Research Protocol:

# Safety and Efficacy Evaluation of a low-cost CPAP device for hypoxemic COVID-19 patients: A Pilot Study

**Submitted to:**

Bangladesh Medical Research Council (BMRC)

Mohakhali, Dhaka-1212, Bangladesh.


**Principal Investigator:**

Dr. Taufiq Hasan Al Banna, Assistant Professor

Department of Biomedical Engineering

Bangladesh University of Engineering and Technology (BUET)

**Co-Principal Investigator**

Dr. Robed Amin (MBBS, FCPS)

Professor, Department of Medicine

Dhaka Medical College & Hospital, Dhaka – 1000.


**Date of Submission**

December 10, 2020

# ANNEXURE - A

## Application for Ethical Clearance

**1. Principal Investigator(s):**

Name: Dr. Taufiq Hasan Al Banna

Qualification: B.Sc., M.Sc., Ph.D. (UT Dallas, TX, USA)

Detail Address: 1111, mHealth Lab, Biomedical Engineering, Bangladesh University of Engineering and Technology (BUET), Dhaka – 1205.

Mobile: 01817579844 Telephone (Off./Res): 55167100 (Ex. 6597)

e-mail: taufiq@bme.buet.ac.bd

**2. Co-Investigator(s):**

1. Name: Prof. Dr. Md. Robed Amin

Qualification: M.B.B.S, F.C.P.S.

Detail Address: Dhaka Medical College, Dhaka, Bangladesh.

Mobile: 01711725787 e-mail: robedamin@yahoo.com

2. Name: Dr. Md Khairul Islam

Qualification: M.B.B.S, M.C.P.S., F.C.P.S.

Detail Address: Dhaka Medical College, Dhaka, Bangladesh.

Mobile: 01717696207 e-mail: Khairul0696207@gmail.com

3. Name: Dr. Forhad Uddin Hasan Chowdhury

Qualification: M.B.B.S, F.C.P.S.

Detail Address: Dhaka Medical College, Dhaka, Bangladesh.

Mobile: 01712101875 e-mail: drmarufsomc@gmail.com

4. Name: Md. Mohiuddin Sharif

Qualification: M.B.B.S, M.P.A.

Detail Address: Dhaka Medical College, Dhaka, Bangladesh.

Mobile: 01717539682 e-mail: mohiuddinsharif.fmc@gmail.com

3. **Place of the Study/Institution(s):** Department of Medicine, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh.

4. **Title of Study:** Safety and Efficacy Evaluation of a low-cost CPAP device for hypoxemic COVID-19 patients: A Pilot Study

5. **Type of Study:** Prospective, Interventional study.

6. **Duration of Study:** 3 months

7. **Total Cost:** Tk. 10,00,000/-

8. **Funding Agency:** N/A.

**Circle the appropriate answer to each of the following**
***(If not Applicable write NA)***

**1. Source of Population:**

(a) ILL Participant (Yes) No

(b) Non ILL Participant Yes (No)

(c) Minors or persons under guardianship Yes (No)

**2. Does the study involve?**

(a) Physical risks To the subjects (Yes) No

(b) Social Risks Yes (No)

(c) Psychological Risks to subjects Yes (No)

(d) Discomfort to Subjects (Yes) No

(e) Invasion of the body Yes (No)

(f) Invasion of Privacy Yes (No)

(g) Disclosure of Information damaging to Subject or others Yes (No)

**3. Does the study involve?**

(a) Use of records, (Hospital, medical, Death, birth or other) (Yes) No

(b) Use of fetal tissue Or abortus Yes (No)

(c) Use of organs or Body fluids Yes (No)

**4. Are subjects clearly informed about?**

(a) Nature and purposes of study (Yes) No

(b) Procedures to be followed including alternatives used (Yes) No

(c) Physical risks (Yes) No

(d) Private questions N/A

(e) Invasion of the Body N/A

(f) Benefits to be Derived (Yes) No

(g) Right to refuse to participate or to withdraw from study (Yes) No

(h) Confidential handling of data (Yes) No

(i) Compensation where there are risks or loss of working time or privacy is involved in any particular procedure N/A

**5. Will signed consent form/verbal consent be required?**

(a) From Subjects (Yes) No

(b) From parent or guardian (if subjects are minors) N/A

**6. Will precautions be taken to protect anonymity of subjects** (Yes) No

***Note: If the final instrument / questionnaire is not completed prior to review, the following information should be included in the abstract.***

1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.

