MINUTES OF THE 27TH CLINICAL STUDIES COMMITTEE (CSC) MEETING, HELD ON 24TH JUNE 2021.

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The 27th Meeting of the CSC was held on 24th June 2021 through Zoom under the chairmanship of Dr. Abdur Rashid, Director Pharmacy Services Division / Chairman (CSC). At the Committee Room-II, 4th Floor, Drug Regulatory Authority of Pakistan, Islamabad.

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

Sr. No.	**Name**	**Designation**
01	Dr. Abdur Rashid.	Chairman CSC / Director, Division of Pharmacy Services-DRAP.
02	Ahmad Din Ansari.	Secretary CSC / Additional Director, Division of Pharmacy Services-DRAP.

3. Following members attended the meeting online through Zoom:

01	Dr. Faiza Bashir.	Chairman, Pakistan Health Research Council or his nominee, Islamabad.
02	Prof. Dr. Javed Akram.	Professor of Medicine, Physician, Vice Chancellor, University of Health Sciences, Lahore.
03	Dr. Farhana Badar.	Biostatistician & Epidemiologist, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.
04	Dr. Aamir Jaffary	Sindh Institute of Urology & Transplantation (SIUT), Karachi Co-opted Member.
05	Prof. Dr. Rizwana Chaudhri	HOD Gynecologist Holy Family Hospital, Rawalpindi Co-opted Member.
06	Prof: Dr. Mushtaq Ahmed	Professor of Cardiology, Bach Khan Medical College, Mardan, KPK Co-opted Member.
07	Raeef Ahmed	Representative of Pharma Bureau Observer.

4. Meeting started with the recitation of holy verses of the Quran by Ahmad Din Ansari, Secretary CSC. Secretary, CSC welcomed all the members & introduced himself & presented the agenda of the meeting.

AGENDA ITEM - I: **CONFIRMATION OF THE MINUTES OF THE 26TH CLINICAL STUDIES COMMITTEE MEETING.**

1. Confirmation of Minutes of 26th CSC meeting, held on 31st May 2021. Since the occurrences of COVID pandemic majority of the meetings are being conducted online through Zoom.

2. The members are requested to confirm the minutes electronically. Confirmatory email will be made part of the minutes to satisfy legal provision.

Submitted for consideration of CSC.

Decision:

All the Members of the CSC unanimously confirmed the Minutes of 26th CSC meeting held on 31st May 2021.

AGENDA ITEM - II:

REQUEST FOR APPROVAL OF M/S AGA KHAN HOSPITAL FOR WOMEN, KARIMABAD, KARACHI TO ACT AS CLINICAL TRIAL SITE TO CONDUCT CLINICAL STUDY TITLED "AZITHROMYCIN & CEFEXIME TREATMENT OF TYPHOID IN SOUTH ASIA TRIAL (ACT-SOUTH ASIA TRIAL).F.NO.15-26/2021 DD (PS)

Application submitted by Dr. Sayed Mairajuddin Shah (CNIC-42201-3587009-7), Chief Operating Officer (COO) Secondary Hospital, Aga Khan University Hospital Karachi, for approval of M/s Aga Khan Hospital for Women, Karim Abad, Karachi, dated 01st March 2021, the site is situated at AKHW, Karim Abad, 6-D, Shahra-e-Pakistan, Federal "B" area, Karachi. Wherein the request has been made to license the subject site with DRAP to act as Clinical Trial Site for Phase-IV Clinical Trials. Application is on prescribed form-I along with a prescribed fee of Rs.100000/- paid vide challan number 2060429, dated 02nd March 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 2060429, dated 02nd March 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).	The Aga Khan University Order, 1983 is attached.
4	Details of premises including layout plan	Attached.

	of the site.	
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. As powers conferred by CSC to Chairman CSC/Director Pharmacy Services for constitution of panel for inspection, Chairman CSC reconstituted the following panel for inspection of subject Clinical Trial Site as follows:

i.	*Dr. Abdur Rashid, Chairman CSC-DRAP (Coordinator)*
ii.	*Prof. Dr. Aamir Jaffrey, SIUT Karachi.*
iii	*Prof. Dr. Raza Shah, Director H.E.J. ICCBS, Karachi.*
iv	*Dr. Naseem Salahuddin, The Indus Hospital, Karachi.*
v	*Dr. Najam Us Saquib, Additional Director, In charge DRAP-Karachi.*

4. Due to unavailability of some panel members Chairman CSC conducted inspection with following experts on 10th June 2021:

i.	*Dr. Abdur Rashid, Chairman CSC-DRAP (Coordinator)*
ii.	*Dr. Muhammad Iqbal Afridi, Ex Dean JPMC, Karachi.*
iii	*Prof. Dr. Raza Shah, Director H.E.J. ICCBS, Karachi.*
iv	*Dr. Najam Us Saquib, Additional Director, In charge DRAP-Karachi.*

5. After inspection, panel submitted report with following remarks:

Keeping in view that it is a separate hospital of Aga Khan University (51 bedded), infrastructure, human resource, training, SOPs, documentation, waste management recommends Aga Khan Hospital for Women, Karim Abad Fed.B area, Block-7, Gulberg Town Karachi for Clinical Trial Site.

