A Feasibility Study Evaluating a Novel Mask (Nasal Reservoir Cannula) Plus Standard Nasal Cannula vs. Standard Nasal Cannula Alone for Supplemental Oxygen Delivery in the Treatment of Hospitalized Pediatric Patients with Hypoxemia due to Severe Pneumonia

Investigational Device: Mask (Nasal Reservoir Cannula)

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PROTOCOL SYNOPSIS

Title: A feasibility study evaluating a novel mask (nasal reservoir cannula) plus standard nasal cannula vs. standard nasal cannula alone for supplemental oxygen delivery in the treatment of hospitalized pediatric patients with hypoxemia due to severe pneumonia.

Disease:
Hypoxemia due to severe pneumonia.

Objectives:
The primary objective of this feasibility study is to collect preliminary information to aid in the design and conduct of future trials evaluating the safety and efficiency of a novel mask (nasal reservoir cannula) plus standard nasal cannula vs. standard nasal cannula alone for supplemental oxygen delivery in the treatment of hospitalized pediatric patients with hypoxemia due to severe pneumonia. This study is intended to provide information on intervention delivery and implementation, trial conduct, availability of patients and recruitment rates, protocol adherence, and effect sizes and outcomes to guide power calculation and design of a more definitive future study.

Our long-term goal is to conduct definitive studies to evaluate whether the addition of a novel mask (nasal reservoir cannula) to a standard nasal cannula during supplemental oxygenation is safe and more efficient (compared with a standard nasal cannula alone) in reducing the total amount of oxygen needed per cylinder for adequate oxygen delivery in pediatric patients with hypoxemic respiratory illness in resource-limited settings.

Study Design:
The study is an open-label, prospective, feasibility study of hospitalized pediatric patients with hypoxemia due to severe pneumonia. Following study eligibility, patients will receive baseline assessments followed by supplemental oxygen per standard of care before being equally randomized to one of the following two groups:

- Group A: Each patient will receive oxygen for 1 hr using a novel mask (nasal reservoir cannula) plus standard nasal cannula (Period 1), followed by a 1-hr period of continued use of the standard nasal cannula delivery (Period 2).
- Group B: Each patient will receive oxygen for 1 hr using a standard nasal cannula (Period 1), followed by a 1-hr period of continued use of the novel mask (nasal reservoir cannula) plus standard nasal cannula (Period 2).

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

- Age $\geq$ 1 year and $\leq$ 6 years of age.
- Severe pneumonia based on World Health Organization (WHO) criteria.

- $SpO_2 \geq 85\%$ and $< 94\%$ by pulse oximetry on room air.
- Hospital admission based on clinician judgment.
- Written informed consent from parent(s)/guardian(s) of subjects must be obtained before any study procedure is performed.
- Body weight ≥ 8 kg and ≤ 26 kg

Exclusion Criteria:

- Hypercapnia ($pCO_2 > 55$ mm Hg or 7.32 kPa) on room air
- Acidosis / lactic acidosis (pH < 7.20 and/or lactate > 3 mmol/L) on room air
- $SpO_2 < 85\%$ or $\geq 94\%$ by pulse oximetry on room air
- SICK score > 2.4
- Hemoglobin < 7 g/dL
- Facial abnormalities or trauma precluding use of nasal prongs.
- Requirement of intubation or noninvasive or invasive positive-pressure ventilation.
- Suspected or known pneumothorax.
- Body weight < 8 kg and > 26 kg
- Hemodynamic instability based on clinician judgment.
- $SpO_2 < 90\%$ by pulse oximetry on oxygen, measured at the end of the enrollment and before initiation of Period 1.

Investigational Device:
Mask (nasal reservoir cannula)

Procedures:

- All patients will receive standard of care for their underlying disease according to World Health Organization (WHO) recommendations, including availability of standardized care of oxygen therapy.
- Safety evaluations will consist of vital signs (respiratory rate, temperature, blood pressure, heart rate), physical examination, clinical laboratory, and adverse event information. Clinical laboratory tests for safety assessment will include metabolic panels, complete blood count, continuous transdermal end-tidal carbon dioxide (CO_2) monitoring, blood gases (P_aO_2, P_aCO_2, pH, base excess), peripheral blood oxygen saturation (SpO_2), and blood lactate.
- Efficacy will be measured throughout the hospitalization by continuous monitoring of transdermal end-tidal carbon dioxide (CO_2), blood gases (P_aO_2, P_aCO_2, pH, base excess), peripheral blood oxygen saturation (SpO_2), and blood lactate. Signs of inflammation in children that can kill (SICK) score will be calculated from physical

exam and SpO_2 data. The amount of oxygen used from a cylinder during Period 1 through 2 will be measured.

- At screening, severe pneumonia by WHO criteria, peripheral blood oxygen saturation (SpO_2 by pulse oximetry) on air, capillary blood gas with lactate to evaluate for hypercapnia/acidosis, hemoglobin (rapid) and complete blood count (CBC) to evaluate for anemia / leukocytosis, SICK score to evaluate degree of illness, and body weight will be obtained to determine study eligibility.
- Baseline (pre-treatment): Once eligibility criteria are met, physical examination, including vital signs and capillary refill time; blood glucose (point of care); malaria rapid diagnostic test; and concomitant medication information will be obtained. In addition, a metabolic panel will be recorded *only* if obtained as standard of care. Any baseline assessment obtained during the screening period will be used as the baseline value. Patients will be placed on supplemental oxygen consistent with standard of care. Based on the body weight of the patients the size (small or large) of the nasal reservoir cannula to be used during the intervention periods will be determined.
- Period 1 (Group A: nasal reservoir cannula plus nasal cannula for 1 hr, Group B: standard nasal cannula alone) will include:

  Period 1 (1 hr):

  - Continuous monitoring of transdermal end-tidal carbon dioxide (CO_2) with recording every 15 min.
  - Continuous monitoring of SpO_2 by pulse oximetry with recording every 15 min.
  - Record vital signs every 15 min.
  - Record oxygen flow (L/min) every 15 min.
  - Record concomitant medication information.
  - Record adverse events.

  End of Period 1:

  - Physical examination, including capillary refill time; capillary blood gases (P_aO_2, P_aCO_2, pH, base excess, lactate); and SICK score.
- Period 2 (Group A: nasal cannula for 1 hr, Group B: nasal reservoir cannula with standard nasal cannula alone) will include:

  Period 2 (1 hr):

  - Continuous monitoring of transdermal end-tidal carbon dioxide (CO_2) with recording every 15 min.
  - Continuous monitoring of SpO_2 by pulse oximetry with recording every 15 min.
  - Record vital signs every 15 min.

- Record oxygen flow (L/min) every 15 min.
- Record concomitant medication information.
- Record adverse events.

End of Period 2:

- Physical examination, including capillary refill time; capillary blood gases (P_aO_2, P_aCO_2, pH, base excess, lactate); and SICK score.

- Study duration is from the beginning of Period 1 to end of Period 2 (approximately 2 hour).

Sample Size and Number of Sites:

- The target sample size for the study (up to 20 patients) is consistent with feasibility studies for other clinical interventions. Planned number of sites: 1 (Department of Pediatrics, Makerere University, Kampala, Uganda).

Removal of Subjects from Investigational Study Treatment or Assessment:

A subject may be prematurely discontinued from investigational device treatment or study assessment if the investigator or subject's parent(s)/guardian(s) requests such discontinuation for any reason.

