## PEER REVIEW HISTORY

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## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Technology to improve reliable access to oxygen in Western Uganda: Study protocol for a phased implementation trial in neonatal and paediatric wards. |
| **AUTHORS** | Bagayana, Sheillah; Subhi, Rami; Moore, Graham; Mugerwa, Joseph; Peake, David; Nakintu, Eleanor; Murokora, Daniel; Rassool, Roger; Sklar, Marc; Graham, Hamish; Sobott, Bryn |

## VERSION 1 – REVIEW

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| **REVIEWER** | Waldemar Carlo<br>University of Alabama at Birmingham, Pediatrics |
| **REVIEW RETURNED** | 03-Sep-2021 |

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| **GENERAL COMMENTS** | Methods<br>It is unclear what will be the baseline use of pulse oximeters to detect hypoxemia and availability of oxygen to treat those patients with detected hypoxemia. If there are not universal use of pulse oximeters and availability of supplemental oxygen, then it would be obvious that introducing these capabilities will improve the measures. Similarly, it is essential to determine what the knowledge of identifying hypoxemia and using oxygen therapy is during baseline. It is obvious that if knowledge is inadequate, any teaching should improve practice.<br>This project will prioritize facilities with poor baseline oxygen supplies so bias is likely as any introduction of oxygen monitoring and delivery resources is going to increase its use so it is unclear what the study will add to the scientific and clinical literature.<br>One to two hospitals will be added every month. However, the method for selecting the order will not be randomized. What will determine the order?<br>The expected dates of conducting the studies are not stated.<br>It is unclear what resources will be available long term for the pulse oximeters and oxygen delivery systems. Where will the funds to sustain the system come from? How about the resources for personnel training and work? How about other incidental costs?<br>It is concerning that the current oxygen delivery system could be displaced and then not be available after the study is completed.<br>Is it known that the proposed system will be the most cost-effective? There is a risk that the costs may be higher than with other or future systems. It is possible that it will be more expensive to maintain than the current system.<br>Long term, is it better to introduce a new system rather than improve the current one?<br>The survey is generic and not specific to this study. For example, even though this is a single country study, one of the questions asks which country is the respondent from. |

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| **REVIEWER** | Payam Vali<br>UC Davis Department of Medicine |
| **REVIEW RETURNED** | 25-Nov-2021 |

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| **GENERAL COMMENTS** | The authors present a protocol paper of a phased implementation study comparing the proportion of hypoxaemic children receiving oxygen pre- and post-implementation of a novel oxygen system (FREO2) within and between facilities in Western Uganda.<br><br>The FREO2 is driven by a mains-powered oxygen concentrator, with the ability to switch automatically between low-pressure oxygen storage device (LPOS) and cylinder oxygen in power interruptions. The proposed study aims to test whether the FREO2 oxygen system can improve getting oxygen to children who need it.<br><br>Positive results from this study could have a significant impact on improving the lives of children in low and middle-income countries.<br><br>The manuscript is well written and the reporting checklist for clinical trials is complete.<br><br>I have the following comments/suggestions<br><br>1. Can the authors elaborate how much oxygen can be stored within the Low Pressure Oxygen Storage (LPOS)? How long does the FREO2 system take to fill the LPOS to capacity?<br>2. Can the authors clarify if each patient needs its own FREO2 system or if the system can be can be shared between several patients?<br>3. How will the researchers determine how many systems each facility will need?<br>4. Can the authors clarify if data will be collected on the type of respiratory support provided (e.g. nasal cannula, high flow, invasive vs. non-invasive ventilation)?<br>5. The respiratory management of neonates, particularly newly borns in the first few days of life, is very different from the older infant or child. Neonates often rely more on pressure and benefit from continuous positive pressure (e.g. bubble CPAP) and would not necessarily need much oxygen. Can the authors clarify if the FRO2 system can blend O2 with air and be equipped with an oxygen blender?<br>6. How will the facility-selection questionnaire be sent to the hospitals, by e-mail or by regular mail?<br>7. In the FREO2 Oxygen for Health Centres Survey (appendix 1), did the authors intend to include a link (where stated “Add in link to plain description of technology” and “Add in link to plain language statement of survey”? Do all facilities have reliable Internet to access these links?<br>8. Figure 1: can the authors clarify what "PROTECT" and "Prioritizer" are? |

