

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Pulse Oximetry and Oxygen Services for the Care of Children with Pneumonia Attending Frontline Health Facilities in Lagos, Nigeria (INSPIRING-Lagos): Study Protocol for a mixed-methods evaluation
<b>AUTHORS</b>	Graham, Hamish; Olojede, Omotayo; Bakare, Ayobami Adebayo; McCollum, Eric D.; Iuliano, Agnese; Isah, Adamu; Osebi, Adams; Seriki, Ibrahim; Ahmed, Tahlil; Ahmar, Samy; Cassar, Christine; Valentine, Paula; Olowookere, Temitayo Folorunso; MacCalla, Matt; Uchendu, Obioma; Burgess, Rochelle; Colbourn, Timothy; King, C.; Falade, Adegoke; Consortium, INSPIRING

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Timothy Ore Commission for Hospital Improvement, Department of Health
<b>REVIEW RETURNED</b>	29-Nov-2021

<b>GENERAL COMMENTS</b>	<p>The authors' secondary outcome, 14-day pneumonia case-fatality rate, should be the primary outcome, and their primary outcome (correct management of hypoxaemic pneumonia involving administration of oxygen therapy, referral, and presentation to hospital) should be the secondary, process outputs, NOT outcomes. Any consideration given to stratification for co-morbidities? A cluster randomised controlled trial will most likely present stronger evidence (as in the protocol by Fatima Mir and colleagues on the impact of pulse oximetry on hospital referral acceptance in children under five years with severe pneumonia in the district of Jamshoro in rural Pakistan, published in BMJ Open in 2021).</p> <p>Not sure this protocol will yield substantially new insights on the cost effectiveness of pulse oximetry and oxygen therapy in health facilities (in Lagos State, Nigeria). The issue is already well-researched. For example, in a study published in Nature on 2 December 2015, Jessica Floyd and colleagues evaluated the impact of pulse oximetry on childhood pneumonia mortality in resource-poor settings (15 countries with the highest burden worldwide). They estimated that, assuming access to supplemental oxygen, pulse oximetry has the potential to avert up to 148,000 deaths if implemented across the 15 countries. Integrated management of childhood illness alone has a relatively small impact on mortality owing to its low sensitivity. They found that the combination of pulse oximetry with integrated management of childhood illness is highly cost-effective, with median estimates from US\$2.97 to \$52.92 per disability-adjusted life year averted in the 15 countries analysed. On 24 June 2021, Yiming Huang and others demonstrated (in a paper published in JAMA Network Open) the cost-effectiveness of pulse oximetry and oxygen therapy for treating hypoxemia in young children in low and middle income countries, relative to no oxygen.</p>
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<b>REVIEWER</b>	Andrew Argent Red Cross War Memorial Childrens Hospital, Paediatric Intensive Care Unit
<b>REVIEW RETURNED</b>	02-Dec-2021