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1 LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BUN	blood urea nitrogen
CBC	complete blood count
CO_2	carbon dioxide
CRF	case reporting form
dL	deciliter
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
hr	hour(s)
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
kg	kilogram
kPa	kilopascals
MCV	mean corpuscular volume
mg	milligram
min	minutes
mm Hg	millimeters mercury
O_2	oxygen
PCO_2	Partial pressure of carbon dioxide in arterial blood
P_aCO_2	Partial pressure of carbon dioxide in blood
PO_2	Partial pressure of oxygen in blood
P_aO_2	Partial pressure of oxygen in arterial blood
RBC	Red blood cell
SAE	serious adverse event
SpO_2	peripheral capillary oxygen saturation
SICK	Signs of inflammation in children that can kill
UNICEF	United Nations Children's Emergency Fund
WHO	World Health Organization

2 INTRODUCTION

2.1 Pediatric Respiratory Illness and Hypoxemia in the Developing World

Pneumonia is the leading infectious cause of death among children less than 5 years of age (Liu et al., 2015). Estimates indicate that 922,000 children died from pneumonia in 2015, accounting for 15% of all deaths of children under 5 years of age (World Health Organization 2015). Hypoxemia is a major fatal complication of pneumonia, and the risk of death increases with increasing severity of hypoxemia (Djelantik et al., 2003).

Childhood pneumonia can be especially difficult to diagnose and treat in low-resource settings, and is the leading cause of death among children under 5 years in the developing world (Ginsberg et al., 2015). Indeed, more than half of the world's annual new pneumonia cases are concentrated in just five countries where 44% of the world's children aged less than 5 years live: India (43 million), China (21 million) and Pakistan (10 million) and in Bangladesh-Indonesia and Nigeria (6 million each) (World Health Organization 2016a). Major risk factors for childhood pneumonia in the developing world include malnutrition, low birth weight (≤ 2500 g), non-exclusive breastfeeding (during the first 4 months of life), lack of measles immunization (within the first 12 months of life), indoor air pollution, and crowding. These factors also contribute to other respiratory and systemic illnesses that result in hypoxemia. The main bacterial causes of clinical pneumonia in developing countries are *S. pneumoniae* and *Haemophilus influenzae type b*, and the main viral cause is respiratory syncytial virus, but estimates of their relative importance vary in different settings.

In low-resource settings, early detection of pneumonia or other hypoxemic respiratory illness, identification of a pathogen, and initiation of treatment is challenging but potentially life-saving. In particular, hypoxemia is a common and potentially lethal complication of acute respiratory infection in children in resource-poor settings, especially among those with severe disease. In these settings, hypoxemia can also occur in children with illnesses of infectious origin that are not primarily due to lower respiratory tract infection, such as acute sepsis, meningitis, and severe malaria, or due to different forms of shock syndrome such as hypovolemic shock due to diarrhea, trauma, and cardiac conditions. In developing countries, instruments for measuring arterial oxygen saturation are not available in most settings, which complicate the ability of health providers to detect hypoxemia in children with acute respiratory infections. In these situations, clinical signs are used to guide the initiation and use of oxygen therapy (World Health Organization 2016b). Besides availability of instruments to measure oxygenation, oxygen delivery systems for neonate and pediatric patients with hypoxemia are a critical resource as mainstay of treatment. However, oxygen supplies are also unavailable or inadequate throughout much of the developing world (Duke et al., 2006). In the setting of resource-poor hospitals, the cost, maintenance, local availability of compressed air (for oxygen

cylinders), power, and logistics remain challenges for the adequate care of pediatric hypoxemic patients (Coghill et al., 2011). The critical necessity of providing better access to quality and sustainable uninterrupted oxygen systems is underscored by their impact and cost-effectiveness, which compares favorably with other higher profile child survival interventions such as new vaccines (Duke et al., 2010).

2.2 Limitations of Oxygen Delivery in the Developing World

Deficiencies in the delivery and sustainability of oxygen to hypoxemic infants and children vary significantly in the developing world (Catto et al., 2011). Oxygen cylinders, which contain the gas in compressed form, are the standard storage form of oxygen in most poorly resourced or remote health facilities. Cylinders do not require an electrical supply but are expensive, difficult to transport, and require regular replenishment (Duke et al., 2010). In contrast, oxygen concentrators are machines that can concentrate oxygen at the bedside by absorption of nitrogen from atmospheric air; they are a less expensive and more reliable alternative for providing oxygen treatment, as long as there is an ability to maintain them and a reliable power supply (World Health Organization 2016b). Central piped oxygen is impractical for most hospitals in resource-limited countries.

Regardless of the source of oxygen, methods of delivery to the patient also vary but ideally should be safe, simple, effective, and inexpensive (World Health Organization 2016b). Nasal prongs (also called cannula) and nasal or face masks are the most efficient means of delivery of oxygen to balance safety and efficacy for long-term oxygen delivery in hypoxemic patients. Standard flow rates for oxygen through nasal prongs or nasal catheters are 0.5-1 L/min for neonates, 1-2 L/min for infants, and 1-4 L/min for older children (World Health Organization 2016b).

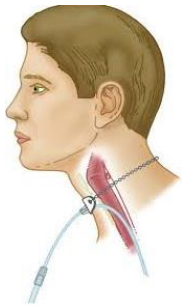
Methods of oxygen conservation (termed “oxygen conserving devices”) have included both changing the interface (e.g., reservoir cannulas and transtracheal catheters) and changing the oxygen delivery system. Reservoir cannulas, a more common oxygen-conserving device, function by storing oxygen in the reservoir space during exhalation, making that oxygen available as a bolus upon the onset of the next inhalation (Soffer et al., 1985; Tiep and Carter, 2016). Oxygen is conserved because the patient breathes a higher concentration of oxygen without increasing flow from the oxygen tank or concentrator. Reservoir cannulas increase the percent of oxygen in the air that the patient inhales over that delivered by standard nasal cannula and usually enable a reduction in the oxygen flow setting of approximately 25 to 50 percent while maintaining the same pulse oxygen saturation. The development of oxygen conserving devices was based on efforts to improve the portability of oxygen therapy by reducing the liter flow and thereby enabling patients to use a smaller and lighter ambulatory system, or a standard system for longer time periods (Hofmann 1994). Other advantages include a reduction of overall costs of long-term oxygen therapy and the ability to treat refractory hypoxemia more effectively.

Tables 1 and 2 show typical gas, liquid, and concentrator oxygen systems – and oxygen-conserving devices (American Thoracic Society 2015), many of which are not readily available or practical in resource-limited settings.