6. Concluding status / remarks of inspection panel:

Recommended for approval.

7. It is submitted that the application was submitted for approval of subject site for Phase-IV Clinical Trails.

Submitted for consideration of CSC.

Decision:

After due deliberation / discussion & pursuance to the recommendations of the inspection panel, CSC unanimously granted approval to issue licence in the name of M/s Aga Khan Hospital for Women, Karim Abad, F.B. Area, Karachi to act as Clinical Trial Site for Phase-IV Clinical Trials.

AGENDA ITEM - III:

REQUEST FOR APPROVAL OF M/S AGA KHAN HOSPITAL FOR WOMEN, GARDEN, KARACHI TO ACT AS CLINICAL TRIAL SITE TO CONDUCT CLINICAL STUDY TITLED "AZITHROMYCIN & CEFEXIME TREATMENT OF TYPHOID IN SOUTH ASIA TRIAL (ACT-SOUTH ASIA TRIAL).F.NO.15-27/2021 DD (PS)

Application submitted by Dr. Sayed Mairajuddin Shah (CNIC-42201-3587009-7), Chief Operating Officer (COO) Secondary Hospital, Aga Khan University Hospital Karachi, for approval of M/s Aga Khan Hospital for Women, Garden, Karachi, dated 01st March 2021, the site is situated at AKHW, 515 Gold Street, Garden East, Karachi. Wherein the request has been made to license the subject site with DRAP to act as Clinical Trial Site for Phase-IV Clinical Trials. Application is on prescribed form-I along with a prescribed fee of Rs.100000/- paid vide challan number 2060427, dated 02nd March 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 2060427, dated 02nd March 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).	The Aga Khan University Order, 1983 is 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	Attached.

	services, emergency handling, etc.	
8	Undertaking on stamp paper	Attached.

3. As powers conferred by CSC to Chairman CSC/Director Pharmacy Services for constitution of panel for inspection, Chairman CSC reconstituted the following panel for inspection of subject Clinical Trial Site as follows:

i.	*Dr. Abdur Rashid, Chairman CSC-DRAP (Coordinator)*
ii.	*Prof. Dr. Aamir Jaffrey, SIUT Karachi.*
iii	*Prof. Dr. Raza Shah, Director H.E.J. ICCBS, Karachi.*
iv	*Dr. Naseem Salahuddin, The Indus Hospital, Karachi.*
v	*Dr. Najam Us Saquib, Additional Director, In charge DRAP-Karachi.*

4. Due to unavailability of some panel members Chairman CSC conducted inspection with following experts on 10th June 2021:

i.	*Dr. Abdur Rashid, Chairman CSC-DRAP (Coordinator)*
ii.	*Dr. Muhammad Iqbal Afridi, Ex Dean JPMC, Karachi.*
iii	*Prof. Dr. Raza Shah, Director H.E.J. ICCBS, Karachi.*
iv	*Dr. Najam Us Saquib, Additional Director, In charge DRAP-Karachi.*

5. After inspection, panel submitted report with following remarks:

Keeping in view the infrastructure, human resource, expertise, Pharmacy, waste management, stand by generator, documents, pathological laboratory, x-ray testing facility in main again Hospital, panel recommends Aga Khan Hospital for women, Garden East, Golden Street, Postal Code 74100 Karachi for Clinical Trial Site.

6. Concluding status / remarks of inspection panel:

Recommended for approval.

7. It is submitted that the application was submitted for approval of subject site for **Phase-IV** Clinical Trails.

Submitted for consideration of CSC.

Decision:

After due deliberation / discussion & pursuance to the recommendations of the inspection panel, CSC unanimously granted approval to issue licence in the name of M/s Aga Khan Hospital for Women, Garden-East, Karachi to act as Clinical Trial Site for Phase-IV Clinical Trials.

AGENDA ITEM - IV:

REQUEST FOR APPROVAL OF M/S NATIONAL INSTITUTE OF CHILD HEALT, KARACHI TO ACT AS CLINICAL TRIAL SITE TO CONDUCT CLINICAL STUDY TITLED "ANTI-CORONAVIRUS THERAPIES TO PREVENT PROGRESSION OF COVID-19. F.NO.15-28/2021 DD (PS)

Application is submitted by Prof. Sayed Jamal Raza (CNIC-42000-0493240-3), Executive Director, M/s National Institute of Child Health, Karachi, dated 31st March 2021, the site is situated at NICH, Rafiqui Shaheed Road Karachi. Wherein the request has been made to license the subject site with DRAP to act as Clinical Trial Site. Application is on prescribed form-I along with a prescribed fee of Rs.100000/- paid vide challan number 2060431, dated 02nd March 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 2060431, dated 02nd March 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).	Applied site is a tertiary care hospital, working under Provincial Government.
4	Details of premises including layout plan of the site.	Details of facility are attached. Layout plan is not provided.
5	Details of the section-wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	List of some equipment is attached. Applied site is a Tertiary Care Provincial Hospital.
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. As powers conferred by CSC to Chairman CSC/Director Pharmacy Services for constitution of panel for inspection, Chairman CSC reconstituted the following panel for inspection of subject Clinical Trial Site as follows:

i.	*Dr. Abdur Rashid, Chairman CSC-DRAP (Coordinator)*
ii.	*Prof. Dr. Aamir Jaffrey, SIUT Karachi.*
iii	*Prof. Dr. Raza Shah, Director H.E.J. ICCBS, Karachi.*
iv	*Dr. Naseem Salahuddin, The Indus Hospital, Karachi.*
v	*Dr. Najam Us Saquib, Additional Director, In charge DRAP-Karachi.*

