan.
19	Name of Monitors & Clinical Research Associate	M/s IQVIA Solutions Pakistan (Pvt) Ltd., Karachi. • Sadia Altaf & Sadia Hashmi-Karachi. • Asjid Ali Arshad-Islamabad. • Mahir Ahmed & Muhammad Asif Mahmood-Lahore.
20	Evidence of registration in country of origin.	**Not provided.**
21	Copy of registration letter (if registered in Pakistan)	**Not applicable.**
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	Approximately 07 Months.
23	Undertaking on Stamp paper	Attached.

07. After initial scrutiny following shortcomings were recorded:

i. Original DRAP's copy of fee challan need to be provided.
ii. Provisional approval letter of NBC is attached but final NBC approval need to be provided.
iii. Investigator's Brochure for comparator NeisVac-C/Men C Vaccine (Comparator) is not provided.
iv. Summary of IB for both Flucelvax Quadrivalent (QIVc) (Active) & NeisVac-C/Men C Vaccine (Comparator) is not provided.
v. CoPP of any IMPs (i.e. Active, Placebo or Comparator) is not provided.
vi. NeisVac C is mentioned as comparator. Whereas in protocol Men C is mentioned as comparator. Clarify that, why there is difference in name of comparator.
vii. Evidence of registration in country of origin for Active & Comparator is not provided.
viii. Financing & Insurance details should be part of protocol as per ICH-GCP guidelines.

08. Accordingly, shortcomings communicated to Principal Investigator & nominated CRO for fulfillments vide letter bearing even number dated, 07th September, 2022.

09. Applicant/PI, Dr. Fatima Mir, submitted reply dated 26th September, 2022. Summary of submitted reply along with attachments is as follows:

Sr.	Descriptions / Shortcomings	Reply	Remarks
01	Original DRAP's copy of fee challan need to be provided.	Kindly see the attached original fee challan. Refer to **Index # 1**. (Page 908/Corr.)	---

02	Provisional approval letter of NBC is attached but final NBC approval need to be provided.	Kindly see the attached the NBC approval letter. Refer to **Index # 2.** (Page 910/Corr.)	NBC approval reference letter No.4-87/NBC-844/22/, dated 25th August, 2022 is provided.
03	Investigator's brochure for comparator NeisVac-C/Men C Vaccine (Comparator) is not provided.	Investigator's brochure for comparator NeisVac-C/Men C Vaccine cannot be provided as this is a registered product. Kindly see the attached SmPC for NeisVac-C/Men C Vaccine (including the marketing authorization holder details). Refer to **Index# 3**. (Page 911-919/Corr.)	---
04	Summary of IB for both Flucelvax Quadrivalent (QIVc) (Active) & NeisVac-C/Men C Vaccine (Comparator) is not provided.	• Summary of IB for Flucelvax Quadrivalent (QIVc) already shared. IB for Flucelvax Quadrivalent (QIVc) (IP) attached again for your reference. Refer to Index # 4.1 • The SmPC (Refer to Index # 3), QP, and CoA for NeisVac-C/Men C Vaccine. Refer to Index # 4.2. (Page 911 & 932/Corr.)	---
05	CoPP of any IMPs (i.e. Active, Placebo or comparator) is not provided.	Kindly see the attached GMP as the sponsor is unable to provide the CoPP. Refer to Index # 5. (Page 933-934/Corr.)	i. Catalent Pharma Solution Inc., 10381 Decatur Road, Philadelphia, 19114, United States. (933-934/Corr.) ii. CSL Behring GmbH, Emil-von-Behring-Straße 76, 35041, Marburg, Germany. (935-940/Corr.) iii. Seqirus Netherlands B.V., Pasheuvelweg 28, Amsterdam, 1105BJ, Netherlands. (941-943/Corr.) iv. Catalent Germany Schorndorf GmbH, Steinbeisstr. 1-2, Schorndorf, Baden-Wuerttemberg, 73614, Germany. (944-946/Corr.) v. Seqirus Vaccines Limited, Gaskill Road, Speke, Liverpool, L24 9GR, United Kingdom. (947-951/Corr.) vi. Seqirus Inc., 475 Green Oaks Pakway, Holly Springs, NC, 27540-7976, United States. (952-953/Corr.)
06	NeisVac-C is mentioned as comparator. Whereas in protocol Men-C is mentioned as comparator. Clarify that, why there is difference in name of comparator.	Men-C vaccine and Neisvsc-C are one and the same. Men-C vaccine is the generic name while, Neisvac-C® is the brand name manufactured by Pfizer. Please refer to page 9 & 10 of the protocol for clarity on the matter as it states: "the non-influenza vaccine is a conjugate vaccine for prevention of invasive disease caused by Neisseria meningitides sero group C (MenC vaccine)." "Men-C vaccine (Neisvac-C®, Pfizer)"	---
07	Evidence of registration in country of origin for Active & Comparator is not provided.	• Kindly see the attached the evidence registration of the Flucelvax Quadrivalent (QIVc) (IP). Refer to Index # 6.	---

		• Refer to Index # 3 for the marketing authorization holder details (market authorization number by Pfizer healthcare Ireland: PA0822/183/001) in SmPC for NeisVac-C/Men C Vaccine (Comparator).	
08	Financing & Insurance details should be part of protocol as per ICH-GCP guidelines.	As per ICH GCP E6 (R2) guidelines section 5.9 outlines that, "The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution." Hence, the Finance and insurance are separate documents as a multicenter study. Kindly see the attached the Insurance documents. Refer to Index # 7.	Insurance documents attached (957-974/Corr.)

10. As applicant submitted reply for all shortcomings so the application is complete.

11. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to approve the Clinical Trial titled, "A Phase-III, Randomized, Observer-Blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus-Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine When Administered in Healthy Subjects Aged 6 Months through 47 Months (SEQIRUS)", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s):

Clinical Trial Site(s)	**PI/Co-PI**
Aga Khan University Hospital, Karachi	Dr. Fatima Mir (National-PI)
Shifa International Hospital, Islamabad.	Dr. Ejaz A. Khan, Site-PI
Avicenna Medical college and Hospital, Lahore.	Dr. Aneela Zareen, Site-PI
Central Park Teaching Hospital, Lahore.	Dr. Muhammad Fakharul Zaman, Site-PI
Al-Shifa Trust Eye Hospital, Islamabad.	Dr. Ume Sughra, Site-PI

AGENDA ITEM XVI:

APPLICATION FOR LICENSE TO ACT AS BIO ANALYTICAL LAB AT INSTITUTE OF BIOLOGICAL BIOCHEMICAL & PHARMACEUTICAL SCIENCES (IBBPS), AT DOW UNIVERSITY OF HEALTH SCIENCES, KARACHI. F. No.15-15/2019-DD (PS)

Application was from Dr. Sadia Asim, Director, Institute of Biological, Biochemical & Pharmaceutical Sciences (IBBPS), At Dow University of Health Sciences, Karachi, dated 26th April, 2019, wherein the request has been made to license their firm with DRAP to act as a Bio Analytical Laboratory, on prescribed Form-I of the Bio-Study Rules 2017, with fee OF Rs.300000/- submitted Vide challan no. 1932881.

02. It is submitted that application evaluated according prerequisites as mentioned in Form-I of the Bio-Study Rules 2017:

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.	Attached.
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.	Attached
	Fee	Attached
	Undertaking	Attached

03. Chairman CSC/Director Pharmacy Services nominated following panel for inspection of Contract Research Organization (CRO) & Bioanalytical Laboratory at M/s Institute of Biological, Biochemical & Pharmaceutical Sciences (IBBPS), At Dow University of Health Sciences, Karachi.:

i.	**Dr. Abdur Rashid** Chairman CSC/Director, Division of Pharmacy Services-DRAP.
ii.	**Prof. Dr. Nisar Hussain Shah** Dean Faculty of Pharmacy, Bahauddin Zakariya University, Multan
iii.	**Prof. Dr. Ali Jawa** University of Health Sciences, Lahore.
iv.	**Dr. Farhana Badar** Biostatistician, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.
v.	**Shafqat Hussain Danish** Assistant Director-DRAP.

04. Chairman CSC/Director Pharmacy Services scheduled the inspection on 9th & 10th November 2020 & also informed that after above inspections, panel will also visit M/s Indus Hospital, Karachi, to verify progress of ongoing clinical trials at the site.

05. Due to some concerns panel revised by the then Chairman CSC.

06. Reference to discussion & informal meeting carried out in the office of Director Pharmacy Services, between Director (PS) & representatives (Dr. Sadia Asim & others) of IBBPS, Dow University of Health Sciences, Ojha Campus, Karachi on 20th June 2022.

07. Matter regarding prerequisites of Form-IIA of the Bio-Study Rules, 2017, specifically requirement of GMP & CoPP Certificate for reference product discussed in detail. Further, Dr. Sadia Asim, Director, IBBPS, DUHS, Karachi claimed that, their application for Bio-Analytical Laboratory is still pending.

08. Director (PS)/Chairman CSC desired to forward the case details for further deliberations. Accordingly, brief regarding application is as follows:

- Application received on 26th April, 2019
- After initial evaluation shortcoming letter was issued on 04th July, 2019
- Applicant submitted reply on 09th July, 2019
- Application placed before CSC in its 5th Meeting held on 08th August 2019 and it was decided that, the inspection panel constituted for BA/BE Studies also inspect Bio-Analytical Laboratory. (Minutes attached at Page 84/Corr.)
  "The CSC after deliberation, deferred the case & decided that the panel constituted for BA/BE Centre with also inspect the Bio Analytical Laboratory."

- After re-evaluation & approval inspection letter issued on 26th August 2019
- Applicant submitted letter for readiness for inspection on 28th September 2020
- Applicant forwarded letter on 29th September to withdraw the letter submitted on 28th September 2020 for readiness for inspection.

- Inspection panel again constituted & letter issued on 23rd October 2020 & due to unavailability of some panel members Chairman CSC again constituted the panel & letter issued on 08th December 2020.
- Till date inspection panel haven't submitted inspection report & neither applicant submitted any application for inspection.

09. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation deferred the case. The Division of Pharmacy Services, will coordinate with the applicant for readiness for inspection of applied Bio-Analytical Laboratory.

Further, applicant is directed to submit the response within 30 days positively, afterwhich the Chairman CSC will nominate experts for inspection as powers delegated by the Committee and if the applicant fails to reply within 30 days the application will be liable for rejection.

AGENDA ITEM XVII:

REQUEST FOR ISSUANCE OF LICENCE TO ACT AS CRO AT M/S TRUST FOR VACCINE & IMMUNIZATION, KARACHI. F. No.15-05/2022 DD (PS)

Application submitted by Dr. Zamir Hussain Suhag (CNIC:41306-5785631-9), Director - Technical, M/s Trust for Vaccines & Immunization, situated at Suite #301, 3rd floor, Al-Sehat Centre, Adjacent to Regent Plaza Hotel, Rafiqui Shaheed Road, Karachi, dated 07th March 2022, received on 15th March 2022. Wherein the request has been made to license their firm with DRAP to act as Clinical Research Organization (CRO), the application is on prescribed Form-I of the Bio-Study Rules 2017 without prescribed processing fee of Rs.300000/-.

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

S. No.	Required Documents / Information	Page No.	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	02-03	Attached
2	Fee	---	Prescribed processing fee of Rs.300000/- is not provided.
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).	10 - 30	• FBR Certificate with NTN number 3553904-6, dated 16th May 2010. • Trust Deed • Certificate from Sub. Registrar under Trust Act 1882.
4	Details of premises including layout plan of the site.	---	Not provided.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	--	Not applicable as applied for CRO.
6	Names and qualifications of the above sections along with their staff.	---	Not provided.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	--	Not applicable as applied for CRO.
8	Undertaking on stamp paper	---	Not provided.

03. After initial scrutiny following shortcomings were observed:

i. Prescribed processing fee of Rs.300000/-, notified vide S.R.O. 1047(I)/2019 dated 12th September 2019, is not provided. (Copy attached).
ii. Details of premises including layout plan of the site of the CRO is not provided.
iii. Names and qualifications of the requisite sections for CRO along with their staff is not provided. (Copy attached).
iv. Undertaking on stamp paper is not provided.

04. Accordingly, shortcomings were shared vide letter bearing even number dated 29th March, 2022. Applicant, Dr. Zamir Hussain Suhag, submitted reply dated 06th July, 2022. Applicant provided following requisite documents:

i. Prescribed processing fee of Rs.300000/-, deposited vide challan no. 55951330942, dated 09th June, 2022.
ii. Layout plan of the proposed site for subject CRO.
iii. Names and qualifications of the staff/officials of requisite sections required to work as a CRO.
iv. Undertaking on stamp paper.

05. Accordingly, Chairman CSC/Director constituted following expert panel for inspection, to verify the facilities available at proposed site & its feasibility to act as CRO.

i.	**Dr. Ahson Siddiqui,** CEO, Sindh Health Care Commission, Karachi.
ii.	**Dr. Awais Ahmed Juno**, Ph.D. Pharmacy Practice, Assistant Director, CDL-Karachi.
iii.	**Area F.I.D, Karachi.**

06 Inspection panel report is awaited.

087. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation deferred the case as inspection panel report is awaited.

Further, it was decided, in case of unavailability of any member the Chairman CSC will re-nominate another expert for inspection as powers delegated by the Committee.

AGENDA ITEM XVIII:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "FINDING TREATMENTS FOR COVID-19: A PHASE-II, MULTI-CENTRE, ADAPTIVE PLATFORM TRIAL TO ASSESS ANTIVIRAL PHARMACODYNAMICS IN EARLY SYMPTOMATIC COVID-19 (PLATCOV)", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-18/2022-PS (CT)

Application was submitted by Dr. Muhammad Asim Beg (CNIC: 42201-0543067-7), Principal Investigator PLATCOV Study, Professor and Consultant Parasitologist, Institutional Lead for APMEN, Former Chair Hospital Ethics Committee, Department of Pathology & Microbiology, Aga Khan University Hospital, Stadium Road, Karachi dated 15th September, 2022, wherein request has been made for approval of subject Phase-II Clinical Trial, which will be carried out at Aga Khan University Hospital, Karachi. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide challan no. 374049140, dated 24th August, 2022. The trial is also enlisted on U.S National Trial Registry with identification number ***NCT05041907*** (https://www.clinicaltrials.gov/ct2/show/NCT05041907)

02. The details regarding trial, sponsor & responsible party is as under:

i. **Sponsor/Responsible Party:** University of Oxford, UK.
ii. **Funded by:** Wellcome Trust Grant ref :223195/Z/21/Z through the COVID-19 Therapeutics Accelerator.
iii. **Contact information:** William Schilling, MD +662 203 6333 william@tropmedres.ac
Prof. Nicholas J White, +662 203 6333 nickw@tropmedres.ac

iv. **Brief Summary:**

The trial will develop and validate a platform for quantitative assessment of antiviral effects in low-risk patients with high viral burdens and uncomplicated
COVID-19 to determine in-vivo antiviral activity. In this randomized open label, controlled, group sequential adaptive platform trial, we will assess the performance of three distinct types of intervention relative to control (no treatment):
A: Newly available and repurposed potential antiviral drugs;
B: Positive control: monoclonal antibodies initially but subsequently any therapeutic that is shown to accelerate the rate of viral clearance C: Novel small molecule drugs that have gone through phase 1 testing
PLATCOV study is supported by the Wellcome Trust Grant ref: 223195/Z/21/Z through the COVID-19 Therapeutics Accelerator.

v. **Study Description:**

Condition or Disease	Intervention/Treatment	Phase
COVID-19	1. Favipiravir (200 mg tablet) (Trade Name: FAVUZA) 2. Nitazoxanide (500 mg tablet) (Trade Name: IZATO) 3. Molnupravir (200 mg Capsule) (Trade Name: MONUVIR) 4. Nirmatrevir/ritonavir (Nirmatrevir 150 mg tablet; Ritonavir: 100 mg tablet) (Trade Name: PAXOVIR) 5. Fluoxetine (20 mg tablet) (Trade Name: FLUX) 6. Ensitrelvir (Each tablet contains Ensitrelvir fumaric acid 125 mg). 7. B REGN-COV2 (600 mg Casirivimab/600 mg Imdevimab) 8. Sotrovimab (500 mg /8 ml) 9. A combination of Molnupiravir and Nirmatrevir/ritonavir (Trade Name: MONUVIR and PAXOVIR) L0. Evusheld (150 mg of the tixagevimab and 150 mg of the Cligavimab)	Phase-II

vi. **Arms & Interventions:**

Arms	Intervention/treatment
Active Comparator: Positive control (monoclonals)	Drug: Monoclonal antibodies Monoclonal antibodies: 600mg casirivimab/ 600mg imdevimab given once on D0
Experimental: Favipiravir	Drug: Favipiravir Favipiravir 1800mg BD D0 and 800mg BD for a further 6/7.
Experimental: Ivermectin [This arm is now closed to recruitment]	Drug: Ivermectin Ivermectin 600micrograms/kg/day for 7/7.
Experimental: Remdesivir [This arm is now closed to recruitment]	Drug: Remdesivir Remdesivir 200mg D0 and 100mg for a further 4/7.
Negative control group	Other: No treatment No treatment (except antipyretics- paracetamol)
Experimental: Fluoxetine	Drug: Fluoxetine Fluoxetine 40mg OD for 7/7
Experimental: Molnupiravir	Drug: Molnupiravir Molnupiravir 800mg BD for 5/7
Experimental: Nirmatrelvir/ritonavir (e.g. PAXLOVID™)	Drug: Nirmatrelvir/ritonavir (e.g. PAXLOVID™) Nirmatrelvir 300mg BD for 5/7 Ritonavir 100mg BD for 5/7
Experimental: Nitazoxanide	Drug: Nitazoxanide Nitazoxanide 1.5g BD 7/7

vii. **Purpose of trial:** The purpose of this study is to evaluate, Quantitative evidence of antiviral activity in patients with COVID-19 is required to justify phase III clinical trials of putative antivirals

There are many potential therapeutics for COVID- 19 and a much larger number of vaccines are in development. Vaccines are the solution but there are concerns over incomplete protection, vaccine hesitancy and waning protective effects over time. Many people over the next 2-3 years will get COVID-19 with substantial morbidity

and hundreds of thousands of deaths. For all these reasons effective therapeutics are needed urgently. There is no optimised or validated approach to assess rapidly potential antiviral therapeutics in COVID-19. Drugs are currently selected for clinical study based on activity in cell culture systems (in-vitro) and animal models in-vivo. Unfortunately, the animal models are not sufficiently good to be included in the drug development critical pathway. In order to identity effective antivirals and optimise their dosing. phase 3 studies must be designed appropriately. and progress is as rapid as possible, in vivo antiviral effects must be characterized adequately. This can be achieved in natural COVID-19 infections at an early stage of the disease using the following design.

The proposed trial will develop and validate a platform for quantitative assessment of antiviral effects in low-risk patients with high viral burdens and uncomplicated COVID- 19.

In this randomised open label. controlled. group sequential adaptive platform trial. we will assess the performance of three distinct types of intervention relative to control (no treatment):

A: Newly available and repurposed antiviral drugs; and if available:
B: "Positive control" (e.g., monoclonal antibodies); and later:
C: Small molecule drugs that pass phase 1 testing.

viii. **Trial Monitoring:**

There will be no designated monitor or clinical research associate, however sponsor will do central monitoring of the data entered in defined software. Moreover, an independent Data Safety and Monitoring Board (DSMB) will be set up consisting of qualified volunteers with the necessary knowledge of clinical trials. The DSMB will receive summary reports from MORU as defined per charter or per ad-hoc request, prior to each meeting. An interim report will be prepared by the Trial Statistician for the pre-specified interim analysis. In case of safety concerns, additional information or formal interim analyses can be requested by the DSMB.

The DSMB will meet formally at the following time points:

- Before the study starts
- After the first 50 patients have been accrued into the study (10 per arm)
- At additional time-points as indicated by the DSMB after their review, if deemed necessary.

All DSMB recommendations will be communicated to site PIs. The site PI will be responsible for submitting the written DSMB summary reports with recommendations as applicable to local/national ethics committees and other applicable groups.

ix. **Number of subjects to be recruited:** **1500** Subjects (Globally)

x. **Anticipated cost of the project: Not provided**

xi. **Study design & details:**

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	**1500** participants (Globally) **250** Subjects from Pakistan.
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open label)
Primary Purpose:	Treatment
Official Title:	Finding Treatments for COVID-19: A Phase 2 Multi-centre Adaptive Platform Trial to Assess Antiviral Pharmacodynamics in Early Symptomatic COVID-19 (PLATCOV)
Estimated Study Start Date :	30th September, 20212
Estimated Primary Completion Date :	August, 2024
Estimated Study Completion Date :	August, 2024

03. The study carried out under the supervision of Dr. Muhammad Asim Beg (PI). The trial comprises of following objective(s);

Primary Outcome Measures:

i. Rate of viral clearance for newly available and repurposed drugs [Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for each newly available and repurposed drug compared with the no antiviral treatment control i.e. those not receiving study drug

ii. Rate of viral clearance for positive controls (e.g. monoclonal antibodies) [Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for positive controls (e.g. monoclonal antibodies) compared with the no antiviral treatment control i.e. those not receiving study drug

iii. Rate of viral clearance for small novel molecule drugs [Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for small novel molecule drugs compared with the no antiviral treatment control i.e. those not receiving study drug

Secondary Outcome Measures:

i. Viral kinetic levels in early COVID-19 disease [Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for each therapeutic arm compared with the no antiviral treatment control i.e. those not receiving study drug

ii. Number of antiviral treatment arms that are shown to be effective i.e. a positive signal (>90% probability of >12.5% acceleration in viral clearance) [Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for each therapeutic arm compared with the no antiviral treatment control i.e. those not receiving study drug

iii. Rates of viral clearance by treatment arm, as compared against REGN-COV2 (monoclonal antibody cocktail) monoclonal antibody cocktail) or other licensed and available therapeutics with evidence of accelerated viral clearance (monoclonal antibody cocktail) [Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for each therapeutic arm compared with positive control (e.g. REGN-COV-2 a monoclonal antibody cocktail) or other licensed and available therapeutics with evidence of accelerated viral clearance.