**VERSION 1 – AUTHOR RESPONSE**

**Reviewer: 1**

**Dr. Waldemar Carlo, University of Alabama at Birmingham**

**Comments to the Author:**

**Methods**

**It is unclear what will be the baseline use of pulse oximeters to detect hypoxemia and availability of oxygen to treat those patients with detected hypoxemia. If there are not universal use of pulse oximeters and availability of supplemental oxygen, then it would be obvious that introducing these capabilities will improve the measures. Similarly, it is essential to determine what the knowledge of identifying hypoxemia and using oxygen therapy is during baseline. It is obvious that if knowledge is inadequate, any teaching should improve practice.**

Oxygen and pulse oximetry are seemingly simple interventions, but countries have struggled to scale them up, and coverage remains patchy. In this study, we aim to add to the tool-kit of policy makers and clinicians by proposing and testing technological adaptations. To learn whether the FREO$_2$ system is appropriate across Uganda, we sought to test it across a broad range of representative facilities (both public and private), with varying baseline access to oximetry and oxygen, case-loads, staffing, training and quality of care. And to promote ownership by facilities, the twenty facilities are not pre-selected, but identified as the project progresses, in discussion with district health officers, stakeholders, and facility managers. This approach, while limiting the evaluation (eg. not allowing randomisation nor control of confounders), more accurately reflects real life, and allows for more organic adoption.

Baseline assessment of pre-existing pulse oximetry and oxygen is described in the Methods and Analysis (Site Selection):

*"Eligible facilities are visited, and a baseline assessment (appendix 2), using a standardised tool is completed. The assessment collects more detailed information on admissions numbers, pneumonia burden, pre-existing oxygen supplies, access to pulse oximetry, oxygen costs, staffing and biomedical support. Selection and recruitment of facilities is unblinded and non-randomised."*

We have clarified that there will be assessment of prior knowledge and training in the Methods and Analysis (Implementation):

*"Following baseline assessment, staff will receive refresher training in the diagnosis of hypoxaemia (+/- provision of pulse oximeters). Prior knowledge and training will be assessed, including a brief pre-training quiz with clinical questions on pulse oximetry and oxygen therapy based on WHO guidelines."*

**This project will prioritize facilities with poor baseline oxygen supplies so bias is likely as any introduction of oxygen monitoring and delivery resources is going to increase its use so it is unclear what the study will add to the scientific and clinical literature.**

The study is measuring whether appropriate technology, that has potential to improve oxygen reliability and reduce costs, can be successfully adopted and incorporated in daily clinical practice in facilities with low resources, and lead to improvement in measurable practice outcomes. Countries continue to struggle to roll out pulse oximetry and oxygen with existing approaches. This is partly because of unreliable power, equipment breakdown, cost, limited capacity for maintenance and repair, transport… This work seeks to address some of these challenges, partly by adapting appropriate technology (eg. low pressure storage and voltage conditioning) and by conceptualising oxygen as a service (implementation of equipment plus maintenance, training and ongoing support). We prioritise facilities with poor baseline oxygen because that is where the unmet need is, and where we need more evidence - not of whether oxygen works, but of how to ensure every patient who needs it receives it.

**One to two hospitals will be added every month. However, the method for selecting the order will not be randomized. What will determine the order?**

We describe the process for facility selection in the Methods and Analysis (Site Selection). We work closely with the Ministry of Health to align the implementation with national priorities. As mentioned above, we highlight in the manuscript that the selection and implementation order is unblinded and non-randomised.