4. Due to unavailability of some panel members Chairman CSC conducted inspection with following experts on 10th June 2021:

i.	*Dr. Abdur Rashid, Chairman CSC-DRAP (Coordinator)*
ii.	*Prof. Dr. Aamir Jaffrey, SIUT Karachi.*
iii	*Prof. Dr. Raza Shah, Director H.E.J. ICCBS, Karachi.*
iv	*Dr. Ahson Siddiqi, Co-Opted Member CSC.*
v	*Dr. Najam Us Saquib, Additional Director, In charge DRAP-Karachi.*

5. After inspection, panel submitted report with following remarks:

Keeping in view the infrastructure, human resource, In-door and out facilities, x-ray laboratory facilities, IT, documents, waste management and presence of Principal Investigator in Aga Khan University, the panel recommends the Clinical Trial Site of National Institute of Child Health, Rafique Shaheed Road, Karachi.

6. Concluding status / remarks of inspection panel:

Recommended for approval.

7. It is submitted that the subject clinical trial site is a Government Hospital & proposed for a **Phase-IV** Clinical Trail.

Submitted for consideration of CSC.

Decision:

After due deliberation / discussion & pursuance to the recommendations of the inspection panel, CSC unanimously granted approval to issue licence in the name of M/s National Institute of Child Health, Rafiqui Shaheed Road, Karachi to act as Clinical Trial Site for Phase-IV Clinical Trials.

AGENDA ITEM - V:

REQUEST FOR APPROVAL TO IMPORT STUDY MEDICINES FOR RESEARCH PROJECT TITLED AS "AZITHROMYCIN & CEFEXIME TREATMENT OF TYPHOID IN SOUTH ASIA TRIAL (ACT-SOUTH ASIA TRIAL). F.NO.03-51/2020 DD (PS).

Application submitted by Prof. Dr. Farah Naz Qamar, Associate Professor, Department of Pediatrics & Child Health, Aga Khan University Hospital, Karachi, dated 24th December 2020, on prescribed Form-II along with a fee of Rs.200000/- deposited vide challan no.1908194, dated 08th December 2020. Wherein request has been made for registration & approval of subject clinical trial, which will be carried out at following clinical trial sites:

i. Aga Khan University Hospital, Garden East, Karachi
ii. Aga Khan University Hospital for Women, Karim Abad, Karachi.
iii. National Institute of Child Health (NICH), Karachi.

2. The details regarding sponsor & responsible party is as under:
   i. **Sponsor:** Oxford University Clinical Research Unit, Vietnam.
   ii. **Collaborators:**
      a. University of Oxford.
      b. Medical Research Council.
      c. Department for International Development, United Kingdom.
      d. Wellcome Trust.
   iii. Information provided by (Responsible Party):
      Oxford University Clinical Research Unit, Vietnam.
3. The trial comprises of following objectives;

i. Primary Outcome Measures :

Treatment Failure [Time Frame: Within 28 days of treatment initiation]

A composite outcome of treatment failure by the 28th day after the initiation of treatment will be defined by either of the following events: 1.Clinical failure: persistence of fever on day 7 (168 h) post treatment initiation OR The need for rescue treatment as judged by the Trial Clinician OR The development of any complication (e.g., clinically significant bleeding, fall in the Glasgow Coma Scale score, perforation of the gastrointestinal tract) OR Syndromic enteric fever relapse within 28 days of initiation of treatment. 2.Microbiological failure: a positive blood-culture for S. Typhi or S. Para typhi on day 7 of treatment regardless of the presence of fever (microbiological failure) OR blood culture-confirmed typhoid fever relapse within 28 days of initiation of treatment.

ii. Secondary Outcome Measures :

a. Fever clearance time (FCT) in patients in each treatment arm [Time Frame: at least 2 days]. The FCT will be the time from the first dose of a study drug until a temperature of < 37.5°C (axillary); < 38.0°C (oral) has been achieved.
b. Time from onset of treatment to treatment failure [Time Frame: Within 28 days of treatment initiation]. The time to treatment failure will be the time from the first dose of a study drug until an event occurs defined as a treatment failure.

c. Time from symptom onset to treatment failure [Time Frame: Within 28 days of treatment initiation]. The time to treatment failure will be the time from the day of the first symptom until an event occurs defined as a treatment failure.
d. Adverse event [Time Frame: Within 90 days]. Adverse events will be graded (grade 3/4 adverse events, serious adverse events, adverse events of any grade leading to modification of study drug dose or interruption/early discontinuation);
e. Faecal carriage of S.Typhi or S.Paratyphi [Time Frame: One- and three-month follow-up]. Positive culture of faeces sample for S.Typhi or S.Paratyphi.
f. cost effectiveness of treatment [Time Frame: Initiation of treatment and one-month follow-up visit]. The incremental cost-effectiveness ratio (ICER) will comprise of the total costs per case, real outpatient and in-patient costs, total direct and indirect costs for the family and healthcare system and health outcomes converted to Disability Adjusted Life Years (DALYs). The cost per DALY averted will be compared against multipliers of the gross domestic product/capita in each of the four countries to establish the cost-effectiveness of the combination regimen.

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.200000/- deposited vide challan no.1908194, dated 08th December 2020.
3	Investigator Brochure (s)	Attached but not as per ICH-GCP guidelines.
4	Final protocol	Attached. Version 1.3
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Bangladesh, India, Nepal & Pakistan.
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.	i. Azithromycin 250mg Tablets(200 Strips) ii. Azithromycin 500mg Tablets (416 Strips) iii. Azithromycin Suspension 15ml (100 bottles) iv. Azithromycin Suspension 30ml (600 bottles) v. Cefixime 100mg DT (2300 Strips) vi. Cefixime 400mg (668 Strips)
9	Site of the trial	1. Aga Khan University Hospital, Garden East, Karachi 2. Aga Khan University Hospital for Women, Karim Abad, Karachi. 3. National Institute of Child Health

		(NICH), Karachi.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref:No.4-87/NBC-492/20/505, dated 19th October 2020.
12	CV's of the Investigators	CVs of following (P.Is) are attached: i. Prof. Dr. Farah Naz Qamar, AKUH, Karachi. ii. Dr. Sonia Qureshi, AKUH, Karachi.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Attached.
14	Pre-clinical/clinical safety studies	Articles Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Not provided & claimed that as all drugs used in the trial are already registered & widely used worldwide so not applicable.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	375 Subjects
19	Name of Monitors & Clinical Research Associate	CV of Naveed Ahmed is attached.
20	Evidence of registration in country of origin.	Relevant documents are not provided, whereas Patient Information Leaflets (PIL) of following are attached; i. Azithro-100/Azithro-200 (Azithromycin) Oral Suspension. ii. Azithro-250/Azithro-500 (Azithromycin) Tablets iii. Fixim-200/Fixim-400 (Cefixime) Tablets.

		iv. Fixim DT-100 (Cefixime) Dispersible Tablets. All above drugs manufactured by M/s National Healthcare (Pvt) Ltd, Nepal.
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	36 Months
23	Undertaking on Stamp paper	Attached.

5. Further, it is informed that due to current scenario they might exclude COVID-19 positive patients even if they were randomized & included in the study. Therefore applicant (PI) recalculated the quantities of study drug to be procured as follows:

S.No.	Name of drug	Quantity
01	Azithromycin 250mg	200 Strips
02	Azithromycin 500mg	416 Strips
03	Azithromycin Suspension 15ml.	100 Bottles
04	Azithromycin Suspension 30ml.	600 Bottles
05	Cefixime 100 mg DT	2300 Strips
06	Cefixime 400 mg	668 Strips.

Submitted for consideration of CSC.

6. Dr. Sonia form Aga khan University Hospital/ Representative of Principal Investigator joined the meeting through Zoom link, presented the case before expert members of the committee and also responded the queries made during discussion of the case.

Decision:

The CSC after deliberation / detailed discussion decided to grant approval for registration of the Phase-IV clinical trial titled "Azithromycin & Cefixime Treatment of Typhoid in South Asia Trial (ACT-South Asia Trial)".

AGENDA ITEM - VI:

APPLICATION FOR APPROVAL OF M/S ZAINAB PUNJWANI MEMORIAL HOSPITAL, KARACHI TO ACT AS CLINICAL TRIAL SITE. F.NO.15-34/2021 DD (PS).

Application submitted by Dr. Imtiaz Bashir (CNIC-42301-5409018-9), Director, Zainab Punjwani Memorial Hospital, Karachi, dated 20th May 2021, the site is situated at Muhammadi Habib Road, Numaish, Karachi. Wherein the request has been made to license the subject site with DRAP to act as Clinical Trial Site. Application is on prescribed form-I along with a prescribed fee of Rs.100000/- paid vide challan number 40883786, dated 20th May 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. Application is for conducting Clinical Phase I to Phase IV (Phase I,II,III and IV).(
2	Prescribed processing fee	Rs.100000/- paid vide challan number 40883786, dated 20th May 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).	Provisional licence number SHCC/DLA/PL/0058/2020, dated 27/07/2020 is attached, issued by the Healthcare Commission Sindh. Applicant further informed that the Sindh Health Care Commission presently is not active. On receipt of regular license, a copy will also be shared.
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. As powers conferred by CSC to Chairman CSC/Director Pharmacy Services for constitution of panel for inspection, Chairman CSC reconstituted the following panel for inspection of subject Clinical Trial Site as follows:

i.	*Dr. Abdur Rashid, Chairman CSC-DRAP (Coordinator)*
ii.	*Prof. Dr. Aamir Jaffrey, SIUT Karachi.*
iii	*Prof. Dr. Raza Shah, Director H.E.J. ICCBS, Karachi.*
iv	*Dr. Naseem Salahuddin, The Indus Hospital, Karachi.*
v	*Dr. Najam Us Saquib, Additional Director, In charge DRAP-Karachi.*

4. Due to unavailability of some panel members Chairman CSC conducted inspection with following experts on 08th June 2021:

i.	*Dr. Abdur Rashid, Chairman CSC-DRAP (Coordinator)*
ii.	*Prof. Dr. Muhammad Iqbal Afridi, Ex Dean JPMC, Karachi.*
iii	*Prof. Dr. Raza Shah, Director H.E.J. ICCBS, Karachi.*
iv	*Dr. Najam Us Saquib, Additional Director, In charge DRAP-Karachi.*

5. After inspection, panel submitted report with following remarks:

Keeping in view the Infrastructure, human resource, training, space, emergency handling, waste management and other facilities, recommends the approval for Clinical Trial Site of Zainab Panjwani Memorial Hospital, 2/228 Muhammad Ali Habib Road, Numaish Churangi, Karachi.