Table 1. Gas, Liquid and Concentrator Oxygen Systems

Features	Concentrator	Cylinder (Compressed Gas)	Liquid
			
Reliability	Good with regular maintenance	Good but gauges may become inaccurate	Generally good but connector may freeze
Cost	Least expensive but cost of electricity born by patient	Higher	Highest
Powerwall current	Required	Not required	Not required
Transfilling	Good only on special units that allow transfilling	Limited	Excellent
Ambulatory use	Good with transfill systems to gas plus conserver	Good with conserver	Good alone and with conserver
Stationary weight	35-50 lb	H cylinder 200 lb	Reservoir 120 lb
Use time at 2 L·min^{-1}	Continuous	2.5 days	8.9 days, special system >30 days
Portable weight	Portable units are not presently available	E cylinder 22 lb with cart	6 lb with no conserver
Use time at 2 L·min^{-1}	Unlimited	5 h	4 h
Portable weight with conserver	See gas transfill portable with conserver	M6 cylinder 4.5 lb	3.4 lb with conserver
Use time at 2 L·min^{-1}	See gas transfill portable with conserver	12 h	10 h

Table 2. Comparison of Oxygen-Conserving Devices

Conserving Device	Reservoir Cannula	Demand Pulse Delivery	Transtracheal Catheter
			
Conserving method	Store during exhalation	Early inspiration delivery	Store at end exhalation; bypass upper airway dead space
Efficiency gain [1] (savings)	2:1-4:1	2:1-7:1	2:1-3:1
Reliability	Good	Mechanically complex	Mucus plug possible
Comfort	Adequate-good	Adequate-good	Good
Cosmetics	Obtrusive	Adequate	Best
Cost	Low	Higher	Highest
Unique advantages	Inexpensive Easy initiation Reliable	Most efficient Alarms programmable	Cosmetics No nasal/ear irritation Good compliance
Disadvantages	Bulky on face Poor performance for pediatric patients	Mechanically complex Failure is possible Poor performance for pediatric patients	Special care + training Surgical complications Mucus plugs

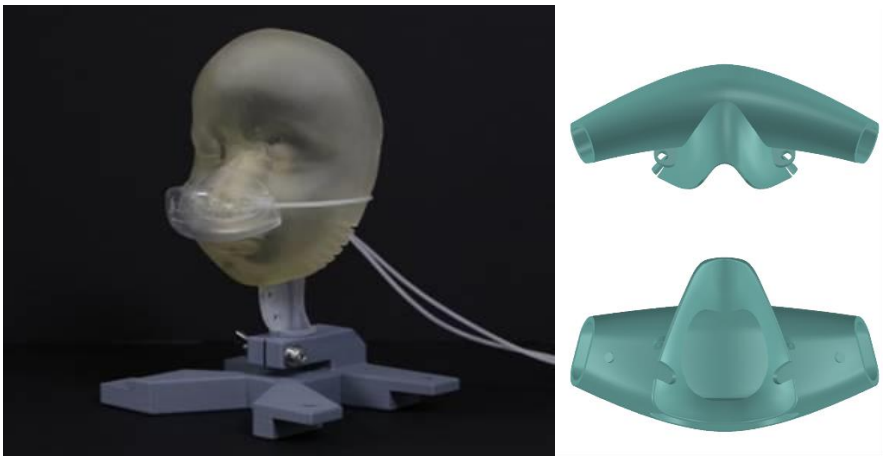
2.3 Global Good/Intellectual Ventures Pediatric Mask (Nasal Reservoir Cannula)

Improving oxygen delivery and extending oxygen supplies to ill patients with respiratory distress can reduce fatalities in resource-poor settings. Global Good has developed a low cost oxygen mask (nasal reservoir cannula) to more efficiently deliver oxygen to the pediatric patient by increasing dead space to recapture a portion of expelled oxygen using

[1] Efficiency gain is based on adult patients. Most conserving devices are not approved for pediatric use.

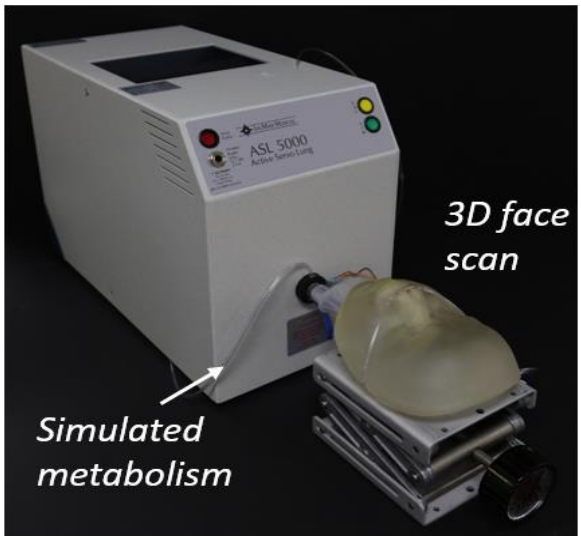
the spatial distribution of the nasal reservoir cannula volume and length of surface seal. This nasal reservoir cannula fits over a standard nasal cannula (also termed prong) (see Fig. 1 below). The system is designed to reduce administered oxygen to deliver an equal or higher fraction of inspired oxygen (FiO_2) per oxygen delivered (L/min) compared with a standard nasal cannula alone. Please refer to the device brochure (Appendix I) for instructional details on the nasal reservoir cannula.

Figure 1. Novel Nasal Reservoir Cannula



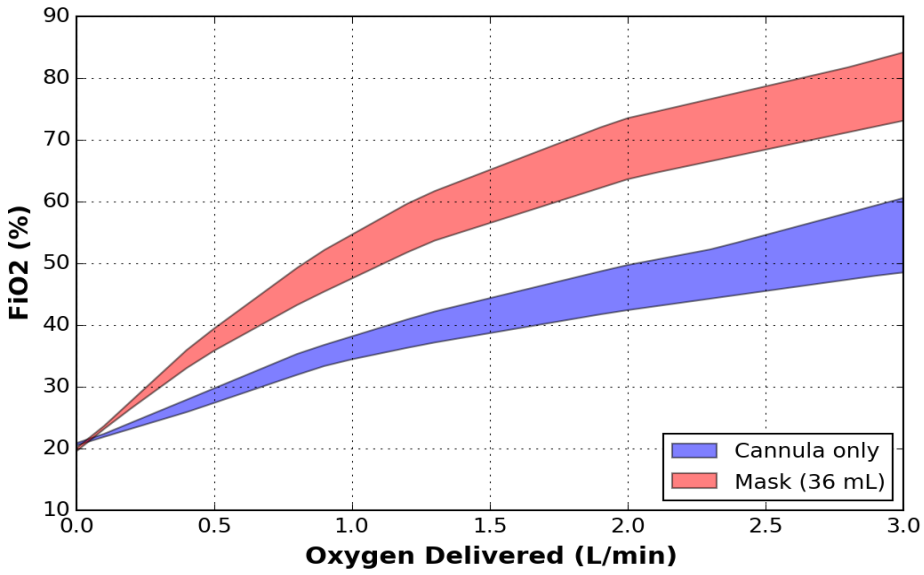
Mask performance was evaluated using a breathing simulator developed at the Global Good Laboratory (Bellevue, WA). The system consists of a breathing simulator (ASL 5000, IngMar Medical, Pittsburgh, PA) paired with an anatomically correct airway and face constructed by 3D printing computerized tomography scan data (Fig. 2). Carbon dioxide was titrated into the lung to simulate metabolism. The end-tidal carbon dioxide (CO_2), which is equivalent to the maximal concentration of carbon dioxide at the end of an exhaled breath, and FiO_2 were measured. An array of breathing waveforms was tested to bound mask performance.

Figure 2. Pediatric Breathing Simulator



For hospitalized patients with hypoxic respiratory illnesses, the minimal oxygen delivered recommended by the World Health Organization (WHO) is in ranges typically used in low-flow nasal cannulas; in vitro experiments on the breathing simulator indicate that the novel nasal reservoir cannula may be able to provide the same or higher FiO_2 at approximately 2.5-times lower oxygen flow rate (L/min) compared with a standard nasal cannula alone (Global Good, data on file; see Fig. 3). This can result in less oxygen used than conventional delivery systems, which may be valuable for resource limited settings where oxygen supplies are limited.