<b>GENERAL COMMENTS</b>	<p>General Comments</p> <p>Thanks for the opportunity to review this important study. The authors have provided a protocol which will provide comprehensive (but detailed) information on the impact of providing pulse oximetry and oxygen services for children with pneumonia in Lagos.</p> <p>The study is carefully designed, and seems appropriate to achieve the goals.</p> <p>The position of children with COVID-19 in the study (particularly if they do not have pneumonia) could be clarified. The potential impact of the COVID-19 pandemic on the implementation of this study could be addressed in more detail, as it may have substantial consequences (change in numbers of expected children at centres; change in parental behaviour; change in healthcare procedures and potential interference with the implementation of the project).</p> <p>It would also be useful to have a little more clarity about the role of procedures such as nasogastric feeding (particularly in the context of providing oxygen therapy); administration of antibiotics and fluids.</p> <p>Specific Comments</p> <p>Title</p> <p>The study only admits children with pneumonia and COVID-19 infection, so I am not sure that the title should refer to: “acutely unwell children attending frontline health facilities”. The study clearly excludes unwell children with other conditions.</p> <p>Introduction</p> <p>The introduction reads well and provides an excellent context for the study.</p> <p>Throughout this document it feels as if patients with COVID-19 infections have been included as an afterthought and without particular attention to detail. Firstly it would be interesting to know exactly how many children under 5 years of age are presenting to healthcare systems with COVID-19, and then what the mode of presentation is. Clearly some of the children may present with features of “pneumonia”, in which case they would be included as part of the study. If children presented with other features of COVID infection which are not primarily related to the respiratory system, I am not sure that it makes sense to include them into this study, particularly if there are delays in the diagnostic testing, and if presumption of COVID-19 brings multiple other factors into play (isolation, isolation of caregivers / parents etc).</p> <p>Methods</p> <p>Settings</p> <p>The authors have clearly described the settings that will be used within the study. I am not clear as to how representative these units are of care at equivalent centres throughout the region (the authors state that the 7 state facilities were “purposefully selected” on the basis of need).</p>
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	<p>Just for clarity – would children from the clinics be referred to the secondary care centres within the study?</p> <p><b>Data Collection</b> The authors state that “Each data collector will be responsible for one to two clinics, aiming to screen all children under-five who present to the clinic with an acute infection for eligibility before they have been routinely assessed by the HCW.” If a data collector is responsible for &gt;1 clinic, how can they screen “all children ... who present .... eligibility before they have been ...by the HCW”? Do the clinics have opening hours that don’t overlap?</p> <p><b>Impact Evaluation</b> <b>Outcomes</b> The authors state that: ‘Correct management’ is defined as the child receiving oxygen treatment and being referred to and subsequently attending hospital (all three criteria need to be met).” Are there not other components of “correct management” including the administration of appropriate antimicrobial therapy, provision of appropriate fluids / feeds?</p> <p>It is not clear how hypoxaemic patients will be referred to secondary level institutions. Will these patients actually be transferred on oxygen to those institutions?</p> <p><b>Sample size</b> The authors have provided a number for the original sample size. After review of the baseline data they recalculated the numbers, but have not provided the details of numbers to be recruited; estimated numbers with completed follow up (they assume 75 per month, but do not suggest the proportion of patients entered into the study who are likely to complete follow-up). They have not provided a basis for the estimate of 10% hypoxaemia.</p> <p><b>Analysis</b> The phrase: “1) changes in incidence have occurred; 2) identifies the most likely time for the change point, which we can link to the intervention and other key events.” does not read well and needs updating.</p> <p><b>Tables</b> <b>Table 1</b> <b>Process</b> The introduction of nasogastric feeding as part of the package of care comes as something of a surprise in this table.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Timothy Ore, Commission for Hospital Improvement

Comments to the Author:

The authors' secondary outcome, 14-day pneumonia case-fatality rate, should be the primary outcome, and their primary outcome (correct management of hypoxaemic pneumonia involving administration of oxygen therapy, referral, and presentation to hospital) should be the secondary, process outputs, NOT outcomes. Any consideration given to stratification for co-morbidities? A cluster randomised controlled trial will most likely present stronger evidence (as in the protocol by Fatima Mir and colleagues on the impact of pulse oximetry on hospital referral acceptance in children under five years with severe pneumonia in the district of Jamshoro in rural Pakistan, published in BMJ Open in 2021).

Thanks to Reviewer 1 for your thoughtful comments. Measuring mortality impact on primary care interventions is challenging, and based on preliminary data we will not be adequately powered to make mortality the primary outcome – but we felt it is nonetheless important to report as a secondary outcome. Therefore, we chose a composite practice outcome that reflects what should happen based on existing evidence (correct management of hypoxaemic pneumonia involving administration of oxygen therapy, referral, and presentation to hospital). Your example of Fatima Mir’s elegant protocol is another example of using such distal practice outcomes as a primary outcome measure (accepted referral). Unlike Fatima Mir’s study, we are conducting this as external evaluators of an established program implemented by an NGO and local government, and this prevented us setting it up as a cluster randomised trial. We accept the lack of randomisation as a limitation for impact results, and have addressed this by using time-series analysis (which means we can still account for time –i.e. how our primary and secondary outcomes change over time in relation to intervention coverage–, and clustering and facility level) and by conducting a robust mixed-methods process evaluation.

Not sure this protocol will yield substantially new insights on the cost effectiveness of pulse oximetry and oxygen therapy in health facilities (in Lagos State, Nigeria). The issue is already well-researched. For example, in a study published in Nature on 2 December 2015, Jessica Floyd and colleagues evaluated the impact of pulse oximetry on childhood pneumonia mortality in resource-poor settings (15 countries with the highest burden worldwide). They estimated that, assuming access to supplemental oxygen, pulse oximetry has the potential to avert up to 148,000 deaths if implemented across the 15 countries. Integrated management of childhood illness alone has a relatively small impact on mortality owing to its low sensitivity. They found that the combination of pulse oximetry with integrated management of childhood illness is highly cost-effective, with median estimates from US\$2.97 to \$52.92 per disability-adjusted life year averted in the 15 countries analysed, On 24 June 2021, Yiming Huang and others demonstrated (in a paper published in JAMA Network Open) the cost-effectiveness of pulse oximetry and oxygen therapy for treating hypoxemia in young children in low and middle income countries, relative to no oxygen.