Other Outcome Measures:

i. Rates of hospitalisation by treatment arm (hospitalisation for clinical reasons) [Time Frame: Days 0-28]
Number of hospitalisations up to Day 28 in a treatment arm with an increased rate of viral clearance compared with the negative control i.e. patients not receiving study drug.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed processing fee	Rs. 200,000/- deposited vide challan no. 374049140, dated 24th August, 2022
3	Investigator Brochure (s)	**PIL** of following approved products IMPs are attached:

		vi. Paxovir (Nirmatrevir 150 mg & Ritonavir: 100 mg) Tablets (17/Corr.) **vii.** Monuvir (Molnupravir) Capsules Mfg:by ESKYEF Pharma Bangladesh (18/Corr.). **viii.** FAVUZA (Favipiravir 200 mg) Mfg:by Sami Pharma, Pakistan (19/Corr.) **ix.** Izato (Nitazoxanide) 500 mg tablet Mfg:by Sami Pharma, Pakistan (21/Corr.) **x.** Flux (Fluoxetine 20 mg tablet) Mfg: By Hilton Pharma, Pakistan. (22-23/Corr.) **xi.** Xocova (Ensitrelvir fumaric acid 125 mg) Tablets Mfg: By Shionogi & Co., Ltd. Japan (24-30/Corr.) **xii.** Xevudy (Sotrovimab) 500 mg /8 ml concentrated solution for infusion Mfg: By GlaxoSmithKline, UK (208-217/Corr.) **Investigators Brochure** of following IMPs is attached: i. S-217622, Mfg: By Shionogi Inc., USA. (31-207/Corr.) * IB/PIL of following IMPs are not provided. i. Hydroxychloroquine ii. Remdesivir iii. Lopinavir/Ritonavir iv. Miglustat v. Ivermectin vi. REGN-COV2 with Casirivimab & Imdevimab) vii. Nebulized Unfractionated Heparin viii. Fluvoxamine ix. AZD7442 (Evusheld) ** Clarification required that, why different origin IMPs are utilized in a MRCT. *** There is a difference between IMPs mentioned on US Trial registry, Trial protocol & IMPs used in Pakistan for a same study. Clarification required.
4	Final protocol	Attached Protocol No. VIR21001 Version 0.3, dated 23rd August, 2022
5	Informed consent and participant information sheet (Urdu to English)	Attached.
6	List of participating countries	Thailand, Brazil, Laos & Pakistan. * Some are unconfirmed sites.
7	Phase of trial.	Phase – II * As the site has no Bioanalytical facilities, so clarification regarding PK/PD Assay need to be submitted that, where theses assay/tests will be conducted
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.	The approximate required quantity of each IMPs will be as follows: i. FAVUZA (Favipiravir 200 mg tablet) Total 3960 Tablets ii. IZATO (Nitazoxanide 500 mg tablet) Total 2520 tablets iii. MONUVIR (Molnupravir 200 mg Capsule) Total 2400 capsules

		iv. Nirmatrevir/ritonavir (Nirmatrevir: 150 mg tablet; Ritonavir: 100 mg tablet) a. Nirmatrevir: Total 1200 tablets b. Ritonavir: Total 600 tablets v. Fluoxetine (20 mg Flux tablet) Total 840 Tablets vi. Ensitrelvir (Each tablet contains Ensitrelvir fumaric acid 125 mg) Total 420 Tablets vii. B REGN-COV2 (600 mg Casirivimab/600 mg Imdevimab) Total 60 vials viii. Sotrovimab (500 mg/8 ml) Total 60 vials ix. A combination of Molnupiravir and Nirmatrevir/ritonavir a. Molnupiravir: Total 2400 tablets b. Nirmatrevir: Total 1200 c. Ritonavir: Total 600 tablets x. Evusheld (150 mg of the tixagevimab and 150 mg of the Cligavimab) Total 120 vials
9	Site of the trial	M/s Aga Khan University Hospital, Karachi. * As the site has no Bioanalytical facilities, so clarification regarding PK/PD Assay need to be submitted that, where theses assay/tests will be conducted
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	AKUH IRB/ERC approval, dated 05th August, 2022 for a period of **one year** (w.e.f.05-Aug-2022) is attached. Amendment letter issued on 09th September, 2022 is also attached.
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No. 4-87/COVID-111/22/123, dated 10th August, 2022 (for a period of **Six** months). Approval of amendment reference letter No. 4-87/COVID-111/22/331, dated 15th September, 2022 (for a period of **Six** months) is also attached.
12	CV's of the Investigators	CVs of following experts are attached. **xviii.** Dr. Muhammad Asim Beg (PI) (AKUH)(308-337/Corr.) **xix.** Dr. Farah Naz Qamar (Co-PI) (400-412/Corr.) **xx.** Dr. Abdul Momin Kazi (Co-PI) (358-383/Corr.) **xxi.** Dr. Syed Faisal Mahmood (Co-Investigator) (338-347/Corr.) **xxii.** Dr. Najia Bano Ghanchi (Ph.D. Biotechnology) (Co-Investigator) (384-398/Corr.) **xxiii.** Dr. Aisha Ilyas (Co-Investigator) (414-416/Corr.) **xxiv.** Dr. Junaid Iqbal (Ph.D. Microbiology) (Co-Investigator) (348-357/Corr.)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following manufacturer(s) are attached: i. M/s SAMI Pharmaceuticals (Pvt.) Ltd., Karachi. ii. M/s ESKAYEF Pharmaceuticals Ltd., Gazipur, Bangladesh iii. M/s Hilton Pharma (Pvt.) Ltd., Karachi. iv. M/s Shionogi Pharma Co., Ltd., Osaka, Japan (For S-217622 IMPs) CoPP/ Registration Certificates of following manufacturer(s) are provided:

		v. FAVUZA (Favipiravir 200mg) Tablets. vi. IZATO (Nitazoxanide 500mg) Tablets. vii. MONUVIR (Molnupravir 200 mg) Capsule (CoPP for Ukraine is attached) viii. PAXOVIR (Nirmatrevir150 mg) tablet (CoPP for Ukraine is attached) ix. FLUX (Fluoxetine 20 mg) Total 840 Tablets (Registration letter of FLUX 20mg Capsules is attached instead of Tablets) x. B REGN-COV2 (600 mg Casirivimab/600 mg Imdevimab) Total 60 vials (CoPP attached for 300mg+300mg single dose vial instead of 600+600mg) COA is attached for following: xi. S-217622 IMPs GMP Certificate of following are not provided: i. M/s Roche Registration GmbH, Germany. ii. M/s GENENTECH Inc., Hillsboro, Oregon, USA. iii. Manufacturer of Ritonavir 100mg tablet iv. Manufacturer of Ensitrelvir fumaric acid 125 mg v. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion vi. Any other manufacturer whom IMPs details not attached with dossier. CoPP of the following are not provided: i. Ritonavir 100mg tablet ii. Ensitrelvir fumaric acid 125 mg iii. Sotrovimab (500 mg/8 ml) Infusion iv. Evusheld Tixagevimab 150mg & Cligavimab 150mg) v. CoPP of other IMPs, which is not included in the list with dossier.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Not provided.
17	Adverse Event Reporting Form	ADR reporting form as per CIOMS is not provided.
18	No of patients to be enrolled in each center.	250 subjects from Pakistan 1250 subjects from Brazil, Thailand, Laos & other two countries (Yet unconfirmed) Total 1500 Subjects (Globally).
19	Name of Monitors & Clinical Research Associate	There will be no designated monitor or clinical research associate, however sponsor will do central monitoring of the data entered in defined software. Moreover, an independent Data Safety and Monitoring Board (DSMB) will be set up consisting of qualified volunteers with the necessary knowledge of clinical trials.
20	Evidence of registration in country of origin.	Registration Certificates/CoPP of following product(s)/manufacturer(s) are attached: **i.** FAVUZA (Favipiravir 200 mg) Mfg:by Sami Pharma, Pakistan (578 & 583/Corr.)

		ii. Izato (Nitazoxanide) 500 mg tablet Mfg:by Sami Pharma, Pakistan (579/Corr.) **iii.** Monuvir (Molnupravir) Capsules Mfg:by ESKYEF Pharma Bangladesh (587-588/Corr.). **iv.** Flux (Fluoxetine 20 mg tablet) Mfg: By Hilton Pharma, Pakistan. (596-597/Corr.) **v.** Paxovir (Nirmatrevir 150 mg & Ritonavir: 100 mg) Tablets Mfg:by ESKYEF Pharma Bangladesh (602-603/Corr.). **vi.** Ronapreve (Casirivimab/Imdevimab 300mg/300mg) 1 Single Dose Vial + 1 Single Dose Vial, Solution for Injection / Infusion Mfg:by Hoffmann-La Roche Ltd., Switzerland. (617-641/Corr.). * It need to be clarified that, as it is a MRCT so why IMPs from different origin are utilized at different international Clinical trial Site(s)
21	Copy of registration letter (if registered in Pakistan)	Registration Certificates/CoPP of following product(s)/manufacturer(s) are attached: **i.** FAVUZA (Favipiravir 200 mg) Mfg:by Sami Pharma, Pakistan (578 & 583/Corr.) **ii.** Izato (Nitazoxanide) 500 mg tablet Mfg:by Sami Pharma, Pakistan (579/Corr.) **iii.** Monuvir (Molnupravir) Capsules Mfg:by ESKYEF Pharma Bangladesh (587-588/Corr.). **iv.** Flux (Fluoxetine 20 mg tablet) Mfg: By Hilton Pharma, Pakistan. (596-597/Corr.) * It need to be clarified that, as it is a MRCT so why IMPs from different origin are utilized at different international Clinical trial Site(s)
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	Approximately 03 Years & 28 Days for individual patient involvement.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings were recorded:

i. There is a difference in IMPs mentioned in application, US Trial Registry & in the protocol. Clarification required.
ii. Anticipated cost of the project is not mentioned.
iii. The IMPs (S-217622, Manufactured by Shionogi Inc., USA) is not part of the intervention mentioned in attached protocol. Attached protocol is for AZD7442 (Evusheld). Clarification need to be provided.
iv. Investigator's Brochure / PIL (for registered products) of following IMPs are not provided.

   a. Hydroxychloroquine
   b. Remdesivir
   c. Lopinavir/Ritonavir
   d. Miglustat
   e. Ivermectin
   f. REGN-COV2 with Casirivimab & Imdevimab)
   g. Nebulized Unfractionated Heparin
   h. Fluvoxamine
   i. AZD7442 (Evusheld)

v. Clarification required that, why different origin IMPs are utilized in a Multi-Regional Clinical Trial (MRCT).
vi. There is a difference between IMPs mentioned on US Trial registry, Trial protocol & IMPs used in Pakistan for a same study. Clarification required.
vii. Proposed Clinical Trial Site has no Bioanalytical facilities, so clarification regarding PK/PD Assay (as required in Phase-II CT) need to be submitted that, where theses assay/tests will be conducted.

viii. GMP Certificate of following are not provided:

a. M/s Roche Registration GmbH, Germany.
b. M/s GENENTECH Inc., Hillsboro, Oregon, USA.
c. Manufacturer of Ritonavir 100mg tablet
d. Manufacturer of Ensitrelvir fumaric acid 125 mg
e. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion
f. Any other manufacturer whom IMPs details not attached with dossier.

ix. CoPP of the following are not provided:

a. Ritonavir 100mg tablet
b. Ensitrelvir fumaric acid 125 mg
c. Sotrovimab (500 mg/8 ml) Infusion
d. Evusheld Tixagevimab 150mg & Cligavimab 150mg)
e. CoPP of other IMPs, which is not included in the list with dossier.

x. ADR reporting form as per CIOMS is not provided.
xi. It need to be clarified that, as it is a MRCT so why IMPs from different origin are utilized at different international Clinical Trial Site(s).

06. In the view of above, shortcomings communicated vide letter bearing even number dated 12th October, 2022, response is awaited.

07. Secretary CSC presented the case before the Committee. The expert members, Prof. Munawar Alam Ansari & Prof. Fazel e Subhan, expressed their concerns regarding the title & scope of the trial with respect to the term "Pharmacodynamics".

09. Dr. Muhammad Asim Beg (PI) (who joined the meeting through Zoom) responded to the questions raised during the discussion.

10. As a result the Committee of Experts advised the PI for revision of trial subject & its scope in regard to "Pharmacodynamics", as it's a very broad term & need to be more specific.

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of following shortcomings as per Form-II of the Bio-Study Rules, 2017:

i. There is a difference in IMPs mentioned in application, US Trial Registry & in the protocol. Clarification required.
ii. Anticipated cost of the project is not mentioned.
iii. The IMPs (S-217622, Manufactured by Shionogi Inc., USA) is not part of the intervention mentioned in attached protocol. Attached protocol is for AZD7442 (Evusheld). Clarification need to be provided.
iv. Investigator's Brochure / PIL (for registered products) of following IMPs are not provided.

a. Hydroxychloroquine
b. Remdesivir
c. Lopinavir/Ritonavir
d. Miglustat
e. Ivermectin
f. REGN-COV2 with Casirivimab & Imdevimab)
g. Nebulized Unfractionated Heparin
h. Fluvoxamine
i. AZD7442 (Evusheld)

v. Clarification required that, why different origin IMPs are utilized in a Multi-Regional Clinical Trial (MRCT).
vi. There is a difference between IMPs mentioned on US Trial registry, Trial protocol & IMPs used in Pakistan for the same study. Clarification is therefore required.

vii. Proposed Clinical Trial Site has no Bioanalytical facilities, so clarification regarding PK/PD Assay (as required in Phase-II CT) need to be submitted that, where theses assay/tests will be conducted.

viii. GMP Certificate of following are not provided:

a. M/s Roche Registration GmbH, Germany.
b. M/s GENENTECH Inc., Hillsboro, Oregon, USA.
c. Manufacturer of Ritonavir 100mg tablet
d. Manufacturer of Ensitrelvir fumaric acid 125 mg
e. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion
f. Any other manufacturer whom IMPs details not attached with dossier.

ix. CoPP of the following are not provided:

f. Ritonavir 100mg tablet
g. Ensitrelvir fumaric acid 125 mg
h. Sotrovimab (500 mg/8 ml) Infusion
i. Evusheld Tixagevimab 150mg & Cligavimab 150mg)
j. CoPP of other IMPs, which is not included in the list with dossier.

x. ADR reporting form as per CIOMS is not provided.

xi. It need to be clarified that, as it is a MRCT so why IMPs from different origin are utilized at different international Clinical Trial Site(s).

The applicant is directed to reply within 30 days positively.

AGENDA ITEM XIX:

REQUEST FOR APPROVAL OF CLINICAL TRIAL UNIT (CTU) AT ZIAUDDIN UNIVERSITV. CLIFTON CAMPUS, KARACHI. TO CONDUCT CLINICAL RESEARCH AT DR. ZIAUDDIN HOSPITAL. CLIFTON CAMPUS. KARACHI". F. No.15-13/2022-DD (PS)

Application submitted by Dr. Nida Hussain, Pro-Chancellor & CEO of CTU, Ziauddin University, Clifton Campus, Karachi dated 08th June 2022. Wherein the request has been made to license their firm with DRAP to act as Clinical Trial Unit/Clinical Trial Site, the application is on prescribed Form-I of the Bio-Study Rules, 2017 with prescribed processing fee of Rs.100000/-, paid vide challan number 397123528200, dated 06th June 2022.

02. After initial scrutiny summary of the application & attached documents is as follows:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached.
2	Prescribed processing fee	Rs.100000/- paid vide challan no. 397123528200, dated 06th June 2022.
3	Particulars regarding the legal status of the applicant i.e. in the case of proprietorship the names of proprietors and their addresses, in the case of a 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.	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.	Attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling, etc.	Attached.
8	Undertaking on stamp paper	Attached.

03. It is submitted that, constitution of inspection panel is prerogative of the CSC under 13 (3) (c) of the Bio-Study Rules, 2017, reproduced as under:

> *"Inspection of the premises prior to grant of license, approval of clinical trial, BA or BE study and during and after the completion of the trial or study, if so desired, by a panel constituted by the CSC and any co-opted member under sub-rule (6) of rule 13, any site where clinical trial and BA or BE study is planned to be conducted, to satisfy itself of the observance of, conditions, guidelines or criteria as notified by the DRAP;".*

04. Re-nomination of CSC & its notification is under process. Whereas previously notified CSC delegated (Minutes of 2nd, 6th & 7th CSC meeting are attached) its power of inspection panel constitution to the Chairman CSC/Director Pharmacy Services Division, to save time & to lower the work burden on the Committee.

05. Refer to pre-paras it was proposed that, the Director Pharmacy Services/Chairman CSC may constitute experts' panel for inspection of CTU, Ziauddin University, Clifton Campus, Karachi for verification of facilities available at the CTU/CTS to carry out Phase-III & IV Clinical Trials as per the Bio-Study Rules, 2017 & ICH-GCP guidelines.

06. Accordingly, following expert panel was constituted by Chairman CSC:

i. Chairman/ Secretary CSC
ii. Dr. Aamir Jaffary, SIUT, Karachi
iii. Dr. Ahson Siddiqui, CEO, Sindh Health Care Commission, Karachi.
iv. Dr. Saif Ur Rehman Khattak
v. Area FIDs

07. Inspection panel coordinator forwarded report on 30th September, 2022, in reference to this Division's letter even number dated 09th June, 2022.

08. Nominated Experts panel inspected the subject site on 04th September, 2022 & submitted inspection report with following remarks:

The CTU has the basic infrastructure with detailed organogram, trained and competent staff, adequate system of documentation, organized data management system, secured storage of material and retention/ archiving of related records. Some minor observations have also been noted which have been discussed with the management for rectifications as continuous improvement.

Keeping in view the overall arrangements and facilities provided by the management of the CTU, the inspection team recommends for approval of the CTU by the CSC.

- **Remarks of the Inspecting Panel: Recommended for approval**

09. Before discussion of the subject application, Dr. Mirza Tasawer Baig, Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi & Clinical Pharmacist at Dr. Ziauddin Hospital, Karachi, left the committee room for decision of the instant case, to avaoid impact of affiliation with his parent department or any conflict of interest.

10. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after discussion in the light of inspection report of the Panel of Experts and its recommendation decided to approve "M/s Ziauddin University Hospital, Clifton Campus, Karachi, Sindh, to act as Clinical Trial Site for Phase-III & Phase-IV Clinical Trials only, under the Bio-Study Rules, 2017.

AGENDA ITEM XX:

APPLICATION FOR LICENSE TO ACT AS CLINICAL RESEARCH ORGANIZATION (CRO) OF M/S PROMEDIX (PRIVATE) LIMITED, MULTAN.

The case is an application from Mr. Muhammad Tahir, CEO, Promedix, Multan, wherein they have requested for license to act as Clinical Research Organization for Promedix (Private) Multan.

2. Application on Form-I along with prescribed Fee Rs.300030 vide slip No. 77903404624 dated 27.12.2021 has been submitted. The application was evaluated according to pre-requisites as mentioned in Form-I of the Bio-Study Rules notified vide SRO 697(I)/2018, as following: -

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed fee challan	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).	FBR Taxpayer Registration Certificate and SECP Certificate of Incorporation are attached.
4	Details of premises including layout plan of the site.	Layout plan attached.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Following Functionality/ divisions has been given. 1- Medical Function to provide medical oversight and inputs, to develop protocol and related documents etc.

		2- Regulatory Submission Team to prepare regulatory / bioethical committee required dossier, corresponds with regulatory persons, submit regular updates and seek approvals from the authorities. 3. Clinical operations - the team provide end - to - end services for clinical research from feasibilities till close - out visits. 4- Data Management the team design and ensure the data collection parameters, perform quality analysis, raise risk areas for focus and perform interim analysis to predict and track progress of the trial. 5- Biostatistics The team help to design and study end points parameters and its statistical significance, help in sample size calculation for particular protocol, perform analysis on results and predict data interpretation of the research in process. 6- Medical Writing - The team develops report, study updates, medical information and publication, safety updates in consultation with medical function team, interpret the results from data collected in the light of objectives of the protocol and prepare medical information for communication with different stakeholders. 7- Quality Assurance - This team is to ensure quality parameters are inherited with the performance of the team in all aspects. Services for quality assurance / audit for internal and external teams lies with this team. 8- IT Team catered services for software development according to protocol. development of eCRF, online regular engagement of team members, maintenance of electronic record keeping and e - archiving services are provided by the IT team. 9. Admin & finance - This team monitor, track and record day - to - day administrative and financial aspects of the organization. 10- Human Resources - This team is responsible for hiring of qualified HR for the CRO. It also engages team for their continuous development and look after hiring, firing and other HR related matters from day - to - day activities. 11- Training & Development - Development of required skills for the assigned tasks, co monitoring, regular training for the required services, their development and appraisal suggestion and improvement of week areas in consultation of HR and senior management is done by Training & Development Team

6	Names and qualifications of the above sections along with their staff.	The Name and CVs of each division lead has been submitted. - Medical function - Dr. Hafiz Muhammad Zia Ul Hassan 2- Regulatory Submission Team Dr. Muhammad Farooq 3- Clinical Operations- Dr. Ahmad Kamal (RPh , Pharm - D) 4- Data Management and IT Team - Mr. Rehman Gull 5- Biostatistics - Mr. Arif Hussain 6. Medical Writing - Dr. Hafiz Muhammad Zia 7- Quality Assurance - Dr. Muhammad Farooq 8. Admin & Finance - Mr. Muhammad Tahir 9- Human Resources - Mr. Farooq Amjid 10. Training & Development - Dr. Ahmad Kamal (RPh , Pharm - D)
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Not applicable as applied for CRO.
8	Undertaking on affidavit	E-Stamp attached.

4. The application was placed before Clinical Studies Committee (CSC) in its 34th Meeting held on 13th January 2022. The CSC decided as follows:

"*The CSC after detailed discussion and deliberation decided to delegate the power to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference. The CSC further decided that panel members shall be informed at least five (05) days before inspection of the proposed site to act as CRO.*"

5. Accordingly following inspection panel was constituted by the Chairman CSC for the inspection of said premises to act as CRO.

i. Dr. Faisal Usman, Assistant Professor, Faculty of Pharmacy, Bahauddin Zakariya University (BZU), Multan.

ii. Dr. Masud-Ur-Rehman, Director Pharmacy Services Division, DRAP, Islamabad.

6. The Panel was requested to verify the facilities as per requirements of Form-I of Bio-Study Rules 2017, required equipment, SOPs, expertise and fitness of the site to act as CRO.

7. The is the inspection report of M/s Promedix, Multan along with attendance list and layout plan, handed over by Director (PS) on 16.04.2022.

8. As per attached attendance list, Medical function Team - Dr. Hafiz Muhammad Zia Ul Hassan, Data Management and IT Team - Mr. Rehman Gull, Biostatistics - Mr. Atif Hussain, Medical Writing team - Dr. Hafiz Muhammad Zia, Human Resources team- Mr. Farooq Amjid were absent. Only three technical persons whose CVs were submitted with initial applications were present as per attendance sheet.

9. The panel recommended the M/s Promedix for approval with following remarks;

"*the technical staff owner has been working in the MNCs CRO, so all staff & personal are well aware of functions of CROs, their responsibility and credibility is upto mark. QA system need further strengthening*"

10. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for re-inspection & delegated the power to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference.

AGENDA ITEM XXI:

APPLICATION FOR LICENSE FROM NIH TO ACT AS CLINICAL TRIAL SITE FOR PHASE I, II, III & IV. (F. No.15-03/2022 DD (PS))

The case is an application with covering letter from Mst. Ghazala Parveen Chief BPD, National Institute of Health, Islamabad and Form-I signed from Major General Aamir Ikram, ED NIH, Islamabad wherein they have requested for Phase-I study specific site titled "Phase I dose escalation study of orally administered PAX-1 in patients with moderate COVID-19". A meeting of Director Pharmacy Services and disk officer was held with Executive Director NIH and Chief BPD, NIH on 22.02.2022. It was decided that NIH will apply for generalized Clinical Trial Site instead of trial Phase I dose escalation study of orally administered PAX-1 in patients with moderate COVID-19" specific Phase-I and trial Immunology & Safety of Heterogenous Combination of COVID-19 Vaccine available under Emergency Use Authorization in Pakistan: A Randomized Phase-II Trial specific phase-II. The applicant said that they will withdraw the trial specific applications or will request to change the trial specific sites applications to Generalized trial site application.

2. Accordingly, Mst. Ghazala Parveen has submitted the letter ISB-BPD-ADMN-43 dated 23rd February 2022 along with revised Form-I and other documents, wherein she has stated that that application may be considered for generalized clinical trial site application. The application submitted the Fee of Rs. 200,000/- vide slip number 097352412478 on 27.01.2022. The same Fee was used in previously submitted two trial specific applications. Now applicant intend to convert the trail specific applications in generalized application as per discussion in para 1/N. Guidance required regarding Fee.

3. The application has been evaluated in the light of documents submitted in above mentioned applications and according pre-requisites as mentioned in Form-I of the Bio-Study Rules 2017, details regarding attached documents are as follows:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Rs. 200,000/- vide slip number 097352412478 on 27.01.2022.
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).	The establishment of NIH Islamabad was conceived during early 1960s. In July 1967 the nucleus of this activity started functioning with the name of National health center in newly established capital, Islamabad. Various independently working organization like Bureau of laboratories and directorate of Nutrition survey and research were shifted in the premises of NHC. Later, during 1974proper integration of all these independently working units took place under the name of national health laboratories, Islamabad. The NIH has five major Divisions i.e. Public Health Laboratory division, Biological Production Division, Nutrition division, drugs Control and traditional Medicine Division and field Epidemiology & Disease Surveillance Division. Beside this a college of Medical Laboratory Technology, Allergy Centre and support departments facilitate financial, administrative and engineering functions of the institute.
4	Details of premises including layout plan of the site.	Applicant has attached layout plan of Zoonotic & Vector Laboratory, Main Virology Building, Measles & RotaVirus Laboratory, Molecular Biology Laboratory, Public Health Laboratory Division, Drugs Control & Traditional Medicine Division and layout plan of Clinical trial site.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	List of testing equipment present in Department of Hematology, Cytogenic, Virology, Histopathology, Microbiology, Parasitology, Chemical pathology, Endocrinology & Special Chemistry, QC laboratory, Bacteriology, MVPL, BPD, New Sera Laboratory, TCVPL and Biology Production unit is attached.
6	Names and qualifications of the above sections along with their staff.	List of officers/officials working in the different divisions of NIH, Islamabad along with staff working at proposed CTS is attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Details of Islamabad hospital, *Isolation Hospital and infectious treatment center h*ave been provided.
8	Undertaking on stamp paper	Attached.

4. After evaluation it was found that National Institute of Health, Islamabad has applied for change of trail specific CTS to the generalized Clinical Trial Site. The application has been evaluated in tabulated form.

5. The following panel was constituted by the Director, Pharmacy Services, DRAP;

a. Prof. Brig. (R), Muzammil Hassan Najmi, Professor of Pharmacology, Foundation University, Islamabad
b. Mst. Tehreem Sara, Federal Inspector of Drugs, DRAP, Islamabad.
c. Malik Muhammad Asad, Deputy Director, Division of Pharmacy Services, DRAP, Islamabad.
d. Mr. Shafqat Hussain, Assistant Director, Division of Pharmacy Services, DRAP, Islamabad (Coordinator).

6. The panel conducted the inspection on 04th October, 2022 & has submitted the inspection report with following remarks:

"In view of the observations mentioned in the CTS checklist, panel appreciated the commitment toward continual improvement. The panel is of the opinion that the management has presented the case professionally. However, the observation was note as mentioned in the performa above. Hence the panel unanimously recommends the CTS for grant of phase III & IV (vaccine related trials) subject to fulfilment/ compliance of above mentioned observations."

The observation recorded by the panel are mentioned below;

i. Dedicated dispensing area is available. However, handling under aseptic conditions is required.

ii. Household refrigerator is available (Haier). However, panel suggested Pharma grade storage facility at CTU for IMPs storage.

iii. Inspection panel suggested that a Data Safety Monitoring Board (DSMB) needs to be established.

iv. Revision of SOPs (safety/ incident reporting) is suggested.

v. Panel suggested for access control system under lock & key.

vi. Panel suggested improvements in dedicated facility/ are for archival of record.

7. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberations decided to approve "M/s National Institute of Health, Park Road, Chak Shahzad, Islamabad, for Phase-III & Phase-IV (Vaccine related) Clinical Trials only, under the Bio-Study Rules, 2017.

Further, the Committee delegated the power to the Chairman CSC for constitution of panel to verify the suggested improvements (CAPA) by expert inspection panel.

AGENDA ITEM XXII:

APPLICATION FOR APPROVAL OF M/S NATIONAL UNIVERSITY OF MEDICAL SCIENCES, ISLAMABAD, TO ACT AS CRO (F. No.15-48/2021 DD (PS)).

The case is an application from Brig Muhammad Azhar Shams, SI(M) (Rtd), CNIC:37101-8831686-5, Registrar of M/S National University of Medical Sciences (NUMS), C/O Military Hospital, Abid

Majeed Road, Rawalpindi, Pakistan. Wherein the request has been made to license with DRAP to act as Clinical Research Organization (CRO).