Figure 3 Oxygen Flow and FiO_2 of Novel Mask (Nasal Reservoir Cannula)



3 OBJECTIVES

The primary objective of this feasibility study is to collect preliminary information to aid in the design and conduct of future trials evaluating the safety and efficiency of a novel mask (nasal reservoir cannula) plus nasal cannula vs. nasal cannula alone for supplemental oxygen delivery in the treatment of hospitalized pediatric patients with hypoxemia due to severe pneumonia. This study is intended to provide information on intervention delivery and implementation, trial conduct, availability of patients and recruitment rates, protocol adherence, and effect sizes and outcomes to guide power calculation and design of a more definitive future study.

Our long-term goal is to conduct definitive studies to evaluate whether the addition of a novel mask (nasal reservoir cannula) to a standard nasal cannula during supplemental oxygenation is safe and more efficient (compared with standard nasal cannula alone) in reducing the total amount of oxygen needed per cylinder for adequate oxygen delivery in pediatric patients with hypoxemic respiratory illness in resource-limited settings.

4 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

The study is an open-label, prospective, feasibility study of hospitalized pediatric patients ≥ 1 year and ≤ 6 years of age with hypoxemia due to severe pneumonia. The primary objective of this feasibility study is to collect preliminary information to aid in the design and conduct of future trials evaluating the safety and efficiency of a novel mask (nasal reservoir cannula) plus standard nasal cannula vs. standard nasal cannula alone for supplemental oxygen delivery in the treatment of hospitalized pediatric patients with hypoxemia due to pneumonia in resource-poor settings. This study is intended to provide valuable information on the intervention delivery and implementation, trial conduct, availability of patients and recruitment rates, protocol adherence, and effect sizes and outcomes to guide power calculation and design of a more definitive future study.

Patients meeting entry criteria will receive baseline assessments followed by supplemental oxygen per standard of care. Patients will then be equally randomized to one of the two following groups:

- Group A: Each patient will receive oxygen for 1 hr using a novel mask (nasal reservoir cannula) plus standard nasal cannula (Period 1), followed by a subsequent 1-hr period of continued use of the standard nasal cannula delivery (Period 2).
- Group B: Each patient will receive oxygen for 1 hr using a standard nasal cannula (Period 1), followed by a 1-hr period of continued use of the novel mask (nasal reservoir cannula) plus standard nasal cannula (Period 2).

Patients with a body weight of 8-13 kg will receive treatment with a small 30 ml mask and patients with a body weight of 14-26 kg will receive treatment with a large 50 ml mask.

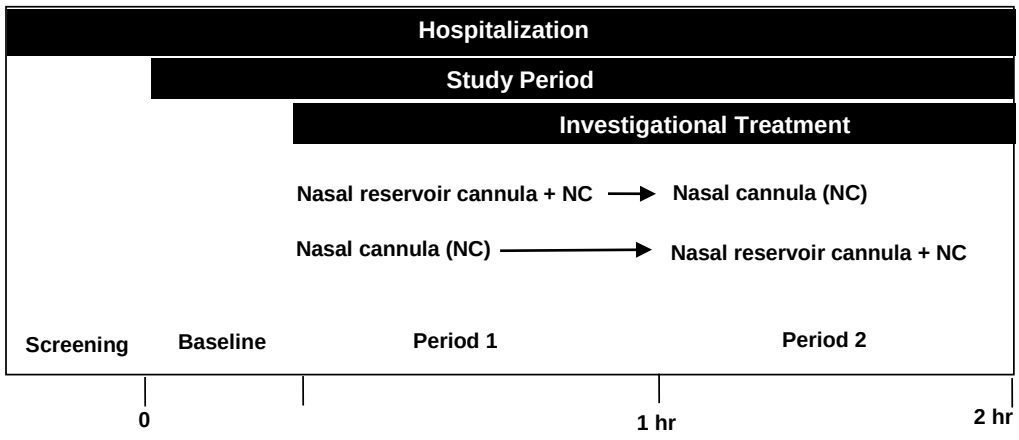
Safety evaluations will consist of vital signs (respiratory rate, temperature, blood pressure, heart rate), physical examination, clinical laboratory, and adverse event information. Clinical laboratory tests for safety assessment will include hemoglobin (rapid) and complete blood count; capillary blood gases (at screening and 2 time points during the study) to evaluate P_aO_2, P_aCO_2, pH, base excess, lactate; continuous oxygen saturation (SpO_2) and transdermal end-tidal carbon dioxide (CO_2) monitoring; blood glucose (point of care); malaria rapid diagnostic test; and results of comprehensive metabolic panels for patients in whom these are clinically indicated and obtained as part of routine care.

Efficacy will be measured throughout the hospitalization by continuous monitoring of transdermal end-tidal CO_2, capillary blood gases (P_aO_2, P_aCO_2, pH, base excess, lactate), and peripheral blood oxygen saturation (SpO_2). Signs of inflammation in children that can

kill (SICK) score will be calculated from physical exam and SpO_2 data. The amount of oxygen used from a cylinder during Period 1 through 2 will be measured.

The study design is illustrated below.

Figure 4. Illustration of Study Design



4.2 Outline of Schedule

4.2.1 Screening and Baseline Evaluations:

4.2.1.1 Screening Evaluations

The following screening assessments must be done to determine eligibility for study participation. Written consent from parents(s)/guardian(s) will be obtained before conducting any study procedures.

- Screen for age and weight entry criteria (see Section 5).
- Medical history.
- Physical examination including body weight.
- Severe pneumonia (based on WHO criteria).
- Peripheral blood oxygen saturation (SpO_2) by pulse oximetry on air.
- Capillary blood gas with lactate (P_aO_2, P_aCO_2, pH, base excess, lactate) to evaluate for acidosis and hypercapnia.
- Completion of SICK score form (based on physical exam and SpO_2) data.
- Rapid hemoglobin and complete blood count (CBC).

- Malaria rapid diagnostic test.
- Point of care blood glucose.
- Comprehensive metabolic panel will be obtained *only* if indicated as part of standard care.

4.2.1.2 Baseline (Pre-treatment) Evaluations

Once eligibility criteria are met, baseline assessments are obtained. Any baseline assessment obtained during the Screening period will be used as the baseline value.

- Vitals signs and capillary refill time.
- Record concomitant medication information.
- Determine mask size to be used in line with body weight. Patients with a body weight of 8-13 kg will receive treatment with a small 30 ml mask and patient with a body weight of 14-26 kg will receive treatment with a large 50 ml mask.
- Peripheral blood oxygen saturation (SpO_2) by pulse oximetry on oxygen.

4.2.2 Investigational Treatment Periods

4.2.2.1 Period 1

Patients will be placed on supplemental oxygen consistent with standard of care.

(Group A): Nasal Reservoir plus Nasal Cannula (1 hr duration)

(Group B): Nasal Cannula (1 hr duration)

- Continuous monitoring of peripheral blood oxygen saturation (by pulse oximetry) with recordings every 15 min.
- Continuous end-tidal carbon dioxide (CO_2) monitoring with recordings every 15 min.
- Record vital signs every 15 min.
- Record oxygen flow (L/min) every 15 min.
- Record concomitant medication information.
- Record adverse event information.
- Physical examination, including capillary refill time; capillary blood gases (PaO_2, $PaCO_2$, pH, base excess, lactate); and completion of SICK score form *at end of Period 1*.