**The expected dates of conducting the studies are not stated.**

We have clarified this in the text ('Methods and Analysis), and made clearer reference to Figure 3:

*"Post Oxygen System data will be collected for 3 months, in the same way as for the pre-intervention period, and will begin 2 weeks following equipment installation to account for a 'wash-out' period. The post-intervention period for the last enrolled facility is expected to complete in November 2022 (Figure 3)."*

**It is unclear what resources will be available long term for the pulse oximeters and oxygen delivery systems. Where will the funds to sustain the system come from? How about the resources for personnel training and work? How about other incidental costs?**

Pulse oximeters provided in the course of the program will be the property of health facilities and available to them beyond the program duration. The $FREO_2$ system will be supported for an additional 12 months after project completion, while facilities (or the Ministry of Health) choose to either enter into an agreement with $FREO_2$ Uganda to provide ongoing maintenance, training and support for a fee, or transition to a different system.

The overarching goal of the program is to combine a social enterprise with appropriate technology to sustainably improve access to reliable oxygen in Western Uganda. Determination of an affordable and fair fee for service is critical for ensuring FREO2 Uganda is viable and we are actively working with the MoH at multiple levels to ensure alignment with national objectives.

We have clarified this in the "Ethical considerations" subheading:

*"The $FREO_2$ system will be supported for an additional 12 months after project completion, while facilities (or the Ministry of Health) choose to either enter into an agreement with FREO2 Uganda to provide ongoing maintenance, training and support for a fee, or transition to a different system."*

**It is concerning that the current oxygen delivery system could be displaced and then not be available after the study is completed.**

We address this concern in the 'Ethical considerations' section:

"*There is a risk that the $FREO_2$ oxygen system may displace existing oxygen systems (cylinders or concentrators) and deskill facility staff in routine upkeep and maintenance of these systems. To*

*mitigate this, this project will prioritise facilities with poor baseline oxygen supplies, where the intervention is not detracting from already functioning oxygen systems."*

In addition, as detailed above, a facility's oxygen supply is supported for a 12 months period beyond the project duration to allow for a transition to either an ongoing agreement with FREO2 or an alternate oxygen source.

**Is it known that the proposed system will be the most cost-effective? There is a risk that the costs may be higher than with other or future systems. It is possible that it will be more expensive to maintain than the current system.**

Several peer-reviewed publications have demonstrated that oxygen concentrators can be more cost-effective and reliable in low resource settings under certain conditions. Access to reliable power, technical support and training have been critical to the sustainability of oxygen systems that included concentrators. In this project we will work with facilities for which the pre-existing oxygen supply is unreliable, prohibitively expensive or insufficient. We do not know whether the FREO2 system is more cost-effective, but the hypothesis that this is the case is based on the system's ability to store oxygen, the robustness of the equipment, and the provision of technical support that optimises equipment longevity. A major objective of this trial is to learn what it costs to have reliable oxygen in peripheral/remote health facilities for which this is an ongoing challenge.

**Long term, is it better to introduce a new system rather than improve the current one?**

Our aim is not to replace functioning existing systems but to provide facilities with a suite of solutions that can be used to solve complex (and expensive) problems. The problems with cylinders (cost and transport) and traditional concentrators (short life time, maintenance and repairs) are ubiquitous in these settings, particularly for smaller, more remote facilities. Our aim is that this technology can go some way in providing facilities with solutions to support their oxygen systems. Beyond the project facilities can choose to use the FREO2 system as the primary oxygen source, or to supplement/back-up other systems. As mentioned, facilities are supported for 12 months following the evaluation to transition to an ongoing agreement with FREO2 or to another oxygen system.

**The survey is generic and not specific to this study. For example, even though this is a single country study, one of the questions asks which country is the respondent from.**

The relevant question on the survey - Question 4 - reads 'county' and not 'country'.

**Reviewer: 2**

**Dr. Payam Vali, UC Davis Department of Medicine**

**Comments to the Author:**

The authors present a protocol paper of a phased implementation study comparing the proportion of hypoxaemic children receiving oxygen pre- and post-implementation of a novel oxygen system (FREO2) within and between facilities in Western Uganda.

The FREO2 is driven by a mains-powered oxygen concentrator, with the ability to switch automatically between low-pressure oxygen storage device (LPOS) and cylinder oxygen in power interruptions. The proposed study aims to test whether the FREO2 oxygen system can improve getting oxygen to children who need it.

Positive results from this study could have a significant impact on improving the lives of children in low and middle-income countries.

The manuscript is well written and the reporting checklist for clinical trials is complete.

I have the following comments/suggestions

**1. Can the authors elaborate how much oxygen can be stored within the Low Pressure Oxygen Storage (LPOS)? How long does the FREO2 system take to fill the LPOS to capacity?**

LPOS can hold up to approximately 1400 litres. The rate that LPOS fills depends on immediate patient demand for oxygen. If patient demand is zero and the concentrator is producing 10 LPM, then 140 minutes are required to fill LPOS.

We have clarified the volume in the Introduction, paragraph 5:

*"As an additional tool to improve the applicability, cost and efficiency of concentrators, particularly in rural and isolated facilities, the FREO$_2$ Oxygen System (Figure 1) combines a robust oxygen concentrator with a Low Pressure Oxygen Storage (LPOS) device able to store 1400 litres of oxygen."*

**2. Can the authors clarify if each patient needs its own FREO2 system or if the system can be can be shared between several patients?**

Each patient does not require their own FREO2 system. Each patient does have their own volumetric flow meter (VFM), mounted on the wall next to their bed, where HCWs can readily adjust individual flow rates. One FREO2 system can supply up to 4 patients simultaneously.

We have clarified this in the Methods and Analysis:

*"Flow is split, with individual patient flow metres at the bed-side, such that one FREO$_2$ system can supply up to 4 children simultaneously."*

**3. How will the researchers determine how many systems each facility will need?**

We have added detail of this in the Methods and Analysis (Phase 2 - FREO2 oxygen system and oxygen therapy training)::

*"The number of systems required by facilities is determined by the case-load, and projected number of hypoxaemic admissions. Based on admission numbers of the level IV facilities in Uganda, and a hypoxaemic prevalence of 10% of all admissions, we expect that one system per facility will be sufficient."*

**4. Can the authors clarify if data will be collected on the type of respiratory support provided (e.g. nasal cannula, high flow, invasive vs. non-invasive ventilation)?**

The facilities involved will mostly only have capacity to provide low flow oxygen, and the FREO2 system is designed for this purpose. Some facilities may have capacity to provide neonatal bubble CPAP in a special care unit - where this is the case, it is separate to the FREO2 system.

**5. The respiratory management of neonates, particularly newly borns in the first few days of life, is very different from the older infant or child. Neonates often rely more on pressure and benefit from continuous positive pressure (e.g. bubble CPAP) and would not necessarily need much oxygen. Can the authors clarify if the FRO2 system can blend O2 with air and be equipped with an oxygen blender?**

The FREO2 system currently only provides low flow, concentrated (>90%) concentrator oxygen. There are efforts in place to develop low cost neonatal air:oxygen blending technology.

**6. How will the facility-selection questionnaire be sent to the hospitals, by e-mail or by regular mail?**

The facility selection questionnaire will be emailed to hospitals. Short-listed facilities are visited in-person to assess suitability for inclusion in the program.

We have clarified this in the Methods and Analysis: Site selection:

*"A facility-selection questionnaire will be sent out by email to 60 facilities, within 90 minutes driving distance from the FREO$_2$ office (appendix 1).*

**7. In the FREO2 Oxygen for Health Centres Survey (appendix 1), did the authors intend to include a link (where stated "Add in link to plain description of technology" and "Add in link to plain language statement of survey"? Do all facilities have reliable Internet to access these links?**

Thank you for pointing this out. We have included the documents as Appendix 1a and Appendix 1b. All facilities have sufficient internet access to allow regular communication with the FREO2 team.