2. The application evaluated according to pre-requisites as mentioned in Form-I of the Bio-Study Rules notified vide SRO 697(I)/2018, summary of submitted documents is as follows:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed fee challan	Photocopy provided, original required to be submitted
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).	Copy of National University of Medical Sciences attached.
4	Details of premises including layout plan of the site.	Just two room layout attached without proper work place distribution to justify operations being done as CRO.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Not applicable as applied for CRO.
6	Names and qualifications of the above sections along with their staff.	Details regarding CVs of minimum division/departments required to work as CRO is need to be submitted.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Not applicable as applied for CRO.
8	Undertaking on affidavit	Attached

3. In light of evaluations following deficiencies were communicated to the applicant vide this office letter No. F.15-48/2021 dated 1st November 2021: -

i. Original fee challan DRAP copy need to be submitted.
ii. Justification being done as CRO is required as just two room layout attached without proper work place distribution.
iii. Details regarding minimum divisions/departments required to work as CRO need to be submitted as per decision of CSC taken in its 2nd meeting.
iv. CVs of technical staff/ officials employed by the applicant mentioning their assigned tasks should be furnished as the submitted information is proposed designated CRO personal.

4. The applicant submitted their reply on 17th December 2021 and case was placed before CSC in its 34th meeting held on 13.01.2022 and decision was as follows;

"The CSC after detailed discussion and deliberation decided to constitute the following panel for verification of facility available at the site to act as CRO"

i. Prof. Dr. Muzammal Hassan Najmi, Prof. of Pharmacology, Foundation University, Islamabad.

ii. Dr. Masud Ur Rehman, Chairman CSC/ Director Pharmacy Services, DRAP, Islamabad.

iii. Dr. Rizwana Chaudhary, Ex-HOD Gynecology, Holy Family Hospital, Rawalpindi.

5. The panel conducted inspection on 03.03.2022 of NUMS to act as CRO and submitted inspections report. The panel has recommended the CRO for approval with following remarks.

"*Inspection of the NUMS was done carefully. The staff, the equipment, the protocols SOP were found upto the mark, with professionalism and enthusiasm shown by the authorities of NUMS, the committee unanimously decided to grant them status of CRO NUMS.*"

6. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and in the light of expert inspection panel recommendations decided to approve M/s National University of Medical Sciences (NUMS), C/O Military Hospital, Abid Majeed Road, Rawalpindi, to act as Contract Research Organization (CRO), under the Bio-Study Rules, 2017.

AGENDA ITEM XXIII:

APPLICATION FOR APPROVAL AND REGISTRATION OF CLINICAL TRIAL TITLED "PHASE-I, OPEN-LABEL, TWO-COHORT STUDY OF ORALLY ADMINISTERED PAX-1 IN PATEINTS WITH MODERATE COVID-19".

The case is application from Major General Prof. Dr. Aamer Ikram, Executive Director, National Institute of Health, Islamabad, with covering letter Mst. Ghazala Perveen, CO-PI, wherein request has been made for registration & approval of subject cited Clinical Trial, which will be carried out at following clinical trial sites:

i. National Institute of Health, Islamabad.

2. Application is on prescribed Form-II, along with Prescribed fee of Rs.200000/-, deposited vide challan number 6164550672, dated 16th November 2021.

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 6164550672, dated 16th November 2021**. Original Fee challan required.**
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	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.	1728 Tablets (48 cartons). **Justification required.**
9	Site of the trial	National Institute of Health, Islamabad. **The Site is trial specific approved Clinical Trial site**.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached ***Prof. Dr. Maj. Gen. Aamir Ikram, PI is Chairman IRB and Mst. Ghazala Perveen, CO-PI, is member of IRB, Dr. Faiza Bashir, member IRB is also member of NBC and Nominee for CSC while Dr. Shehzad Hussain, chief DC & TMD has retired from his post.***
11	Approval of National Bio-ethics Committee (NBC)	NBC approval reference No.4-87/COVID-94/NBC/21/703, dated 02 November, 2021
12	CV's of the Investigators	CV of only Major General Prof. Dr. Aamer Ikram is attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	**Not attached.**
14	Pre-clinical/clinical safety studies	Three clinical studies have been attached. Animal pharmacology & Toxicology is attached in Investigator's Brochure.
15	Summary of Protocol	Given in Final Protocol.
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	50 patients approximately

19	Name of Monitors & Clinical Research Associate	Miss Sadaf from M/s Dimension Research CRO.
20	Evidence of registration in country of origin.	Not provided
21	Copy of registration letter (if registered in Pakistan)	Not provided, phase I study
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	06 Months approximately.
23	Undertaking on stamp paper	Not Attached.

4. In the view of above following shortcomings were noticed.

   i. Original DRAP copy of Fee Challan required.

   ii. Justification for IMPs to be imported is required.

   iii. Proposed Clinical trial Site (CTS) is trial specific approved CTS. National Institute of Health is not approved to carry out/ conduct clinical trials for phase-I.

   iv. Prof. Dr. Maj. Gen. Aamir Ikram, PI is Chairman IRB and Mst. Ghazala Perveen, CO-PI, is member of IRB, Dr. Faiza Bashir, member IRB is also member of NBC and Nominee for CSC that is conflict of interest while Dr. Shehzad Hussain, chief DC & TMD has retired from his post.

   v. CV of CO-PI required.

   vi. GMP certificate along with COPP or Free Sale Certificate is required.

   vii. Signed copy of Final Protocol is required.

   viii. Undertaking on stamp paper.

   ix. Soft Copy of the application particularly Final Protocol, Investigator's Brochure and pre-clinical/ clinical, safety studies required.

5. In the view of above, the above mentioned shortcomings were communicated to the applicant vide this office letter No. F.03-01/2022 DD (PS) dated 20th January 2022.

6. In response applicant submitted the following reply on 04th February 2022 in tabulated form.

Query/ shortcoming communicated	**Reply from applicant**
Original DRAP copy of Fee Challan required	DRAP copy of fee challan attached.
Justification for IMPs to be imported is required.	This study is planning to enroll 48 patients (including 20 % dropout rate) . Considering the dropout rate : - 24 patients will receive 5mg (2 tablets of 2.5 mg PAX - 1) for 10 days : 480 tablets (20 tablets / patient) - 24 patients will receive 7.5mg (3 tablets of 2.5 mg PAX - 1) for 10 days : 720 tablets (30 tablets / patient) Number of cartons and blisters provided to patients : Each carton

	contains 3 blisters of drugs where each blister contains 12 tablets (total 36 tablets / carton) . Total number of drugs , cartons to be imported : 1 carton = 36 tablets / patient Import 48 cartons for 48 patients Total number of tablets for 48 patients = 1,728 tablet
Proposed Clinical trial Site (CTS) is trial specific approved CTS. National Institute of Health is not approved to carry out/ conduct clinical trials for phase-I.	National Institute of Health applied to act as clinical trial sites for all phases I , II , II , IV but DRAP issued trial specific .Now we have submitted the fee PKR 100,000 for this to act as clinical trial site for this trial .
Prof. Dr. Maj. Gen. Aamir Ikram, PI is Chairman IRB and Mst. Ghazala Perveen, CO-PI, is member of IRB, Dr. Faiza Bashir, member IRB is also member of NBC and Nominee for CSC that is conflict of interest while Dr. Shehzad Hussain, chief DC & TMD has retired from his post.	Though both. Prof.Dr.Maj.Gen Aamer Ikram and Mst Ghazala Parveen are members of IRB , however none participated in voting due to conflict of interest and there is no signatures on IRB approval letter . Regarding Dr.Shahzad Hussain , Chief DC & TMD , he is not the member of IRB . List of Approved IRB members of National Institute of Health is attached.
CV of CO-PI required.	CV of Co-PI has been submitted.
GMP certificate along with COPP or Free Sale Certificate is required.	GMP certificate of M/s Komipharm International Co., Ltd, republic of Korea is attached.
Undertaking on stamp paper.	**Not attached.**
Soft Copy of the application particularly Final Protocol, Investigator's Brochure and pre-clinical/ clinical, safety studies required.	Will be shared in email.

7. The following queries were communicated vide this office letter No. F.03-01/2022 DD (PS) dated 9th March 2022;

i. The complete composition of IRB i.e. names and designations of members is required.
ii. Composition of IRB is not as per rule 9(2) of Bio-Study Rules 2017.
iii. Contract/ agreement b/w sponsor is required.

8. The applicant submitted the Memorandum of understanding and Composition of IRB.

9. The case was referred to Dr. Saif Ur Rehman Khattak, Director CDL to review the case and generate the report under rule 7 of Bio-Study Rules 2017 on 29.09.2022 and Dr. saif Ur Rehman Khattak has submitted following report.

Technical Assessment / Evaluation of The Application for Approval & Registration of Clinical Trial Titled Phase-I, Open Label Two- Cohort Study for Orally Administered PAX-I (Sodium meta- arsenite) 2.5mg Tablets in Patients with Moderate COVID-19

The application for approval and registration of clinical trial titled Phase-I open label, two cohort study for orally administered PAX-1 tablets (2.5mg, Sodium meta arsenite) in patients with moderate COVlD-19, forwarded to undersigned vide letter No. F.303-0 1 / 2022 DD (ps) dated 29th June. 2022 has been evaluated in detail keeping in view provisions and requirements of GCP & GLP guidelines, the report may be summarized as under: -

l. Evaluation of the application (Form-II) for general information.

- The applicant has provided information required by the application (Form-II) under rule-7 of the Bio-study Rules, 2017, including:
  a. Name of investigational product.
  b. Purpose of the Trial defining the indication along with the anticipated cost of the project and sources of fund.
  c. Phases of the clinical trial to be conducted and its proposed duration.
  cl. Proposed center for trial.
  e. List of participating countries.
  f. Investigator brochure along with summary.
  g. Pre-clinical. Clinical data, safety studies.
  h. Final protocol.
  1. Detail of the investigator.
  J. IRB approval.
  k. Ethical committee composition.
  l. Site approval by the ethics committee / DRAP.
  m. Informed consent.
  n. Summary protocol or synopsis.
  o. Adverse event reporting form.
  p. Name of the monitor or clinical research associate.
  q. Copy of registration letter if registered in Pakistan.
  r. Proposed label of investigational product(s)
  s. Quantity of the investigational product to be used in the trial along with justification.
- Key information of study protocol
  ▶ Study objectives
    - The primary objective of this study is to evaluate the safety of two escalating doses of PAX-I in patients with moderate COVID-19.
    - The exploratory objectives are to assess the efficacy and pharmacodynamics effects of PAX- I in patients with moderate COVID- I9.

Study design

Treatment 10 clays Treatment of 10 days

Data Safety
Monitoring Board

Study population

The study population will be made up of adult patients with confirmed moderate COVID- 1 9 as per WHO criteria. including a positive RT-PCR of any specimen.

, **Study end points**

- Safety end points
  - Incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.
  - Change of ECG. particularly of QT length incidence of Tdp and cardioversion.
  - Change from baseline in vital signs and clinical laboratory test results.
- Exploratory efficacy end points
  - Clinical failure at Day 10, defined as any of:
    - Death
    - Respiratory failure (patient requires intubation and mechanical ventilation)
    - Presence in the Intensive Care Unit (ICU)
  - Clinical improvement. stable disease. or progression assessed through the WHO ordinal scale at Day I0:
    - Uninfected: no clinical or virologic evidence of infection
    - Ambulatory: no limitation of activities
    - Ambulatory: limitation of activities
    - Hospitalized with mild disease: no oxygen therapy
    - Hospitalized with mild disease: oxygen by mask or nasal prongs
    - Hospitalized with severe disease: non-invasive ventilation or high flow oxygen
    - Hospitalized with severe disease: intubation and mechanical ventilation
    - Hospitalized with severe disease: ventilation+ additional organ support: vasopressors, RRT, ECMO
    - Death
  - Clinical improvement, stable disease and progression assessed through the National Early Warning Score 2

(NEWS2).

- Duration of supplemental oxygen.
- Rate of overall survival at Day I 0.
- Time to hospital discharge or "ready for discharge" (i.e. normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2 L supplemental oxygen).
- Time to a negative RT-PCR result for SARS-CoV-2 in nasopharyngeal swabs.

o Endpoints for pharmacodynamics

Serum tumor necrosis factor [TNF)-4, interferon (IFN)-a. interleukin (IL)-I. IL-2, IL-6, IL-7, IL- l 0, C-reactive protein (CRP), granulocyte colony-stimulating factor (G-CSF), interferon gamma-induced protein (IP)- I 0, monocyte chemoattractant protein (MCP)1, macrophage inflammatory protein (MIP) I *a* levels at baseline and at specified times after initiation of study drug.

2. Introduction to the investigational drug.

PAX-1 tablets. by *M/s* komipharm international pvt ltd. Australia, contain sodium meta-arsenite which is an orally bioavailable, water soluble, trivalent arsenical compound with telomerase inhibiting effect. The Tablets were initially developed for the treatment of cancer caused inflammation and pain and also as a cancer treatment.

The tablets are enteric coated modified (delayed) release oral tablets containing 2.5mg rneta-arsenite. The tablets are packaged in special child-resistant and senior-friendly nitrogen filled Alu Alu blisters.

The product is applied now for Phase-I clinical trial in Pakistan through M/s NIH. Park Road. Chak Shehzad, Islamabad.

3. Evaluation of the information on pre-clinical studies.

The data submitted by the applicant on the pre-clinical studies may be summarized as under:

3 l. Summary of pharmacokinetics and pharmacodynamics.

PAX-1 is rapidly and extensively absorbed from the gastrointestinal tract of common laboratory animals after a single oral dose, distributed throughout the body, metabolized in the liver to mono methyl arsenate and/or dimethyl arsenate and excreted primarily in the urine. Some degree of arsenic accumulation was observed only in dogs after repeated dosing for 13 weeks (0.5-2 mg/kg/day) and possibly in pigs after a 14-day daily treatment (approximately 0.58 mg/kg/day).

The mechanism of action underlying the anti-inflammatory effects of PAX-I has not yet been fully elucidated. However, based on the results of the previously described in vivo and ex vivo models, and cell culture models in vitro, as well as the proven interaction between telomerase activity and inflammation, PAX-I is theorized to be a

cytokine-inhibitor which inhibits the production/secretion of crucialpro-inflammatory mediators

3.2. Summary of efficacy.

3.2.l Antiviral activity.

The anti-viral activity of PAX-1 against SARS-CoV-2 was preliminarily investigated in an in vivo experiment wherein. Syrian golden hamsters were infected with SA RS-CoV-2 (NCCP43326) at a concentration of I 04 TCID50/mL followed by a daily oral administration of PAX-1 at doses of 0.9 mg/kg/day. A panel of measurement was performed on 3, 5 and 7day post infection (dpi) including measurement of the body weight, observation of lung histopathology and qRT-PCR quantification of the copy numbers of SARS- CoV-2 structural (E-protein) and RdRP (IP2) genes. From 6 dpi till the end of the experiment. body weights of the infected PAX-I 0.9 mg/kg-treated group of hamsters were significantly higher than those of the infected control group. indicating normalization of the body weight. Furthermore. significantly reduced expression of SARS-Co V-2 E-proteins and RdRP IP2 proteins at 3 dpi was observed in the hamster group that received PAX-1 0.9 mg/kg treatment. indicating that viral replication in lungs was inhibited by treatment with PAX-1 during the early stages of infection. Histopathological examination of lungs revealed that PAX-1 treatment caused a significant reduction in infiltration of inflammatory cells in interstitial lung at 3 dpi in PAX-I-treated infected group compared to those in the infected control group. At 7 dpi, the PAX-1 0.9 mg/kg-treated group showed significantly reduced infiltration of inflammatory cells in the alveolar cavity compared to the infected control group. This body of evidence shows the antiviral effect of PAX-1 on COVID-19-infected Syrian hamsters.

3.2.2. Anti-inflammatory activity.

PAX-1 at the dose of 1 0mg/kg showed anti-inflammatory activity in a model of rheumatoid arthritis in rats. as well as analgesic activity in the acetic acid- induced pain model and the formalin-induced inflammatory pain model in mice. PAX-1 single oral administration at l .54mg/kg and 2.05mg/kg significantly prolonged the survival rate and significantly suppressed TNF-α. IL-1 and IL-6 in Broncho alveolar lavage fluid (BALF) 111 the Lipopolysaccharide (LPS)-induced Acute Respiratory Distress Syndrome (ARDS) model in mice. Of note. 1.54mg/kg and 2.05mg/kg PAX-1 doses are equivalent to 7.5mg and 10mg human equivalent dose (HED) in a 60-kg adult patient. respectively. In LPS-stimulated murine

RAW 264.7 macrophages. PAX-I showed significant and dose-dependent inhibitory effects on crucial inflammatory mediators, i.e. Nitric Oxide (NO) production. Inducible Nitric Oxide Synthase (iNOS). Tumor Necrotic Factor-a (TNF-a) and Interleukin-I (IL-1) levels. and to a lesser extent prostaglandin E2 (PGE2) production and cyclooxygenase-2 (COX-2) levels. via the inactivation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), mitogen-activated protein kinase (MAPK) and protein kinase B (Akt) signaling pathways. PAX- I also reduced the LPS-induced secretion of TNF-a, IL-I and IL-6 in a concentration-dependent manner in rat primary peritoneal macrophages. at concentrations which preserved cell viability and function.

The proven in-vivo anti-inflammatory activity of PAX-1in the mouse model of lipopolysaccharide-induced ARDS, which is the closest proxy to the indication of COVID-19 pneumonia, making the drug valuable candidate for the treatment of COVID-19 pneumonia.

3.2.3. Safety pharmacology.

As regards safety pharmacology. the single oral administration of PAX-1 was devoid of any effects on the cardiovascular system, respiratory system and CNS in dogs (up to 4 mg/kg), rats (12 mg/kg) and mice (16 mg/kg), respectively. Only a decrease in body temperature was observed after the single oral administration of 16 mg/kg PAX-1 in mice. Moreover. in toxicokinetic or toxicity studies no effect considered to be of specific CNS or cardiovascular origin was seen in mice dosed at up to 65mg/kg/day (Oral), rats dosed at up to 63 mg/kg/day (Oral) and pigs dosed at up to 0.6 mg/kg/day (Oral). for two weeks, or in rats and Beagle dogs dosed at up to 12 or 2 mg/kg/day (Oral), respectively, for 13 weeks.

PAX-1 has been shown not to be point mutagen but was able to induce chromosomal abnormalities in standard test system *in vitro* and *in vivo.* Literature data indicated that sodium arsenite is carcinogenic in several animal carcinogenicity models and teratogenic in hamsters, mice. rats and rabbits. Male fertility seems also to be affected by sodium arsenite treatment in mice and rats.

4. Evaluation of the information on previous clinical studies.

As per data provided in the investigators brochures, nine studies have been performed on PAX-1 in cancer patients four of which were phase I (evaluating maximum tolerated dose) and five phase II (evaluating efficacy).

All these studies have been conducted on the pharmacokinetics, efficacy and safety of the investigational product for the treatment of a variety of cancer types. No study has been conducted to date in patients affected by COVID-19 pandemic. The

pharmacokinetics and pharmacodynamics. efficacy and safety data of the investigational product may be summarized as under:

4.1. Summary of clinical pharmacokinetics and pharmacodynamics

Absorption: Pharmacokinetics data with PAX-I have been generated in four studies: study IPSS-D008, KNX-10-02, IPSS-D039 and UMGCC-0805 (combination with cisplatin). Overall, Study IPSS-D008, KNX-10-02 and IPSS-D039 demonstrate an approximately linear relationship between Cmax and the administered dose.

Furthermore, study UMGCC-0805 support s this conclusion showing that PAX- I may follow a concentration-dependent pharmacokinetics.

In study KNX-10-02 higher total daily dose of PAX-1 resulted in higher trough plasma concentrations at the steady-state. with doses equal to or greater than 10 mg/day producing trough plasma concentrations more than 50 ug/ L. The range of mean trough plasma concentration of total arsenic on day 29 (one day after treatment was interrupted after a 28-day cycle) was 0.480 ~ 0.998 µmol/L over the dose ranges. In study KNX-10-02 the steady-state level of total arsenic was achieved after day 22 in all dose regimens tested (from 5 to 15 mg /day).

In study UMGCC-0805 the steady-state was reached after day 8. The discrepancy may be attributed to the fact that total arsenic level reflects overall status of inorganic arsenic species and its subsequent methylated species.

Furthermore. studies IPSS-D008 and KNX-10-02 shO\v that during the washout period. plasma levels of PAX-I fall to pre-dose levels.

Metabolism: Study UMGCC-0805 indicates a prevalence of methylated arsenic species in plasma after PAX-1 oral administration. This result is suppo11ed by results from study KNX-10-02. where the plasma concentration of dimethyl arsenate appears to be almost double compared with the one of inorganic arsenic species. Moreover. data from the controlled-ingestion studies indicate that both sodium arsenite and sodium meta-arsenite are extensively methylated in humans. with OMA being the main methylated metabolite excreted.

Excretion: In the KNX-10-02 study, it was estimated that a time-weighted average exposure of 50 arsenic /m3 would lead to an average urinary excretion of 220µg arsenic (sum of inorganic arsenic, MMA and DMA) per gram creatinine. Furthermore. the means of total arsenic excreted at day 7 after daily oral administration of PAX-1 were 2303, 3956, 3586 and 4537 µg at total daily doses of 5. l 0. 12.5, and 15 mg. respectively. The T½ at day 28 tended to decrease over the dose ranges.

4.2. ***Summary of efficacy***

None of the studies conducted formally investigated PAX-I as an anti-inflammatory agent in pneumonia and respiratory inflammation. Information on the efficacy of PAX-I in the relief of pain/inflammation comes from three of the clinical trials performed: KNX- 11-01. KNX-11-02 and KNX-08-01. In these studies, pain level was evaluated as a possible indicator of inflammation. Results from the pain score analysis together with evaluation

of the concomitant analgesics administered in four patients of study ICNX-11-01 suggest that in these patients PAX-1 might have provided an analgesic effect in combination with existing analgesic treatment.

Data from the other two studies demonstrated either no change or increase in pain levels after treatment compared with baseline. However, considering that all patients in which pain was evaluated in these studies were affected by advanced or metastatic cancer. it is difficult to draw a clear conclusion concerning a potential effect of PAX I in reduction of inf1ammation in humans.

4.3.*Summary of safety*

Safety of PAX- I was assessed in all clinical trials conducted with PAX-1.

4.3.1. <u>Adverse Drug Reactions</u>

4.3. I. I. Adverse ***Drug Reactions to 12.5mg, 15mg and 20mg/day doses of PAX-1:***

Overall, dose limiting toxicities (DLTs) were reported for the following PAX-1 doses: 12.5 mg/day, 15 mg/day and 20 mg/day. The reported DLTs were a Grade 3 prolongation of QTc interval (2 treated with 20 mg/day in the combination study and 2 treated with PAX- I 12.5 mg/day). Grade 3 neutropenia (1 subject treated with PAX-1 12.5 mg/day). Grade 3 increase in ALT levels (3 subjects treated with PAX-1 15 mg/day) and Grade 3 increase in GGT levels (I subject treated with PAX- I 15 mg/day).

The most common adverse drug reactions (ADRs) possibly. probably or likely drug-related (>one event) reported in the monotherapy studies \\'ere: nausea (66), neutropenia (62), vomiting (59). constitutional symptoms (42), fatigue (42), anemia (36), dyspnea (30), decreased appetite (29),

prolonged QT (22), pruritus (20), anorexia (19). rash (18). ALT increased

(17). diarrhea (l 4), AST increased (13), thrombocytopenia (12). constipation (11) and edema (I0).

4.3.1.2. Adverse Drug Reactions to 2.5mg, 5mg and 7.5mglday doses of PAX-I: For the 2.5, 5 and 7.5 mg/day doses the most frequent ADRs (>one event) were nausea (13), vomiting (8). diarrhea (7). constipation (5) and decreased appetite (5). The most frequent severe ADRs occurring \\ere neutropenia (52). ALT increased (12), AST increased (10). anemia (8). prolonged QT (9), neutrophil count decreased (6). platelet count decrease (5), thrombocytopenia (5) and dyspnea (5). There was an increase in frequency and severity for the common drug-related adverse events with increasing PAX-1 doses. Doses between 2.5 -7.5 mg/day were better tolerated.

4.3.2. **Severe Adverse Drug Reactions 2.5mg and 7.5mg/day doses:** The severe ADRs

occurring at doses between 2.5 and 7.5 mg/day of PAX-1 were platelet count decrease (2). neutropenia (1), diarrhea (1), sudden death (I). atrial fibrillation (1) and cardioversion (1). One sudden death was reported in 7.5mg /day dose level. The causal relationship of the sudden death was deemed as unknown by the Investigator. Overall, fourteen serious adverse events (SAEs) possibly. probably. or likely related to PAX-1 treatment were reported in the monotherapy studies. The reported drug related SAEs were: dyspnea (three events at the 17.5 mg/day dose level and one at 10mg/day). diarrhea (two events at the 7.5 mg/day dose level). nausea and vomiting (one event each at the 12.5 mg/day dose level), decreased appetite (one event at the 5 mg/day dose level), atrial fibrillation and cardioversion (one event each at the 2.5mg/day dose level), therapy cessation and oedema (one event each at the 1 7.5 mg/day dose level) and prolonged QT (one event at the 20 mg/day dose level).

The most common toxicities observed in the phase combination study were nausea and vomiting and cytopenia. Significant, but not dose limiting, neutropenia and thrombocytopenia (> grade 3) were observed at the 15 mg and 17.5mg doses. Causality of these events was not reported.