Both the Floyd 2015 and Huang 2021 papers are excellent examples of cost-effectiveness estimates, relying heavily on non-primary data on the impact of oxygen/POx on child pneumonia mortality (specifically a single study from Papua New Guinea<sup>1</sup>). Aside from these papers, others have reported on program cost and cost-effectiveness – including our recent systematic review and meta-analysis which includes 4 studies from 3 countries (an additional study from Papua New Guinea and 2 studies from Laos and Papua New Guinea).<sup>2</sup> However, there is great need for better primary data from a variety of contexts and deeper exploration of costs beyond just program/equipment cost. We have previously reported on the importance of understanding the economic cost of oxygen from both provider and patient perspectives,<sup>3</sup> and this will be one of the first studies to comprehensively evaluate this. Our study also includes private facilities for which there is very little data on costs or cost-effectiveness despite them comprising a large proportion of facilities in many locations such as in urban Nigeria, our study setting.

Reviewer: 2

Dr. Andrew Argent, Red Cross War Memorial Childrens Hospital

Comments to the Author:

General Comments

Thanks for the opportunity to review this important study. The authors have provided a protocol which will provide comprehensive (but detailed) information on the impact of providing pulse oximetry and oxygen services for children with pneumonia in Lagos.

The study is carefully designed, and seems appropriate to achieve the goals.

The position of children with COVID-19 in the study (particularly if they do not have pneumonia) could be clarified. The potential impact of the COVID-19 pandemic on the implementation of this study could be addressed in more detail, as it may have substantial consequences (change in numbers of expected children at centres; change in parental behaviour; change in healthcare procedures and potential interference with the implementation of the project).

This protocol reflects adaptation to an emerging COVID-19 situation in early 2020. At that stage the epidemiology and clinical features of COVID-19 in children was unclear. We expected most to exhibit respiratory signs and meet WHO diagnostic criteria for pneumonia/severe pneumonia but there had also been reports of a cohort with 'silent hypoxaemia'. Therefore we opted to include all suspected COVID-19 cases in children in analysis. We have described some of the potential impacts of COVID-19 pandemic in the Intervention section (page 8), including the need for an adaptive study design. We have discussed the risks and assumptions as it relates to COVID-19 pandemic in Ethics/Dissemination (page 14-15), and added it as a key limitation in the Strengths and Limitations summary.

It would also be useful to have a little more clarity about the role of procedures such as nasogastric feeding (particularly in the context of providing oxygen therapy); administration of antibiotics and fluids.

Clinical training and protocols were all according to WHO IMCI guidelines, including encouraging the use of pulse oximetry for all acutely unwell children, provision of oxygen if SpO<sub>2</sub><90%, administration/prescription of appropriate antibiotics, and supplemental feeding as required. We did not require NGT placement for oxygen therapy (and we did not address CPAP or high-flow therapy where NGT placement may be more important). We have revised the Methods to clarify this.

*The stabilisation rooms will be implemented alongside broader capacity-building activities targeting primary care HCW practices (preventive and curative). This will include training on WHO's IMCI guidelines, pulse oximetry and oxygen therapy, immunization, and nutrition (Table 4). This includes guidance to conduct pulse oximetry on all acutely unwell children, provide oxygen using nasal prongs to those with low blood oxygen levels (SpO<sub>2</sub><90%), prescribe appropriate antibiotics, and arrange transfer to an admission facility for those requiring inpatient care (typically by private vehicle) as per WHO IMCI guidelines.*

#### Specific Comments

##### Title

The study only admits children with pneumonia and COVID-19 infection, so I am not sure that the title should refer to: "acutely unwell children attending frontline health facilities". The study clearly excludes unwell children with other conditions.

We have revised the title to better reflect the focus on children with pneumonia.

*Pulse Oximetry and Oxygen Services for the Care of Children with Pneumonia Attending Frontline Health Facilities in Lagos, Nigeria (INSPIRING-Lagos): Study Protocol for a mixed-methods evaluation*

##### Introduction

The introduction reads well and provides an excellent context for the study.

Throughout this document it feels as if patients with COVID-19 infections have been included as an afterthought and without particular attention to detail. Firstly it would be interesting to know exactly how many children under 5 years of age are presenting to healthcare systems with COVID-19, and then what the mode of presentation is. Clearly some of the children may present with features of

“pneumonia”, in which case they would be included as part of the study. If children presented with other features of COVID infection which are not primarily related to the respiratory system, I am not sure that it makes sense to include them into this study, particularly if there are delays in the diagnostic testing, and if presumption of COVID-19 brings multiple other factors into play (isolation, isolation of caregivers / parents etc).

See response to related question earlier. The original protocol was developed prior to the emergence of COVID-19 and this protocol paper reflects the revised protocol developed early in the pandemic during 2020. At that stage the clinical and epidemiological features of COVID-19 in children was poorly defined. We expected most to exhibit respiratory signs and meet WHO diagnostic criteria for pneumonia/severe pneumonia but there had also been reports of COVID-19 patients with ‘silent hypoxaemia’. Therefore we opted to include all COVID-19 positive children in analysis. We have revised to clarify this in Outcomes (page 9).

*COVID-19 is defined as either PCR-test confirmed or based on a clinical diagnosis according to local guidelines. At the time of developing this protocol we knew little about the epidemiology or clinical features of COVID-19 in children and, while many presented with signs of respiratory infection, there had been reports of ‘silent/happy hypoxia’. Therefore, we elected to include any children with COVID-19 infection irrespective of respiratory signs.*

## Methods

### Settings

The authors have clearly described the settings that will be used within the study. I am not clear as to how representative these units are of care at equivalent centres throughout the region (the authors state that the 7 state facilities were “purposefully selected” on the basis of need).

There is considerable variability in size and function of primary care facilities within Lagos state, and between states. This selection included facilities of a range of sizes and covering all geographic areas - but was not done randomly. It is likely to be reasonably representative of the variety of peri-urban primary care settings in Nigeria but may not represent more rural settings. Our original intention had been to include all primary care facilities and a random sample of private facilities, but given the COVID-19 pandemic, and the rapid need for oxygen in the context, we changed our approach to be collaborative with the Ministry of Health response.

Just for clarity – would children from the clinics be referred to the secondary care centres within the study?

Yes. Children requiring admission (e.g. for oxygen therapy) would be referred to an admitting facility (usually the secondary care centre).

### Data Collection

The authors state that “Each data collector will be responsible for one to two clinics, aiming to screen all children under-five who present to the clinic with an acute infection for eligibility before they have been routinely assessed by the HCW.” If a data collector is responsible for >1 clinic, how can they screen “all children ... who present .... eligibility before they have been ...by the HCW”? Do the clinics have opening hours that don’t overlap?

Thank you. This is an important point that we had not made clear in the manuscript. We have revised to provide clearer detail, and fuller description of the data collection process. Our original intention was to obtain representative, but not complete, recruitment across facilities by having data collectors attend facilities as set time periods according to a monthly roster. To increase the number and proportion of participants captured we have subsequently recruited additional data collectors so that

>80% of clinic time is now covered with a data collector. This will be reported as a deviation from protocol.

*Study employed clinical data collectors will be responsible for recruitment and data collection in participating facilities. Each data collector will be responsible for one to two clinics, visiting each clinic at scheduled times each week according to a monthly roster that ensures we recruit at different times and days in each facility to maximise representativeness of data. During scheduled clinic visits, data collectors will screen all children under-five who present to the clinic with an acute infection for eligibility before they have been routinely assessed by the HCW. This assessment involves a directed history and physical examination to identify clinical features of pneumonia and COVID-19, including pulse oximetry and auscultation (using standard and digital stethoscopes). After identifying those who meet eligibility criteria, data collectors will obtain consent, complete an additional medical and socio-economic questionnaire and arrange for phone follow-up. Following the HCW consultation, data collectors will enquire about caregiver intentions for onward care and extract routine clinical data from the HCW's clinical notes (including diagnosis, treatment and referral decision, vital signs and clinical observations). The data collector will inform the HCW if they find any signs that meet referral criteria and document whether this results in any change in patient management.*

## Impact Evaluation

### Outcomes

The authors state that: 'Correct management' is defined as the child receiving oxygen treatment and being referred to and subsequently attending hospital (all three criteria need to be met)." Are there not other components of "correct management" including the administration of appropriate antimicrobial therapy, provision of appropriate fluids / feeds?

We have focussed the primary outcome on selected aspects of management that are most related to the intervention and are able to be assessed objectively. We do collect data on other aspects of quality of care that will be included in our process evaluation (detailed in Annex 2).

It is not clear how hypoxaemic patients will be referred to secondary level institutions. Will these patients actually be transferred on oxygen to those institutions?

Completion of referral to a facility is a well-recognised barrier to appropriate care and we have selected it as a key component of the 'correct management' composite primary outcome. We hypothesise that the use of pulse oximetry and availability of oxygen at primary care facilities will improve both immediate treatment of hypoxaemia (with oxygen) and greater referral success. The intervention training includes discussion about referral but the intervention does not have a major emphasis on improving other aspects of the referral pathway, and we as the research team are not intervening in the referral process. The intervention does not include portable oxygen for transport. Formative research suggests that most referrals are done by private vehicle (not ambulance), and therefore wouldn't have access to oxygen. We expect that this trend will continue and we are collecting information on this at follow-up, alongside the costs related to referral. We have added a comment to address portable oxygen and referral.

*The project will establish "stabilisation rooms" within the outpatient areas of participating primary facilities, designed to allow for short-term oxygen delivery for children with hypoxaemia prior to transfer to hospital (or admission to the ward). These stabilisation rooms are intended to support both short-term COVID-19 and longer-term paediatric pneumonia care needs, and will consist of the following intervention components:*

1. *Pulse oximeters, equipped with both paediatric and adult re-usable probes;*
2. *Medical oxygen supply delivered through newly installed oxygen concentrators powered from mains supply, generators and/or solar power;*
3. *Clinical guidelines, job aids and clinical training*

*Secondary health facilities that admit children will also be supported with pulse oximeters and oxygen concentrators for use on the wards to support safe care of patients referred for inpatient care. The intervention does not include portable oxygen for transport or direct referral support.*

#### Sample size

The authors have provided a number for the original sample size. After review of the baseline data they recalculated the numbers, but have not provided the details of numbers to be recruited; estimated numbers with completed follow up (they assume 75 per month, but do not suggest the proportion of patients entered into the study who are likely to complete follow-up). They have not provided a basis for the estimate of 10% hypoxaemia.

We used data from our baseline period of July 2020 – January 2021 to update our sample size, which is where we get the 10% hypoxaemia value from. This is also in-line with other studies in primary care settings (e.g. McCollum et al., 2016 – 9.3% at health centres in Malawi). Similarly, the 75 children with completed follow-up per month is based on data collected in this time period, where we have a successful follow-up completion rate of around 85%. However, as stated above, the uncertainties around care-seeking behaviours and impact of COVID-19 mitigations on respiratory infection epidemiology means these assumptions are still uncertain. We have revised for clarity.

*We had originally calculated a sample size based on the case fatality rate (CFR) as a primary outcome, assuming a baseline CFR of 4% and 1920 eligible children recruited. In this scenario, we had 72% power to detect a 50% reduction in CFR<sup>32</sup> but recognised this was uncertain given the COVID-19 context and lack of baseline data. We therefore reviewed the data from August 2020 – January 2021 and found lower than expected CFR making this scenario unfeasible. We used this data to update the sample size for the new primary outcome of “correct management of hypoxaemic pneumonia cases”, based on using a pre-post analysis. Using the following numbers extracted from the 6-month baseline data, we will be able to detect a minimum 15% increase in correct management: 75 children with completed follow-up per month; 24-month data collection period; intra-cluster correlation 0.05; 10% hypoxaemic; 5% correctly managed pre-intervention. This means we should be able to detect a significant difference if the intervention results in  $\geq 20\%$  of hypoxaemic children being correctly managed.*

#### Analysis

The phrase: “1) changes in incidence have occurred; 2) identifies the most likely time for the change point, which we can link to the intervention and other key events.” does not read well and needs updating.

Revised for clarity.

*We will be able to assess whether care has improved and identify the most likely time for the change point, which we can link to the intervention and other key events.*

#### Tables

##### Table 1

##### Process

The introduction of nasogastric feeding as part of the package of care comes as something of a



surprise in this table.

This is not meant to imply nasogastric feeding as part of oxygen therapy – we have revised Table 1 to separate “(i) oxygen and (ii) nasogastric feeding” for clarity. Rather, nasogastric feeding is a secondary point of interest as previous work has identified similar barriers to acceptability amongst caregivers as oxygen treatment, and inappropriate use – including one study by members of our team in which failure to use nasogastric tubes may have contributed to excess pneumonia mortality.<sup>4</sup>

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Timothy Ore Commission for Hospital Improvement, Department of Health
<b>REVIEW RETURNED</b>	23-Feb-2022
<b>GENERAL COMMENTS</b>	Much improved version.
<b>REVIEWER</b>	Andrew Argent Red Cross War Memorial Childrens Hospital, Paediatric Intensive Care Unit
<b>REVIEW RETURNED</b>	16-Feb-2022
<b>GENERAL COMMENTS</b>	I am grateful to the authors for their responses to the issues raised by the reviewers. I have no further suggestions.