2. Examples of the type of specific question to be asked in the sensitive areas.

3. An indication as to whom the questionnaire will be presented to the committee for review.

---

**We agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects or any changes of the Methodology before making any such changes.**

_____

**Signature**

**Dr. Taufiq Hasan Al Banna**
Assistant Professor, Department of Biomedical Engineering (BME)
Bangladesh University of Engineering and Technology (BUET),
Dhaka - 1000, Bangladesh.

**Date: 10/12/2020**

**Name of Co-investigator (S)** **Signature:**

1. Dr. Robed Amin (MBBS, FCPS)
   Professor, Department of Medicine
   Dhaka Medical College & Hospital

2. Dr. Md Khairul Islam (MBBS, MCPS, FCPS)
   Junior Consultant, Department of Medicine
   Dhaka Medical College & Hospital

3. Dr. Forhad Uddin Hasan Chowdhury (MBBS, FCPS)
   Registrar, Department of Medicine
   Dhaka Medical College & Hospital

4. Dr. Md. Mohiuddin Sharif (MBBS, MPA)
   Indoor Medical Officer, Department of Medicine
   Dhaka Medical College & Hospital.

**** Include all the Investigator, Co-Investigators.***

# ANNEXURE - C

- **Project Title:** Safety and Efficacy Evaluation of a low-cost CPAP device for hypoxemic COVID-19 patients: A Pilot Study

- **Summary:** The aim of this study is to evaluate the preliminary safety and performance of a low-cost locally-made Venturi-based Non-invasive Positive Pressure Ventilator (NIPPV) device for hypoxemic COVID-19 patients. The device administers Continuous Positive Airway Pressure (CPAP) therapy using the jet-mixing or Venturi effect to increase the volume flow rate of oxygenated air from a pressurized cylinder by entraining the atmospheric air. To provide CPAP therapy, this high flow of oxygenated air is delivered to the patient via a low-cost non-vented mask with a tight seal with a High-Efficiency Particulate Air (HEPA) filter connected to the exhalation limb. The tight seal and HEPA filter ensures a minimal risk of aerosol generation and thus the device can be used without a negative pressure room. The system consists of the developed Venturi-based flow-generator, a standard 22mm breathing tube, a standard Y-connector, a non-vented CPAP mask (e.g., snorkel mask, helmet), a HEPA filter, and a Positive End Expiratory Pressure (PEEP) valve. The bench-top testing of the device is done in the laboratories of BUET and was verified that the device performs within the CPAP guidelines provided by the Medicines and Healthcare products Regulatory Agency (MHRA), UK. This study aims to assess the safety of and efficacy of the device in three different steps: (1) design validation, (2) clinical feasibility and (3) pilot clinical trial for safety and efficacy evaluation. Only if the device successfully passes the parts 1 and 2, we will proceed to the final clinical trial in step 3. In this final step, we aim to conduct a randomized controlled trial (RCT) evaluating for non-inferiority of the CPAP intervention compared to standard HFNO treatment. The number of ventilator-free days will be used as the primary outcome for efficacy, while patient recovery, death, or need of intubation and other adverse events will be used as secondary outcomes.

- **Introduction:**

  The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been devastating to our communities worldwide. In Bangladesh, the first confirmed case of the virus was found in March 2020. According to the World Health Organization[1], most COVID-19 patients have uncomplicated or mild illness (81%), while some develop severe illness requiring hospitalization and oxygen therapy (14%). Finally, about 5% of patients become critically requiring ICU admission and possibly mechanical ventilation. COVID-19 primarily affects the respiratory system, while severe cases may lead to acute respiratory failure[1], requiring oxygen therapy. According to WHO

guidelines, supplemental oxygen therapy should be administered to any patient showing emergency signs or having SpO2 < 90%. Oxygen delivery devices can be progressively used in the following order: nasal cannula (up to 5 L/min), Venturi mask (6–10 L/min), and non-rebreather masks (10–15 L/min) with a target of achieving an $SpO_2$ > 90% (non-pregnant adults)[1, 2]. If the patient's condition worsens, the WHO recommends a trial of High-Flow Nasal Oxygenation (HFNO) or non-invasive positive pressure ventilation (NIPPV), including: continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP)[3, 4]. The patient is recommended for intubated mechanical ventilation as the last resort only if these non-invasive treatment pathways have failed[5].

In the context of low-resource community hospitals, various limitations and resource constraints must be taken into account while deciding the most effective clinical treatment pathway. Although HFNO devices are effective, they are expensive (above Tk. 5,00,000 for reputable brands) and difficult to import. In many cases, local suppliers may ask for more than double the original price. In this situation, the use of low-cost CPAP devices as an intermediary treatment may be considered in order to avoid intubation[5,14]. Since CPAP is an aerosol-generating procedure[2], either negative-pressure room or helmet-based non-vented masks need to be used. While constructing negative-pressure rooms are expensive, helmet-based masks are not readily available worldwide. To address this challenge, a facial snorkel interface was used by Italian doctors as an alternative to helmet-based masks[21]. Currently, there is no study comparing a snorkel and a helmet used as CPAP masks. However, the snorkel mask is known to meet the N95 fit-test to be used as a Powered Air-purifying Respirator (PAPR)[22,23]. Since the snorkel mask is designed for breathing under-water, it may be reasonably assumed that it can be used as a non-vented mask for NIPPV applications. These masks are more readily available for purchase in the local market, and thus are viable low-cost options in the context of Bangladesh.

**Objectives:**

In this study, we aim to evaluate the efficacy and safety of a low-cost CPAP system designed mainly in the context of a low-resource hospital with specific limitations in mind. The device is thoroughly tested in laboratory conditions. The device is capable of providing a PEEP of up to 20cm $H_2O$, flow-rate of at least 35 L/min (further technical details provided in Appendix F) for different operating pressure settings, and an $FiO_2$ of up to 100% with a secondary oxygen source. The device is manufactured using widely available components in Bangladesh. The objectives of the study are as follows:

*Study objectives:*

- Evaluation of the device on healthy volunteers to identify the scope for design improvements.
- Determine the feasibility of using the device in a clinical setting on

adults with respiratory distress and hypoxemia.
- Safety and efficacy evaluation of the CPAP device compared to HFNO for severely ill COVID-19 patients that have not responded to the WHO low-flow oxygen therapy.

*Study hypothesis:*
- The developed low-cost CPAP is comfortable for healthy volunteers, and using the device is intuitive and straightforward.
- The developed low-cost CPAP device is feasible for treating hypoxemic COVID-19 patients
- The developed low-cost CPAP device is equivalent (or non-inferior) compared to HFNO for severely ill COVID-19 patients who have not responded to standard WHO low-flow oxygen therapy in terms of the number of days without a ventilator.

**Rationale:**
The study addresses the shortage of medical equipment required during the ongoing pandemic. COVID-19 and other respiratory diseases cause about 1,22,400 deaths every year in Bangladesh[25]. The two main reasons for the high mortality rate are limited treatment facility and delay in diagnosis. Among the top causes of death in Bangladesh, several of these diseases – lung cancer, lower respiratory infections, COPD, and tuberculosis – are related to air pollution[26,27]. Thus, the development of low-cost CPAP devices will significantly benefit the marginalized population in Bangladesh living in areas with limited treatment facilities.

The proposed device is designed specifically considering the resources available in Bangladesh. Firstly, it is powered entirely by a pressurized oxygen cylinder and does not use any electric components. Thus, it is suitable to use even during power outages. Secondly, we made sure that every component the device uses is available in the local market. This means an established supply-chain for the component exists. For example, we propose to use a snorkel mask for oxygen delivery, which is generally imported from China. However, it is a widely available item in Bangladesh. Similarly, our CPAP system uses a 22mm adult breathing circuit, which is also available in the market. A metallic connector is used as an interface between the flow-generating device and the oxygen flow-meter that can withstand the high-pressure of the oxygen cylinder. This metallic connector is also constructed in a local workshop using brass and nickel plating for oxygen proofing.

In the previous section, we pointed out that the international guidelines offer different opinions in regard to the use of HFNO vs. NIPPV for severe COVID-19 patients. As the HFNO devices are highly expensive and are not widely available in Bangladesh, even if the proposed low-cost CPAP can be found to be non-inferior in treating severe COVID-19 patient compared to HFNO, the implications would be significant as the price difference is astronomical (CPAP device pricing at Tk. 5,000 vs. above Tk. 5,00,000 for

HFNO). Since the developed CPAP can be mass-produced locally, it can be easily distributed across different regions of Bangladesh. Therefore, we rationalize the objective of comparing our CPAP device with HFNO treatment. Currently, to the best of our knowledge, there is no scientific literature comparing these two treatments for COVID-19 patients.

We are not aware of a commercially available CPAP device that is priced in the range less than Tk. 10,000. Our main innovation is the flow-generating device that has a manufacturing price of Tk. 2,000. This component uses the jet mixing principle (sometimes incorrectly referred to as the Venturi effect) uses the highly pressurized oxygen to generate a high-velocity supersonic flow – which then pulls-in room air through an entrainment port. In essence, our flow generating device works as an air oxygen blender capable of generating a flow of 61 L/min with an FiO2 between 40 - 100% using a secondary oxygen cylinder. Similar devices to our CPAP system includes the Phillips Respironics Whisperflow[28] and UCL-Ventura[29] (Comparison with other devices are shown in Annexure F). The UCL-Ventura device is reverse engineered from the Whisperflow device by researchers at University College London (UCL) and Mercedes-AMG. These devices use the same working principle as ours but offer more sophisticated controls and thus are more expensive. In fact, at the beginning of the project, we have attempted to manufacture the UCL Ventura device, which is open-sourced. However, we quickly realized that the precise manufacturing capabilities required are not available in Bangladesh.

- **Methodology:**
  In the following sections, we first describe the details of the proposed CPAP design followed by the different parts of the study. The study will be conducted in three different parts: (i) Design validation on healthy volunteers, (ii) Feasibility testing in clinical settings, (iii) Pilot study for safety and efficacy testing in clinical settings.

**Proposed CPAP design:**

The current status of the proposed low-cost CPAP system is shown in Fig. 1 while using with a snorkel mask. Other non-vented masks (CPAP mask, helmet/hood) can also be used. The system consists of a flow generator, 22mm breathing circuit, Y-connector, HME filter (optional), snorkel mask interface (only when snorkel mask is used), HEPA filter, and PEEP valve. The system ensures adequate flow delivered to the subject while minimizes aerosol generation by using the snorkel mask instead of conventional CPAP masks. The HEPA filter at the outlet blocks the virus from entering the atmosphere from the air exhaled by the patient. The flow generator device with two oxygen ports and one air entrainment port is shown in Fig. 2. During laboratory tests, for various iterations of the device, different output flow-rates were found for different settings of PEEP the valve. Full technical evaluation is performed and are described in Annexure F.

Fig. 3. Shows the different type of non-vented CPAP masks that our device is compatible with. These masks have a tight seal around the face (or neck for helmet) of the patient and thus there is no risk of aerosol generation from the mask. The only exhalation port in the mask is covered with a HEPA filter followed by the PEEP valve. Further details about the CPAP device can be found in the OxyJet website: http://mhealth.buet.ac.bd/oxyjet/

The device is capable of delivering at least 35L/min flow for most settings of the device. This ensures that the system meets the peak inspiratory flow demand of the patient during inhalation. Variation of FiO2 with PEEP setting while a single O2 source is used. If a higher FiO2 is required, the 2nd oxygen inlet can be used, and up to 80% FiO2 can be achieved. Further details and technical specifications are provided in Annexure F.

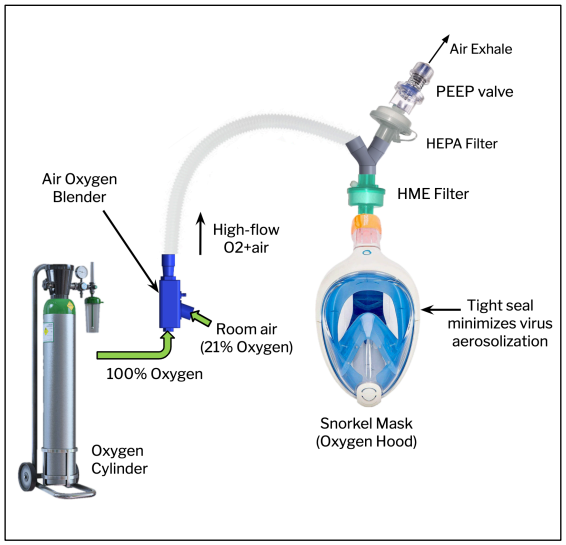


Fig. 1: OxyJet CPAP system showing the flow generator, breathing circuit, Y-connector, HME filter (optional), snorkel mask interface (for snorkel mask only), HEPA filter, and PEEP valve. The proposed setup ensures adequate flow delivered to the subject while minimizes aerosol generation. The HEPA filter at the outlet blocks the virus from entering the atmosphere from the air exhaled by the patient, ensuring airborne precaution.

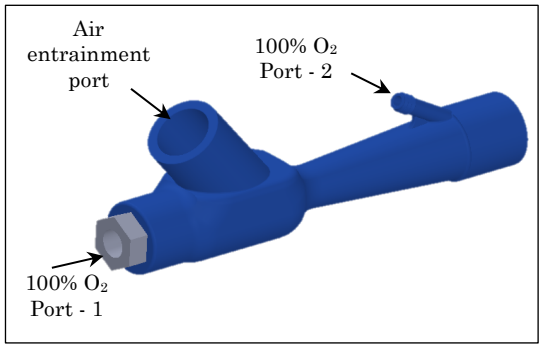


Fig. 2: OxyJet flow generator showing two $O_2$ inlets and one air entrainment port.


Fig. 3: Alternative non-vented masks that can be used with the system. We have already tested the device with a helmet and CPAP and snorkel mask available in the market.

We use an inlet HEPA filter to block viruses or dust particles from entering the device and an outlet HEPA filter to ensure the virus of the exhaled air does not contaminate the environment. In this way, the device can be made safe to be used in the general ward of the tertiary level hospitals of Bangladesh without requiring a negative-pressure room.

**Phase-3 Study Design: Randomized Controlled Trial**

The aim of this phase of the study is to evaluate the safety and efficacy of the proposed CPAP device. Every set of CPAP system provided to the

patients will be individually and thoroughly tested by Department of Biomedical Engineering (BME), BUET. Thus we will ensure that each of the device functions as specified. The various aspects of this final and most important component of the study are described below.

*Sample size calculation:* In this non-inferiority trial, we define the primary efficacy outcome as the number ventilator-free days (or in avoidance time of intubation) from the day of enrollment up to 10 days. To simplify the trial, we only observe the patients for 10 days. Assuming that

$$N_{\text{vent-free}} = \text{No. of ventilator-free days since enrollment}$$

we formulate the primary outcome as follows:

$$\mu = \begin{cases} N_{\text{vent-free}} & \text{if } N_{\text{vent-free}} \leq 10 \\ 10 & \text{else} \end{cases}$$

Thus, the primary outcome will be a continuous variable between 0-10. Assuming an equal allotment between the control and experimental arm, and no true difference in the outcome measure between the two arms, we may use the following formula for calculating the sample size for each group of the non-inferiority trial:

$$N \geq \frac{2\,\sigma^2 (Z_{1-\beta} + Z_{1-\alpha})^2}{d^2} \qquad (1)$$

where,

| | | |
|---|---|---|
| $N$ | = | Required sample size for the non-inferiority trial |
| $\sigma^2$ | = | Estimated variance of the primary outcome |
| $\alpha$ | = | Significance level |
| $1-\beta$ | = | Confidence interval (power) |
| $Z_{1-\alpha}$ | = | The $Z$-score for the confidence level $\alpha$ |
| $Z_{1-\beta}$ | = | The $Z$-score for the confidence interval $\beta$ |
| $d$ | = | Non-inferiority margin |

In order to estimate $\sigma$, we need to approximate the standard deviation of the primary outcome. We assume that the mean and standard deviation for ventilator-free days for the HFNO group (control arm) can be approximated by 24 and 8, according to the FLORALI trial[30]. In this trial, a total of 40 patients were observed for up to 28 days to obtain these statistics. Since our primary outcome is limited to 10 days, we assume a Gaussian distribution ($\mu = 24$ and $\sigma = 8$) for the primary outcome of the FLORALI trial and calculate the standard deviation for the limited region of the distribution between 0 and 10. This results in a standard deviation of 1.44. We use this value as an approximation of $\sigma$ in the equation (1) above.

The following steps are straightforward. Assuming a significance level of 5% ($\alpha = 0.05$), 95% confidence interval ($1-\beta = 0.95$), and non-inferiority

margin of 1.5 days, we find the sample size required for this non-inferiority trial for each arm is found to be:

$$N = 20$$

Thus, we will require a total of 40 subjects (equal allocation) for this study. However, we acknowledge that this is a small number of samples, which was calculated based on a set of simplifying assumptions. The different aspects of the RCT part of the study are summarized in Table V.

Table V: Summary of the non-inferiority trial evaluating the effectiveness of the CPAP therapy compared to HFNO

| **Aspects of the study** | **Description** |
|---|---|
| Location | Internal Medicine Ward, Dhaka Medical College & Hospital (DMCH), Dhaka, Bangladesh. |
| Study type | Interventional non-inferiority trial |
| Allocation | Block randomized (block size = 4) |
| Intervention model | Parallel assignment |
| Masking | None (open-label) |
| No. of subjects | Total 40 (20 on each arm of the trial) |
| Objective | Evaluate the safety and efficacy of the CPAP therapy compared to HFNO therapy |
| Study Population | *Inclusion criteria*<br>• Age ≥ 18 years<br>• Confirmed or suspected COVID-19 patient (by RT-PCR).<br>• Patients having severe pneumonia and hypoxemia ($SpO_2$ ≤90%) who did not respond to standard oxygen therapy (non-rebreather mask on 15L/min at 100% $FiO_2$).<br><br>*Exclusion criteria*<br>• Severely hypoxemic patients (SpO2≤85%)<br>• Patients with low respiratory drive or requiring cardiopulmonary resuscitation<br>• Patients with contraindications for CPAP<br>• Pregnant status<br>• Age > 65 years |
| Procedure | *Experimental arm:*<br>• Administer CPAP: $FiO_2$ of 40% and 10cm PEEP<br>• Titrate PEEP to 5cm or 15 cm if required<br>• Deliver additional oxygen via secondary port if a higher $FiO_2$ is required. |

| Aspects of the study | Description |
|---|---|
| | *Control arm:*<br>• Administer HFNO<br>• Adjust flow-rate and FiO2 as per standard HFNO treatment protocol |
| Outcomes / end-points | *Primary outcome/endpoint*<br>• The number of ventilator-free days up to 10 days (efficacy).<br><br>*Secondary outcomes/endpoint*<br>• Recovery of the patient (efficacy)<br>• Death or need of intubation within 10 days since enrollment (safety)<br>• Oxygen toxicity or other adverse events according to CTCAE scale. |
| Data Collection | *Data collected during enrollment*<br>• Patients clinical condition (pulse, BP, etc.)<br>• Date and time of enrollment<br>• Vitals (SpO2, respiratory rate)<br><br>*Data collected during trial (Every 6-8 hours)*<br>• Patients vitals (SpO2, BP, respiratory rate, pulse).<br>• Date and time of follow-up.<br><br>*Data collected during discharge*<br>• Patients clinical condition<br>• Date and time of discharge<br>• Date and time of intubation (if applicable)<br>• Vitals (SpO2, respiratory rate)<br>• Description of any adverse events |
| Data Analysis | • Mean value of the primary and secondary outcomes<br>• Standard deviation of the primary and secondary outcomes<br>• Statistical t-test to determine if the difference of mean value is significant |

*Procedure:* The main objective during the trial is to keep the oxygen saturation of the patient above 90%. Thus, during enrollment we will recruit subjects who did not respond to 15L/min of low-flow oxygen therapy (SpO2 < 90%). After enrollment the CPAP or HFNO therapy will be administered, if saturation falls below 90% and remains in that value for more than 120 minutes (for either experimental or control arm), the patient will be again shifted to a higher form of treatment, which in this case is intubation & mechanical ventilation in an ICU (if available). The control and experimental arms of the treatment are described in the flow diagram shown in Fig. 5.

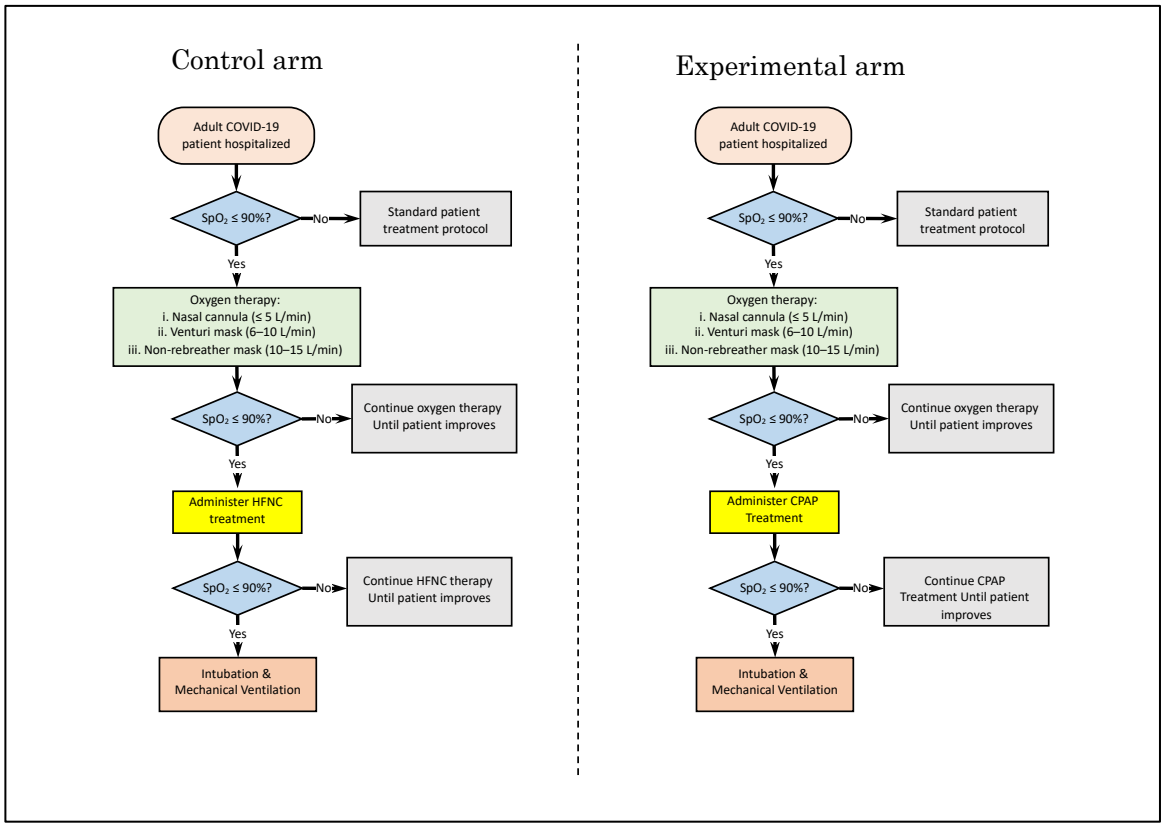


Fig. 5: Clinical pilot study flow diagram for HFNO vs. CPAP treatment.

- **References:**


1. W H O. Clinical management of COVID-19: interim guidance, 27 May 2020. Tech. Rep. (2020).
2. Whittle, J. S., Pavlov, I., Sacchetti, A. D., Atwood, C. & Rosenberg, M. S. Respiratory support for adult patients with COVID-19. J. Am. Coll. Emerg. Physicians Open1, 95–101 (2020).
3. Rhodes, A. et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016.Intensive care medicine43, 304–377 (2017).
4. Rimensberger, P. C., Cheifetz, I. M., Group, *et al.* Ventilatory support in children with pediatric acute respiratory distress syndrome: proceedings from the pediatric acute lung injury consensus conference. Pediatr. Critical Care Medicine 16, S51–S60 (2015).
5. Directorate General of Health Services (DGHS). National Guidelines on Clinical Management of Coronavirus Disease 2019 (COVID-19). Tech. Rep. (2020).
6. Mollah, S. & Saad, M. Crisis of Oxygen Cylinders: Demand sky high, prices too (2020).
7. Abdullah, M. Number of ICU beds insufficient to combat covid-19 pandemic (2020).
8. Forbes. The countries with the most critical care beds per capita [infographic]. https://www.forbes.com/sites/niallmccarthy/2020/03/12/the-countries-with-the-most-critical-care-beds-per-capita-infographic/#317ad40c7f86 (Accessed on 08/05/2020).
9. Ñamendys-Silva, S. A. Respiratory support for patients with covid-19

infection. The Lancet Respir. Medicine8, e18 (2020).
10. Rochwerg, B. et al. Official ERS/ARS clinical practice guidelines: non-invasive ventilation for acute respiratory failure. Eur. Respir. J.50 (2017).
11. Slessarev, M., Cheng, J., Ondrejicka, M. & Arntfield, R. Patient self-proning with high-flow nasal cannula improves oxygenation in covid-19 pneumonia. Can. J. Anesth. 1–3 (2020).
12. Lawton, T. *et al.* Reduced ICU demand with early CPAP and proning in covid-19 at Bradford: a single centre cohort. medRxiv(2020).
13. Ashish, A. *et al.* Early CPAP reduced mortality in covid-19 patients. audit results from Wrightington, Wigan and Leigh Teaching Hospitals NHS foundation Trust. medRxiv (2020).
14. Duan, J. *et al.* Use of high-flow nasal cannula and non-invasive ventilation in patients with covid-19: A multi-center observational study. The Am. J. Emerg. Medicine(2020).
15. NHS, B. Guidance for the role and use of non-invasive respiratory support in adult patients with coronavirus (confirmed or suspected) 2020 26 march 2020 version 2. Publ. approval reference 1559 (2020).
16. Simonds, A.et al. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. Heal. technology assessment (Winchester, England)14, 131–172 (2010).
17. Ing, R. J.et al. Role of helmet-delivered non-invasive pressure support ventilation in covid-19 patients. J. Cardiothorac. Vasc. Anesth. (2020).
18. Marini, J. J. & Gattinoni, L. Management of covid-19 respiratory distress. Jama (2020).
19. Radovanovic, D.et al. Helmet CPAP to treat acute hypoxemic respiratory failure in patients with covid-19: a management strategy proposal. J. clinical medicine9, 1191 (2020).
20. Gattinoni, L. et al.Covid-19 pneumonia: different respiratory treatments for different phenotypes? (2020).
21. Alhazzani, W.et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (covid-19).Intensive care medicine1–34 (2020).
22. Cavallo, L., Marcianò, A., Cicciù, M. & Oteri, G. 3d printing beyond dentistry during covid 19 epidemic: A technical note for producing connectors to breathing devices.Prosthesis2, 46–52 (2020).
23. Kechli, M. K., Lerman, J. & Ross, M. M. Modifying a full-face snorkel mask to meet N95 respirator standards for use with coronavirus disease 2019 patients. A&a Pract.14, e01237 (2020).
24. Greig, P., Carvalho, C., El-Boghdadly, K. & Ramessur, S. Safety testing improvised covid-19 personal protective equipment based on a modified full-face snorkel mask. Anaesthesia (2020).
25. The Daily Star. Respiratory diseases skyrocketing in Bangladesh. https://www.thedailystar.net/health/respiratory-diseases-skyrocketing-bangladesh-1565779 (Accessed on 08/05/2020).
26. Alam, D. S., Chowdhury, M. A., Siddiquee, A. T., Ahmed, S. & Clemens, J. D. Prevalence and determinants of chronic obstructive pulmonary disease (COPD) in Bangladesh. COPD: J. Chronic Obstr. Pulm. Dis.12, 658–667 (2015).
27. Khalequzzaman, M. *et al.* Indoor air pollution and its impact on children under five years old in Bangladesh. Indoor air17,297–304 (2007).

28. Glover, G. & Fletcher, S. Assessing the performance of the Whisperflow continuous positive airway pressure generator: a bench study. Br. Journal Anaesthesia 102, 875–881 (2009).
29. UCL-Ventura breathing aids for Covid-19 patients. https://www.ucl.ac.uk/healthcare-engineering/covid-19/ucl-ventura-breathing-aids-covid-19-patients (Accessed on 08/05/2020).
30. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, Devaquet J. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. New England Journal of Medicine. 2015 Jun 4;372(23):2185-96.