MINUTES OF The 22nd MEETING OF CSC TO HELD ON 23rd March 2021.

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The 22nd Meeting of the CSC was held on 23rd March 2021 through Zoom under the chairmanship of Dr. Abdur Rashid, Director Pharmacy Services Division / Chairman (CSC). At the office of Director Pharmacy Services, 3rd 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	Abdul Sattar Sohrani.	Secretary CSC, Additional Director, Division of Pharmacy Services-DRAP.

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.
04	Dr. Faiza Bashir.	Chairman, Pakistan Health Research Council or his nominee, Islamabad.
05	Dr. Aamir Jaffary	Sindh Institute of Urology & Transplantation (SIUT), Karachi Co-opted Member.
06	Prof: Dr. Mushtaq Ahmed	Professor of Cardiology, Bach Khan Medical College, Mardan, KPK Co-opted Member.

4. Meeting started with the recitation of holy verses of the Quran by Abdul Sattar Sohrani, Secretary CSC. Chairman, CSC welcomed all the members & appreciated active participation of members online through Zoom.

AGENDA ITEM - I: CONFIRMATION OF THE MINUTES OF THE 21ST CLINICAL STUDIES COMMITTEE MEETING.

1. Confirmation of Minutes of 21st CSC meeting, held on 22nd March 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:

Minutes of the 21st meeting of CSC were confirmed by the committee.

AGENDA ITEM - II:

CLINICAL TRIAL OF INDIGENIOUS VENTILATORS (PAKVENT-I VENTILATOR).

Application is from Muhammad, CNIC No. 36302-0466539-7 from M/s Project Management Organization wherein he has applied for clinical validation of Pakvent-1 Ventilator. The application is on Form-II of the Bio-Study Rules 2017 along with fee challan of Rs.200,000/.

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 Challan No. 2077447 dated 14.01.2021.
3	Investigator Brochure (s)	Attached but not as per ICH guidelines.
4	Final protocol	Clinical validation protocol for Pakistan manufactured ventilator system (PMVS) prepared by PEC is attached. **Annex-I**
5	Informed consent and participant information sheet (Urdu to English)	Attached. **Annex-II**
6	List of participating countries	Pakistan.

7	Phase of trial.	**Final Trial.** Phase of trial needs to properly described i.e. Phase I.II,III or 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.	01 ventilator
9	Site of the trial	CMH Rawalpindi (Approved in 21st CSC meeting)
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)	Attached. Ref:No.4-87/EMD-VENT-02/NBC/21/1123 dated January 08, 2021.
12	CV's of the Investigators	Not Attached
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not Attached
14	Pre-clinical/clinical, safety studies	No clinical and safety studies Attached
15	Summary of Protocol	Not Attached
16	Summary of Investigator Brochure	Attached but not as per ICH guidelines.
17	Adverse Event Reporting Form	Attached
18	No of patients to be enrolled in each center.	Not Attached
19	Name of Monitors & Clinical Research Associate	Capt. Raheel, Maj. Mudassar
20	Evidence of registration in country of origin.	Not attached
21	Copy of registration letter (if registered in Pakistan)	Not Attached
22	Sample of label of the investigational product /	Not Attached

	drug.	
22	Duration of trial	03 Months
23	Undertaking on stamp paper.	Not Attached

3. After evaluation, as per checklist provided in bio-Study Rules 2017, following shortcomings were observed.

i. Investigator Brochure (s) is not as per ICH guidelines.
ii. Clinical validation protocol for Pakistan manufactured ventilator system (PMVS) prepared by PEC is attached instead of final protocol.
iii. Written as **Final Trial.** Phase of trial needs to properly described i.e. Phase I, II, III or IV.
iv. Separate application on Form-I is required for approval of clinical trial site i.e. CMH Rawalpindi.
v. Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members, is not attached.
vi. GMP certificate along with COPP & free sale certificate of the investigational product is not attached.
vii. CV's of the Investigators not attached.
viii. Pre-clinical/clinical, safety studies are not attached.
ix. Summary of Protocol not attached.
x. Summary of Investigator Brochure is not as per ICH guidelines.
xi. No of patients to be enrolled in each center not described.
xii. Evidence of registration in country of origin not attached.
xiii. Copy of registration letter (if registered in Pakistan) not attached.
xiv. Sample of label of the investigational product / drug not attached.
xv. Undertaking on stamp paper not attached.

4. After scrutiny of the documents above mentioned shortcomings has been noted and requested due to limited knowledge of ventilators that file may be evaluated by person having some know how about ventilators or may be evaluated by seniors having grip on the ventilators.

5. Application has not been evaluated by any person having the knowledge on ventilators.

6. Further it is added that Expert group for Assessment/ evaluation of locally manufactured devices (Ventilators) was constituted by DRAP vide letter No. 16-5/2020 dated 3rd April & 4th April 2020. The third meeting of Expert Committee of Locally manufactured Ventilators. 3rd Meeting of expert committee on evaluation / Assessment of locally manufactured ventilators was held on 3rd July, 2020 and decided as follows: -

Decision:

In the end of meeting, Maj Gen Aslam Khan said that he won't agree with clinical testing of ventilators in the absence of simulator for ventilators. Since the ventilators have not gone through the routine procedures 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. Abdur 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 and Research Council (PHRCH) under Ministry of National Health Services Regulation and Coordination. If the committee decided to go through the NBC then PEC should apply to NBC as an applicant for all the ventilators. After the approval of Expert Committee on ventilators the PEC would individually apply to Clinical Study Committee as per the provision of Bio-Study Rules, 2017.

7. Further the DRAP vide letter No.F.6-5/2020-MD dated 13.04.2020 advised that "No ventilators shall be used on patients without prior approval of expert group on ventilators".

8. The decision of the Expert Group on ventilators was placed in CSC meeting held on 27.11.2020 and CSC decided as following;

Decision of 16th CSC meeting:

Dr. Muhammad 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.***

9. Accordingly, letters were written to Engr. Brig. Tariq Javaid (PEC), Dr. Faiza Bashir (NBC-PHRC) and three manufacturers.

10. The application was presented before CSC in its 19th meeting held on 12th February 2021 & CSC decided as follows:

Decision of 19th CSC meeting:

The CSC after detailed deliberation decided to constituted a sub-committee which will be comprised of following experts:

i. *Biomedical engineers*
ii. *Anesthetist*
iii. *Pulmonologist*
iv. *Dr. Faiza Basheer*
v. *Prof. Dr. Javed Akram*
vi. *Dr. Abdur Rasheed*
vii. *Any other expert co-opted by the sub-committee.*

II. The Sub-committee will develop TORs & proforma for evaluation & inspection of ventilator trial applications.

III. CSC constituted following panel for inspection of ventilators trial application of Lahore region:

i. *Prof. Dr. Javed Akram, V.C. UHS, Lahore. (Chairman)*
ii. *Dr. Farhana Badar*
iii. *Dr. Faheem Butt, Pulmonologist (from Shaukat Khanum Cancer Hospital & Research Center.*
iv. *Biomedical engineers (from Sheikh Zayed Hospital, Lahore.)*
v. *Prof. Dr. Sajjad Kazmi, Sheikh Zayed Hospital, Lahore.*

IV. CSC constituted following panel for inspection of ventilators trial application of Islamabad region:

i. *Dr. Abdur Rashid, Chairman CSC-DRAP (Chairman)*
ii. *Maj. Gen. (Retd) Aslam*
iii. *Brig. (Retd) Muzammil Hassan Najmi*
iv. *Prof. Dr. Iqbal Memon, HOD Anesthesia, PIMS, Islamabad.*
v. *Dr. Afrasayab, Biomedical Engineer, NUST, Islamabad.*
vi. *Muhammad Mubashir Aslam, G.M. Plant, Innovative Health Technology, NUST, Islamabad.*

V. Inspection panel may co-opt any relevant experts for the inspection. Further it is also decided that application for ventilators included in this meeting, inspection will be carried out without proforma.

VI. Proforma will be developed by sub-committee later on.

11. The subject application was placed before CSC in its 21st meeting held on 22nd March 2021 & the CSC decided as follows:

Decision:

CSC after detailed deliberation decided to deferred the case for further discussion after evaluation of trial protocol. Protocol will be shared with all CSC members for evaluation &

review after which the application will discussed in the next CSC meeting which will be held on 23rd March 2021.

12. As decided in the 21st CSC meeting technical documents (i.e. Protocol & informed consent form etc.) were forwarded to all CSC experts for review & evaluation under sub-rule 4 of rule 7 of the Bio-Study Rules 2017, on 22nd March 2021.

13. Prof. Brig. (R), Muzammil Hassan Najmi forwarded following comments:

i. The consent form in English is elaborate and covers all necessary aspects. The "BA ILM IJAZAT NAMA" given as annexure to the validation protocol is, on the other hand, sketchy. Particularly it does not mention the right of the patient to refuse participation in the trial. It is suggested that the Consent Form in English should be translated into Urdu and should be used for the purpose of obtaining the consent.
ii. Only one member of the Clinical Validation Team has signed the protocol. It should be signed by all the members who have contributed in preparation of this protocol.
iii. The clinical end points for termination of the use of test ventilator should be clearly identified and included in the protocol.
iv. The composition of team of investigators conducting the trial in CMH has not been mentioned. The Principal Investigator, Co PI and other members of the team should be identified and should sign the protocol.
v. The method for collection of data and its statistical analysis has not been included.

14.

Submitted before committee of clinical validation protocol as per Acceptance Test Procedure (ATP).

Decision:

CSC after detailed deliberation & discussion decided as follows:

i. The specifications/features approved by the Pakistan Engineering Council (PEC) contain that the ventilator has built in compressor. Whereas the presentation by the manufacturing team was about the ventilators without compressor. At this stage use of ambient air may not be a good idea in view of contaminated environment so use of built in medical grade compressor/centralized compressed air be considered. As discussed & agreed by the Project Management Organization team that the compressor will be added in the ventilators as approved by the PEC or the existing version of ventilator to be tested may be provided and endorsed by the PEC.

ii. Since the PI plans to adopt a new methodology in the Clinical Validation Study, the PI has to come up with a new inclusion and exclusion criteria, informed consent process, data collection plan, sample size, and all other related aspects. It was also decided that the Consent Form in English as well as in Urdu & should be used for the purpose of obtaining the consent from the subject or his/her next of kin.

iii. The clinical end points for termination of the use of test ventilator should be clearly identified and included in the protocol. The Principal Investigator, Co PI and other

members of the team should be identified and should sign the protocol. The method for collection of data and its statistical analysis should be part of the protocol.

iv. According to the new proposed plan, the test ventilator will be trialed initially on elective surgical subjects who will be administered intravenous anesthesia. Its stated limitation according to the protocol submitted is that this ventilator is not meant to work for more than one day & ICU subjects may require ventilation for several days, it may eventually develop into such use after clinical validation in the elective operative subjects (ASA Category 1).

v. Total number of adult subjects should be mentioned in the amended protocol. Patient safety may not be compromised during the testing of ventilators & trial of the ventilators will be under active supervision of investigation & manufacturing teams to avoid any mishap.

vi. Principal Investigator will modify/amend the protocol as presented & discussed in the meeting. This amended protocol will be approved by IRB of Combined Military Hospital, Rawalpindi & subsequently by NBC-PHRC.

vii. The approved amended protocol will be submitted to Division of Pharmacy Services along with prescribed fee for approval of amended protocol, which will be placed before the CSC for its consideration.