4.2.2.2 Period 2

(Group A): Nasal Cannula Alone (1 hr duration)

(Group B): Nasal Reservoir and Cannula Alone (1 hr duration)

- Continuous monitoring of peripheral blood oxygen saturation (by pulse oximetry) with recordings every 15 min.
- Continuous end-tidal carbon dioxide (CO_2) monitoring with recordings every 15 min.
- Record vital signs every 15 min.
- Record oxygen flow (L/min) every 15 min.
- Physical examination, including capillary refill time; capillary blood gases (PaO_2, $PaCO_2$, pH, base excess, lactate); and completion of SICK score form *at end of Period 2*.

5 DISCUSSION OF DESIGN

The study is an open-label, prospective, feasibility study of hospitalized pediatric patients with hypoxemia due to severe pneumonia. Patients meeting entry criteria will receive supplemental oxygen consistent with standard of care. Patients will be equally randomized to one of two groups. Group A will receive supplemental oxygen for 1 hr using a novel mask (nasal reservoir cannula) plus standard nasal cannula for 1 hr, followed by a 1 hr period using the standard nasal cannula only. Group B will receive treatment in the reverse order (treatment with standard nasal cannula alone for 1 hr followed by a 1-hr period of novel nasal reservoir cannula plus nasal cannula). Patients with a body weight of 8-13 kg will receive treatment with a small 30 ml mask and patient with a body weight of 14-26 kg will receive treatment with a large 50 ml mask.

The design of this study is consistent with the primary objective of collecting preliminary information to aid in the conduct of a more definitive trial evaluating the safety and efficiency of a novel nasal mask plus nasal cannula (vs. nasal cannula alone) in reducing the total amount of oxygen needed per cylinder for adequate oxygen delivery in pediatric patients with hypoxemic respiratory illness in resource-limited settings. Information on the feasibility of intervention delivery and implementation, trial conduct, availability of patients and recruitment rates, protocol adherence, and effect sizes and outcomes to guide future power calculations and designs will be of value in the design of future trials. The assessments used in this trial are standard assessments for the evaluation of pediatric patients with hypoxemia and severe pneumonia.

6 STUDY POPULATION

The investigators and treating physicians participating in this study have expertise in the diagnosis and management of pediatric patients with hypoxemia and severe pneumonia. The participating institution is the Department of Pediatrics, Makerere University, Kampala, Uganda.

Subjects with hypoxemia and pneumonia will be diagnosed based on history, physical examination, and laboratory indices. Inclusion criteria for this study include patients (age ≥ 1 year and ≤ 6 years) with severe pneumonia based on WHO criteria that require hospitalization and have hypoxemia (SpO_2 <94%) by pulse oximetry on air.

Participation in this study is voluntary. The nature of the study will be fully explained to each parent(s)/guardian(s) of the patient during the informed consent process. Both verbal and written explanations will be provided to ensure understanding at all literacy levels. The parent(s)/guardian(s) will have the opportunity to ask questions. The participant information sheet and informed consent document (see Appendix E) will be available in English and Luganda. Parents unable to write may document consent with a thumbprint. The informed consent document will then be signed by the patient's parent(s)/guardian(s) and the person performing the consent discussion, and retained by the investigator according to Good Clinical Practice (GCP) guidelines. All documents will be retained at the study site for 3 years beyond study completion according to GCP guidelines. A copy of the signed informed consent (and any signed assent) document will be given to the subject or their parent(s)/guardian(s), or both.

Eligibility for enrollment will be based on the results of screening for the following inclusion and exclusion criteria.

6.1 Inclusion Criteria

Patients may be included in the study only if they meet **all** of the following criteria:

[1] Age ≥ 1 and ≤ 6 years.

[2] Severe pneumonia based on WHO criteria (see Appendix B).

[3] SpO_2 ≥ 85% and < 94% by pulse oximetry on room air.

[4] Hospital admission based on clinician judgment.

[5] Written informed consent from parent(s)/guardian(s) of subjects must be obtained before any study procedure is performed.

[6] Body weight ≥ 8 kg and ≤ 26 kg

Exclusion Criteria:

Patients meeting any of the following criteria **will not** be eligible to participate in the study:

[1] Hypercapnia (pCO_2 > 55 mm Hg or 7.32 kPa) on room air

[2] Acidosis / lactic acidosis (pH <7.20 and/or lactate >3 mmol/L) on room air

[3] SpO_2 < 85% or ≥ 94% by pulse oximetry on room air

[4] SICK score > 2.4

[5] Hemoglobin < 7 g/dL

[6] Facial abnormalities or trauma precluding use of mask and nasal prongs.

[7] Requirement of intubation or noninvasive or invasive positive-pressure ventilation.

[8] Suspected or known pneumothorax.

[9] Body weight < 8 kg and > 26 kg

[10] Hemodynamic instability based on clinician judgment.

[11] SpO_2 < 90% by pulse oximetry on oxygen, measured at the end of the enrollment and before initiation of Period 1.

6.2 Removal of Subjects from Investigational Device Treatment or Assessment

6.2.1 Early Discontinuation of Investigational Device Treatment

A subject must prematurely discontinue investigational device (nasal reservoir cannula) treatment under any of the following circumstances:

- The subject's parent(s)/guardian(s) wishes investigational device treatment to be discontinued for any reason.
- The investigator wishes the subject to discontinue investigational device treatment, especially, but not limited to the investigator concluding that further treatment puts the subject at unacceptable risk.
- The subject develops a condition or begins a therapy that would have excluded entry into the study (e.g., hypercapnia, acidosis, hemodynamic instability, requirement of intubation or positive pressure ventilation).

A parent(s)/guardian(s) has the right for the subject to discontinue investigational device treatment at any time for any reason without prejudice to current or future medical care by the investigator or other physician at the institution.

6.2.2 Subject Withdrawal from the Study

A subject must be withdrawn from the study (and discontinue any investigational device treatment) if the subject's parent(s)/guardian(s) requests such study discontinuation. The

reason for withdrawal must be recorded in the subject's case reporting form (CRF). Subjects who withdraw from the study will not be replaced.

7 TREATMENTS

7.1 Subject Assignment

After informed consent documents are signed, patients who meet all eligibility criteria will begin study treatment.

7.2 Method of Assignment to Treatment

This is an open-label trial and each subject will sequentially receive supplemental oxygenation followed by sequential periods of both investigational treatment (nasal reservoir cannula plus nasal cannula) and standard of care treatment (supplemental oxygenation through nasal cannula alone). Patients will be randomized so that the order of initial treatment (nasal reservoir cannula plus nasal cannula vs. nasal cannula) is balanced between subjects. Patients with a body weight of 8-13 kg will receive treatment with a small 30 ml mask and patients with a body weight of 14-26 kg will receive treatment with a large 50 ml mask. All subjects will receive standard of care for their underlying disease according to WHO recommendations, including availability of standardized care of oxygen therapy.

8 ADVERSE EVENT REPORTING

8.1 Definition of Adverse Event

For purposes of this trial, an adverse event (AE) will be defined as **any** new unfavorable or unintended sign, symptom, or disease or change of an existing condition, which occurs during or after treatment, whether or not considered treatment-related. If clinically significant laboratory values lead to or are associated with clinical symptom(s), the diagnosis should be reported as an AE. Lack of treatment effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish (or evaluate for) a treatment effect.

8.1.1 Reporting Procedures for All Adverse Events

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the subject to discontinue the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up is left to the discretion of the investigator.

Adverse event information will be collected through the study period. The investigator is responsible for assessing and recording all AEs. Each AE will be recorded and classified for intensity, seriousness, and causality. All AEs either observed by the investigator or reported by the subject will be recorded regardless of causality. The investigator will follow the subject until an AE resolves or stabilizes.

8.1.2 Adverse Event Relationship to Study Treatment or Procedure

The relationship of an AE to the study treatment or procedure should be based on the judgment of the investigator and assessed using the following the guidelines:

- Definitely: Previously known toxicity of study treatment or procedure; or an event that follows a reasonable temporal sequence from administration of the study treatment or procedure; that follows a known or expected response pattern to the suspected study treatment or procedure; that is confirmed by stopping or reducing the dosage of the study treatment or procedure; and that is not explained by any other reasonable hypothesis.
- Probably: An event that follows a reasonable temporal sequence from administration of the study treatment or procedure; that follows a known or expected response pattern to the suspected study treatment or procedure; that is confirmed by stopping or reducing the dosage of the study treatment or procedure; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
- Possibly: An event that follows a reasonable temporal sequence from administration of the study treatment or procedure; that follows a known or expected response pattern to

that suspected of study treatment or procedure; but that could readily have been produced by a number of other factors.

- Unrelated: An event that can be determined with certainty to have no relationship to the study treatment or procedure.

8.1.3 Serious Adverse Event Definition and Reporting Procedures

For purposes of this trial, a serious adverse event (SAE) is defined as an AE that suggests a significant hazard or side effect, regardless of the relationship to study treatment. An SAE includes, but may not be limited to, any event that:

- Results in death.
- Is life-threatening. This definition implies that the subject, in the view of the investigator, is at immediate risk of death from the event. It does not include an event that, had it occurred in a more serious form, might have caused death.
- Requires inpatient hospitalization or prolongs existing hospitalization.
- Results in persistent or significant disability/incapacity.

Any SAE that meets the above definition and occurs in a subject during the course of the study must be reported to the sponsor by telephone within 24 hours of the investigator becoming aware of the event. In addition, a SAE reporting form must be completed by the investigator and faxed to the study sponsor within 24 hours of the investigator becoming aware of the event. In addition, the site investigator must report SAEs to their local Institutional Review Board/Institutional Ethics Committee (IRB/IEC) in accordance with the IRB/IEC's standard operating procedures and policies.

Medical and scientific judgment will be exercised in deciding whether classification of an adverse event as serious is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the outcomes listed in the definition above. These should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependence or abuse.

Please refer to the Data and Safety Monitoring Plan (Appendix H) for further details, including stopping rules.

8.1.4 Laboratory Tests

Clinical laboratory tests will be performed at the times specified in the Study Schedule (see Appendix A) and will follow the local and regular protocol for patients with respiratory distress. All clinical laboratory assessments will be analyzed at the participating site's local laboratory. Clinically significant laboratory abnormalities (see Appendix F), which

are new or worsen during the study period, will be reported as AEs or SAEs as appropriate based on the above definitions.

8.1.5 Withdrawal due to Worsening of Clinical Status

An individual subject will be withdrawn from the study if he or she develops a condition or begins a therapy during the study period that would have excluded entry into the study (e.g., hypercapnia, acidosis, SICK score >2.4, hemodynamic instability, requirement of intubation or positive pressure ventilation, SpO_2 < 90% on oxygen). Additionally, the on-site pediatrician/Co-Principal Investigator may discontinue investigational device treatment at any time if she feels that further treatment puts the subject at unacceptable risk.

9 QUALITY CONTROL AND QUALITY ASSURANCE

The investigator agrees to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standard of GCP; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator must allow study-related monitoring, audits, and inspection by the IRB/IEC, sponsor (or designee), government regulatory agencies, and, if applicable, University compliance and quality assurance groups of all trial-related documents and procedures.

The investigator shall prepare and maintain accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations.

10 DATA ANALYSIS METHODS

10.1 Determination of Sample Size

The target sample sizes for this study (up to 20 patients) are consistent with feasibility studies for other clinical interventions (Billingham et al., 2013).

10.2 Efficacy Variables

10.2.1 Signs of Inflammation in Children that can Kill (SICK) Score

The SICK score is a severity of illness score that incorporates vital signs, oxygenation (SpO_2), age, and physical examination information (mental status, capillary refill time) with associated weighting for each variable to provide a score from 1 to 7 (Kumar et al, 2003). The SICK score, which can be easily calculated, was initially intended to provide a severity of illness score to prioritize care for more sick children who needed urgent management in resource-limited settings. In resource-limited settings, the SICK score has paralleled clinical recovery or deterioration during therapy in hypoxemic children with respiratory illness (Turnbull et al, 2016).

10.2.2 Laboratory Efficacy Parameters

Laboratory efficacy parameters related to oxygenation will be collected by continuous monitoring of peripheral blood oxygen by pulse oximetry (SpO_2); continuous transdermal end-tidal carbon dioxide (CO_2) monitoring; capillary blood gases (e.g., SpO_2, P_aO_2, P_aCO_2, pH, base excess); and blood lactate.

10.3 Safety Variables

Safety evaluations will include collection of adverse event, physical examination, vital sign, and clinical laboratory data. Hemoglobin rapid test, malaria rapid test, and blood glucose (point of care) will be obtained along with complete blood count (CBC), which may include hemoglobin, hematocrit, erythrocyte or red blood cell count (RBC), mean cell volume (MCV), segmented neutrophils, juvenile neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, cell morphology, reticulocyte count.

Metabolic panel will be done based on local standard of care for patients with respiratory distress, but may include evaluation of

- Metabolic panel: Serum concentrations of sodium, potassium, chloride, total bilirubin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin.

Safety evaluation will also involve the collection of data from: continuous transdermal end-tidal carbon dioxide (CO_2) monitoring, capillary blood gases (P_aO_2, P_aCO_2, pH, base excess), peripheral blood oxygen saturation (SpO_2), and blood lactate.

10.4 Oxygen Cylinder Use and Flow

The amount of oxygen (L) used from a cylinder and average oxygen flow (L/min) during Period 1 through 2 will be collected or calculated.

10.5 Statistical and Analytical Plans

10.5.1 General Considerations

The full analysis population will include all randomly assigned subjects who have received study treatment. All variables will be summarized by descriptive statistics for each treatment group. The statistics for continuous variables will include mean, median, standard deviation, and number of observations. Categorical variables will be tabulated using frequencies and percentages.

10.5.2 Handling of Missing Data

Missing data will not be imputed.

10.5.3 Subject Disposition

Study subject disposition will be summarized by treatment group. Subjects who discontinued study drug prematurely or withdrew from the study will be summarized and listed, with reason for early termination/withdrawal.

10.5.4 Subject Characteristics

Demographic and other baseline characteristics will be summarized by treatment group.

10.5.5 Efficacy Analyses

Data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum and maximum) for continuous variables and frequency and percentages of categorical variables. Tests of significance will be done only on an exploratory basis.

10.5.6 Safety Analyses

Treatment-emergent AEs are defined as AEs occurring after the first initiation of treatment until completion of treatment. Duration of treatment will be summarized by treatment group. The incidence of all reported AEs and treatment-related AEs will be tabulated by treatment group. AEs will be classified by system organ class and verbatim term.

AEs will be listed and summarized by treatment group, verbatim term, severity, seriousness, and relationship to study drug. In the event of multiple occurrences of the same AE with the same verbatim term in one subject, the AE will be counted once as the worst occurrence. The incidence of AEs will be tabulated by system organ class and

treatment group. AEs leading to premature discontinuation of study drug or withdrawal from the study will be summarized and listed in the same manner.

10.5.7 Stopping Rules

A comprehensive evaluation of data relevant to stopping rules will occur after enrollment of the first 10 participants. This study will be stopped at this time if: (1) the majority of investigators find that the harm to study participants outweighs the benefit of the scientific evidence to be accrued by continuing the trial; (2) new information from sources outside the trial provides definitive information that the intervention is effective or harmful; (3) any new information becomes available that necessitates stopping the trial; and (4) other situations occur that might warrant stopping the trial.

11 ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

The investigator is responsible for presenting the risks and benefits of study participation to the subject's parent/guardian or legally authorized representative in simple terms using the informed consent document. The investigator will ensure that written informed consent is obtained from each parent/guardian or legally authorized representative by obtaining the appropriate signatures and dates on the informed consent document before the performance of protocol evaluations or procedures.

11.1 Ethical Review

The sponsor will obtain documentation by the applicable local IRB/IEC of approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing IRB/IEC are provided in the investigator file.

The sponsor will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments.
- Informed consent document and updates.
- Relevant curricula vitae, if required.
- Required safety and SAE reports.
- Any additional submissions required by the site's IRB/IEC.

The sponsor will retain the following documentation, if applicable:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

11.2 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the 2013 version of the Declaration of Helsinki or the applicable guidelines on GCP, and all applicable federal, state, and local laws, rules, and regulations.

All data recorded in the CRF for subjects participating in this study will be transcribed from medical records. After reading the protocol, the investigator will sign the protocol signature page and return it to the sponsor or designee.

11.2.1 Investigator Information

The contact information and qualifications of the principal investigator and sub-investigators, and name and address of the research facilities are included in the investigator file.

11.2.2 Protocol Amendments and Study Termination

The sponsor will initiate changes to the protocol as necessary (with the exception of changes to eliminate an immediate hazard to a study subject) and seek approval by the IRB/IEC prior to implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol violations must be reported to the local IRB in accordance with IRB policies. The sponsor may terminate the study at any time. The IRB must be advised in writing of study completion or early termination.

11.2.3 Study Documentation, Privacy, and Records Retention

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the investigator for a minimum of 5 years (or longer if required by the local IRB/IEC).

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the applicable regulatory agencies and applicable IRB/IEC with direct access to original source documents.

Records containing subject medical information must be handled in accordance with the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and consistent with the terms of the subject authorization contained in the informed consent document for the study. Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the informed consent document. Furthermore, CRFs and other documents should be completed in strict accordance with the instructions provided by the sponsor-investigator, including the instructions regarding the coding of subject identities.

11.3 Study Finances

This study is financed through Global Good/Intellectual Ventures. Global Good/Intellectual Ventures holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies, which apply to this trial.

11.4 Publications

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

12 REFERENCES

American Thoracic Society, 2015. Oxygen sources and delivery devices. Accessed at: https://www.thoracic.org/copd-guidelines/for-health-professionals/management-of-stable-copd/long-term-oxygen-therapy/oxygen-sources-and-delivery-devices.php.

Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC Med Res Methodol*. 2013; 13:104.

Catto AG, Zgaga L, Theodoratou E, et al. An evaluation of oxygen systems for treatment of childhood pneumonia. *BMC Public Health*. 2011;11 Suppl 3:S28.

Coghill M, Ambalavanan N, Chatburn RL, et al for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Global Network for Women's and Children's Health Research. Accuracy of a Novel System for Oxygen Delivery to Small Children. *Pediatrics*. 2011; 128(2): e382–e387.

Djelantik IG, Gessner BD, Sutanto A, et al. Case fatality proportions and predictive factors for mortality among children hospitalized with severe pneumonia in a rural developing country setting. *J Trop Pediatr*. 2003; 49(6):327-32.

Duke T, Keshishiyan E, Kuttumuratova A, et al. Quality of hospital care for children in Kazakhstan, Republic of Moldova, and Russia: systematic observational assessment. *Lancet*. 2006, 367 (9514): 919-925.

Duke T, Graham SM, Cherian MN, et al the Union Oxygen Systems Working Group. Oxygen is an essential medicine: a call for international action. *Int J Tuberc Lung Dis*. 2010; 14(11): 1362–1368.

Ginsburg AS, Delarosa J, Brunette W, et al. mPneumonia: Development of an innovative mHealth application for diagnosing and treating childhood pneumonia and other childhood illnesses in low-resource settings. *PLoS One*. 2015;10(10):e0139625.

Hoffman LA. Novel strategies for delivering oxygen: reservoir cannula, demand flow, and transtracheal oxygen administration. *Respir Care.* 1994; 39: 363-376.

Kumar N, Thomas N, Singhal D, Puliyel JM, Sreenivas V. Triage score for severity of illness.*Indian Pediatr*. 2003;40(3):204-10.

Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet*. 2015; 385(9966):430–40.

Modi P, Munyaneza RB, Goldberg E, et al. Oxygen saturation can predict pediatric pneumonia in a resource-limited setting. *J Emerg Med*. 2013;45(5):752-60.

Soffer M, Tashkin DP, Shapiro BJ, et al. Conservation of oxygen supply using a reservoir nasal cannula in hypoxemic patients at rest and during exercise. *Chest* 1985; 88:663-668.

Tiep B, Carter R. Portable oxygen delivery and oxygen conserving devices. In: *UpToDate*, Stoller JK (Ed), UpToDate, Waltham, MA. (Accessed on May 26, 2016).

Turnbull H, Conroy A, Opoka RO, Namasopo S, Kain KC, Hawkes M. Solar-powered oxygen delivery: proof of concept. *Int J Tuberc Lung Dis*. 2016 20(5):696-703.

World Health Organization 2013. Pocket book of hospital care for children. Guidelines for the management of common illnesses with limited resources, 2nd ed. WHO: Geneva, Switzerland

World Health Organization 2015. Pneumonia. Fact sheet N°331. Accessed at: http://www.who.int/mediacentre/factsheets/fs331/en/

World Health Organization 2016a. Epidemiology and etiology of childhood pneumonia. Accessed at: http://www.who.int/bulletin/volumes/86/5/07-048769/en/

World Health Organization 2016b. *Oxygen therapy for children.* WHO: Geneva, Switzerland.

APPENDIX A:
SCHEDULE OF EVENTS

Activity	Screening	Period 0 (Baseline)	Period 1 (1 hr)	Period 2 (1 hr)
		Group A	Nasal reservoir + nasal cannula	nasal cannula
		Group B	Nasal cannula	Nasal reservoir + nasal cannula
Recruitment/Informed Consent	X			
Medical history	X			
Physical examination	X		X (end of period)	X (end of period)
Severe pneumonia (based on WHO criteria) [a]	X			
SpO_2 85-93% on room air (pulse oximetry)	X			
Capillary blood gas with lactate	X		X (end of period)	X (end of period)
Signs of inflammation in children that can kill (SICK) score	X		X (end of period)	X (end of period)
Hemoglobin rapid test	X			
Complete blood count (hematology panel)	X			
Malaria rapid diagnostic test	X			
Blood glucose (point of care)	X			
Comprehensive metabolic panel [b]	X			
Determine nasal reservoir size		X [d]		
SpO_2 >90% on oxygen (pulse oximetry)		X		
Vital signs [c]		X [f]	record values every 15 min	
Record concomitant medication information		X	X	X
Continuous transdermal end-tidal CO_2 monitoring			record values every 15 min	
Continuous SpO_2 monitoring (during supplemental O_2)			record values every 15 min	
Record oxygen flow (L/min)			record values every 15 min	
Record adverse event information			X	X

a. Severe pneumonia based on World Health Organization criteria (Appendix B).
b. Comprehensive metabolic panel will be obtained only if indicated as part of standard of care.
c. Vitals signs: blood pressure, respiratory rate, heart rate, and temperature. Obtain at baseline (pretreatment) and every 15 minutes from the beginning of Period 1 through end of Period 2. Any values obtained during Screening period may be used as Baseline values.
d. Patients with a body weight of 8-13 kg will receive treatment with a small 30 ml mask and patients with a body weight of 14-26 kg will receive treatment with a large 50 ml mask.

APPENDIX B:

World Health Organization (WHO) Definition of Severe Pneumonia

(World Health Organization 2013)

Sign or symptom	Classification	Treatment
Cough or difficulty in breathing with: ■ Oxygen saturation < 90% or central cyanosis ■ Severe respiratory distress (e.g. grunting, very severe chest indrawing) ■ Signs of pneumonia with a general danger sign (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions)	**Severe pneumonia**	– Admit to hospital. – Give oxygen if saturation < 90%. – Manage airway as appropriate. – Give recommended antibiotic. – Treat high fever if present.

APPENDIX C:

SIGNS OF INFLAMMATION IN CHILDREN THAT CAN KILL (SICK) SCORE

(from Kumar et al., 2003)

Table 1: Scoring of abnormal clinical variables[7]

Variable	Abnormal range
Temperature	>38°C < 36°C
Heart rate	Infant >160 per minute Child >150 per minute
Respiratory rate	Infant >60 per minute Child >50 per minute
Systolic blood pressure	Infant <65 mm Hg Child <75 mm Hg
SpO_2	<90%
Capillary refill time	≥3 seconds
A Alert	Anyone except A
V Responds to voice	
P Responds to pain	
U Unresponsive	

Based on SIRS and APLS[8,9]

Table 2: Weight (Regression coefficient) for each variable* developed in previous study[7]

Variable	Weight
Heart rate	0.2
Respiratory rate	0.4
Blood pressure (systolic)	1.2
Temperature	1.2
SpO_2	1.4
Capillary filling time	1.2
AVPU	2.0
Age (months)	
≥ 60	0.0
≥ 12 to <60	0.3
≥ 1 to <12	1.0
<1	2.2

*Based on multiple logistic regression analysis

APPENDIX D
PROTOCOL SIGNATURE PAGE

By signing this protocol, the investigator agrees to conduct the study in accordance with the protocol, generally accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study. In addition, the investigator agrees to provide the sponsor-investigator with accurate financial information to allow the sponsor to submit complete and accurate certification and disclosure statements as required by regulations.

By signing this protocol, the sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written procedures to ensure that the trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the study.

Investigator's Signature	Print Name	Date
Investigator's Signature	Print Name	Date
Site Address and Telephone		
Sponsor's Medical Expert's Signature		Date

APPENDIX E
MASK FEASIBILITY STUDY
PARTICIPANT INFORMATION SHEET AND CONSENT FORM

STUDY TITLE: A Feasibility Study Evaluating a Novel Mask (Nasal Reservoir Cannula) Plus Standard Nasal Cannula vs Standard Nasal Cannula Alone for Supplemental Oxygen Delivery in the Treatment of Hospitalized Pediatric Patients with Hypoxemia Due to Severe Pneumonia

Investigators and Collaborators	*Institutions*
Michael Hawkes	*University of Alberta, Edmonton, Canada*
Akos Somoskovi	*Global Good/Intellectual Ventures Laboratory, Bellevue, WA, USA*
Hellen Aanyu-Tukamuhebwa	*Department of Paediatrics and Child Health, Mulago National Referral Hospital and College of Health Sciences, Makerere University*
Ezekiel Mupere	*Department of Paediatrics and Child Health, College of Health Sciences, Makerere University*
Alfred Onubia Andama	*Department of Medicine, College of Health Sciences, Makerere University*

Who is carrying out this study?

Investigators and collaborators from the Department of Pediatrics and Child Health at Mulago Hospital, and Makerere University are carrying out this project. All research at Makerere University must be approved by the Institutional Review Board, who carefully evaluate research, and must agree that it is important, relevant, follows nationally and internationally agreed research guidelines, and that it will be conducted properly and participants' safety and rights are being respected.

What is this study about?

In this study, we are looking at how oxygen (a clean, odorless gas necessary for life) is given to children with low oxygen levels due to lung infections like pneumonia. We want to learn more about a new device that is loosely worn over the nose (nasal mask), and used to decrease the total amount of oxygen needed for adequate oxygen supply in sick children with low oxygen levels due to lung infections like pneumonia. Twenty children will be enrolled in the study.

Why do you want my child to participate and what does it involve?

You are being asked to allow your child to participate in a study that will help us assess whether the new nasal mask added over the standard method of care (nasal cannula: a lightweight tube with two prongs placed in the nose to provide a mixture of air and oxygen) can safely and adequately deliver oxygen. Since your child has low oxygen levels and is being admitted for treatment, we would like to enroll your child. Your child will receive the same treatment as children not enrolled in the study. In addition to what is normally provided to patients, additional physical and blood testing will occur to ensure safety of your child. These additional safety and monitoring tests for your child are not normally provided during routine care at Mulago Hospital. For children in this study, a Study Nurse will complete a form to collect information about your child's hospitalization, including how your child's body is working, what problems are causing your child to be sick, and any

treatments given to your child.

All of your child's study records will be kept private. Your child will be assigned a study ID number and your name will not be used. We will only refer to you by an identification number. All of your child's records will be kept in a locked filing cabinet at Mulago Hospital. Only people working on the study will be able to look at these records. Any reports that come out of this study will not have your child's name or anything that could identify your child.

What happens during the study?

During the study your child will use the conventional nasal cannula alone for 1 hour and will use the nasal cannula with the mask placed over it for a second hour. The order in which your child will receive the mask in combination with the nasal cannula either during the first or during the second hour will be randomized, which means using chance methods (like flipping a coin) to assign patients the order of treatment. After the two-hour test period, oxygen treatment will be continued with the standard nasal cannula alone. The mask is unique in that its form and fit provide more nasal coverage to the patient while loosely sitting on the nose. This means that the mask takes up more space over your child's nose (and goes onto their cheeks), but it is not tightly secured. The study pediatrician or nurse will need to draw blood three times during the study (once at the beginning, once after the first hour wearing the cannula or mask + cannula, and once at the end). