

**Minutes of 16<sup>TH</sup> MEETING OF CSC TO BE HELD ON 27<sup>th</sup> NOVEMBER 2020.**

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1. The 16<sup>th</sup> CSC Meeting was held on 27<sup>th</sup> November 2020 through Zoom under the chairmanship of Dr. Abdur Rashid, Director Pharmacy Services Division / Chairman (CSC). At the Committee Room, 4<sup>th</sup> 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, Divison of Pharmacy Services.
02	Muhammad Arif Chaudhry.	Secretary CSC / Additional Director, Divison of Pharmacy Services.

3. Following members attended the meeting online through Zoom:

01	Prof. Nadeem Irfan Bukhari.	Professor of Bio-Pharmaceutics & Pharmacokinetics, University of Punjab, Lahore.
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. Member CSC.
04	Dr. Naseem Salahuddin.	Director, Infectious Diseases Indus Hospital, Karachi Co-opted CSC Member.
05	Dr. Aamir Jaffary	Sindh Institute of Urology & Transplantation (SIUT), Karachi Co-opted Member.
06	Dr. Rizawa Chaudri	Shifa Tameer e milat university. Islamabad. Co-opted Member.
07	Dr. Mushtaq Ahmed	Professor of Cardiology, Bach Khan Medical College. Mardan Co-opted Member.

3. Mr. Muhammad Adnan Faisal Saim, Deputy Director, Pharmacy Services Division, Mr. Rana Ahsan Ul Haq Athar Assistant Director, Pharmacy Services Division, assisted the Secretary CSC for evaluation & presentation of the cases.

4. Meeting started with the recitation of holy verses of the Quran by Dr. Muhammad Fakhruddin Amir, Director, Division of Medical Devices and Medicated Cosmetics.

5. Chairman, CSC welcomed all the members. He briefed the members of the meeting, regarding the meeting agenda. Chairman, CSC also thanked members for their active participation online through Zoom.

**1. CONFIRMATION OF THE MINUTES OF THE 15<sup>TH</sup> CLINICAL STUDIES COMMITTEE MEETING.**

1.1 Minutes of 15<sup>th</sup> CSC meeting are placed for confirmation of CSC members.

1.2 Submitted for perusal, discussion and decision of CSC.

1.3 **Decision of 15<sup>th</sup> CSC meeting:**

*All the members confirmed the minutes of 15<sup>th</sup> CSC which was held on 12<sup>th</sup> October, 2020.*

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**2. APPLICATION FOR APPROVAL TO ACT AS CRO AT M/S PRECISION HEALTH CONSULTANTS (PHC) GLOBAL (PVT) LIMITED KARACHI. F. No.15-56/2020 DD (PS).**

2.1 Application from Muhammad Imran Khan, CEO of M/s Precision Health Consultants (PHC) Global (Pvt.) Limited, House # 241, 1<sup>st</sup> floor, Bahadurabad #03, 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. 2051401, dated 15<sup>th</sup> October 21, 2020.

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

<b>S. No.</b>	<b>Required Documents / Information</b>	<b>Remarks</b>
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Fee	Attached
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	SECP Registration Certificate No. A035856, with Corporate Universal Identification No. 016597 is attached
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.	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.	Not applicable as applied for CRO.
8	Undertaking	Attached

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

**Decision of 16<sup>th</sup> CSC meeting:**

*CSC after detailed deliberation decided to authorize the Chairman CSC for the constitution of inspection panel for the inspection of M/s Precision Health Consultant (PHC) Global (Pvt.) Limited, Karachi. The case will be again placed before the CSC for further deliberations and decisions after submission of inspection report.*

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**3. APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIAL SITE FROM NATIONAL INSTITUTE OF HEALTH SCIENCES.**

FR (page 01 – 96/corr.) is an application from Mst. Ghazala Perveen Chief BPD, national Institute of Health sciences, Islamabad, wherein the major General prof. dr. Aamer Ikram SI (M), Executive Director, NIC number 51401-0924270-9 application has requested for grant of license to act as a Clinical Trial Site. 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	Page No.	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	04-05	Attached
2	Prescribed processing fee	03-03	Fee challan of Rs.100,000/- attached submitted vide slip No. 2003111.
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	07-10	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

	partners and in the case of company the name and address of the company and its directors).		Nutrition survey and research were shifted in the premises of NHC. Later, during 1974 proper 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.	11-33	Attached
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	34-72	List of testing equipment Attached. But details of treatment/ patient handling facilities of trial center not provided.
6	Names and qualifications of the above sections along with their staff.	73-88	Attached
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	89-95	Islamabad hospital <i>Isolation Hospital and infectious treatment center</i> Detail are provided.
8	Undertaking on stamp paper	---	Not provided.

3. After evaluation it was found that national institute of Health Islamabad has applied for the clinical trial site but allied facility details of Islamabad hospital has been provided. Applicant may be asked about the premises where trial of Covid vaccine is to be run either it is some specific department of NIH or at Islamabad hospital, off Jinnah Avenue, Islamabad. Applicant may also be asked to submit undertaking on stamp paper.

4. Submitted for perusal of CSC.

**Decision of 16<sup>th</sup> CSC meeting:**

***CSC after detailed deliberation decided to authorize the Chairman CSC for the constitution of inspection panel for the inspection of NIH to act as clinical trial site and Islamabad Hospital, off Jinnah Avenue, Islamabad for COVID-19 Vaccine Phase III Trial. The***

*case will be again placed before the CSC for further deliberations and decisions after submission of inspection report.*

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**4. SUBMISSION REVIEW OF PROTOCOL FOR CANSINO AD5-COV-PHASE III VERSION 1.3 BY NATIONAL INSTITUTE OF HEALTH, ISLAMABAD ISSUANCE OF PROTOCOL AMMENDMENT (APPROX. 18000 PARTICIPANTS) BY NIH, ISLAMABAD.**

Mst ghazala Perveen Chief CBD has submitted of fee of Rs. 25000/- vide challan No. 2003110 for review of protocol for CanSino Ad5-Cov-phase III version 1.3 communicated vide this office letter dated 30.09.2020.

**(Soft copy of Revised Protocol for CanSino Ad5-nCoV Phase III Version 1.3 is attached)**

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As per page 56, 57 of revised Protocol for CanSino Ad5-nCoV Phase III Version 1.3

**Country Samples size range % Total enrollment**

Pakistan 8000-14000 20%- 35%	Russia 5000-10000 12.5%-25%
Argentina 5000-10000 12.5%-25%	Chile 3000-5000 7.5%-12.5%
Saudi Arabia 5000-8000 12.5%-20%	Mexico 5000-8000 12.5%-20%

*Percent of total enrollment is based on a sample size of 40, 000 participants.*

Mst Ghazala Perveen Chief CBD, NIH , Islamabad has requested to please issue approval letter of protocol amendment (Approx. 18,000)

Mst Ghazala Perveen Chief CBD has submitted of fee of Rs. 25000/- vide challan No. 2003112 for review of protocol for CanSino Ad5-Cov-phase III version 1.4 vide letter No.ISB-BPD-ADMN-File-43 dated 10.11.2020 and as per page 68 of this protocol;

**Total sample size 40000-54000**

Pakistan	18000	Mexico	15000
Chile	5000	Argentina	8000
Russia	8000		

**Soft copy of Revised Protocol for CanSino Ad5-nCoV Phase III Version 1.4 is attached)**

It was proposed that the both revised protocol may be forwarded to experts for review under Rule 7 (4) of Bio-Study Rules 2017 and applicant may be asked for subject recruitment details and conduction of systemic safety observation.