Considering the known property of arsenic agents in prolongation of QT/QTc interval, QT and QTc time prolongation were closely monitored in all clinical trials conducted and these events were mainly reported in subjects treated with PAX-1 doses ranging from 10 to 20 mg /day. The safety data support the use of oral doses of 5 and 7.5 mg /day of PAX-1 in future clinical trials.

5. Justification for indication in patents with moderate COVID-19.
The applicant has submitted under benefits/Risk assessment as under:

- *Known Potential Risks*

  A known property of arsenic agents is prolongation of QT/QTc interval. In the studies performed with PAX-1, QT and QTc time prolongation were closely monitored and these events were mainly reported in subjects treated with PAX-1 doses ranging from 10 to 20 mg/day. At the doses planned to be tested in the future dose-finding study or lower, only one patient treated at the 5 mg/day dose exhibited QTc prolongation. In one study, a statistically significant increase in heart rate and QTc interval was reported at the final visit compared with baseline in subjects treated with 7.5 mg/day PAX-1, however, none of the abnormal changes were clinically significant. During the studies performed with PAX-1 so far, clinically significant differences for levels of some hematological parameters and liver enzymes were reported for the PAX-1 doses ranging from 10 to 20 mg /day, including Grade 3 neutropenia (7 subjects) and thrombocytopenia (2 subjects). For the planned PAX-1 doses or lower only one event of severe drug-related neutropenia (grade 3) and one event of severe drug-related platelet count decrease were reported in the 7.5 mg/day group.

- *Known Potential Benefits*

  In COVID-19 infectious pneumonia, the overproduction of early response pro-inflammatory cytokines (TNF-a, IL-6, and lL-113) results in what has been described as a cytokine storm, leading to an increased risk of vascular hyper-permeability. multiorgan failure, and eventually death when the high cytokine concentrations are unabated over time: Therefore, therapeutic strategies under investigation are targeting this hyper-inflammation syndrome, but this must be balanced with maintaining an adequate inflammatory response for pathogen clearance. PAX-1, with its antiviral activity and specific actions on the functions of pro-inflammatory cytokines to reduce cytokine storm without the nonspecific effects of immunosuppressive drugs, such as corticosteroids, may give physicians more time to provide supportive treatment and represents a new treatment strategy for patients with moderate COVID-19.

Assessment of potential risks and benefits

To date, therapeutic options for COVID-19 pneumonia remain limited. In light of the considerations stated above, the potential benefits of the future studies planned with PAX-1 appear to outweigh its potential risks.

6. Recommendations

Evaluation of the information submitted in support of the application especially the potential benefits/Risks assessment, it is recommended that permission to conduct the titled study may be granted subject to:

i. ***Prior approval of the clinical site by DRAP as no approval could be provided by the applicant with the application however, stated that they have applied for the same.***

ii. ***Assessment of suitability of the clinical site in terms of facilities for the titled study by the CSC.***

iii. ***Assessment of the laboratory other than the clinical site if planned to be used for conducting any test related to the study.***

iv. ***Instructions to conduct the trial under strict supervision and monitoring for any severe adverse event or adverse event including the known QT/QTc time prolongation.***

Dr. Saif Ur Rehman Khattak
Director CDL, Karachi

11. Later the applicant submitted amended consent form (ICF) version 1.2 in urdu and English along with approval from IRB. Following are queries of this office.

i. NBC approval required.
ii. CTS not approved for Phase-I clinical trials.
iii. Justification for Phase-I trial in Pakistan instead of the country of origin.

12. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation and in the light of recommendations by Dr. Saif Ur Rehman Khattak, Director Central Drugs Laboratory (CDL), Karachi, decided to defer the case for rectification of following shortcomings and fulfillment of requirements:

i. Prior approval of the clinical site by DRAP as no approval could be provided by the applicant with the application.
ii. Assessment of suitability of the clinical site in terms of facilities for the titled study by the CSC.
iii. Assessment of the laboratory other than the clinical site if planned to be used for conducting any test related to the study.
iv. Instructions to conduct the trial under strict supervision and monitoring for any severe adverse event or adverse event including the known QT/QTc time prolongation.

AGENDA ITEM XXIV:

APPLICATION FOR APPROVAL AND REGISTRATION OF CLINICAL TRIAL TITLED "A RANZOMIZED, BLINDED, PARALLEL CONTROLLED PHASE III STUDY TO EVALUATE THE IMMUNOGENICITY AND SAFETY OF SARS CoV-2 mRNA VACCINE (LRVNA009) AS HETEROLOGOUS BOOSTER IN PARTICIPANTS AGED 18 YEARS AND OLDER VACCINATED 2 DOSES INACTIVATED SARS-CoV-2 VACCINE" (F. No.03-07/2022-DD (PS)).

The Case is from Muhammad Khurram Zaki Khan, CEO Dimension Research CRO & SMO, Karachi, wherein he has requested for registration and approval of subject mention trial/ study.

2. Application is on prescribed Form-II from M/s Dimension research CRO, along with Prescribed fee of Rs.200000/-, deposited vide slip number 0377603156, dated 24th July 2022.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached. **Form-II not signed.**
2	Fee	Prescribed fee of Rs.200000/-, deposited vide slip number 0377603156, dated 24th July 2022
3	Investigator Brochure (s)	Attached
4	Final protocol	Attached. **Not signed by PI and sponsor**
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Pakistan
7	Phase of trial.	Phase – 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.	SARS-CoV-2 mRNA Vaccine (LVRNA009) 550 +138 boxes. Inactivated SARS-CoV-2 (Vero Cell) (CoronaVac) 550+50 boxes. **Justification required for 138, 50 extra Boxes.**
9	Site of the trial	National Institute of Health, Islamabad.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB approval attached. **Mrs. Ghazala Parveen is Sub-Investigator and also member of IRB.**
11	Approval of National Bio-ethics Committee (NBC)	NBC approval reference No.4-87/NBC-798/22/2331, dated 17th June 2022 (a New approval required)
12	CV's of the Investigators	CVs of Major General Prof. Dr. Aamer Ikram, Mrs. Ghazala Parveen and Dr. Omera Naseer are attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP certificate of M/s Ningbo Rongan Bio-Pharmaceutical co., Ltd is attached **with scope of Inspection "Preventive Biological Products [Rabies Vaccine (Vero Cell) for Human Use, Freeze dried]"** **GMP Certificate with IMPs manufacturing or IND approval is required.** **GMP Certificate, CoPP for CoronaVac is required.**
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Provided in protocol.
16	Summary of Investigator Brochure	**Not attached.**
17	Adverse Event Reporting Form	**Applicant has attached Unique Case Reporting Form instead of Adverse Event Reporting Form**
18	No of patients to be enrolled in each center.	1,100 subjects.
19	Name of Monitors & Clinical Research Associate	Mrs. Sadaf Khuram Miss Maleeha Arshad

		Miss Wajeeha Nuzhat Of M/s Dimension Research CRO
20	Evidence of registration in country of origin.	Drug Under Phase III Trial **Evidence in country of origin for CoronaVac is required.**
21	Copy of registration letter (if registered in Pakistan)	**Registration letter for CoronaVac is required.**
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	From start of enrolment till data lock will be approximately 20 months.
23	Undertaking on stamp paper	Attached.

4. In the view of above following are the observations;

i. Form-II is from CEO of a CRO instead of responsible party i.e. PI or Sponsor.
ii. Form-II not signed.
iii. Justification required for 138, 50 extra Boxes to be imported/ purchased.
iv. Mrs. Ghazala Parveen is Sub-Investigator and also member of IRB that is conflict of interest.
v. GMP certificate of M/s Ningbo Rongan Bio-Pharmaceutical co., Ltd is attached with scope of Inspection "Preventive Biological Products [Rabies Vaccine (Vero Cell) for Human Use, Freeze dried]" GMP Certificate with IMPs manufacturing or IND approval is required.
vi. GMP Certificate, CoPP for CoronaVac is required.
vii. Investigator Brochure not attached.
viii. Evidence in country of origin for CoronaVac is required.
ix. Registration letter for CoronaVac is required.
x. The published data for Phase-I & II along with study protocol for Phase-I & II are required.
xi. NIH is not approved as CTS for generalized clinical trials.
xii. Agreement and details/ procedure for sample transfer not attached.

5. **The shortcomings were communicated vide this office letter No.F.03-07/2022 DD (PS) dated 3rd October 2022 and reply is still awaited.**

6. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for rectification of following shortcomings and fulfillment of requirements as per Form-II of the Bio-Study Rules, 2017:

i. Form-II is from CEO of a CRO instead of responsible party i.e. PI or Sponsor.
ii. Form-II not signed.
iii. Justification required for 138, 50 extra Boxes to be imported/ purchased.

iv. *Mrs. Ghazala Parveen is Sub-Investigator and also member of IRB that is conflict of interest.*

v. *GMP certificate of M/s Ningbo Rongan Bio-Pharmaceutical co., Ltd is attached with scope of Inspection "Preventive Biological Products [Rabies Vaccine (Vero Cell) for Human Use, Freeze dried]" GMP Certificate with IMPs manufacturing or IND approval is required.*

vi. *GMP Certificate, CoPP for CoronaVac is required.*

vii. *Investigator Brochure not attached.*

viii. *Evidence in country of origin for CoronaVac is required.*

ix. *Registration letter for CoronaVac is required.*

x. *The published data for Phase-I & II along with study protocol for Phase-I & II are required.*

xi. *NIH is not approved as CTS for generalized clinical trials.*

xii. *Agreement and details/ procedure for sample transfer not attached.*

AGENDA ITEM XXV:

APPROVAL OF CLINICAL TRIAL TITLED "COMPARATIVE PHARMACOKINETICS OF CHOLCALCIFEROL FROM M/S RAWALPINDI MEDICAL UNIVERSITY RAWALPINDI (F. No.03-06/2022 DD (PS)).

The case is an application from Prof. Dr. Muhammad Umar, Rawalpindi Medical University, Rawalpindi, wherein the applicant has requested for approval of subject Clinical Trial "COMPARATIVE PHARMAKOKINETICS OF TWO DIFFERENT ORAL DELIVERY SYSTEM OF CHOLCALCEFEROL". The application is on Form-II as prescribed in the Bio-Study Rules 2017. Fee of Rs. 200,000/- submitted vide Slip No. 122382130574 dated 30th June 2022 is attached with application.

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:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed processing fee	Fee of Rs.200,000 submitted vide Slip No. 122382130574 dated 30th June 2022
3	Investigator Brochure (s)	**Investigator Brochure is not as per ICH/ GCP guidelines.**
4	Final protocol	Attached.
5	Informed consent and participant information sheet (Urdu to English)	Attached **but it does not cover the subject/ participant health insurance.**
6	List of participating countries	Pakistan.
7	Phase of trial.	As per Form II the proposed trial is of Phase III **but as per page 262, it Phase IV trial.**
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Quantity of Investigational; SunnyD STAT softgel Capsule 15

		Plcebo SunnyD Stat softgel capsule 15 SunnyD Insta Ampoule 15 Placebo SunnyD Insta Ampoule 15
9	Site of the trial	Department of Medicine of M/s Rawalpindi Medical university Rawalpindi (CTS0055)
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Refernce No 217/IREF/RMU/2022 dated 05.02.2022 is attached. **Composition and Notification of IRB not attached.** **Approval from IRB is signed by Prof. Dr. Muhammad Umar who also PI of the study.**
11	Approval of National Bio-ethics Committee (NBC)	**NBC approval not attached.**
12	CV's of the Investigators	CV of Prof. Dr. Muhammad Umar, VC, RMU, Rawalpindi attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP certificate for Scotmann Pharmaceutical and COPP for Sunny D insta Injection for 5mg/ml is attached. Free sale certificate for Sunny D state soft gel is attached. **Whereas GMP certificate for Scotmman Pharmaceutical (H&OTC) Division is not attached.**
14	Pre-clinical/clinical safety studies	Miscellaneous articles for Vitamin D3 100,000 international units is attached. **Some of copies not readable.**
15	Summary of Protocol	**Not attached**
16	Summary of Investigator Brochure	**Not attached.**
17	Adverse Event Reporting Form	CIOMS form attached.
18	No of patients to be enrolled in each center.	**Not attached.**
19	Name of Monitors & Clinical Research Associate	Prof. Dr. Fazlur Rehman. **The application to IRB has also been submitted by Prof. Dr. Fazlur Rehman.**
20	Evidence of registration in country of origin.	N/A
21	Copy of registration letter (if registered in Pakistan)	Enlistment No. 00639.0007 Sunny D state soft gel 200,000 IU attached. Registration No. 063450 Sunny D Insta Ampoule is attached.
22	Sample of label of the investigational product / drug.	Commercial packs with laser printing "*FOR TRIAL PURPOSE ONLY NOT FOR SALE*". Labels for placebo not attached.
22	Duration of trial	8 months.
23	Undertaking on stamp paper.	Attached**.**

3. After evaluation of the application, following shortcomings were noticed which needs clarification by the applicant.

i. Investigator Brochure is not as per ICH/ GCP guidelines.
ii. Informed consent does not cover the subject/ participant health insurance.
iii. As per Form II the proposed trial is of Phase III but as per page 262, it Phase IV trial.
iv. Composition and Notification of IRB not attached.
v. Approval from IRB is signed by Prof. Dr. Muhammad Umar who also PI of the study.
vi. NBC approval not attached.
vii. GMP certificate for Scotmman Pharmaceutical (H&OTC) Division is not attached.
viii. Summary of Protocol not attached.
ix. Summary of Investigator Brochure not attached.
x. No of patients to be enrolled in each center not attached.
xi. Clinical trial monitor is Prof. Dr. Fazalur Rehman and he is also applicant who has applied in IRB.
xii. Quantities of drug to be used in clinical trial is not justified.
xiii. Applicant has not attached permission to manufacture placebo.
xiv Some copies in preclinical studies are not readable.
xv Soft copy of application is required.
xvi. Further as per undersigned understanding, it seems BA/BE studies while RMU is not approved BA/BE center.

4. **The shortcomings were communicated vide this office letter No.F. 03-06/2022-DD (PS) dated 24th June 2022 with request to clarify/ explain shortcomings/ queries with in seven (07) working days and applicant has not replied yet.**

5. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for rectification of following shortcomings and fulfillment of requirements as per Form-II of the Bio-Study Rules, 2017:

i. Investigator Brochure is not as per ICH/ GCP guidelines.
ii. Informed consent does not cover the subject/ participant health insurance.
iii. As per Form II the proposed trial is of Phase III but as per page 262, it Phase IV trial.
iv. Composition and Notification of IRB not attached.
v. Approval from IRB is signed by Prof. Dr. Muhammad Umar who also PI of the study.
vi. NBC approval not attached.
vii. GMP certificate for Scotmman Pharmaceutical (H&OTC) Division is not attached.
viii. Summary of Protocol not attached.
ix. Summary of Investigator Brochure not attached.
x. No of patients to be enrolled in each center not attached.
xi. Clinical trial monitor is Prof. Dr. Fazalur Rehman and he is also applicant who has applied in IRB.
xii. Quantities of drug to be used in clinical trial is not justified.
xiii. Applicant has not attached permission to manufacture placebo.
xiv. Some copies in preclinical studies are not readable.
xv Soft copy of application is required.
xvi. Further as per undersigned understanding, it seems BA/BE studies while RMU is not approved BA/BE center.

AGENDA ITEM XXVI:

APPROVAL OF CLINICAL TRIAL TITLED "SAFETY AND EFFICACY OF APIXABAN IN COVID-19 COAGULOPATHY PATIENTS WITH RESPIRATORY SEVERITY UNDER CRITICAL CARE" (F. No.03-02/2022 DD (PS)).

Case is an application from Prof. Dr. Muhammad Umar, Rawalpindi Medical University, Rawalpindi, wherein the applicant has requested for approval of subject Clinical Trial "SAFETY AND EFFICACY OF APIXABAN IN COVID-19 COAGULOPATHY PATIENTS WITH RESPIRATORY SEVERITY UNDER CRITICAL CARE". The application is on Form-II as prescribed in the Bio-Study Rules 2017. Fee of Rs. 200,000/- submitted vide Slip No. 35132282067 is attached with application.

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:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed processing fee	Fee of Rs.200,000 submitted vide Slip No. 35132282067 is attached
3	Investigator Brochure (s)	**Leaflet of ECRU tablet attached.**
4	Final protocol	Attached. **Detail regarding insurance of subjects not included in protocol. Signed protocol by sponsor and PI is required.**
5	Informed consent and participant information sheet (Urdu to English)	Attached **but it does not cover the subject/ participant insurance.**
6	List of participating countries	Only Pakistan.
7	Phase of trial.	Phase III **but as per US Trial Registry it Phase IV trial.**
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Quantity of Investigational product (20 tablets per patients' x 40 patients= 80 Tables) 2.5 mg Tablets twice daily for 10 days duration of the trial. **As per calculation quantity is 800 tablets instead of 80 tablets.**
9	Site of the trial	Infectious Diseases Department/ Department of Medicine of M/s Rawalpindi Medical university Rawalpindi (CTS0055)
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Not attached

11	Approval of National Bio-ethics Committee (NBC)	NBC approval Ref: No. 8-87/COVID-102/21/969 is attached.
12	CV's of the Investigators	CV of Prof. Dr. Muhammad Umar, VC, RMU, Rawalpindi attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Registration Letter, GMP certificate, ISO 9001:2015 attached.
14	Pre-clinical/clinical safety studies	**Full prescribing information of Eliquis Tablets is attached.**
15	Summary of Protocol	attached
16	Summary of Investigator Brochure	**Not attached.**
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	40 **but as per US Trial Registry the number of subjects is 30.**
19	Name of Monitors & Clinical Research Associate	Prof. Dr. Fazlur Rehman. Dr. Imran Arshad.
20	Evidence of registration in country of origin.	Registration letter of locally manufactured drug ERCU attached
21	Copy of registration letter (if registered in Pakistan)	Registration letter of locally manufactured drug ERCU attached
22	Sample of label of the investigational product / drug.	**Not provided.**
22	Duration of trial	3 months.
23	Undertaking on stamp paper.	**Not provided.**

3. After evaluation of the application, following shortcomings has been noticed and need clarification by the applicant.

i. Original DRAP copy of Fee Challan is required.

ii. Signed protocol by applicant and sponsor is required.

iii. Details regarding the insurance of the subjects not included in the protocol.

iv. Informed consent does not cover the subject insurance.

v. Quantity of IMPs is not justified.

vi. Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.

vii. Pre-clinical/clinical safety studies in COVID patients required.

viii. No of subjects in application is 40 while as per US Trial registry is 30.

ix. Sample of label of the investigational product / drug not provided.

x. As per US Trial registry (NCT 05088928) Phase of trial is IV but as per application phase is III.
xi. As per column 19 of Form II of IMP is 2.5mg twice daily while as per US trial registry its once daily.
xii. Phase II trial data establishing the preliminary efficacy of the drug in treatment group required.
xiii. Investigator Brochure, COPP or Free Sale Certificate, GMP/ Registration of Rivaroxaban is required.
xiv. Clinical indication of Rivaroxaban in covid-19 coagulopathy patients with respiratory severity under critical care is required.
xv. Undertaking on stamp paper not attached.
xvi. Justification for using such a small group of subjects for Phase III required.
xvii. Anticipatory cost of the project mention in Form-II (Rs.2000/-) is not justified.

4. The above mentioned shortcomings were communicated vide this office letter No.F.03-02/2022 DD (PS) dated 2nd February 2022. The applicant submitted their reply on 14.02.2022 to the queries. The representatives of the applicant also visited the office. The reply submitted was also discussed with them. He agreed that submitted reply does not cover the shortcomings/ queries mentioned in letter. Later on following letter was written to the applicant vide No. F.03-02/2022 DD (PS) dated 24th February 2022.

Dr. Muhammad Umar,
Vice Chancellor,
Rawalpindi Medical University,
Rawalpindi.
SUBJECT: APPROVAL OF CLINICAL TRIAL TITLED "SAFETY AND EFFICACY OF APIXABAN IN COVID-19 COAGULOPATHY PATIENTS WITH RESPIRATORY SEVERITY UNDER CRITICAL CARE".

Reference to your submitted reply dated 14-02-2022 for approval of subject application, it is informed that the reply does not cover the shortcomings / queries communicated vide this office earlier letter dated 02.02.2022

2. The matter was also discussed at length on 18-02-2022 with your representative M. Bilal and on 23-02-2022 with M. Bilal and Ms, Syeda Saba It was agreed to submit reply afresh as per shortcomings / queries communicated vide above referred letter. Hence, it is once again advised to clarify / explain the points not addressed in the reply and furnish your response in the light of shortcomings / queries mentioned in this office letter dated 02.02.2022 within seven (07) working days to proceed further in the matter.

-SD-
Assistant Director (PS)

5. The applicant has not replied yet.

6. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for rectification of following shortcomings and fulfillment of requirements as per Form-II of the Bio-Study Rules, 2017:

i. Original DRAP copy of Fee Challan is required.
ii. Signed protocol by applicant and sponsor is required.
iii. Details regarding the insurance of the subjects not included in the protocol.
iv. Informed consent does not cover the subject insurance.

v. *Quantity of IMPs is not justified.*
vi. *Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.*
vii. *Pre-clinical/clinical safety studies in COVID patients required.*
viii. *No of subjects in application is 40 while as per US Trial registry is 30.*
ix. *Sample of label of the investigational product / drug not provided.*
x. *As per US Trial registry (NCT 05088928) Phase of trial is IV but as per application phase is III.*
xi. *As per column 19 of Form II of IMP is 2.5mg twice daily while as per US trial registry its once daily.*
xii. *Phase II trial data establishing the preliminary efficacy of the drug in treatment group required.*
xiii. *Investigator Brochure, COPP or Free Sale Certificate, GMP/ Registration of Rivaroxaban is required.*
xiv. *Clinical indication of Rivaroxaban in covid-19 coagulopathy patients with respiratory severity under critical care is required.*
xv. *Undertaking on stamp paper not attached.*
xvi. *Justification for using such a small group of subjects for Phase III required.*
xvii. *Anticipatory cost of the project mention in Form-II (Rs.2000/-) is not justified.*

AGENDA ITEM XXVII:

APPLICATION FOR LICENSE TO ACT AS BA/BE STUDY CENTER FROM M/S DEFENCE SCIENCE AND TECHNOLOGY ORGANIZATION (DESTO) LAB., ISLAMABAD (F. No.15-14/2022 DD (PS)).

The case is an application from Dr. Sumera Mahboob, Deputy Chief Manager, Defense Science & Technology Organization, Chattar, Islamabad, wherein the request has been made to license their premises work as BA/BE study Center. The application is on prescribed Form-I of the Bio-Study Rules along with fee of Rs.300000/- deposited vide slip No.909297512, dated 16.06.2022.

2. It is submitted that application evaluated according pre- requisites as mentioned in Form-I of the Bio-Study Rules, 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	Rs.300000/- deposited vide slip No.909297512, dated 16.06.2022 is 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).	Public Sector Organization, working under Ministry of Defence established on 11th July 1963 (Notification attcahed). In 2005 it came under SPD in 2009 it became part of NESCOM, SPD. **The notification regarding its working under SPD and then NESCOM, SPD along with authority letter are required.**

4	Details of premises including layout plan of the site.	Only layout attached.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	List of equipment is attached.
6	Names and qualifications of the above sections along with their staff.	List of staff along with their CVs attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	As per submitted details followings are allied facilities. 1. Medical center equipped with essential medical and lab equipment. 2. 2x Doctors (1 PMO & 1 SMO). 3. 5x Nursing Staff. 4. 5 x Patients Beds. 5. Wheel Chairs 6. 4 x Ambulances (2 fully cardiac equipped). 7. NESCOM Hospital. 8. MoU signed with NIH for animal Study.
8	Undertaking on stamp paper	Attached.

3. The evaluation has been given above in tabulated form. As per u/s understanding there are very minor queries/ shortcomings that can be verified by the panel if constituted by the CSC.

4. The following panel was constituted by the Director Pharmacy Services and was communicated vide letter No. F.15-14/2022 DD (PS) dated 7th July 2022. The panel visited the M/s Desto Lab. on 30th August 2022 and it was found that firm has equipment as per provided list but Nursing staff and dedicated site/ unit to retain subjects were not available. The matter was discussed with DESTO management and they requested that they will inform the panel after construction of site/ unit to retain the subjects, for revisit/ re-inspection of the site.

5. **The applicant has not informed the panel to date for re-inspection.**

6. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberations decided to defer the case for re-inspection. Further, the Committee delegated the powers to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference.

AGENDA ITEM XXVIII:

APPLICATION FOR RENEWAL OF LICENSE TO ACT AS CENTER, CLINICAL TRIAL SITE, FROM NISHTAR MEDICAL UNIVERSITY & HOSPITAL, MULTAN (F. No.15-22/2019 DD (PS)).

The case is the letter from Prof. Rizwana Chaudhri wherein she has enclosed application of Prof. Dr. Mehnaz Khakwani, for renewal of licence for Nishtar Medical University & Hospital, Multan to act as a clinical trial site (licence No. CTS-007). The application is on Form-III of Bio-study Rules 2017 along with fee deposit slip of Rs. 100,000/-

2. The application has been evaluated below in tabulated form according to pre- requisites as mentioned in Form-III of the Bio-Study Rules 2017.

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached. **Stamp paper signed but application has not been signed. Previously applied for phase III but now at time of renewal has been applied for phase III & IV.**
2	Prescribed processing fee	Fee Slip number05212678705 dated 22.07.2022 of Rs.100,000/- 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).	Nishtar Medical University (Formerly Nishtar Medical College) is a Public sector health sciences university located in Multan.
4	Details of premises including layout plan of the site.	Applicant has provided details of Nishtar Medical university and Hospital and also attached its layout plan. **The details including layout plan of Clinical Trial Site is required.**
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	**Details of machinery and equipment required for clinical studies not attached.**
6	Names and qualifications of the management.	**Details of management to be provided.**

7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Labour room has its own pharmacy and blood bank services. All the required emergency medicines are available in the pharmacy. The labour room provides services for SVD, VBAG and instrumental deliveries like forceps and ventouse. The labour room is facilitating to deal with high risk obstetrical cases like eclampsia, placental abruption, cardiac patients and management of post partum hemorrhage. In operation theatre all sorts of caesarean sections from primary cesarean section to complicated obstetrical cases like placenta previa with morbid adherence, placental abruption, high order caesarean section and re-open laparotomies.
8	Undertaking on stamp paper	Attached **but has been issued in favor of Shifa Hospital Islamabad instead of DRAP.**

3. Previously the application was submitted by Prof. Dr. Huma Quddusi and renewal has been applied by Prof. Dr Mehnaz Khakwani. Further, as per IRB notification Dr. Mehnaz Khawkwani is member of IRB and also investigator of the trial.

4. In the light of above following are the observations.

i. Application not signed by the applicant.
ii. Initially application was submitted to act as Clinical trial Site for Phase-III but at the time of renewal application is for Phase III & IV.
iii. The details including layout plan of Clinical Trial Site is required.
iv. Details of machinery and equipment required for clinical studies not attached.
v. The details of management may be provided.
vi. Stamp paper has been issued in favor of Shifa Hospital instead of DRAP.
vii. Prof. Dr. Mehnaz Khakwani is Investigator of the trial and also member of the IRB that is conflict of interest.
viii. Initially application was submitted by Prof. Dr. Huma Qudusi and renewal by Prof. Dr. Mehnaz Khakwani. What is the status of Prof. Dr. Huma Qudusi?

5. In the **light of above, the shortcomings were communicated vide this office letter No.F.15-22/2019 DD (PS) dated 31st August 2022 but reply is still awaited.**

6. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberations decided to defer the case for rectification of shortcomings and fulfillment of requirements as per Form-III of the Bio-Study Rules, 2017. Further, applicant is directed to provide requisite documents within 30 days positively.

AGENDA ITEM XXIX:

REQUEST FOR EXTENTION OF REGISTERATION OF ABDUL WAHEED TRUST HOSPITALS/ INSTITUTIONS AS PHASE-II CLINICAL TRIAL SITE (F. No.15-09/2022 DD (PS)).

The case is an application from Abdul Waheed Sheikh CNIC No.35201-1304557-7, Chairman, M/s Abdul Waheed Trust located at Avicenna Medical college & Hospital phase IX, DHA, Bedian road, Lahore wherein he has applied for Clinical Trial Site situated at Avicenna Medical college & Hospital, Phase IX, Bedian Road Lahore for Phase II. As per covering letter, the applicant has written that Abdul Waheed Trust is seeking approval as clinical trial site for Protocol Number TG2018V01 specific phase II site approval for trial titled as "A Global Multicenter, Randomized, Double -Blind, Parallel controlled Clinical Study to evaluate the Immunogenicity and safety of Different Production Scales and Batches of Recombinant SARS-CoV-2 Fusion Protein vaccine in Adults aged 18-59 Years". Application is on Form -I of the Bio-Study Rules 2017 with prescribed fee of Rs. 100,000/-.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Fee challan of Rs.100,000/- attached submitted vide slip No. 021275670104 dated 4th March 2022.
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. The applicant is Chairman of the trust.
4	Details of premises including layout plan of the site.	Layout plan of Avicenna hospital, Avicenna Medical college, Avicenna dental college and Hospital, Gulfreen Nursing College and Institute of Allied Health sciences is attached. **The details of Clinical Trial Site including its layout plan is required.**
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	**Not Attached**

6	Names and qualifications of the above sections along with their staff.	**Not Attached.**
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Attached
8	Undertaking on stamp paper	Attached.

3. After evaluation, it was noticed that application is from Abdul Waheed Sheikh , chairman Abdul Waheed Trust. Under the Umbrella of Abdul Waheed Trust, Avicenna Medical college, Avicenna Hospital, Avicenna dental College and hospital, Gulfreen Nursing College and Institute of Allied Health sciences are working. Applicant has attached the documents of all above mentioned institutions in his application.

4. Applicant may be asked to reply the following shortcomings;

i. Where the Clinical Trial Site is located? Is it a specific site or whole Abdul Waheed Trust?

ii. The details of Clinical Trial Site including its layout plan is required.

iii. Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.

iv. CVs of Staff working in Clinical Trial Site and analytical or Bio-analytical Lab and Abdul Waheed Sheikh are required.

5. The shortcomings/ queries were communicated vide this office letter No. F.15-09/2022 DD (PS) dated 21st April 2022.

6. The applicant submitted the reply on 27.04.2022 but not addressed the above mentioned queries. As per previously submitted Form-I, the CTS is located at Avicenna Medical College, as per site MAP its located in Avicenna Dental College Building and as per clinical trial layout MAP it is Avicena Hospital. Instead of analytical/ bio-analytical lab, applicant has enclosed list of Diagnostic Lab. Applicant has attached staff list working at CTU but list of staff working at analytical/ bio-analytical lab is not attached. Again shortcomings were communicated vide this office letter of even number dated 15th June 2022 and applicant submitted the reply on 23.06.2022 as following;

i. Abdul Waheed Trust and all its constituent institutions including: Avicenna Medical College, Avicenna Dental College, Avicenna Hospital, Gulfreen Nursing College, Institute of Allied Health Sciences and Avicenna Clinical Research Center, Student and Doctors Hostels are located on the same site of 23 acres as given in the site map earlier in Annex - A. The Clinical Trial Site Avicenna Clinical Research Center ' is located on the second floor of Avicenna Dental College block. CTS has been highlighted in yellow and labeled in Annex - A for your perusal.

ii. The details of Clinical Trial Site and its layout attached. Its location has been specified in para i above.

iii. For the requested Phase - II approval we have provided a justification letter (copy attached as Annex - C) regarding TG2108V01 Trial Specific Phase - II Site Approval. For this Phase - II trial

standard sampling / testing will not be performed at the Clinical Trial Site and shall be outsourced as follows: a. The RT - PCR sampling is outsourced to Central Laboratory in Pakistan b. For immunogenicity testing, as per protocol; samples will be taken at site level and further investigation will be performed in the laboratory outside Pakistan. Only Blood Urine Pregnancy Test (UPT), rapid IgG and testing will be performed at site level. Therefore, due the above reason, we do not need bioanalytical lab facility at the Clinical Trial Site as testing will not be performed Site. RT - PCR and immunogenicity testing will not be performed at the Clinical Trial Site and this testing will be outsourced as mentioned in point above, we do not need banalytical lab staff for this trial.

7. As per reply the applicant the CTS is located at 2nd floor of Avicenna Medical College and it was considered as trial specific for Protocol Number TG2018V01 specific phase II site approval for trial titled as "A Global Multicenter, Randomized, Double -Blind, Parallel controlled Clinical Study to evaluate the Immunogenicity and safety of Different Production Scales and Batches of Recombinant SARS-CoV-2 Fusion Protein vaccine in Adults aged 18-59 Years").

8. Accordingly, the following panel for inspection was constituted by the Director, Pharmacy Services Division;

ii. Prof. Dr. Javed Akram, VC, UHS, Lahore.
iii. Dr. Farhana Badar, Biostatician, SKCH&RC, Lahore.
iv. Mist. Majida Mujahid, Additional Director, DRAP, Lahore.
v. Rana Ahsan-ul-Haq Athar, AD (PS), DRAP, Islamabad.

9. **The panel visited the site on 5th September 2022 and following the queries the applicant requested for some time for re-inspection. The applicant has requested for re-visit but inspection was not conducted due to non-availability of members.**

10. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberations decided to defer the case for re-inspection. Further, the Committee delegated the powers to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference.

AGENDA ITEM XXX:

APPLICATION FOR APPROVAL OF REHMAN MEDICAL CENTER, PESHAWAR TO ACT AS CLINICAL TRIAL SITE FOR PHASE-II CLINICAL TRIALS (F. No.15-07/2022 DD (PS)).

The case is an application on Form-I of Bio-Study Rules 2017 from Dr. Dewan Talha Ashfaq NIC number 4200024481493 M/s Rehman Medical Institute, Hayatabad, phase-v, Peshawar, wherein applicant has applied for clinical trial site for clinical trials of Phase-II. The covering letter of the application is from Kholood Janjua where he/she has that the site is seeking protocol number TG2108V01 specific phase-II site approval for below mentioned trial titled "A Global, Multi-center, Randomized, double-Blind, Parallel-Controlled Clinical Study to evaluate the immunogenicity and Safety of Different Production Scales and Batches of Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01) in Adults Aged 18-59 years". The application is on Form-I of the Bio-Study Rules 2017 with fee of Rs. 100,000/-.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached. **The ID card Number on Stamp Paper is not correct.**
2	Prescribed processing fee	Fee challan of Rs.100,000/- attached submitted vide slip No. 78721978330 dated 11th March 2022.
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).	Applicant has attached certificate of incorporation of Rehman Medical Institute, ISO 9001:2015 certificate and Taxpayer Profile inquiry. **Legal status of the applicant is required** 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).**
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.	List of all medical equipment is attached. **Particularly list of equipment and machinery required for analytical/ Bio-analytical laboratory and Clinical trial site is required.**
6	Names and qualifications of the above sections along with their staff.	List of staff of CTU and HOD is attached. **The CVs of staff of CTU and Bio-Analytical Lab is required.**
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Attached
8	Undertaking on stamp paper	**ID Card Number on stamp paper is not correct.**

3. After evaluation, following shortcomings were found
   i. Particulars regarding the legal status of the applicant (Dr. Dewaan Talha Ashfaq and Kholood Janjua) 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) is required.
   ii. The ID card copies of both the applicants required.
   iii. The list of equipment and machinery required for analytical/ Bio-analytical laboratory and Clinical studies (particularly for phase- II) is required.
   iv. The CVs of staff working in CTU and Bio-analytical Lab is required.
   v. Stamp Paper from applicant with correct CNIC number is required.
4. The shortcomings were communicated vide this office letter No.F.15-07/2022 DD (PS) dated 13th April 2022. The applicant submitted the following in response to above mentioned letter.

Query communicated by this office	Reply of the Applicant
Particulars regarding the legal status of the applicant (Dr. Dewaan Talha Ashfaq and Kholood Janjua) 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) is required.	Applicant has attached the copy of CERTIFICATE OF INCORPORATION issued by THE COMPANY REGISTERATION OFFICE. **We may ask for the appointment/ Authority letter of the applicants and name and addresses of the Directors.**
The ID card copies of both the applicants required.	Attached.
The list of equipment and machinery required for analytical/ Bio-analytical laboratory and Clinical studies (particularly for phase- II) is required.	Applicant has attached the machinery for CTS. Further they submitted that they are applying for study specific phase-II approval and this particular would not require any bio-analytical testing at the hospital. All the samples will be shipped to the study sponsor and will be analyzed at at central laboratory.
The CVs of staff working in CTU and Bio-analytical Lab is required.	CVs of staff working at CTU is attached but they wrote that they are not applying for Bio-analytical laboratory.
Stamp Paper from applicant with correct CNIC number is required	They wrote that shared earlier bear correct CNIC number. **As per previously submitted stamp paper CNIC number is 00024481493 while correct number is 4200024481493 (as per Form-I)**

5. The following queries were communicated vide this office letter of even number dated 15th June 2022.

a. Appointment/ Authority letter of the applicants along with names and addresses of Directors.
b. The Stamp paper with correct CNIC number. As per previously submitted stamp paper bears CNIC number is 00024481493 while correct number is 4200024481493 (as per Form-I).

6. The Head of HR submitted Service/ appointment verification letter for Ms. Khlood Janjua and Authority letter for Dr. dewaan Talha Ashfaq with following wording.

"This is to certify that Dr. Dewan Talha Ashfaq s/o Mr. Dewan Ashfaq Ahmed is a regular employee of Reman Medical Institute, Peshawar since 15th September, 2020 and is presently working as Director operations.

This certificate is issued on the request of the employee and does not constitute any liability towards RMI or undersigned."

7. Again the following letter of even number dated 2nd August 2022 was written;

Dr. Dewan Talha Ashfaq,
M/s Rehman Medical Institute,
Hayatabad, phase-v,
Peshawar.

SUBJECT: APPLICATION FROM REHMAN MEDICAL INSTITUTE PESHAWAR FOR LICENSE TO ACT AS CLINICAL TRIAL SITE FOR PHASE-II FOR CLINICAL STUDY TITLED "A Global, Multicenter, randomized, Double Blind Parallel-Controlled Clinical Study to Evaluate the Immunogenicity and Safety of Different Production scales and batches of recombinant SARS-CoV-2 Fusion Protein vaccine (V-01) in Adults Aged 18-59 Years".

I am directed to refer to your reply submitted dated 04.07.2022 in response to this office letter dated 15.06.2022 for above mentioned trial specific CTS for Phase-II.

2. It is to inform that stamp requires the name of signatory at signature place on stamp paper describing the undertaking. Further since the clinical trial site is institution based instead of person, the liability of institution is required which was observed as denied as per appointment/ Authority letter

issued by the RMI, the institute and HR Head as per response dated 04-07-2022 from the institution/organization. Hence, in current scenario the application can't be entertained.

3. In view of above, you are advised to explain your position, do need full and submit clarification within seven (07) working days if you intend to proceed further with your application for the trial site.

-SD-
Assistant Director (Pharmacy Services)

Copy to;
1. CEO/ Head of Rehman Medical Institute, Hayatabad, phase-v, Peshawar.
2. Head of HR, Rehman Medical Institute, Hayatabad, phase-v, Peshawar

8. The reply was submitted by Mr. Imran Nabi, Head of HR, RMI, Peshawar in response to this office letter wherein he has stated that;

i. New stamp paper has been signed and stamped by the concerned authorized person i.e. Dr. Dewan Talha Ashfaq.

ii. Kindly consider the Authority letter sent to you dated 21.07.2022 in which it is clearly mentioned that Dr. Dewan talha Ashfaq has been authorized by RMI for correspondence with DRAP on behalf of RMI clinical trial unit. On stamp paper the signature of Dr. Deewan talha Ashfaq has been copy paste instead of original signature. Further, the letter written to Dr. Deewan Talha Ashfaq was returned.

9. Accordingly, following letter was written by this division on 22.09.2022 and reply is still awaited.

Head of HR (Mr. Imran Nabi,),
M/s Rehman Medical Institute,
Hayatabad, phase-v,
Peshawar.

SUBJECT: APPLICATION FROM REHMAN MEDICAL INSTITUTE PESHAWAR FOR LICENSE TO ACT AS CLINICAL TRIAL SITE FOR PHASE-II FOR CLINICAL STUDY TITLED "A Global, Multicenter, Randomized, Double Blind Parallel-Controlled Clinical Study to Evaluate the Immunogenicity and Safety of Different Production scales and batches of recombinant SARS-CoV-2 Fusion Protein vaccine (V-01) in Adults Aged 18-59 Years".

I am directed to refer to your reply submitted dated 17.08.2022 in response to this office letter dated 02.08.2022 for above mentioned trial specific CTS for Phase-II.

2. It is to inform that this office letter of even number dated 02.08.2022 was written to Dr. Dewan Talha Ashfaq, who is the applicant of subject CTS and copied to CEO and Head of HR of M/s Rehman Medical Institute, Peshawar. The letter written to Dr. Dewaan Talha Ashfaq was returned with the comments that *"this person is not not working here anymore, must be returned"*. The stamp paper submitted in above mentioned reply does not bear the original signature of Dr. Dewaan Talha Ashfaq, prima facie the signatures have been copied and pasted. On further inquiry this office came to know that applicant Dr. Ashfaq Talha Awan has resigned from M/s Rehman Medical Institute, Peshawar.

3. In light of above, you are advised to explain your position, do need full and submit clarification within seven (07) working days to proceed further in the matter.

-Sd-
Assistant Director (Pharmacy Services)

Copy to;
1. Dr. Dewaan Talha Ashfaq, Rehman Medical Institute, Hayatabad, phase-v, Peshawar.

10. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberations decided to reject the case and advised for submission of new application.

AGENDA ITEM XXXI:

APPLICATION FOR RENEWAL OF CTU AT AGA KHAN UNIVERSITY HOSPITAL, KARACHI TO ACT AS CLINICAL TRIAL SITE FOR PHASE-I, II, III & IV CLINICAL TRIALS. F. No.15-11/2019 DD (PS)

Application submitted by Dr. Saeed Sadiq Hamid (CNIC:42000-0516220-5), Director, Clinical Trial Unit, Aga Khan University Hospital, Stadium Road, Karachi, dated 07th September, 2022, received on 13th September, 2022. Wherein the request has been made for renewal of licence issued vide licence No. CTS-0003, dated 10th October, 2019, to act as CTU/CTS at Aga Khan University Hospital, Karachi. The application is on prescribed Form-III of the Bio-Study Rules 2017

with prescribed processing fee of Rs.100000/- paid vide challan No. 945048800, dated 06th September, 2022.

02. The above mentioned site license will be expired on 09th October, 2022 & different trials are active at the site. Now applicant submitted application for renewal of the site to act as CTU/CTS & to conduct Phase I, II III & IV Clinical Trials.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-III of the Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Rs.100000/- paid vide challan No. 945048800, dated 06th September, 2022
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.	Attached.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	List attached but equipments are not fulfilling requirement of tests required in Phase-I & Phase-II Clinical trials & the list of minimum equipments required for a bioanalytical assay in Phase-I/II Clinical Trials. Further there is no approved Bioanalytical laboratory at proposed site. Justification/reply from applicant need to be submitted.
6	Names and qualifications of the above sections along with their staff.	List of staff working at CTU, AKUH is attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Attached.
8	Undertaking on stamp paper	Attached.

04. After initial scrutiny following shortcoming(s) were observed:

vii. List of section wise equipment and machinery required for analytical or bio-analytical and clinical studies attached but equipments mentioned in the list are not fulfilling requirement of tests/assay required in Phase-I & Phase-II Clinical trials (i.e. Pharmacokinetic & Pharmacodynamics Studies). Further there is no approved Bioanalytical laboratory at proposed trial site. Justification/reply for management of Phase-I & II Clinical Trial assay & bioanalytical requirements need to be submitted by applicant.

05. Accordingly, after approval shortcomings communicated to applicant vide letter bearing even number dated 03rd October, 2022.

06. Applicant submitted reply in reference to this Division's letter dated 03rd October, 2022. Reply is reproduced as under:

i. *Some of our international Phase 2-3 clinical trials require Pharmacokinetic / Pharmacodynamics samples to be taken as part of the protocol. These samples are sent to central laboratories overseas that are designated by the sponsors. We therefore do not perform Pharmacokinetic/Pharmacodynamics studies at our site currently. However, in the future we may be able to set up the required analytical equipment for such studies.*

ii. *We have not yet performed a Phase I study, and can obtain permission to do such studies separately whenever the need arises. So kindly proceed with our renewal application accordingly, and specific the clinical trials phases that the CSC approves our unit for.*

07. In view of above, it is proposed that, a panel of expert may be nominated by CSC/Chairman CSC for verification & availability of facilities, skilled & trained human resources & equipment required for Phase-I, II, III & IV Clinical Trials.

08. Further it is proposed that, "Scope of Clinical Trial Site" needs to be mentioned on each license.

09. Submitted for constitution of panel of experts for inspection & consideration of CSC:

10. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and deliberations decided to approve the site subject to inspection panel recommendation & the Committee delegated the powers to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference.

Further, the Committee directed to applicant to provide details regarding Bio-Analytical Laboratories to be utilized in Phase-I & II Clinical Trial(s). In case foreign or Sponsor designated Bio-Analytical Laboratories is involved in PK/PD Assays, regulatory approval of respective country's regulatory body may be provided.

AGENDA ITEM XXXII:

RENEWAL & AMENDMENTS APPROVAL FOR CLINICAL TRIAL TITLED, "A PHASE-III, MATRIX DESIGN, PARTIALLY DOUBLE BLIND, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF 50mg LONAFARNIB / 100mg RITONAVIR BID WITH & WITHOUT 180mcg PEG IFN-ALFA-2A FOR 48 WEEKS, COMPARED WITH PEG IFN-ALFA-2A MONOTHERAPY AND PLACEBO TREATMENT IN PATIENT CHRONICALLY INFECTED WITH HEPATITIS DELTA VIRUS BEING MAINTAINED ON ANTI-HBV NUCLEOS (T) IDE THERAPY (D-LIVR)". F.NO.03-08/2019 DD (PS).

Application for extension/renewal of subject Clinical Trial is from Dr. Saeed Hamid (PI) & Director, Clinical Trial Unit, Aga Khan University, Karachi, dated 10th August, 2022, received on 15th August, 2022.

2. Applicant request is reproduced as under:

Dear Chair,

I am writing with reference to your approval letter for the study title " A PHASE 3, MATRTX DESIGN, PARTIALLY DOUBLE.BLIND, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF 50 IVIG LONAFARNIB/ 1OO 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 (D-LIVR) Reference No.: F.No.03-08/2019-0D (PS)" dated 15 Oct 2021to request one year extension and the approval of the following amendments on behalf of Dr. Saeed Hamid (Pl of D-LIVR study).

We have enrolled 53 patients out of 80 as per approved license No. CT0002. We are expecting last patient last visit in March 2023.

The study has been received the ERC and NBC extension approvals:

- *ERC extension approval: 10 January 2022 (Attached in annexure)*
- *NBC extension approval: 08 March 2022 (Attached in annexure)*

Following are the list of Amendments: (Attached in Annexure)

i. *EIG-LN F-ol1_Protocol Amendment 03_29 Oct2021 Final signed*
ii. *EIG-LNF-011 PA03 Clarification Letter 01 (Global)_2022-03-03a signed*
iii. *EIG-LNF-o11 PA02 Clarification Letter 02 (Global)_202f 06 22*
iv. *LNF IB Ed 9.o_Final 27 Jan 2oz2_si1ned*
v. *Main ICF V6.0PAKV1.0dated 20 Apr 2022 _Track changed English/ Urdu*

ERC and NBC approvals have been received for the above amendments. (Attached in Annexure)

i. *ERC approval letter 16Jun 2022_ PA03, lBv09, ICF v6.0, PA03 clarification letter*
ii. *NBC-384 Amendment Approval letter 07.07.2022_PA03, tBv09, ICF v6.0, PA03 clarification*
iii. *letter*
iv. *ERC approval letter 08 Dec 2021_ PA02 clarification letter 202L 06 22*
v. *NBC-384 Amendment Approval letter 23 Dec 2021_ PA02 clarification Letter 2021 06 22*

DRAP approval of following documents is pending. Submission letter dated O4th Jan 2022 and 1Os Feb 2022 is attached. (Attached in Annexure)

i. *LNF IB Ed 8.0 Final 2lJan2L redline since Ed 7.1 corrected*
ii. *IB V8_Addendum_Eiger_with signature*
iii. *Amendment to Protocol EIG-LNF-011 v.2.O- 22 Sep 2027*

Import license has been taken on L9 Nov 2021for below mentioned quantities.

	Kits Approval	*Kits imported Yet*	*Remaining Kits*
Tablets Lonafarnib and Ritonavir (Active/Placebo)	*960*	*386*	*960-386=574*
PEG IFN-alfa-2a	*420*	*186*	*420-186=234*

3. Applicant also provided Prescribed processing fee of Rs. 25000/- paid vide challan No. 16373567921, dated 11th August, 2022.

4. In view of above, extension in trial duration may be granted as per NBC approved period & amendment may be considered by the CSC.

5. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to approve extension in trial duration as approved by the NBC, for a period of one year w.e.f. 07th July, 2022.

Further, the Committee also approved following proposed amendments for Clinical Trial titled "A Phase 3, Matrix Design, Partially Double-blind, Randomized Study of the Efficacy and Safety of 50

IVIG 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 (D-LIVR)".:

i. *EIG-LN F-011_Protocol Amendment 03_29 Oct2021 Final signed*
ii. *EIG-LNF-011 PA03 Clarification Letter 01 (Global)_2022-03-03a signed*
iii. *EIG-LNF-011 PA02 Clarification Letter 02 (Global)_2021 06 22*
iv. *LNF IB Ed 9.0_Final 27 Jan 2022_signed*
v. *Main ICF V6.0PAKV1.0dated 20 Apr 2022 _Track changed English/ Urdu*

AGENDA ITEM XXXIII:

TRANEXAMIC ACID (TXA) FOR REDUCING POSTPARTUM BLEEDING IN WOMEN WITH ANEMIA: AN INTERNATIONAL, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL (WOMEN-II TRIAL) (F. No.03-03/2019-DD (PS))

The "TRANEXAMIC ACID (TXA) FOR REDUCINGPOSTPARTUM BLEEDING IN WOMEN WITH ANEMIA: AN INTERNATIONAL, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL (WOMEN-II TRIAL)" was approved in July 2019 wherein the PI is Prof. Dr. Rizwana Chaudhary, Principal Scientist GIHD-STMU, Islamabad.

2. Prof. Dr. Rizwana Chaudhary, Principal Scientist GIHD-STMU submitted a letter 21.07.2022 wherein she has stated that she is thankful to DRAP members for supporting Woman 2 Trial. She has applied for drug import licence on 25th April 2022. As per requirement of the licensing department, she hereby applying for approval of quantities mentioned in import licence application (80 drug boxes in total). She has attached the detailed report of drug boxes imported.