6. Concluding status / remarks of inspection panel:

Recommended for approval.

7. After submission of inspection panel report a reply received through email from Harris Shaikh, Admin officer, Zainab Punjwani Memorial Hospital, Karachi, dated 17th June 2021. Wherein email is in reply of this division letter bearing even number dated 04th June 2021. Applicant informed that the applied trial site will conduct Phase-I,II,III & IV clinical trials.

8. It is pertinent to mention here that applied Clinical Trial Site (i.e. Zainab Punjwani Memorial Hospital, Karachi) is a tertiary care private sector hospital & before inspection it was not mentioned in the application that the site will operate for Phase I,II,III & IV clinical studies, it is informed by email after submission of inspection report.

9. After initial evaluation it is observed that subject site has not necessary testing equipment's required for pharmacokinetic/Pharmacodynamic studies in Phase I & II clinical trials as per submitted documents. Accordingly, a letter for clarification was communicated on 21st June 2021 to the applicant/PI and the reply is still awaited.

10. Submitted for consideration of CSC.

Decision:

After due deliberation / discussion & pursuance to the recommendations of the inspection panel, CSC unanimously granted approval to issue licence in the name of M/s Zainab Punjwani Memorial Hospital, Karachi to act as Clinical Trial Site for Phase-III & IV Clinical Trials.

AGENDA ITEM - VII:

APPLICATION FOR APPROVAL OF APPLICATION TO ACT AS CRO AT M/S GLOBAL SCIENTIFIC R&D (PVT) LIMITED KARACHI. F. No.15-25/2021 DD (PS)

Application submitted by Choudhry Muhammad Riaz (CNIC:35202-2768580-9), CEO of M/s Global Scientific R&D (Pvt.) Limited, Plot No. 34/A/78 Hafiz Center, Karachi, Pakistan. 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 along with a fee of Rs.300000/- submitted vide challan No. 0788984, dated 26th March, 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	Fee	Rs.300000/- submitted vide challan No. 0788984, dated 26th March, 2021.
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).	SECP Certificate of incorporation & Acknowledgement certificate, dated 24th March 2021 are 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.	Not applicable as applied for CRO.
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	Attached.

3. As powers conferred by CSC to Chairman CSC/Director Pharmacy Services for constitution of panel for inspection, Chairman CSC reconstituted the following panel for inspection of subject Clinical Trial Site as follows:

i.	*Dr. Abdur Rashid, Chairman CSC-DRAP (Coordinator)*
ii.	*Prof. Dr. Aamir Jaffrey, SIUT Karachi.*
iii	*Dr. Naseem Salahuddin, The Indus Hospital, Karachi.*
iv	*Dr. Ahson Siddiqi, CSC Co-opted member.*
v	*Dr. Saif Ur Rehman Khattak, Director/ In charge CDL, Karachi.*

4. Due to unavailability of some panel members Chairman CSC conducted inspection with following experts on 10th June 2021:

i.	*Dr. Abdur Rashid, Chairman CSC-DRAP (Coordinator)*
ii.	*Dr. Muhammad Iqbal Afridi, Ex Dean JPMC, Karachi.*
iii	*Prof. Dr. Raza Shah, Director H.E.J. ICCBS, Karachi.*
iv	*Dr. Saif Ur Rehman Khattak, Director/ In charge CDL, Karachi.*

5. After inspection, panel submitted report with following remarks:

Keeping in view the QA, QC, IT, HR, Finance, Personal SOPs, Other documents, Pharmacy facility, Biostatistician and other human resources and safety and security measures, panel recommends Global Scientific R & D (Pvt) Ltd., Hafiz Center, Shahra e Faisal Karachi, as Contract Research Organization (CRO)

6. Concluding status / remarks of inspection panel:

Recommended for approval.

Submitted for consideration of CSC.

Decision:

After due deliberation / discussion & pursuance to the recommendations of the inspection panel, CSC unanimously granted approval to issue licence in the name of M/s Global Scientific R&D (Pvt.) Limited, Plot No. 34/A/78 Hafiz Center, Karachi, to act as Contract Research Organization (CRO).

AGENDA ITEM- VIII:

APPROVAL OF REVISED GUIDELINES FOR CONDUCT OF CLINICAL TRIAL

Revised "Guidelines for Conduct of Clinical Trial" are attached as annexure-I. For technical evaluation, these revised guidelines forwarded to experts through email on 30th May 2021, for review & evaluation. Dr. Farhana Badar & Dr. Aamir Jaffary shared their comments. Comments/ input of both experts have been incorporated in the revised guidelines.

Submitted for perusal, discussion and decision of CSC.

Decision:

After due deliberation / discussion the CSC unanimously approved the "Revised Guidelines for Conduct of Clinical Trials" after necessary rephrasing where required.

AGENDA ITEM- IX:

SIGNED PROTOCOL VERSION 2.0 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".

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

i. Aga Khan University Hospital, Karachi.
ii. The Indus Hospital, Karachi.
iii. Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.
iv. Shifa International Hospital, Islamabad.
v. University of Health Sciences, Lahore

2. The case was submitted as a fresh application on prescribed Form-II of the Bio-Study Rules 2017 along with a fee of Rs.200,000/- for new trial.

3. Applicant/PI didn't inform or clarified that the application is in continuation of previously approved single dose vaccine trial.

4. As application was not accompanied with IRB/ERC approvals & doesn't informed by the PI, so the application was treated as new/fresh application/case & placed before CSC for consideration.

5. The case was placed before CSC in its 26th meeting held on 31st May 2021. The CSC decided as follow.

The CSC after detailed deliberation decided to approve 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" subject to submission of IRB approvals of the following Clinical Trial Sites:

i. Aga Khan University Hospital, Karachi.
ii. The Indus Hospital, Karachi.
iii. Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.
iv. Shifa International Hospital, Islamabad.
v. University of Health Sciences, Lahore.

It is pertinent to mention that National Bioethics Committee has already approved this study.

6. The decision of the CSC in the case was communicated to the applicant accordingly and in the light of decision, the IRB approvals should have been furnished by the applicant. Ms. Ghazala Parveen, Chief BPD-NIH/Co-PI of the trial was explained that IRB as well as NBC approval letter need to be submitted in original for further processing of the case telephonically, as the documents on the record are print outs of Whats App communication (even some not legible page & UHS letter is an application to EC for approval and not an IRB approval letter).

i. The applicant was again requested for provision of the above said information vide this division letter dated 11-06-2021. The response to the letter date 02-06-2021 was received in this division on 14-06-2021 wherein IRB approval letters were enclosed however NBC approval letter in original was not still provided as requested.

ii. Perusal of documents submitted by Ms. Ghazala Parveen, Chief BPD-NIH/Co-PI of the trial, revealed that all the IRB/ECs approval were for amendment/addendum/modification in the initially approved trial titled "Phase-III, Double-Blind, Placebo-Controlled, Randomized Clinical Trial of Recombinant Novel Corona Virus Vaccine (Adenovirus Type 5 Vector)." manufactured by M/s CanSino Biologics Inc., & Beijing Institute of Biologicals, China. This trial was approved for a duration of four months, enrolling 10000 subjects & registration letter number CT-0015 was granted as per decision of 13th CSC meeting held on 11th August 2020. Later on, trial was conducted on 18000 Subjects through some amendments.

iii. After completion of Clinical Trial on 18000 Subjects in Pakistan, trail report was submitted to CSC, Committee on Vaccines & Registration Board for grant of Emergency Use Authorization (EUA) which was accorded & the vaccine under reference was included in mass vaccination program as a single dose vaccine. However, the trial report was not found in office record as it has never been submitted to this office/ division.

iv. Applicant also claimed that the applied Clinical Trial is a Global multi country trial & is enlisted on U.S. National Trail Registry & provided identifier number: NCT04526990. When it was checked on U.S. National Trial Registry it was observed that it's a single dose placebo-controlled trial instead of 2nd or booster dose trial as being claimed now by applicant/NIH. The submitted protocol for second dose/booster dose has not been signed by

any Investigator/Sponsor. Later on, Study Protocol was submitted having signatures pages of sponsor, Global PI and Co-PIs on 18.06.2021.

7. As already submitted above in paras that previously approved trial for CanSino Vaccine (CT-0015) was approved for a duration of 04 months by the CSC from the date of issuance of trial registration certificate (i.e. 24th August 2020) was completed on 18000 Pakistani Subjects & EUA has been granted, so how can a completed trial have got Protocol Amendment approval from NBC & IRB of Clinical Trial Sites? It is found that there is a communication gap between NBC, IRB & DRAP or some facts have not been brought on record by the applicant.

8. The matter was discussed at length with Ms. Ghazala Parveen, Chief BPD-NIH/Co-PI in presence of Director PS/ Chairman CSC, Additional Director/ Secretary CSC, Assistant Directors on 21-06-2021 at Pharmacy Services Division of DRAP. Ms. Ghazala Parveen briefed in detail that its protocol amendment instead of new trial and submitted a letter stating that it is the amended version of the protocol of the previously approved Clinical trial Study and requested for issuance of Clinical Study Approval as per amended protocol.

9. In the light of above & perusal of documents on record, following queries needs to be addressed.

i. As per U.S. National Trail Registry & provided identifier number: NCT04526990, it is a single dose trial while as per new amended protocol, it is two doses trial.
ii. If the said trial has not been completed yet then how this vaccine has been issued EUA and have become the part of Mass Vaccination Program as single dose.
iii. If after completion of two doses trial, safety, efficacy and immunogenicity is based on double dose then what will be the fate of people having single dose during mass vaccination.
iv. Second dose will be given to participants after primary outcomes have been achieved. So, clinical trial data of single dose is required before start of second dose to ascertain primary achievements/ objective.
v. Is it safe to conduct phase III Clinical trial without carrying phase II trial with two doses??

7. Above discussion and queries, are submitted for consideration of CSC. The amended protocol as submitted (version 2.0) along with summary of changes is submitted for consideration of CSC.

8. Dr. Ghazala Parween (Co-P.I) joined the meeting through Zoom link & presented the case before members of CSC and also responded some of the queries made during discussion of the case.

9. During the meeting, Dr. Aamir Jafarey raised the point of Conflict of Interest that, when a sitting member is also an applicant, no norms of conduct, anywhere in the world, permit the honorable member to sit through, let alone contribute to the discussion, of his or her own proposal. Dr. Aamir Jafarey had pointed this out and this needs to be minuted. This was seconded twice by Professor Mushtaq Ahmad, and Dr Abdur Rasheed on this also said Noted to be incorporated in the minutes.

Submitted for perusal, discussion and decision of CSC.

Decision:

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 Clinical Trial Sites in the light of their respective IRB approvals:

i. Aga Khan University Hospital, Karachi.
ii. The Indus Hospital, Karachi.
iii. Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.
iv. Shifa International Hospital, Islamabad.
v. University of Health Sciences, Lahore.

2. CSC also approved 16,560 doses of investigational product to be used in this trial.

Note: *The partial minutes of the case were prepared as approved by the CSC during meeting and the decision of CSC was communicated to the applicant vide letter no. F.No.16-27/2021 DD (PS) dated 24th June 2021.*

AGENDA ITEM- X:

EFFECTIVE COMMUNICATION BETWEEN NATIONAL BIO ETHICS COMMITTEE (NBC) & CLINICAL STUDIES COMMITTEE (CSC)

It is submitted that National Bioethics Committee is an important stake holder & responsible for ethical approval of Clinical Studies conducted on Human Subjects in Pakistan.

2. Ethical clearance from NBC is mandatory for approval of Clinical Trial applications from Clinical Studies Committee (CSC).

3. It is proposed that, NBC may be officially requested to share/communicate all approval granted for clinical research.

Submitted for perusal, discussion and decision of CSC.

Decision:

After due deliberation / discussion the CSC unanimously approved the agenda for "Effective Communication between National Bioethics Committee (NBC) & Clinical Studies Committee (CSC)" & decided that National Bioethics Committee will share all approval letter(s) and send copies to Division of Pharmacy Services-DRAP for processing of the respective case.

AGENDA ITEM - XI:

REQUEST FOR REGISTRATION OF CLINICAL STUDY TITLED "ANTI-CORONAVIRUS THERAPIES TO PREVENT PROGRESSION OF COVID-19. F. No.03-57/2021-DD (PS).

Application submitted by Dr. Khawar Kazmi, Visiting Faculty Department of Medicine, Professor & Consultant Cardiologist, Aga Khan University Hospital, Karachi, dated 02nd February 2021, on prescribed Form-II along with a fee of Rs.200000/- deposited vide challan no.0831707, dated 01st February 2021. Wherein request has been made for registration & approval of subject clinical trial, which will be carried out at following clinical trial sites:

S.No.	Clinical Trial Site	Site P.I.	Expected enrollment
01	Aga Khan University Hospital, Karachi. (National Coordinating & Participating Site)	National Coordinator: Dr. Khawar Kazmi. Site P.I. Dr. Zainab Samad.	Inpatient: 50 Outpatient: 150
02	Tabba Heart Institute, Karachi.	Dr. Bashir Hanif, Medical Director & Head of Cardiology.	Inpatient: 50 Outpatient: 100
03	Jinnah Post Graduate Medical Center / Jinnah Sindh Medical University, Karachi.	Dr. Zeeshan Ali, Associate Professor of Medicine.	Inpatient: 50

2. The study is also enlisted at U.S. National Trial Registry under identification number: NCT04324463. The summary regarding sponsor, responsible party & trial is as under:

i. **Sponsor:** Hamilton Health Sciences through its Population Health Research Institute, Canada.

ii. **Collaborators:**
   a. Bayer AG, Leverkusen, Germany.

iii. Information provided by (Responsible Party):
   Population Health Research Institute, Canada.

iv. **Name of Investigational product , including all available names ; trade , generic or INN name etc.**
   a. Anti - inflammatory : colchicine vs. control . (both inpatient and outpatient)
   b. Antithrombotic : acetylsalicylic acid (ASA) vs. control (outpatient only.
   c. Antithrombotic : combination of ASA and rivaroxaban vs. control . (Inpatient only)
   d. Interferon-Beta, subcutaneous injection

v. **Purpose of trial defining the indication along with the anticipated cost of the project and sources of fund**:
   a. The aim of the study is to evaluate anti - inflammatory and anti-thrombotic therapy to determine whether they prevent clinical progression of COVID-19 in outpatients and inpatients . Disease progression and mortality appear to be related to an intense inflammatory response and secondary thrombosis in the pulmonary , cardiac and cerebral vasculature . We will likely need combinations of several widely available

and affordable interventions that target different pathways (e.g. inflammation, thrombosis) to substantially reduce the risk of COVID - 19 disease progression . We need to test these treatments as soon as possible after diagnosis.

b. Source of funding : Hamilton Health Sciences through its Population Health Research Institute (PHRI), Canada.

3. The trial comprises of following primary objectives;

i. Outpatient trial - Colchicine vs. control and Aspirin vs. control [Time Frame: 45 days post randomization] composite of hospitalization or death.
ii. Inpatient trial - Interferon-β vs. control and Colchicine vs. control [Time Frame: 45 days post randomization] invasive mechanical ventilation or death.
iii. Inpatient trial - Aspirin and rivaroxaban vs. control [Time Frame: 45 days post randomization] invasive mechanical ventilation or death

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.200000/- deposited vide challan no.0831707, dated 01st February 2021.
3	Investigator Brochure (s)	Attached.
4	Final protocol	Attached. Version 15.0
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Argentina, Brazil, Canada, Chile, Columbia, Ecuador, Egypt, India, Philippines, Russia, Saudi Arabia, United Arab Emirates, United States of America & Pakistan
7	Phase of trial.	Phase –III As per U.S. National Trial Registry Identifier No. NCT04324463
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.	i. Aspirin 75mg Tablets (7280 Tablets) ii. Colchicine 0.5 mg Tablets (10740 Tablets) iii. Xarelto (Rivaroxaban) 2.5 mg Tablets (5488 Tablets).
9	Site of the trial	1. Aga Khan University Hospital, Karachi 2. Tabba Heart Institute, Karachi. 3. Jinnah Postgraduate Medical Center, Karachi.

10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref:No.4-87/COVID-56/NBC/20/1148, dated 13th January 2021.
12	CV's of the Investigators	CVs of following (P.Is & Co-PIs) are attached: i. Dr. Sayed Khawar Abbas Kazmi, AKUH, Karachi. ii. Dr. Zainab Samad, AKUH, Karachi. iii. Dr. Bashir Hanif, Tabba Heart Institute, Karachi. iv. Dr. Zeeshan Ali, JPMC, Karachi.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP certificates of followings are attached: a. M/s Tiofarma B.V., Benjamin Franklinstraat, Netherlands. b. M/s Bayer AG, Leverkusen, Germany. c. M/s Almac Clinical Services Limited, Northern Ireland, UK. d. GMP certificate of M/s Medreich PLC, Warwick House, Plane Tree Crescent, Feltham, TW13 7HF, United Kingdom. COPP are attached for following IMPs: a. Xarelto (Rivaroxaban) 2.5 mg Tablets. Mfg. by Bayer AG, Leverkusen, Germany. b. Colchicine 0.5mg Tablets, manufactured by M/s Tiofarma B.V., Benjamin Franklinstraat, Netherlands. c. Aspirin 75mg Tablets manufactured by M/s Medreich PLC, Warwick House, Plane Tree Crescent, Feltham TW13 7HF, United Kingdom.
14	Pre-clinical/clinical safety studies	EMA assessment report for Xarelto (Rivaroxaban) is attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting	Attached.

	Form	
18	No of patients to be enrolled in each center.	Attached.
19	Name of Monitors & Clinical Research Associate	Monitoring plan is attached.
20	Evidence of registration in country of origin.	COPP are attached for following IMPs: a. Xarelto (Rivaroxaban) 2.5 mg Tablets. Mfg. by Bayer AG, Leverkusen, Germany. b. Colchicine 0.5mg Tablets, manufactured by M/s Tiofarma B.V., Benjamin Franklinstraat, Netherlands. c. Aspirin 75mg Tablets manufactured by M/s Medreich PLC, Warwick House, Plane Tree Crescent, Feltham TW13 7HF, United Kingdom.
21	Copy of registration letter (if registered in Pakistan)	Copy of registration letter for Xarelto (Rivaroxaban) 2.5 mg Tablets. Mfg. by Bayer AG, Leverkusen, Germany is attached.
22	Sample of label of the investigational product / drug.	Attached for following IMPs: a. Colchicine 0.5mg Tablets. b. Rivaroxaban 2.5mg Tablets. c. Aspirin (ASA) 75mg Tablets.
22	Duration of trial	12 Months
23	Undertaking on Stamp paper	Attached.

5. It is submitted that the application was discussed in the 19th CSC meeting & CSC decided the case follows:

Decision of 19th CSC meeting:

The CSC after detailed deliberation deferred till fulfilment of all prerequisites & clinical trial site(s) approval.

6. Applicant submitted required documents / clarification & proposed Clinical Trial Sites were approved by CSC in its 25th meeting held on 28th April 2021.

7. Technical documents (i.e. Study Protocol & investigator's brochure etc.) were forwarded to all CSC experts for review & evaluation under sub-rule 4 of rule 7 of the Bio-Study Rules 2017, on 01st February 2021.

8. Submitted for consideration of CSC.

9. Dr. Khawar Kazmi (P.I) joined the meeting through Zoom link, presented the case before expert members of the CSC and also responded the queries made during discussion of the case.

Decision:

The CSC after detailed deliberation & discussion decided to grant approval for registration of the Phase-III clinical trial titled "Anti-Coronavirus Therapies to Prevent Progression of COVID-19".