**NBC approval for both revised protocols not attached.**

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**Decision of 16<sup>th</sup> CSC meeting:**

*Dr. Ghazala Perveen Chief CBD (Co-Principle Investigator) explained her case before the CSC. In the light of her presentation, NBC approval and submitted documents, the committee discussed the case in details and following decisions were taken;*

- *The Principle Investigator will submit the detailed report on the progress made in undergoing trials at different approved sites for the consideration of the CSC.*
- *The matter of false reports in the national press also come under discussion and it was decided by the CSC that a comprehensive press release will be issued by CSC for the understating of the public.*
- *The committee further decided to increase the number of volunteers/ participants of trial from 10,000 to 18,000.*

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**5. APPLICATION FOR APPROVAL TO CONDUCT THE WOMAN PHARMACO TXA TRIAL IN PAKISTAN, SHIFA TAMEE-E-MILLAT UNIVERSITY ISLAMABAD.**

**APPLICATION FOR A RANDOMIZED TRIAL TO ASSESS THE PHARMACOKINETICS AND PHARMACODYNAMICS OF INTRAMASCULAR, INTRAVENOUS AND ORAL ADMISTRATION OF TRANEXAMIC AVID IN WOMAEN GIVING BIRTH BY CAESAREAN SECTION.**

This is an application from Dr. Rizwana Chaudhary, head of Translational Research Department, Shifa Tameer e Millat University (STMU) and Haleema Shakur-Still Professor Global e health Clinical Trials, London School of Hygiene and Topical medicina Caple Street, London, wherein they had stated that we are writing to apply for approval from the Drug Regulatory Authority of Pakistan (DRAP) to conduct the WOMAN-PharmacoTXA trial in Pakistan. Please find below list of hospitals taking part in the trial in Pakistan for your consideration: Site names in Pakistan are Institute of Medical Sciences (PIMS) and Federal Government Polyclinic Hospital with Investigators Professor Syeda Batool Mazhar and Dr Naila israr respectively.

2. The trial is organized by an international academic group and is sponsored and coordinated by the London School of Hygiene and Tropical Medicine (LSHTM, University of London). This application is to seek approval for the trial in Pakistan under the supervision of Professor Rizwana Chaudhri.

3. The WOMAN-PharmacoTXA trial aims to answer the question whether giving tranexamic acid by different routes (intramuscular or oral liquid) achieves a good enough level in the blood to reduce bleeding - compared to the standard intravenous dose. To this aim, we will assess pharmacokinetics of intravenous, intramuscular and oral TXA solution in pregnant women. Women

enrolled in this trial will be undergoing a Caesarean Section because they are at high risk of postpartum hemorrhage.

4. They further stated that The WOMAN trial assessed the effects of intravenous TXA in 20,060 women with postpartum hemorrhage, 5282 of them in Pakistan. TXA significantly reduced death due to bleeding with no adverse effects. The WOMAN trial showed that every 15 minutes delay giving tranexamic acid reduced the treatment benefit by 10%. If we can give tranexamic acid by the oral or intramuscular routes, more women are likely to receive the treatment sooner. This is particularly relevant in Pakistan where postpartum hemorrhage is a leading cause of maternal mortality and morbidity. This trial responds to the call by the World Health Organization which states that "research on other routes of TXA administration is a priority.

5. They are looking forward to receiving DRAP response to their application and hoping that Pakistan will be able to join this collaboration soon.

6. It seems like some bioavailability study. The applicant or representative of the applicant well versed with the case may be asked to attend the office to discuss the case.

7. As per discussion following is the administrative evaluation of the case as per check list provided in Bio-Study Rules 2017.

S. No.	Document	Page No.	Remarks
1	Application on prescribed Form-II	01-12	Attached
2	Prescribed processing fee	16-17	Provided vide challan No. 2043618 dated 06.10.2020
3	Investigator Brochure (s)	18-72	Attached
4	Final protocol	73-141	Attached
5	Informed consent and participant information sheet (Urdu to English)	145-162	Attached.
6	List of participating countries	07	Pakistan and Zambia
7	Phase of trial.	07	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.	07	Trial sample is 120 participants with a full set of evaluable samples (30 receiving oral liquid TXA, 30 intramuscular TXA, 30 intravenous and 30 receiving no TXA). There is no limit on the number of patients to be recruited in Pakistan. If randomized to receive Tranexamic Acid participant will receive either: Two ampoules of 0.5g/ml drawn in 10 ml injection.



			<p>Two ampoules of 0.5g/ml split between two 5ml IM injection. Eight ampoules of 0.5g/5ml tranexamic acid given as 40ml oral solution.</p> <p>Further applicant wrote that they estimate about 20% of the participant will drop out or will have missing data, will need to be replaced. In addition, they need to be allowed for possible damage and breakage of ampoules. 500 ampoules of TXA will be purchased.</p>
9	Site of the trial	07	<p>Federal Government services Hospital. Pakistan Institute of Medical Sciences (PIMS).</p>
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	237-238	<p>Copies of IRB approval Federal government Polyclinic and Shaheed zulfiqar Ali Bhutto Medical University is attached. complete composition of committee i.e. names and designation of members is not attached.</p>
11	Approval of National Bio-ethics Committee (NBC)	251	<p>Attached. Ref:No.4-87/NBC-532/20/409, Dated 30<sup>th</sup> September 2020.</p>
12	CV's of the Investigators	204-235	<p>CV of Dr. Syeda Batool Mazhar is attached. CV of Dr. Naila Israr is not attached.</p>
13	GMP certificate along with COPP & free sale certificate of the investigational product.	-----	<p>Not attached.</p>
14	Pre-clinical/clinical safety studies	08	<p>Applicant has stated that TXA has been licensed for clinical use for over 40 years. Preclinical testing would have been well established before being licensed for use in human.</p>
15	Summary of Protocol	81-81	<p>Attached.</p>

16	Summary of Investigator Brochure	23-26	Attached.
17	Adverse Event Reporting Form	193	Attached.
18	No of patients to be enrolled in each center.	12	120
19	Name of Monitors & Clinical Research Associate	11	Dr. Asia kiani, Assistant Professor STMU. Dr. kiran javaid Assistant Professor STMU
20	Evidence of registration in country of origin.	11	Applicant has submitted that its Transamine Injection (005024). They have also stated that the drug will be obtained from the open market and as such will have to be manufactured to GMP standards.
21	Copy of registration letter (if registered in Pakistan)	----	Not Attached.
22	Sample of label of the investigational product / drug.	---	Not provided.
22	Duration of trial	20	01 May 2021 or till completion of patients.
23	Undertaking on stamp paper.	14-15	Attached.

8. Evaluation is based pre-requisite as per Bio-Study rules 2017. After fulfillment of shortcomings, case may be referred to experts for technical evaluation. DFA for shortcomings per checklist provided in Bio-Study rules 2017 is attached please.
9. Following shortcomings were communicated.
- i. Complete composition of committee i.e. names and designation of members of IRB not attached.
  - ii. Detailed CV of the Investigator Dr. Naila Israr is not attached.
  - iii. Evidence of registration of ampoule to be used orally is required.
  - iv. Copy of registration letter for IM, IV and oral liquid required to whom principal investigator wants to use during study.
  - v. Sample of label of the investigational product / drug not attached.

10. Applicant was advised to fulfill the shortcomings within seven (07) working days but reply is still awaited.
  11. Submitted for perusal of CSC.
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**Decision of 16<sup>th</sup> CSC meeting:**

*Dr. Rizwana Chaudhri (Supervisor) and Dr Haleema Shakur -Still (Professor Global Health CT, London School Hygiene and topical Medicines) explained the case before the CSC and after detailed deliberation following decisions were taken with majority of votes;*

- *The Dr. Rizwana Chaudhri and Dr Haleema Shakur -Still will submit the undertaking that no ADRs were reported in Phase 1 trials conducted in France along with detailed SOPs/ Protocol Validation for samples transportation.*
  - *Dr Haleema Shakur -Still will submit the detailed report on the Phase 1 trials as early as possible.*
  - *Fulfilment of all short comings under the Bio-Study Rules mentioned in agenda.*
  - *The committee finally approved the study.*
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## **6. CLINICAL VALIDATION OF PAKISTAN MANUFACTURE VENTILATORS SYSTEM (PMVS)**

A letter received from Engr. Brig. Tariq Javed,(R) wherein he has stated that please find attached the copy of application for clinical validation of PMVS by respective OEMs i.e. PMO, PAEC, M/s Alson Group and NED university. (soft copy enclosed).

**Background:** - Expert Group for Assessment/ Evolution of locally manufactured Medical devices (Ventilators) was constituted vide letter No. 16-5/2020-MD dated 3<sup>rd</sup> April 2020 & 4<sup>th</sup> April 2020. Case of ventilators was in 3<sup>rd</sup> meeting of Expert Committee on evaluation/ assessment of locally manufactured ventilators was held on 3<sup>rd</sup> July 2020 and decided as follow:

**Decisions:** *In the end of meeting Major general Aslam Khan said that he would not agree with clinical testing of ventilators in the absence of simulators for ventilators. Since the ventilators have not gone through the routine procedure of simulation, animals testing, healthy volunteers and patients testing, therefore, testing through simulators for ventilators must be mandatory. In case the testing through simulators is not possible, then DRAP ethic committee approval should be solicited. Ethic committee should decide that due to COVID-19 these ventilators should not go through animal, healthy volunteers and patients testing. Dr.Abdul Rasheed briefed the participants that ethic committee is not in the mandate of DRAP, rather it is working as National Bio-ethic Committee (NBC) in Pakistan Health Research Council (PHRC) under Ministry of National Health Services Regulation & Coordination. If the committee decided to go through the NBC as an applicant for all the ventilators. After approval from NBC the case may be again presented before this committee. After approval of Expert Committee on Ventilators the PEC would individually apply to Clinical study Committee as per the provision of Bio-Study Rules,2017.*

Following were also communicated by Dr Ghazanfar Ali vide letter No. F.16-5/2020-MD dated 13<sup>th</sup> April 2020 that;

1. No locally manufactured Ventilator design/ Prototype be processed by DRAP unless it is wetted/ validated by Pakistan engineering Council (PEC) Experts;
2. No ventilator shall be used on patients without prior approval of expert group on ventilators;
3. Standards for fast Track Acceptance Test Procedure for locally Manufactured mechanical ventilators for ICU (Version 1.1) developed by PEC and approved by Expert Group on ventilators shall be the bench mark for locally manufactured ventilators in Pakistan and the same has been uploaded on DRAP website.

Submitted for perusal of CSC

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**Decision of 16<sup>th</sup> CSC meeting:**

*Dr. Muhamamd Fakhruddin Aamir, Director (MDMC) /Chairman, Medical Device Board gave a detailed presentation for the mechanism to be adopted for the registration of locally manufactured medical devices/Ventilators. The committee after detailed deliberation and discussion made the following decisions;*

- *The Dr. Faiza Bashir (Member, CSC) informed the committee that NBC has asked different queries regarding electromedical devices development from PEC and their reply is still awaited. However, NBC is in the process of developing the SOP/guidelines for the clinical validation of locally manufactured electromedical devices (ventilators etc.) which will be finalized soon. The CSC advised Dr. Faiza Bashir, for sharing of guidelines after finalization, with the committee.*
  - *The applicants will apply to the Division of Pharmacy Services directly along with recommendations of Pakistan Engineering Council under Bio Study Rules, 2017.*
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