3. Applicant has provided list of Expired Drug Boxes at site/ Distribution Center, proof of destruction as site, proof drug destruction at PNCC. As per rule 8 (13) of Bio-Study Rules 2017 (13) The destruction of unused investigational products should be carried out after seeking approval from CSC which shall nominate officers to accompany during the process of destruction of investigational products". Applicant has destroyed without approval from CSC and also has not attached the prescribed fee under miscellaneous heading.

4. Accordingly following letter No.F.03-03/2019 DD (PS) dated 05th August 2022 was written to PI but no response has been received yet.

Prof. Dr. Rizwana Chaudhri,
Head of Translational Research Department,
Shifa Tamer-e-Millat University,
Pitras Bukhari road, Sector H-8/4,
Islamabad.

Subject: APPLICATION AMENDMENT OF CLINICAL TRIAL TRANEXAMIC ACID (TXA) FOR REDUCING POSTPARTUM BLEEDING IN WOMEN WITH ANEMIA: AN INTERNATIONAL, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL (WOMEN-II TRIAL).

I am directed to refer to your application, dated 18th July, 2022, wherein you have requested for approval to import the Investigational Medicinal Products and had submitted the destruction details of previously imported IMPs.

2. As per SRO 1047 (I)/2019, fee for miscellaneous applications is Rs. 25,000/- that has not been deposited with your application. Secondly, as per rule 8 (13) of Bio-Study Rules 2017 (13) The destruction of unused investigational products should be carried out after seeking approval from CSC which shall nominate officers to accompany during the process of destruction of investigational products" while as per this office record you have destroyed the products without approval of CSC.

3. Therefore, it is advised to explain your position regarding queries in para 2 to proceed further in the matter please.

-Sd_
Assistant Director,

5. The letter signed by National coordinator and Chief Investigator of the trial was submitted on 04.08.2022 wherein they have stated that CTS Aziz Bhatti Shaheed Teaching Hospital, Gujrat is withdrawn from the trial site, primarily because of low event rate.

6. The following letter was written to the Prof. Dr. Rizwana Chaudhary on 7th September 2022 but no reply has been received yet.

Prof. Dr. Rizwana Chaudhri,
Head of Translational Research Department,
Shifa Tamer-e-Millat University,
Pitras Bukhari road, Sector H-8/4,
Islamabad.
Subject: APPLICATION AMENDMENT OF CLINICAL TRIAL TRANEXAMIC ACID (TXA) FOR REDUCING POSTPARTUM BLEEDING IN WOMEN WITH ANEMIA: AN INTERNATIONAL, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL (WOMEN-II TRIAL).

I am directed to refer to your application, dated 26th July, 2022, wherein you have informed to withdraw the clinical trial site situated at Aziz Bhatti Shaheed Teaching Hospital, Gujrat.

2. It is informed that you have not attached detailed activities/ progress report with your letter regarding trial site under reference. Further reply to this office letter of even number dated 5th August 2022 (Copy enclosed for ready reference) is still awaited.

3. In view of above, it is advised to submit detailed progress report of said trial including SAEs on CIOMS form, complete activities carried out on the site under reference, trial subject follow up status along with reply to this office letter dated 5th August 2022 to proceed further in the matter please.

-Sd-
Assistant Director,

7. The letter signed by Dr. Rizwana Chaudhary and Haleema Shakur-still was submitted on 31.08.2022, wherein, they have stated that PI of the following sites have been changed due to previous PI retirement.

Site	Previous Investigator	New Investigator
Ayub Teaching Hospital	Prof. Aziz Un Nisa Abbasi	Prof. Ansa Aslam
Bahawal Victoria Hospital Unit - 1	Prof. naheed Fatima	Prof. Sohail Mehmood Chaudhary
Bahawal Victoria Hospital Unit - 2	Prof. Bushra Sher Zaman	Prof. Shakila Yasmin
Civil Hospital Karachi Unit 1	Prof. Fauzia Perveen	Prof. Sarah kazi
Civil Hospital Karachi Unit 3	Prof. Nusrat Shah	Prof. Riffat Jaleel
JPMC karachi Ward 9	Prof. Khadija Bano	Dr. Saba Khan
Nishtar Hospital Unit 1	Prof. hajira Masood	Prof Syda Ali

Applicant submitted that they have notifies NBC and Local Ethics Comittee at the sites. Further they have attached the following documents;
New PI HPICV and CV
New PI GCP Training Certificate
DRAP licence to act as CTS

8. The Hospital/ PI information form is not readable after scanning, further ethics committee approvals not attached. Also fee required under heading of miscellaneous requests is required. Accordingly, following letter was written vide letter of even number dated 21.09.2022.

Prof. Dr. Rizwana Chaudhri,
Head of Translational Research Department,
Shifa Tamer-e-Millat University,
Pitras Bukhari road, Sector H-8/4,
Islamabad.
Subject: APPLICATION AMENDMENT OF CLINICAL TRIAL TRANEXAMIC ACID (TXA) FOR REDUCING POSTPARTUM BLEEDING IN WOMEN WITH ANEMIA: AN

INTERNATIONAL, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL (WOMEN-II TRIAL).

I am directed to refer to your letter, dated 31st August, 2022, wherein you have written to notify the committee about changes of PI at some clinical trial sites.

2. It is informed that some copies of documents (WhatsApp photos) submitted are not readable. Further, ethics committee approvals, detailed activities/ progress report by the previous PI and prescribed fee is not attached with the letter. Also response to this office letters of even number dated 5th August 2022 and 7th September 2022 is still awaited.

3. Hence, you are advised to submit readable copies/ original documents, ethics committee's approvals, detailed activities/ progress report signed by the previous PI, subject follow up details, SAEs on CIOMS from, prescribed fee along with reply to this office letters of even number dated 5th August 2022 and 7th September 2022 within seven (07) working days to proceed further in the matter.

Assistant Director,

9. **The applicant has not submitted the reply to above mentioned letters yet.**

10. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberations decided to defer the case for rectification of all shortcomings and fulfillment of requirements as communicated by the Division.

Further, applicant is directed to provide requisite documents within 30 days, failing which the application is liable to be rejected.

AGENDA ITEM XXXIV:

APPLICATION FOR APPROVAL AND REGISTRATION OF CLINICAL TRIAL TITLED "A GLOBAL MULTICENTER, RANZOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, ADAPTIVE DESIGNED PHASE III TRIAL TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF RECOMBINANT NOVEL CORONA VIRUS VACCINE (ADENOVIRUS TYPE 5 VECTOR) IN ADULTS 18 YEARS OF AGE AND OLDER". (F.No.03-69/2021 DD (PS)).

The subject cited above protocol was approved by CSC in its 27th meeting held on 24th June 2021 with following decision;

a. *The CSC after detailed deliberation and discussion decided to approve the protocol amendments (CS-CTP-AD5NCOV-III Version 2.0) in clinical trial titled "A Global Multicenter, Randomized, Double Blind, Placebo Controlled, Adaptive Designed Phase III Trial to Evaluate the Efficacy, Safety and Immunogenicity of Recombinant Novel Corona Virus Vaccine (Adenovirus Type 5 Vector) In Adults 18 Years of Age and Older". The trial as per amended protocol will be conducted at the following sites in the light of their respective IRB approvals:*
   i. *Agha Khan University, Karachi.*
   ii. *The Indus Hospital, Karachi.*
   iii. *Shaukat Khanum Memorial Cancer Hospital & Research Center, Karachi.*
   iv. *Shifa International Hospital, Islamabad.*
   v. *University of Health Sciences, Lahore.*
b. *CSC also approved 16,560 doses of Investigational products to be used in this trial.*

2. Major General, Prof. Dr. Aamir Ikram, PI, submitted following Comprehensive Annual Progress Report;

Investigator Name/ Site	Random. Subject	Total vaccinated	SAE Update	Covid Expected	PCR + Corona Case	Number of ADRs/ AEFIs	Deviation Major/ Minor
Dr. Ejaz Ahmed Khan/ Shifa International (9201)	5485	5409	25	308	184	124	05
Dr. Salma Abbas/ SKMCH& RC (9202)	1033	1029	8	282	88	Nil	Not any major study deviation
Dr. Faisal Mehmood/ Agha Khan University Hospital (9203)	3111	2899	32	639	165	59	29
Dr. Naseem Salahuddin/ The Indus Hospital (9204)	3169	3036	5	560	80	Nil	18 Minor
Dr. Javed Akram/ UHS, Lahore (9205)	5034	4875	17	201	149	464	35 Major 516 Minor Total 550

3. The applicant was advised to report SAEs on Adverse Event Reporting Form (CIOMS), duly endorsed by IRB in hard and soft copy vide this office letter F.No.03-69/2021 dated 29th December 2021.

4. Meanwhile, Mst. Ghazala Perveen, *Co-PI*, submitted following NTF (change of study plan) on 24th December 2021.

Subject: To cancel blood sample collection on Week 52 post 1" dose and Week 24 post 2nd dose

This memo to file is to document that there will be no blood collection for all study cohorts for Week 52 post 1st dose and Week 24 post 2nd dose for subjects as described below:

1. For subjects who received the first dose, no Week 52 blood samples will be collected.

2. For subject who received the second dose, no Week 24 blood samples will be collected.

3. For subjects who have already completed Week 52 post 1st dose or Week 24 post 2nd dose visit, please send the serum samples to Nexelis according to the protocol.

Considering the efficacy of the vaccine against the symptomatic disease, and the evidence from other vaccines, we believe it may not meaningful to collect so many blood samples to evaluate the efficacy against the asymptomatic disease.

The amendment will not increase the risk of the subjects, only reduced the sampling, we suggest that there is no need to re-sign the informed consent form, only verbally inform subject and however; subject compensation will not be changed and record it in the source document.

5. Likewise, Major General, Prof. Dr. Aamir Ikram, PI, submitted following Comprehensive Progress Report on 27th December 2021;

Investigator Name/ Site	Random. Subject	Total vaccinated	SAE Update	Covid Expected	PCR + Corona Case	Number of ADRs/ AEFIs	Deviation Major/ Minor
Dr. Ejaz Ahmed Khan/ Shifa	5485	5409	27	308	178	(MAE) 121 Not related to vaccine	18

International (9201)							
Dr. Salma Abbas/ SKMCH& RC (9202)	1033	1029	9	301	93	Nil	Not any major study deviation
Dr. Faisal Mehmood/ Agha Khan University Hospital (9203)	3111	2899	0	27	0	0	Not any major study deviation
Dr. Naseem Salahuddin/ The Indus Hospital (9204)	3160	3085	0	30	0	Nil	Not any major study deviation
Dr. Javed Akram/ UHS, Lahore (9205)	5034	4875	0	0	0	0	Not any major study deviation

6. The following letter was written to Mst. Ghazala Parveen, *CO-PI*, in reponse to above letters on 11th January 2022.

Ghazala Parween,
Co-Principal Investigator,
National Institute of Health,
Islamabad.

Subject: A GLOBAL MULTICENTER, RANZOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, ADAPTIVE DESIGNED PHASE III TRIAL TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF RECOMBINANT NOVEL CORONA VIRUS VACCINE (ADENOVIRUS TYPE 5 VECTOR) IN ADULTS 18 YEARS OF AGE AND OLDER.

I am directed to refer to your letter No. ISB-BPD-ADMN-File-43, dated 24th December 2021, wherein you have submitted the change in the study plan regrading subject mentioned Clinical Trial and comprehensive progressive reports of phase III clinical trial of Ad5-nCoV dated 14th October 2021 & 27th December 2021.

2. The requisite fee for amendment in protocol is not attached with submitted change in study plan. Further, due to changes in trial/ study protocol will stand amended so, approval from NBC and all respective IRB approvals also need to be furnished. Moreover, the submitted progress reports varies in SAE updated, Corona Suspected cases, PCR +ve cases and number of ADRs/AEFIs etc.

3. It is therefore advised to submit the requisite fee as per SRO 1047 (I)/2019 dated 12th September 2019 and NBC & IRB approvals regarding the amendment in the study/ trial protocol due to changes made in study plan to further process your request No. ISB-BPD-ADMN-File-43, dated 24th December 2021. You are further directed to clarify the variation/ difference in number of SAEs updated, Corona Suspected cases, PCR +ve cases and number of ADRs/AEFIs etc in submitted progress reports along with detail of each SAE on Serious Adverse Event Reporting Form (CIOMS), duly endorsed by IRB of each site, as hard and soft copy (as was already requested vide this office letter even number dated 29.12.2021).

4. The information/ documents as stated in para 3 above be furnished at earliest to proceed further in the matter.

Assistant Director (PS)

7. Mst. Ghazala Perveen, *Co-PI* of study submitted following Comprehensive Progress Report on 12th January 2022;

Investigator Name/ Site	Random. Subject	Total vaccinated	SAE Update	Covid Expected	PCR + Corona Case	Number of ADRs/ AEFIs	Deviation Major/ Minor
Dr. Ejaz Ahmed Khan/ Shifa International (9201)	5485	5409	27	308	179	(MAE) 121 Not related to vaccine	19

Dr. Salma Abbas/ SKMCH& RC (9202)	1033	1029	9	301	93	Nil	Not any major study deviation
Dr. Faisal Mehmood/ Agha Khan University Hospital (9203)	3111	2899	0	22	3	2	Not any major study deviation
Dr. Naseem Salahuddin/ The Indus Hospital (9204)	3160	3085	0	21	0	Nil	1
Dr. Javed Akram/ UHS, Lahore (9205)	5034	4875	0	0	0	0	0

8. The Mst. Ghazala perveen was again advised by this office letter of even number dated 31.01.2022 to submit SAEs alongwith Serious Adverse Event Reporting Form (CIOMS) duly endorsed by PI/ Co-PI & IRB of each site in hard and soft copy.

9. Mst. Ghazala Perveen, submitted her following reply on 1st February 2022;

"Reference your letter No. 03-69/2021 DD(PS) dated 31 January 2022 regarding the submission of details of SAE. In this regard it may be noted that the above mentioned study was approved on 22nd September 2020 and undersigned has been submitting SAE, along-with monthly reports, but no such form (CIOMS) was demanded during the course of action. Now after passing one and half year these forms have been demanded in this connection, it is intimated that the desired data is very huge and transferring of data is time consuming activity. However, all the sites have been advised to provide the scan copies of these forms

As soon as the data is received, the same will be sent to your good office on e-mail, you are therefore need to provide the email address on which the soft copies can be sent."

10. The Mst. Ghazala Perveen was again advised by this office letter of even number dated 04.02.2022 to submit SAEs along with Serious Adverse Event Reporting Form (CIOMS) duly endorsed by PI/ Co-PI & IRB of each site in hard and soft copy.

11. Mst. Ghazala Perveen, submitted her following reply on 7th February 2022;

"Reference your letter No.03-69/2021-DD(PS) dated 4" February 2022 undersigned is well aware of the study protocols and COIMS forms and all sites recorded the SAES in this forms on regular basis,

As clarified in the previous letter of even No dated 1 February 2022, that this data of SAES is very huge and collection of this data is time consuming activity, further, it has never been demanded separately before by your good office. However, all the sites have been advised to provide the data on urgent basis as soon as it is received will be forwarded to your office.

Further, refer to para 3/N. it is required to provide the referred SRO related to endorsement of CIOM form from Principal Investigator (PI)/Co PI and sites IRBS so that the same can be communicated to all Sites for implementation."

12. Mst. Ghazala Perveen Co-PI, in response to this office letter of even number dated 11th January 2022, submitted fee Rs. 25,000/- for changes in study plan along with NBC approval dated February 2022 (approved for six months only), IRB approval from Agha Khan University Hospital, Indus Hospital & Hospital Network (Expiration date 02 October 2022) on 22nd February 2022.

i. They have not submitted IRB approval from UHS, Lahore, SKMCH&RC, Lahore and Shifa International Hospital, Islamabad despite of letter of this division of even number dated 1st March 2022.

ii. Fresh NBC approval and submitted IRB approvals of Indus Hospital and Agha Khan Hospital required.

13. Major General, Prof. Dr. Aamir Ikram submitted comprehensive progress report on 30th March 2022 for month of February 2022, on 26th April 2022 form month of March 2022 on 18th may 2022 for month of April 2022, on 28th June 2022 for month of May 2022, 25th August for month of July 2022and Development Safety Update Report (DSUR) on 14th May 2022.

14. The Director, Division of Pharmacy Services, nominated following two experts to investigate the matter for finding out root cause of SAEs and review the DSUR. Further, they were requested to generate the report on SAEs and DSUR and same was to be placed before the CSC in its forthcoming meeting. Furthermore, it was requested that confidentiality may be maintained as required. The soft copy of the SAEs & DSUR were sent through email on 04.07.2022;

Dr. Aamir Jaffary, SIUT, Karachi

Prof. Dr. Mushtaq Ahmed, Prof. of cardiology, Bacha Khan Medical College, Mardan.

15. Dr. Aamir Jaffery replied that I am unavailable for these tasks due to current work and travel commitments. Then Dr. Ahson Siddique, CEO, Sindh Healthcare Commission, was nominated to replace Dr. Aamir Jaffary. Both experts were requested to investigate root cause of SAEs and review DSUR on 01.08.2022 through email.

16. Prof. Dr. Mushtaq Ahmed wrote through email that "Would you kindly to send us a hard copy of the same as it is very difficult to go through this in the soft form" and Dr. Ahson Siddique wrote "I would also prefer to receive hard copies of relevant documents". Accordingly, Mst. Ghazala Perveen was requested on 26th August 2022 to submit two sets of hard copy of DSUR, Monthly Progress Report, SAEs on CIOMs form and latest study protocol for onward submission to experts. Instead of submission documents she replied that hard copies of DSUR and SAEs on CIOMS form was provided to your office along with flash drive in February 2022. All study protocols including required documents were submitted in your office along with sodft copies. Further, sites only provide the progress report in the form of SAEs summary but not the CIOMS form. If you are desired CIOMS form of any specific site, kindly intimate because 5 sites are engaged in the study since last two years.

17. She was again communicated vide this office letter of even number dated 04.10.2022 as following and reply is still awaiting.

Ghazala Parveen,
Co-Principal Investigator,
National Institute of Health,
Islamabad.

Subject: A GLOBAL MULTICENTER, RANZOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, ADAPTIVE DESIGNED PHASE III TRIAL TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF RECOMBINANT NOVEL CORONA VIRUS VACCINE (ADENOVIRUS TYPE 5 VECTOR) IN ADULTS 18 YEARS OF AGE AND OLDER.

In continuation to this office letter of even number dated 26.08.2022 and your good office letter ISB-BPD-ADMN-File-43 dated 01.09.2022, it is submitted that SAEs of subject mentioned trials were never reported to this office on CIOMS form (hard copies) while CIOMS form is the part of your submitted application. It is also mentioned that the finding of ERC/IRB were also never submitted to this office. Keeping in view the safety of the subjects participating in the trial, it was decided to take the comments/ opinion/ recommendation from the independent/ unbiased experts. The data was sent to experts through email (as soft copy) while they desired all related documents as hard copy.

2. Hence you are once again requested to submit two sets of DSUR, monthly progress reports, SAEs on CIOMS form and latest study protocol for onward submission to the experts as hard copy. You are again requested to submit the desired documents within three (07) working days positively.

Assistant Director (PS)

Copy to;
1. M/s Dimension Research (CRO & SMO), B-213, Block 2, Gulsitan-e- Johar, Scheme 36, Karachi.

18. **Applicant has not responded to this Division letter yet**

19. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberations decided to defer the case for rectification of the shortcomings and fulfillment of requirements as communicated by this Division.

Further, applicant is directed to provide requisite documents within 30 days, failing which the application is liable to be rejected.

AGENDA ITEM XXXV:

PROTECT TRIAL APPLICATION FOR THE REGISTRATION OF PROTECTS CLINICAL TRIAL TITLED HYDROXYCHLOROQUINE, OSELTAMIVIR AND AZITHROMYCIN FOR THE TRAETMENT OF COVID-19. F.NO.3-21/2020-DD (PS)

Application is from Prof Dr. Javed Akram Vice Chancellor University of Health Sciences, Lahore wherein they have submitted the study close out report as under

"that we are in the final close out report of a Subject study as per Bio Study Rules, 2017. This was a Clinical Trial for mildly symptomatic, RT-PCR positive patients. At the time of recruitment, majority of the participants were admitted to eleven Government Hospitals (including isolation centers) in Pakistan across eight cities. Please note the following key points regarding the study:

• The interim results were released separately on July 20, 2020, in Lahore and

September 04, 2020 in Muzaffarabad.

• No SAE/E reported during the whole study.

• All the hospitalized enrolled patients who became negative to PCR test or became

asymptomatic were shifted for home isolation. No adverse events reported after the

discharge from the hospital facility.

• Study data is archived on dashboard maintained by the University of Health Sciences Lahore and remain available to audit and inspections. The diagnostic data of participants is also archived at the web portal designed by Government of Punjab.

• All the sites are officially closed and close out notification has been sent to their

respective IRBs/ECs. All digital logins and access provided to the sites stand withdrawn

since May 2021.

• The accountability and reconciliation of the investigational product has been done by the site pharmacists with support of central pharmacy/sponsors of investigational

products (IPs).

• The study was paused as required by the Regulatory Authorities in May 2020 and was allowed to be restarted again in mid-June 2020.

• Upon advice of the Chair, National Data Safety & Monitoring Board (meeting attended by Mr. Zeeshan Danish), recruitment for this study was officially notified as finished during January 2021 owing to recruitment failure.

• After the close out, the investigators met with Principal Investigator telephonically to finalize the formalities and accounting of the investigational product leftover at each site. It was also decided to keep study material including, patient's source notes, and informed consent forms archived at sites and the study data to be retained online for any stakeholder's review, audit, or inspection. IPs were sponsored by Getz Pharma and Tegma Pharma.

• The study biostatistician has been un-blinding the trial data for analysis and results will be made available as soon as finalized.

2. **It is submitted that the instant application was placed before CSC in its 9th meeting held on 8th of April 2020 and the decision of CSC is as under:-**

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

3. As per record of this office available on file the applicant failed to reply within one week hence the approval stands deferred as per decision of the CSC and as per record available in this division till date no registration letter was issued as the same was not approved by competent forum. Now the applicant has submitted the final close out report of the study.

4. The request of the applicant is submitted before CSC for guidance and further necessary action on the matter.

5. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberations decided to reject the case due to non-compliance to the CSC decision taken in the 9th meeting of CSC, held on 8th April, 2022.

AGENDA ITEM XXXVI:

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 PLUS TRIAL.

The case is from Dr. Aun Raza consultant physician infectious diseases of M/s Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore, dated 20th September 2021, wherein he has applied for approval/ registration 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 plus trial." Using Inj. Artesunate, Imatinib and Infliximab.**

2. After initial scrutiny, following mandatory pre-requisite may kindly be requested from applicant for further processing the application.

i. Prescribed fee as per S.R.O 1047 (I)/2019 dated 12th September, 2019.

ii. Clarification whether it is a new trial or amendment in already applied trial i.e. an international randomized trial of additional treatments for COVID-19 in hospitalized patients who are all receiving the local standard of care. Solidarity trial using Chloroquine or hydroxychloroquine, lopinavir plus ritonavir and interferon beta.

3. After evaluation of your reply and documents/information furnished on the matter in response to this division letter dated 01st December, 2021, it is requested to submit application on Form-II as fresh application along with all pre-requisite as required under Bio-Study Rules, 2017 due to following reasons vide letter dated 6th January 2022.

i. In Solidarity Trial drugs/IMPs to be used are Hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir and Interferon whereas in Solidarity Plus trial different drugs/IMPs i.e. Artesunate, Imatinib and Infliximab are being used as compared to Solidarity Trial which tantamount to major change in trial/study.

ii. Title of trial is different i.e. Solidarity Trial has been changed to Solidarity Plus Trial.

iii. Protocol of the trial is completely changed.

iv. The last version in Solidarity Trial is 10.0, if we consider it as amendment next version must be 10.1 but in Solidarity Plus Trial Protocol version 1.0 has been drafted afresh supporting it to be a new trial/study.

v. As per WHO ERC / COVID-19 Review Summary – Approval submitted by applicant it is also not clearly mentioned that this is an amendment in Solidarity Trial. However, study/trial protocol ID are different which also indicate the trial under reference a new trial.

4. In view of above and also agreed on telephonic discussion in detail with Dr Sadia representative of applicant, it is therefore advised to apply on prescribed Form-II along with other pre-requisites including prescribed fee so that your application can be evaluated for further processing and its placement before the Competent Forum i.e. CSC for its consideration.

5. the applicant Dr. Aun Raza consultant physician infectious diseases of M/s Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore, forwarded through **what's app**, wherein he has enclosed the copy of Form-II for approval/ registration 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 Acronym: Solidarity Plus Trial)** along with copy of fee challan slip No.256391126292 dated 11.01.2022.

6. The already submitted application has been evaluated in the light of newly submitted Form-II as followings:

7. The details of evaluation as per checklist provided in Bio-Study Rules 2017 are as followings;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Fee	copy of fee challan slip No.256391126292 dated 11.01.2022.
3	Investigator Brochure (s)	SmPC attached instead of investigator Brochure.

4	Final protocol	Attached.
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	52 countries around the world in collaboration with WHO
7	Phase of trial.	Phase 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.	Artesunate 850 vials Imatinib 600 Tablets Infliximab 160 vials
9	Site of the trial	Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore. Pakistan Institute of Medical Sciences (PIMS) Islamabad. Shifa International Hospital, Islamabad. Agha Khan University Hospital AKUH, Karachi. Indus Hospital, 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 Shaukat Khanum Memorial Cancer Hospital and research Center, Indus Hospital, Shifa International Hospital, as amended approval in solidarity trial (Solidarity plus) is attached. Protocol number is the same. Approval from Shaheed Zulfiqar Ali Bhutto medical university for Solidarity plus trial is attached. **Only the composition of IRB of SKCH&RC is attached.** **IRB approval of agha Khan hospital not attached.**
11	Approval of National Bio-ethics Committee (NBC)	**An international randomized trial of additional treatments for covid-19 in hospitalized patients who are all receiving the local standard of care". (Trial Acronym: Solidarity (covid-93)** is **a**ttached
12	CV's of the Investigators	CVs of Dr. Aun Raza, Dr. Faisal Sultan, Salma Muhammad Abbas, Dr. Shahzeb Khan, Dr. Naseem Akhtar, Dr. Ejaz A. Khan, Dr. Nosheen Yasir, Dr. Syed Faisal Mehmood, Dr. Samreen Sarfraz are attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	CoA & GMP certificate for Artisunate of IPCA Laboratory, India is attached. CoA & GMP certificate for Imatinib of Lec pharmaceutical, A Sandoz company, Poslovna is attached.

		CoA & GMP certificate for Infliximab of Jansen, Cilag AG, Switzerland is attached. **COPP or Free Sale Certificate not attached.**
14	Pre-clinical/clinical safety studies	Applicant submitted that its available in SmPC.
15	Summary of Protocol	Trial Standard Operating Procedure and appendix attached.
16	Summary of Investigator Brochure	SmPC attached
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Around 120 patients
19	Name of Monitors & Clinical Research Associate	Clinical Trial Unit of the University of Bern will conduct the global monitoring. Trial Steering Committee and its Executive group, WHO Trial center, Geneva and Global Data and Safety monitoring committee etc. will monitor.
20	Evidence of registration in country of origin.	SmPC attached.
21	Copy of registration letter (if registered in Pakistan)	IMPs are to be imported.
22	Sample of label of the investigational product / drug.	Label of Artesunate (Larinate) & Infliximab (KitNumb) is attached. Label of Imatinib is not Attached.
22	Duration of trial	One year
23	Undertaking on Stamp paper	Not provided.

8. This trial will be carried out in collaboration with WHO and is being managed by R & D blueprint team at WHO Headquarters, Switzerland. Trial governance will be at following levels:

i) **Trial steering Committee-** this will govern the conduct of trial in accord with the agreed international protocol, amended as necessary during the study. The National PI would be part of this committee.

ii) **Executive Group of steering Committee-** For practically a smaller executive group of about 5-9 members of this committee will be setup in consultant with WHO to confer electronically at frequent intervals with WHO to ensure trial steering committee is appropriately informed and consulted.

iii) **WHO Trial Center (Geneva)-** this will be responsible for the conduct of trial and remote central monitoring of collected data.

iv) **Global Data and Safety Monitoring Board-** this independent committee will examine confidential interim analysis of safety and efficacy, reporting them to executive group only if DSMC consider them likely to require publication or change in the conduct of trial.

9. In the light of above scrutiny and discussion of Secretary CSC with chairman CSC, the case has been placed as agenda item for CSC meeting to be held on 13.01.2022 (as its international trial in collaboration with WHO).

10. <u>Submitted for consideration of CSC:</u>

11. Dr. Aun Raza, the applicant / PI of the study also joined the meeting on line through Zoom and presented his case before the CSC.

Decision:

"The CSC after detailed discussion and deliberation decided to approve the trial at the following three sites subject to fulfilment of shortcomings as notified to the applicant during his presentation of the case:

i. *M/s Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore.*
ii. *M/s Shifa International Hospital, Islamabad.*
iii. *M/s Indus Hospital Karachi."*

12 Request from Shaukat Khanum Hospital and Research Center, Lahore wherein they have requested for the inclusion of following two Clinical Trial Sites as applied in initial application in already ongoing trial.

i. Shaheed Zulifqar Ali Bhutto Medical University, Islamabad.
ii. Agha KhanUniversity Hospital, Karachi.

13. On evaluation it is submitted that the case was placed before CSC in its 34th meeting held on 13th January 2022 and the Committee has approved the trial for 3 sites however there were deficiencies regarding below mentioned sites, Now the applicant has submitted the following deficient documents:-

i. IRB approval of Shaheed Zulifqar Ali Bhutto Medical University, Islamabad.
ii. IRB approval of Agha Khan University Hospital, Karachi.
iii. Copy of Clinical Trial Site License of Shaheed Zulifqar Ali Bhutto Medical University, Islamabad.
iv. Copy of Clinical Trial Site License of Agha Khan University Hospital, Karachi

14. It is proposed that we may add the case in the agenda of forthcoming CSC meeting for the inclusion of two sites in already ongoing clinical trial, please.

15. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberations decided to defer the case for further deliberation & due to paucity of time.

AGENDA ITEM XXXVII:

A PHASE-II, GLOBAL MULTI-CENTER, RANDOMIZED, DOUBLE BLIND, PARALLEL, -CONTROLLED, CLINICAL STUDY TO EVALUATE THE IMMUNOGENICITY & SAFETY OF DIFFERENT PRODUTION SCALE & BATCHES OF RECOMBINANT SARS-COV-2 FUSION PROTIEN VACCINE (V-01) IN ADULTS AGED 18-59 YEARS. F. No.03-05/2022 DD (PS)

Application submitted by Muhammad Tanseer Ali, CNIC No. 35401-6440356-9 of M/s Tigermed Consulting Pakistan, 7th Floor, Office No.712-713, High-Q Tower, Plot-1, Gulberg-5, Jail Road, Lahore wherein the applicant has requested for approval & registration of Clinical Trial titled, "*A Phase-I, Global Multi-Center, Randomized, Double Blind, Parallel, -Controlled, Clinical*

Study To Evaluate The Immunogenicity & Safety Of Different Production Scale & Batches Of Recombinant Sars-Cov-2 Fusion Protein Vaccine (V-01) In Adults Aged 18-59 Years"**.** The application is on Form-II of the Bio-Study Rules 2017 along with prescribed fee of Rs.200000/- paid vide challan number 1574048628, dated 07th March 2022.

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:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed processing fee	Fee of Rs.200000/- paid vide challan number 1574048628, dated 07th March 2022.
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	Pakistan only
7	Phase of trial.	Phase II * On protocol Phase-I is mentioned.
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.	Only quantity provided complete details require to be submitted along with justification.
9	Site of the trial	i. Central Park Medical College & Hospital, Lahore. ii. Avicenna Medical College & Hospital, Lahore. iii. Indus Hospital & Health Network, Karachi. iv. Rehman Medical Institute, Peshawar Licenses of sites to act as Clinical trial site are not provided.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	i. Central Park Medical College & Hospital, Lahore. ii. Avicenna Medical College & Hospital, Lahore. iii. Rehman Medical Institute, Peshawar iv. Indus Hospital & Health Network, Karachi IRB approval is not attached.
11	Approval of National Bio-ethics Committee (NBC)	Not provided
12	CV's of the Investigators	CV of Dr. Muhammad Ahmad Dr. Waheed Ahmad, Dr. Fivzia Herekar,

		Dr. Javed Khan Attached. Site wise details of PI required.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided
14	Pre-clinical/clinical safety studies	Phase-II data published by Chinese Medical Journal provided
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	No Attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Total 1696 subjects will be recruited in Pakistan as informed by the applicant.
19	Name of Monitors & Clinical Research Associate	Tigermed Consulting Pakistan, Lahore. Mr. Muhammad Tanseer Ali Country Operation Manager, Faheem Shahzad, CRAs Team, Muhammad Salman Tariq, Abdullah Mir, Husnain Sajjad, Rimsha Shahid, Hasina Sarwar, Fatima Siddique.
20	Evidence of registration in country of origin.	Not attached
21	Copy of registration letter (if registered in Pakistan)	N/A
22	Sample of label of the investigational product / drug.	Provided.
22	Duration of trial	13 Months.
23	Undertaking on stamp paper.	Attached.

3. After evaluation following shortcomings were recorded:
   i) Clarification regarding the Phase of trial.
   ii) IRB approval from Indus Hospital and Health Network, Karachi is required along with composition of committee i.e. names and designation of members.
   iii) Details of drug / trial material to be imported along with Justification for Quantity of drug / trial material to be imported is required.
   iv) Approval of National Bio-ethics Committee (NBC) is not provided.
   v) COPP, Free sale Certificate and evidence of registration in the country of origin (if applicable) required.
   vi) Summary of Investigator Brochure is not provided.
   vii) Licenses of sites to act as Clinical trial site are not provided.
   vii) CV's of the Investigators are provided however Site wise details of PI are not provided.
   vii) Soft Copy of Final Protocol, Investigator Brochure, Pre-clinical data & Safety studies and Phase I & II trial data required for onward submission to Expert is required.

4. Accordingly, shortcomings shared to applicant.

5. Applicant submitted reply in reference to communicated shortcomings:

Queries asked	**Reply of the Firm**
Data of Phase I & II trial may be provided	Attached. Page 562-651

IRB approval from each trial site is required along with composition of committee i.e. names and designation of members.	Following IRB Approvals attached; Chugtai lab, Lahore (page 554-556) Central Park Hospital, Lahore (p.556-557). Aziz Fatima Hospital, Faisalabad. (p.558-559). Avicenna Hospital Lahore. (P.560-561). UHS, Lahore (P.760-763). National Hospital and medical Center (page 764-766).
Separate application for each clinical trial site is required on Form 1 of Bio-Study Rules 2017.	Applications for approximately 04 sites has been submitted and evaluated.
Justification for Quantity of drug / trial material to be imported is required.	The justification of importing the amount of vaccine/ placebo mentioned is to cover the 10000 subjects (three doses) and for any loss due to damage to vial during cold chain transportation and storage and also breakage (page246/corr.). Further, representative of DRK verbally told that they will import vaccine/ placebo as per approval by CSC other medicines mentioned in the list will be purchased locally.
COPP, Free sale Certificate and evidence of registration in the country of origin (if applicable) required.	The product has not been yet registered in any country and hence phase III trial.
Detailed CV of principal investigator for each trial site is required.	CVs of Prof. Waheed Uz zaman Tariq (Chugtai lab) Dr. Aun Raza (SKMH&RC) Dr. Muhammad Ahmed (Central parks Medical College and Hospital) Dr. Waheed Ahmed (Avicenna Medical College and Hospital) Dr. Awais Aslam (Aziz Fatima Hospital) Prof. Muhammad Ishaque (National Hospital and Medical Center) Prof. Javaid Akram (UHS) Are attached. (Page 499-549)
Soft Copy of Final Protocol, Investigator Brochure, Pre-clinical data & Safety studies and Phase I & II trial data required for onward submission to Expert is required.	Has been provided on USB

6. Approximately all quires have been addressed, reference para 4/n, submitted for nomination of Expert for evaluation of Study material under rule 7(4) of Bio-Study Rules 2017, please.

7. Another request from Miss. Maria Song, Senior Manager, wherein she has stated that they have applied for 35,000/- Vaccines for the clinical trial but they have received the letter of quantity 30600/- dated 15.02.2021. In China they have got approval of 35,000/- from different departments and ready for airlift to Pakistan. There is possibility of damage/ breakage during transportation and handling. So, it is requested to permit already requested quantity of 35,000/- to complete the trial in valid time.

8. Accordingly DFA for corrigendum has been prepared and placed please.

9. A request for NOC for import of recombinant Novel Corona Virus Vaccine and placebo for Clinical Trial Study issued by Mrs. Anam Saeed, Assistant Director, DRAP, Lahore and Copy send to Director Pharmacy services and Secretary CSC.

10. Another request sends by DRK Pharma Solutions as “application for change of principal investigator of clinical trial titled “A phase III randomized, double blind, parallel controlled clinical

trial in 18 years of age and above to determine the safety and efficacy of ZF2001, a recombinant novel corona virus vaccine (CHO cell) for prevention of Covid-19"".

. *"Please include in the agenda of forthcoming meeting of CSC to be held on 10.03.2021."*

11. Applicant has submitted that due to some personal reasons Dr. Waheed-Uz-Zaman Tariq has requested to relieve him from this responsibility and same has been accepted by sponsor. Prof. Dr. Javed Akram Principal Investigator at the University of Health Sciences site has been nominated and he has accepted to work as lead investigator as well. Applicant has attached Notification by DRK Pharma solution, Notification by Prof. Waheed Uz zaman Tariq, Chugtai Lab. And Notification by Prof. Javed Akram, U.H.S. Lahore.

12. Reference para & para the request has been added in the agenda of 20th CSC meeting with following queries.

i. Principal Investigator/ Lead Investigator Prof. Dr. Javed Akram is member of CSC. It needs to be considered for conflict of Interest.
ii. Fee of Rs. 25,000/- required under SRO 1047(I)/2019 dated 12th September 2019 under miscellaneous heading.
iii. NBC approval has been issued to Prof. Dr. Waheed Uz Zaman Tariq vide letter No. ref: No.4-87/Covid-57/NBC/21/1134 dated 11th January 2021. Change of PI/ Lead Investigator may approved from NBC.

13. Request from Mr. Azam Jafery, Director Commercial and Operations, DRK Pharma Solutions in which he has stated that they have changed the Laboratory Islamabad Diagnostic Center (IDC) Lahore as Central Laboratory to perform the RT-PCR test in this Clinical trial. Previously Chugtai lab was their central laboratory.

Request has been added in the of 20th CSC meeting with following queries.

i. Fee of Rs. 25,000/- required under SRO 1047(I)/2019 dated 12th September 2019 under miscellaneous heading.
ii. Contract is between Anhui Zhifei Longcom Biopharmaceutical Co., ltd and Mr. Atif Saeed, legal representative of Islamabad Diagnostic Center, plot No. 4, beside Shadman police station, jail road, Shadman II, Lahore. As per Punjab Healthcare Commission has granted permission the Islamabad Diagnostic Center, Lahore to proceed with the collection of collection of samples for COVID-19 PCR testing at IDC, Lahore. This permission was granted keeping in view the emergency situation due to covid-19 pandemic and is subject to review by the commission from time to time. This needs to be clarifies about testing at Islamabad diagnostic Center, Lahore.
iii. Certificate of registration is required for IDC, Lahore from Punjab Healthcare Commission for Laboratory services.

Submitted for perusal of para & para please.

14. Request from Prof. Javed Akram, Principal Investigator Prof. Dr. Javed Akram, the Principal Investigator of Clinical Study/ Trial "A PHASE III RANDOMIZED, DOUBLE-BLIND, PARALLEL-CONTROLLED CLINICAL TRIAL IN 18 YEARS OF AGE AND ABOVE TO DETERMINE THE SAFETY AND EFFICACY OF ZE2001, A RECOMIBINANT NOVEL CORONAVIRUS VACCINE (CHO CELL) FOR PREVENTION OF COVID-19" has requested to include following two new clinical trial sites in Islamabad, in above mentioned Trial.

i. Al-Shifa Trust Eye Hospital, Islamabad.
ii. Shaheed Zulfiqar Ali Bhutto medical university, Islamabad.

15. *"Include in the agenda of CSC to be held on 3rd April as it is already approved Clinical Study of anhui China of eight sites."*

16. IRB approval of both new sites not attached with the application but anyhow in compliance to direction in para 43/n, application has been included in the agenda of 23rd meeting to held tomorrow i.e. 03.04.2021.

17. The case of commencement of A PHASE-III RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED, CLINICAL TRIAL IN 18 YEARS OF AGE & ABOVE TO DETERMINE THE SAFETY & EFFICACY OF ZF2001, A RECOMBINENET NOVEL CORONA VIRUS VACCINE (CHO CELL) FOR PREVENTION OF COVID-19 IN SZABMU, Islamabad was placed in **24th meeting** of CSC held on 07th April 2021 and CSC decided as following;

All the Members of the CSC unanimously decided to withdraw the approval of MCH Unit-II Pakistan Institute of Medical Sciences, Islamabad as ab-initio for clinical study titled, "A PHASE-III RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED, CLINICAL TRIAL IN 18 YEARS OF AGE & ABOVE TO DETERMINE THE SAFETY & EFFICACY OF ZF2001, A RECOMBINENET NOVEL CORONA VIRUS VACCINE (CHO CELL) FOR PREVENTION OF COVID-19", and approved the following clinical trial sites for above mentioned study:

i. *Clinical Assessment Unit, Examination Unit, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad instead of MCH Unit-II, Pakistan Institute of Medical Sciences, Islamabad.*

18. Accordingly, DFAs for withdrawal of MCH Unit-II Pakistan Institute of Medical Sciences, Islamabad and approval Clinical Trial Site situated at Clinical Assessment Unit, Examination Unit, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad instead of MCH Unit-II, Pakistan Institute of Medical Sciences, Islamabad, have been prepared and submitted please.

19. Request submitted by DRK, wherein they have stated that DRK Pharma Solution the licensed Clinical Research Organization having License No CRO-001 dated 11 October 2019 had applied for approval for clinical trial to DRAP, titled as "A PHASE III RANDOMIZED, DOUBLE-BLIND, PARALLEL-CONTROLLED CLINICAL TRIAL IN 18 YEARS OF AGE AND ABOVE TO DETERMINE THE SAFETY AND EFFICACY OF ZE2001, A RECOMIBINANT NOVEL CORONAVIRUS VACCINE (CHO CELL) FOR PREVENTION OF COVID-19" They further wrote that they were given permission to conduct the trial vide letter No. 03-52/2021 DD (PS) Dated 15th February 2021 allotting under license No. 0023. Subsequently on their application for the change of Principal Investigator licenseNo.0033 was issued in March 2021. This application is being submitted in collaboration with the Principal Investigator Professor Javed Akram. The total number of subjects to be recruited (and approved) are 10,000. To date (l7th May 2021) 3804 subjects have been recruited. The trial protocol states that the subjects shall be given vaccine dosage at 0, 1 and 2 months. At the moment second dose has been started and soon the third dose shall also be given. To complete the total number of subjects' further time is required. They have requested for extension for further 6 months. Applicant has also submitted on this application with hand writing that since in this trial we are required to enroll 10,000 subjects from Pakistan. So, far we have screened9470 subjects, out of which 60% subjects are IgM/ IgG positive (60% screening failure). Therefore, it is requested to grant the approval to import additional 10,000 SARs CoV-2 IgM/IgG antibody detection kits to complete recruitment.

20. As per Direction of the Chairman CSC, para 55/n has been placed as agenda item for next forthcoming meeting.

21. The study was approved on 19th March, 2021 by CSC on the following trial sites.

i. Agha Khan University Hospital, Karachi.
ii. University of health Sciences, Lahore,

iii. National Hospital & Medical Center, Lahore.

22. Following is the latest status of recruitment submitted on 7th June, 2021.

Site Name	Screening	Screening Failure	Ist Dose	2nd Dose	3rd Dose
National Hospital & Medical Center, Lahore	1112	426	485	335	74
Avicenna Medical College, Lahore	1841	746	786	400	131
Central Park Medical college, Lahore	3752	1175	1577	916	250
Aziz Fatima Hospital, FSD	1547	557	709	241	43
UHS, Lahore	1688	356	800	470	105
Indus Hospital Karachi	516	250	247	153	7
SZABMU, Islamabad	856	385	365	170	--
Al-Shifa Trust, Rawalpindi	2231	473	1337	247	--

23. Adverse Event/ Serious Adverse Event reporting from different sites. Case wise details are followings.

a. The Subject 100001, with Initials ALRA was enrolled on 17-03-2021 at Central park teaching Hospital. He was injected with a Vial No. X49602 on 17-03-2021 at 12:50 PM. A Grade I adverse event was reported within 30 minutes' observation he Subject was feeling redness at the injection site. The subject contacted the investigator via phone on the morning of 20-03-2021. The subject was complaining of fever and shortness of breath. On evening of 21-03-2021 the subject contacted and complained of fever, cough, body aches, loss of taste. The subject was advised to get admitted. The subject as falling into Suspected Covid case Criteria by definition. He was taking oral Medication. He was Hospitalized and monitored.

   The Subject was Hospitalized and monitored daily. Test reports are attached with Covid Case Monitoring record. Two Swabs were collected and tested in laboratory. The Subject was positive twice and confirmed as Covid-19 case. The severity of case was mild. His symptoms resolved gradually. He was discharged from hospital on 24-03-2021 and sent to complete isolation in home. He is being followed up daily by the investigator. His clinical reports and follow up visits suggest he is recovering from disease and his condition is stable now.

b. Subject Number: 108310 was given 1st Vaccination Dose on 14-04-2021 at Aziz Fatima Trust Hospital. Investigator contacted her for follow up on 22-04-2021, Subject complained of fever from 15-04-2021 to 26-04-2021. Body ache on 14-04-2021, (16 to 17)-04-2021, (19 to 21)-04-2021 Weakness from 14-04-2021 to 24-04-2021 Cough from 14-04-2021 to 17-04-2021. Vertigo from 20-04-2021 to 22-04-2021. She has these symptoms after being vaccinated, at the time of physical examination (14-04-2021) she had not any symptom detailed above. So, she was taking the following medication for those symptoms: Tab Panadol (B.D) 14-04-2021 to 15-04-2021 Tab Rotech (Misoprostol + Diclofenac Sodium) 75mg (B.D) 15-04-2021 to 22-04-2021 Tab Surbex Z (Multivitamin) (OD) 21-04-2021 to 21-04-2021 But she did not improve with medication, she was suspected Covid-19 case and called on 22-04-2021 for first nasal swab to PCR test. The First PCR result was positive (+), On 23-04-2021 Her lab test, Chest X Ray and

PCR test was done, 2nd PCR result was also positive (+). HRCT was advised by doctor, but patient condition was unstable and she was feeling very weak, so she refused for HRCT. All other lab reports were normal but CRP was raised. On Chest X-ray, bilateral infiltrates peripheral middle and lower zone were present. Her Oxygen saturation was 93 percent at the time of measurement at hospital on 23-04-2021. Doctor thinks her condition may be worsen, her life may be endangering and should be hospitalized but she refused. On 24-04-2021, doctor called her for follow-up and she told doctor, yesterday (23-04-2021) after returning to home from hospital, she again measured her oxygen saturation, her oxygen saturation was 70-76 percent at home. And her family arranged oxygen cylinder for her at home. She told other symptoms were more worsen than 23-04-2021, doctor think her life is in endangering situation. On 26-04-2021, doctor asked her again on phone call she told her other family members also developed COIVD-19 symptoms from 25-04-2021, her other symptoms are still persistent but her oxygen saturation is 92 percent without oxygen cylinder today. The main ingredients of the vaccine are NCP-RBD from SARS-COV-2 Spike protein, and (or) aluminum hydroxide adjuvant, which is not the source of infection. In addition, according to the phase I and phase II clinical results of the vaccine, it does not cause COIVD-19 in subjects. Therefore, the infection of subjects with COIVD-19 is possibly unrelated to the vaccine. Follow up on 26-04-2021: Cough improved from grade 3 to grade 2, Fever improved from grade 3 to grade 2. Follow up on 27-04-2021: Oxygen saturation was 97%. Fever 37.5°C Grade 1, cough improved from grade 2 to grade 1. Follow up on 28-04-2021: Oxygen saturation was 99 %. Subject was having weakness of grade 3 and Cough of grade 1. Fever settled completely. Follow up on 29-04-2021: Oxygen saturation was 99%. Weakness was of grade 3 and associated with vertigo of grade 1 and dizziness of grade 2. Cough was persistent and was in grade 1. Follow up on 30-04-2021: Cough was settled. Weakness of grade 2 was present which was associated with vertigo of grade 1 and dizziness of grade 2. Follow up on 03-05-2021: She told that on 01-05-2021 she was having weakness of grade 2 which was associated with vertigo and dizziness of grade I and on 02-05-2021 Weakness of grade 2 was present associated with grade 1 vertigo. Today on 03-05-2021 she was having weakness of grade I associated with Vertigo and dizziness of grade 1. Follow up on 04-05-2021: Weakness of grade 1 was present. No other symptom is present. Follow up on 05-05-2021: Weakness of grade 1 was present. No other symptom is present. So called the subject for nasal swab to PCR test and result was negative (-). Follow up on 07-05-2021: No other symptom is present. And subject all previous symptoms has resolved and get fully recovered. Above mentioned symptoms are not related to Hypertension and Diabetes Mellitus because subject did not complaint weakness, dizziness and vertigo before get covid 19.

Subject started taking following medication for her above symptoms from 23-04-2021 to 05-05-2021 Tab. Xcept (Rivaroxaban) 15mg (1 tablet daily) Tab. Wilgesic (Paracetamol + Orphenadrine) (1 tablet daily) Subject was taking following medication for her above symptoms, from 28-04-2021 to 05-05-2021: Tab, Delta (prednisolone) 5mg (2 tablet daily) Tab. Emflox (Moxifloxacin) 400mg (I tablet daily) Tab. Surbex Z (Multivitamin) (1 tablet daily). Subject was taking following medication for diabetes mellitus and Hypertension. Before 23-04-2021 her RBS level was between 150-190mg/dl. Her diabetes mellitus get worsen from 23-04-2021 (RBS level was 350mg/dl) to 01-05-2021 after that her blood sugar go back down to the previous level. Tab. Vildagliptin + Metformin HCL 50/1000mg (2 tablet daily) Tab. Amlodipine + Valsartan 10/160mg (1 tablet daily) Inj. Lantus (Insulin Glargine) (26 Units / Day) Subject used above mentioned medication before 23-04-2021 Tab. Vildagliptin + Metformin HCL 50/1000mg (2 tablet daily) Tab. Amlodipine + Valsartan 10/160mg (1 tablet daily) Injection Humulin R (from 23-04-2021 onwards) (30 Units in tds) Subject used above mentioned medication from 24-04-2021 to till date.

c. Subject with study number is 088472, Screening wan performed on 05-05-2021 at Avicenna Medical College. His vaccination date (1st dose) as on 06-05-2021. After 30 minutes of observation post vaccination no adverse effects were observed and the subject left. The subject went to the hospital to submit the diary card on May 18, 2021, during which no adverse events occurred, and the contact card was issued on the same day. The researcher contacted the subject on June 4. 2021, but the subject has not answered the call. The researchers called the subjects for follow up at 12:56 pm on June 10, 2021, and notified the subjects to receive the second vaccination. The subject's son answered the phone and told the researchers that his father died in a traffic accident on May 29, 2021. The subject's son told the investigator that the subject had a traffic accident on the way home from got off work on a motorcycle on May 20, 2021 due to a rear-end car collision. The main person responsible was the car driver. The subject was rushed to the General Hospital on the same day rescue him. He died on the morning of May 29, 2021. Death caused by traffic accident was of grade V. Relationship between SAE (Death) and investigational vaccine is Definitely unrelated.

d. Subject was enrolled in a Phase 3, Randomized, Double-blind, Placebo-Controlled clinical trial to determine the safety and efficacy of ZF2001, a Recombinant Novel Coronavirus Vaccine (CHO Cell) for prevention of COVID-19. Subject is 31 years old, female, screening Number 2401049. Subject Number 092453, enrolled at National Hospital & Medical Center, Lahore, had no prior co-morbidities and took no medication previously. After a negative PCR test and antibody test, her first physical examination took place on 27 May 2021. Her vitals and physical examination was within normal limits, after which she received the vaccine (first dose) at 03:19 PM on 27 May 2021. Patient developed high grade (grade 3) fever in the early hours of 8th June 2021. Max. temperature measured was 39.4°C. Fever was relieved partially with PO acetaminophen but would come back again. Patient started taking PO Acetaminophen 1 g thrice daily. Despite this fever was waxing and waning, not falling below 39.7°C according to the subject. By 12 of June 2021 her fever escalated to persist in the range of 38.3-38.8°C and wasn't relieved by Per Oral Acetaminophen. Myalgias (Grade 3): Patient developed myalgias since 8h June 2021 which progressively worsened till, she visited the site on 14 June 2021. The intensity of these were directly proportional to the severity of the fever. Sore Throat with productive cough (Grade 2): Patient complained of sore throat with productive cough since 8 June 2021. Fatigue (Grade 2 which progressed to Grade 3): Patient complained of fatigue since 9 June 2021. Fatigue rapidly worsened proportionally with worsening fever and dyspnea and reached a point where the subject had difficulty walking. 5) Progressive Dyspnea (started from Grade 2 and progressed to Grade 4): On 10 June 2021, patient started developing debilitation dyspnea. Her Respiratory Rate was in 20s which progressively increased so 40s at rest. Air hunger was tangible and she describes as being consistently out of breath. Her dyspnea progressively worsened till 13th June 2021 after which she came in to the site for evaluation the very next day i.e., 14th June 2021. Patient came to us on the 14th of June 2021 with severe dyspnea, high grade fever, rigors, chills, myalgias and productive cough. Her vitals showed 38.8 °C fever and Sp02 88 percent on room air. On examination she had a hyperemic posterior pharynx, accessory respiratory muscles were in use, and auscultation showed poor air entry on the right side with dullness to percussion along with coarse rales heard in the left lower lobe of the lungs. A CT scan of chest was ordered which showed Right Lung Massive Pleural Effusion/Possible Empyema with complete atelectasis. Patient was moved to the ER after the CT scan and was placed of 2 liters of oxygen to maintain saturation. IV acetaminophen Ig. IV Piperacillin/tazobactam 4.5g, dexamethasone 4 mg was given and the patient was also nebulized with Ipratropium 250mcg and Beclomethasone/Salbutamol 800/1600mcg. A call was sent to the Pulmonologist who reviewed the patient and advised and immediate ICU ADMISSION. Subject has been

admitted to the ICU under Pulmonologist on 14 June 2021. Following medicines have been started, IV Moxifloxacin 400mg once a day IV Piperacillin/Tazobactam 4.5g thrice a day IV Acetaminophen lg thrice a day IV Ringer Lactate a rate of 120ml/hour IV Metronidazole 500mg thrice daily IV Omeprazole 40mg once daily Thoracic surgery consult: Video Assisted Thoracoscopic Surgery (VATS) and Decortication recommended. Baseline Labs were sent: Hemoglobin 8.9, TLC 7.1 with left shift (Neutrophils 85%) and lymphopenia (10%). C-reactive protein is 33.99. PT 14/INR 1.3. Liver function tests ALP 296 and GGT 134 with hypoalbuminemia 2.9. ABGS show mixed respiratory and metabolic alkalosis. Subject's medication history Subject had no prior significant medical history, no known allergies, no tangible family history, didn't take any regular medicines, no history of tobacco, illicit drugs or alcohol. She is a housewife, mother of 2 sexually active with her husband. Information of the Investigational product Subject received the 1" dose of vaccine on 27-05-2021 at 03:19 PM, vaccine no X44088. Description of Outcome of SAE. not decided yet Correlation of SAE with investigational drug. According to Principal Investigator the SAE is Severe Dyspnea (Shortness of breath) secondary to Right Lung Massive Pleural Effusion Possibly Empyema with Atelectasis and possibly Not related to the investigational drug/ vaccine, as the subject had no prior medical illnesses or comorbids.

e. The subject No. 092484 was enrolled at National hospital and Medical center, Lahore. The subject was 53 years old, Male subject having Initials MUIB, had a prior history of Hypertension (from 01-01-2018 and) Diabetes Mellitus (from 01-01-2019) and was Non-Compliant regarding medication, remaining findings were found to be normal on his first physical examination on 05-06-2021, and he received his first dose on the 5th June 2021. Before vaccination his PCR for COVID 19 and antibodies were Negative. His Vitals were within normal limits before vaccination. Subject then came for his first follow up visit (V3) on 14-06-2021 and all findings were within normal limits. SAE description: Patient presented to the emergency department on 18h of June 2021. At the time of arrival, patient was BP-less and pulseless with no respiratory effort. Pupils were B/L fixed dilated. Heart sounds and breath sounds were absent. B/L carotid pulses were absent. Corneal reflex was absent. ACLS protocol was started along with Cardiopulmonary resuscitation. ECG was done which showed a straight line. Death was declared at 2:15 PM on the 18th June 2021Patient was non-compliant with his medications regarding diabetes mellitus and hypertension. In Emergency Room: Patient was administered adrenaline (1mg/1ml every 5 minutes for 15 minutes) as per ACLS protocol. Information of the Investigational product (0.5ml/vial that contains 0.25 micro grams of NCP-RBD protein). Description of Outcome of SAE. Patient expired due to cardiopulmonary arrest. Correlation of SAE with investigational drug. The patient was diabetic and hypertensive and non-compliant with medications which most probably resulted in cardiopulmonary arrest. There is no relation of the investigational vaccine with the SAE.

f. Subject's basic information Subject number 103052 having Initials MULM, got screened on 04-05 2021 at Central Park Teaching hospital and received the first dee on 05-05-2021 after passing the inclusion criteria with normal Vitals. He had a history of Diabetes mellitus. No adverse events were observed during the 10-minutes post vaccination. Subject developed the fallowing symptoms: 1. Subject was admitted as a case of Diabetic foot and Un controlled diabetes, along with jaundice His workup for Jaundice shewed deranged Liver Function Tests and highly reactive far Anti-ICV antibodies, along with a finding of Acalculous Cholecystitis on ultrasound abdomen. The Subject cannot confirm the start date of jaundice. Therefore, the subject is now being treated for the new working-diagnosis and having further investigations done, along with a slow response to insulin, resulting in hospitalization. He got admitted on 12-06-2021 to hospital and currently is still admitted. Subject's medication history During hospitalization the subject received the following medication. Injection Insulin (regular) on sliding scale. Injection Tanzo

(Piperacillin) 4.5g TDS Injection Toradol (Ketorolac) 30mg SOS 4 Clinical Investigation: Liver Function Tests: Abnormal values are mentioned below Serum total Bilirubin 10.0.mg/dL Serum Conjugated bilirubin: 7.3 mg/dL Serum ALT :710 U/L Serum AST: 649 U/L. Serum Alkaline Phosphatase: 292 U/L Serum Gamma GT: 1545 U/L Anti-HCV Antibodies (Reactive) 6.17 Hepatitis B and Hepatitis Screening Negative Complete Blood Count CBC results were normal. Lipid Profile: Serum non- HDL Cholesterol was very High 221 Serum Total cholesterol was 226 mg/dL that was on borderline. Serum triglycerides was also high 281 mg/dL Serum HDL Cholesterol was low 5 mg/dL Serum LDL Cholesterol was very High 238 mg/dL. Ultrasound Abdomen (Acalculous Cholecystitis) Serum Electrolytes 966 Sodium level was decreased that was 129 mmol/L. Serum potassium, Serum chloride, serum bicarbonate was Normal HbAlc (Very High) 12.9% Urine Compete examination: Thyroid Profile: Thyroid profile was Normal. Information of the Investigational product Subject received the 1" dose of vaccine on 05-06-2021 (0.5ml/vial that contains 0.25 micro grams of NCP- RBD protein). The decision will be made after the outcome of SAE. Description of Outcome of SAE. The subject is currently stable and still hospitalized. Correlation of SAE with investigational drug. According to doctors, the diagnosis of SAE is Acute Hepatitis C, Uncontrolled Diabetes and Diabetic Foot and is definitely not related to the investigational drug vaccine, as the subject had a history of diabetes before being vaccinated and his liver function tests and jaundice correlate to his new diagnosis of Acute Hepatitis C. Continuation of Investigational Drug: Investigational drug is continued till the Outcome of SAE. Final decision will be taken after the outcome of SAE.

24. Letter from Prof. Javed Akram, PI, wherein he has requested for change in protocol (and related trial documents) received from sponsor of the trial. He has given the following background.

The recombinant novel coronavirus vaccine (CHO cell) jointly developed by Anhui Zhifei Longcom Biopharmaccutical Co., Ltd. and Institute of Microbiology, Chinese Academy of Sciences obtained the NMPA drug clinical trial approval on June 19, 2020, and the proposed indication is "prevention of 2019 coronavirus disease (COVID-19) caused by novel coronavirus infection". After obtaining the initial results of Phase Land Phase II clinical trials of this product, sponsor conducted technical communication of Phase Ill clinical trial protocol for people aged 18 and above with your center on November 4, 2020, It is planned to enroll 28,000 overseas subjects to evaluate the protective efficacy, immunogenicity and safety of COVID-19, and 1,000 domestic subjects to evaluate the safety and immunogenicity. At present, the Phase III clinical trials are being carried out in China, Uzbekistan, Indonesia, Ecuador and Pakistan. As of February 15, 2021, 6830 subjects have been enrolled in Uzbekistan, and the third dose of vaccination has started; In the past two months, 81 suspected cases have been found, and no confirmed cases have been found Considering that since October 2020, the daily number of confirmed cases of COVID-19 in Uzbekistan has been continuously decreasing (statistics of WHO Global Health Observatory), daily number of newly added cases in recent 2 months is below 100, and most of them are mild or asymptomatic infected persons. According to the actual epidemiological situation in Uzbekistan, is difficult to catch effective cases if the original protocol is used for case monitoring. In order to improve the monitoring efficiency of COVID-19 cases in clinical trials, on the basis of referring to the latest technical guidelines, and drawing lessons from the clinical trial experience of products on the market at home and abroad, sponsor of the trial plans to apply for the adjustments to the diagnostic criteria of COVID-19 suspected cases and COVID-19 cases in the Phase III clinical trial protocol of recombinant novel coronavirus vaccine (CHO cells). The changes in the protocol have also been reflected by some changes in the other documents. Hopefully once the new version of the protocol is approved the changes in other documents shall also stand approved, (see Table 1). The summary of the changes and the documents mentioned in Table 1 with reference to the previous and new

document versions is given as attachment to the letter. In view of the fact that this product has started the third dose of vaccination and will enter the monitoring period of vaccine effectiveness and protection 14 days after the third dose, I am eager to get a reply from DRAP as soon as possible.

25. Major revisions of diagnostic criteria for suspected COVID-19 cases and COVID-19 cases in protocol is attached by the applicant (page976-979/corr.) and revised consent form in Urdu and English is attached at page 1133-1169/corr.

26. Applicant is accompanying Fee of Rs.25,000/- along with NBC approval (page 973/corr.). The NBC-PHRC has been issued to Prof. Waheed Uz Zaman Tariq instead of Prof. Dr. Javed Akram, PI. Moreover, IRB approval for amended protocol are not attached. Amended protocol also not attached with application.

27. Applicant may be asked to submit NBC-PHRC approval issued to Dr. Javed Akram, PI, IRB approvals from clinical trial sites, and amended protocol.

28. Progress reports submitted by DRK Pharma Solution regarding the recruitment status of the subjects. The study was approved on 19th March 2021 by CSC on the following trial sites.

i. Agha Khan University Hospital, Karachi.
ii. University of health Sciences, Lahore,
iii. National Hospital & Medical Center, Lahore.

29. Following is the latest status of recruitment submitted on 29th June 2021.

Site Name	Screening	Screening Failure	Ist Dose	2nd Dose	3rd Dose
National Hospital & Medical Center, Lahore	2008	577	1000	429	325
Avicenna Medical College, Lahore	2380	913	101	625	407
UHS, Lahore	5281	1580	2512	1453	801
Central Park Medical college, Lahore	2395	752	1316	576	217
Aziz Fatima Hospital, FSD	1977	440	1015	667	448
Indus Hospital Karachi	1113	383	585	210	147
SZABMU, Islamabad	2086	572	1254	381	127
Al-Shifa Trust, Rawalpindi	3806	576	2654	1368	273

30. Reference para 65/n and 81/n, it is proposed that the status of the recruitment may be placed before CSC in forthcoming meeting.

31. Adverse Event/ Serious Adverse Event reporting from different sites. Prof. Dr. Waheed Ahmad has submitted initial report and summary report of the case. Details are followings.

32. Subject with the initial's JAMA, Study number is 091036, Screening was performed on 22-05-2021, His vaccination (1st dose) was completed on 24-05-2021 at Avicenna Hospital, Lahore. After 30 minutes of observation post vaccination, no adverse events were observed and the subject left. The subject submitted his diary card on 01 June, 2021, during which no adverse events occurred, and the contact card was issued on the same day. The investigator contacted the subject on June 24, 2021 to receive the second vaccination but the subject did not answer the call. The subject's daughter came on June 28, 2021 at 13:05 to submit contact card and death certificate of subject and told the investigator that the subject got fever of 38.8°C (Grade III) on June 06, 2021 which could not be recovered due to self medication of Paracetamol 500 mg twice a day from 06-06- 2021 to 07-06-2021. So, the subject was admitted to Lahore General Hospital on June 08, 2021, He died on June 13, 2021 at 05:45 am due to Cardiopulmonary Arrest which happened due to his past medical history (Cerebrovascular accident). Subject had past medical history called Cerebrovascular Accident

(CVA). According to the Dr's decision, cardiopulmonary arrest was caused by his past medical history (Cerebrovascular accident) which had nothing to do with vaccine. Relationship between SAE (Cardiopulmonary Arrest) and investigational vaccine is Definitely unrelated.

33. Prof. Dr. Waheed Ahmad, in both reports have submitted that SAE start date is 08.06.2021 while actually SAE start date is 06.06.2021. The investigator has claimed that relationship between SAE and investigational vaccine is definitely unrelated while he could not get data of subject (symptom, treatment, clinical findings etc) during subject stay at Lahore General Hospital, Lahore. Further, given reference of protocol version LKM-2020-NCV-GJ01 (version 1.0) on initial report while protocol LKM-2020-NCV-GJ01 (version 1.1). It is strange that how two protocol versions can be used on single patient with single dose while LKM-2020-NCV-GJ01 (version 1.1) not approved by CSC.

34. It is proposed that data regarding SAE of trial vaccine mentioned at para 66/n 84/n may be send to pharmacovigilance center or an expert for evaluation and recommendation of appropriate action regarding the trial. Meanwhile, a panel may be constituted to visit the selected site and CRO to check data integrity.

35. Request from Prof. Dr. Javed Akram, VC UHS, member CSC and PI of the trial titled as "A PHASE I RANDOMIZED, DOUBLE-BLIND, PARALLEL- CONTROLLED CLINICAL TRIAL IN 18 YEARS OF AGE AND ABOVE TO DETERMINE THE SAFETY AND EFFICACY OF ZF2001, A RECOMBINANT NOVEL CORONAVIRUS VACCINE (CHO CELLYEOR PREVENTION OF COVID-19" wherein he has stated that reference to your letter: F. No. 03-52/2021 DD (PS) Dated 16th February 2021, DRK Pharma Solution the licensed Clinical Research Organization having License No CRO-0001 dated 11th October 2019, had applied for approval for clinical trial to DRAP. This trial is being sponsored by Anhui Long com Biopharmaceutical Company China. We were given permission to conduct the trial vide letter No. 03-52/2021 DD (PS) Dated 15th February 2021. I am conducting this trial at my site as the lead investigator and covering the other 8 sites in Pakistan. Now that the government has started the vaccination drive. There is news that every citizen above the age of 18 has to get vaccinated. If the individual cannot provide a vaccine certificate being issued by the government some of the facilities shall be withdrawn. It is requested that since the undergoing trial was approved by the National Ethics Committee and subsequently fulfilling all the requirements by Clinical Study Committee of Pharmacy Division, DRAP. The subjects enrolled are finding it difficult to continue with the follow up in the trial. It is requested that the Government to please issue a certificate (excerpting them from forced vaccination till they complete the trial process) as these subjects are a part of an approved clinical trial. As per protocol 10.000 subjects are to be enrolled and 9000 + plus have been enrolled and vaccinated, some of these subjects (nearly 2000) have been given the 3rd dose. As half of these enrolled are given vaccine and half placebo with the commitment that after the interim analysis. The ones given placebo shall also the vaccinated. Hence covering the whole in trial population being vaccinated in the coming couple of months. Now under these circumstances those who have been given vaccine cannot get another vaccine (as this has not been proven safe) and if they are vaccinated they shall be considered a dropout from the current trial putting the whole trial data in jeopardy. This would be a setback to the scientific contribution from Pakistan. Hoping to get a positive response and further guidelines to follow in this case.

36. Fee of Rs. 25,000/- is required for miscellaneous requests under SRO 1047/2019 dated 12th September 2019 for further processing of the case. Hence, applicant may be asked to submit requisite fee.

37. Para 82/n, 86/n and 88/n are submitted for perusal, approval and guidance please

FR (page /corr.) is the reply from DRK Pharma solutions wherein they have enclosed amended protocol version 1.1 and ICF version 1.3 along with IRB approval from UHS, Lahore, National Hospital & Medical Center, Lahore, Avicenna Medical and Dental college and Hospital, Lahore. Central Park Medical college, Lahore, Aziz Fatima hospital Faisalabad, Indus Hospital, Karachi, Al-Shifa Trust Eye Hospital Rawalpindi and SZABMU, Islamabad. Applicant has also provided the revised NBC-PHRC approval issued to Prof. Dr. javed Akram, PI of the trial.

38. Reference para 112/n, it is submitted that the file may be send to Division of Legal affairs for opinion on Fee of miscellaneous application as per para 88/n.

39. SAEs reported from Central Park Teaching Hospital, Lahore, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Avicenna Hospital, Lahore and Al-Shifa Trust Eye Hospital, Rawalpindi that occurred during clinical trials.

40. It is proposed that data regarding SAE of trial vaccine mentioned may be send to pharmacovigilance section or an expert for evaluation and recommendation of appropriate action regarding the trial.

41. Request from M/s DRK pharma solution for approval of protocol version 1.2 and ICF version 1.4. The applicant has enclosed explanation on applying for revision of protocol, Protocol version 1.2 and ICF version 1.4 English. He has also requested for increase in the total number of subjects from 10,000 to 11,500 (increase of 1500).

42. The applicant may be asked to submit NBC approval, IRB approval from each trial site, soft copy of protocol, comparison of changes in both versions, ICF version 1.3 and changes and Fee for protocol amendment.

43. Para 113/n, 115/n and 117/n are submitted please.

Reference to para 116-117/N, the firm M/s DRK, Pharma, Solutions, Lahore have provided the following documents for amendment in Protocol 1.2 and ICF 1.4 in already approved trial/study:-

i. Copies of IRBs approval for amendment
ii. Prescribed fee of 25000 for amendment
iii. NCB approval for amendment.

Following is the amendment in already approved protocol 1.1and ICF 1.3 summary is as under: -

7.2.1 Diagnostic process for suspected cases

"The investigator confirms whether the definition of suspected case is met and completes a case monitoring form based on the symptom information provided by the subject.

(1) If yes, under the direction of the investigator, arrive at the institution where the study is conducted or at a designated medical facility as soon as possible for the following tests.

Two nasopharyngeal swabs are collected by the site investigator (two swabs are collected for each sampling). One is subjected to real-time RT-PCR and the other is backed up and stored. Besides, respiratory rate (RR), oxygen saturation (SpO2), and oxygenation index (PaO2/FiO2) are tested. The investigators collect RT-PCR test report forms, diagnostic source documents, test report of S gene mutation loci and relevant test reports from all subjects with positive PCR tests:

1) If the RT-PCR test result is positive, the investigator should judge whether it is a COVID-19 case by referring to relevant symptoms and test results of the subject. Once considered as a COVID-19 case, it should be handled in accordance with the local epidemic diagnosis and treatment measures, and samples should be taken again at an interval of 24-48 h for testing. The

ARMS-PCR method is also used to detect the SARS-CoV-2 S gene mutation loci, and the main mutation loci detected are N501Y, A570D, HV69-70del, K417N, K417T, and E484K.

2) If the RT-PCR test is negative, re-sample for testing should be within an interval of 24-48 hours, and test respiratory rate (RR), oxygen saturation (SpO2) and oxygenation index (PaO2/FiO2).

(1) if the test result is positive, the investigator should judge COVID-19 cases according to the related symptoms and test results of the subjects. The SARS-CoV-2 S gene mutation loci detection is also performed.

7.4 Biological sample collection

2) The biological samples collected by each center are divided into two parts. One part is sent to the SARS-CoV-2 nucleic acid testing laboratory for real-time fluorescence quantitative RT-PCR and/or SARS-CoV-2 S gene mutation locus detection (refer to SOP for SARS-CoV-2 nucleic acid testing and SOP for SARS-CoV-2 S gene mutation loci detection); the other part is kept in a qualified laboratory for backup.

If agreed we may place the case in 32nd meeting of CSC, please.

168. Application from DRK Pharma Solutions wherein they have requested for the import of 480 RT-PCR Kits from China as per detailed below to be used in already approved trial. They have submitted that RT-PCR test kits are mandatory for every subject to be tested. Further throughout the clinical trial any subject having symptoms like COVID-19 is also tested with the RT-PCR kits to confirm if the subject is having COVID-19 infection. So far in this clinical trial more than 20,000 subjects were screened, 11500 are given vaccination after confirming that they are COVID-19 negative.

169. The instant case was considered in 26th meeting of CSC (Pages1034/corr) and CSC recommended the import of SARs CoV-2 IgM/IgG antibody detection kits and also decided to ask the applicant to approach the MDMC Division/QA&LT Division for approval of import & clearance of the said kits under provision of relevant rules: -

Medical Device / Components or Raw material	**Manufactured by**	**Total Boxes**	**Test kit per Box**	**Total Quantity**
SARs CoV-2 nucleic acid detection kit (RT-PCR)	Shanghai Fosun Long March Medical Science Co., Ltd.	10	48	480

170. In light of above, it is proposed that we may place the case before CSC, please.

FRs (Pages1038-1103/Corr) are SAEs reported from following sites: -

i. Shaheed Zulifqar Ali Bhutto Medical University, Islamabad. (Pages1038-1084/corr).
ii. National Hospital & Medical Centre, Lahore. (Pages1085-1090/corr).
iii. Avicenna Hospital, Lahore. (Pages1099-1103/corr).
iv. Aziz Fatimah Trust Hospital, Faisalabad. (Pages1091-1098/corr).

176. The Chairman CSC has constituted the following panel of experts to investigate the matter for finding out the root cause of SAEs for Shaheed Zulifqar Ali Bhutto Medical University, Islamabad: -

i. Dr Faiza Bashir, PHRC, Islamabad.
ii. Abdul Mateen, Assistant Director, Pharmacy Services, DRAP, Islamabad.
iii. Dr Abdur Rashid, Director, Pharmacy Services, DRAP, Islamabad.

iv. Rana Ahsan Ul Haq Athar, Assistant Director, Pharmacy Services, DRAP, Islamabad.

177. SAEs ii, iii, iv at 175/N are submitted for constitution of panel of experts to investigate the matter for finding out the root cause of SAEs, please.

Reply M/s DRK, Pharma Solutions, Lahore, an amendment stating that vaccine could get a better protection effect 7 days after the completion of the third dose instead of waiting for the 14th days CDE n China suggested to change the clinical trial protocol to evaluate the efficacy of vaccine after 7 days and they have submitted the following documents: -

i. Amended version of protocol 1.3.
ii. IRB approvals of all the (8) sites.
iii. NBC approval.
iv. Prescribed fee of Rs.25000/.

15. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberations decided to defer the case for further deliberation & due to paucity of time.

Meeting ended with praises to Allah.