**8. Figure 1: can the authors clarify what "PROTECT" and "Prioritizer" are?**

We have added a description to the introduction:

*"This control of oxygen source is achieved by a 'Prioritizer device': a pneumatic switch that can automatically switch between concentrator, LPOS and cylinder oxygen without additional intervention from health workers. A traffic light (Stack Lamp) display communicates the status of the system to nursing staff (green=concentrator oxygen, orange = LPOS oxygen, red= back-up cylinder oxygen). The oxygen concentrator is connected to a PROTECT device, that conditions the mains power to meet the specific electrical requirements of the concentrator."*

And added detail to the caption of Figure 1:

***"Figure 1.** FREO$_2$ Oxygen System, consisting of an oxygen concentrator (a), PROTECT – power conditioning system (b), Prioritizer – pneumatic switch that automatically controls oxygen source (c), back-up cylinder (d), low pressure oxygen storage (e), patient flow-meters (f) and Stack Lamp – traffic light display that communicates the status of the system (g). Image reprinted from Peake et al, and inspired by a similar illustration by David Woodroffe"*

**VERSION 2 – REVIEW**

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| **REVIEWER** | Waldemar Carlo<br>University of Alabama at Birmingham, Pediatrics |
| **REVIEW RETURNED** | 27-Jan-2022 |

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| **GENERAL COMMENTS** | I am still concerned about the design including a reasonable control period and the phased implementation. Given the increased support provided with the implementation, it will be hard to assess the benefits without appropriate controls. With increased availability of oxygen, the proportion of hypoxaemic children who receive oxygen will increase but the important clinical and economic outcomes will be hard to assess.<br>Very objective outcome measures are needed. |

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| **REVIEWER** | Payam Vali<br>UC Davis Department of Medicine |
| **REVIEW RETURNED** | 18-Jan-2022 |

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| **GENERAL COMMENTS** | The authors have satisfactorily responded to my comments/suggestions. Thank you |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer 1 comments:

"I am still concerned about the design including a reasonable control period and the phased implementation. Given the increased support provided with the implementation, it will be hard to assess the benefits without appropriate controls."

The duration of the pre- and post- intervention period was determined by power calculations, based on expected number of hypoxaemic children. It would be unethical to extend a control period – where improved oxygen systems are with-held from children who require it – beyond what is required to document statistically significant outcomes;

In the spirit of aiming to study real life challenges (including financial sustainability), and propose workable solutions for the oxygen access gap, this study is a pragmatic implementation trial. It is imperative to be led by local priorities, adapt to changing environments and take on lessons learned and feedback from on the ground. We had to, therefore, be flexible in choice of facilities and order of implementation. We believe that this aspect of our design strengthens the validity of the results, and enables us to answer questions that are not possible in a controlled trial.

The only support provided to facilities in the pre-intervention period is pulse oximetry (if this was not already in place) and training in how to use it. This is done because it is difficult to document changes in oxygen access in the absence of pulse oximetry. We acknowledge that this may impact on oxygen practices at baseline, and is a limitation of the design.

"With increased availability of oxygen, the proportion of hypoxaemic children who receive oxygen will increase but the important clinical and economic outcomes will be hard to assess. Very objective outcome measures are needed."

The impact of improved oxygen systems on reducing mortality have been well established and recently documented (Lam. BMJ Open 2021). We did not aim to replicated these by designing a clinical trial of patient outcomes.

It is now widely acknowledged that ‘availability’ of oxygen or pulse oximetry in itself does not guarantee that hypoxaemia will be diagnosed and treated in an affected child. Our primary outcome – the proportion of hypoxaemic children (SpO2<90%) who receive oxygen – is objective, and has been proposed as “single most important indicator for evaluating patient access” to oxygen (Graham. BMJ Global Health 2021)

## VERSION 3 – REVIEW

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| **REVIEWER** | Waldemar Carlo<br>University of Alabama at Birmingham, Pediatrics |
| **REVIEW RETURNED** | 20-Apr-2022 |

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| **GENERAL COMMENTS** | Accepted. I do not have further comments. |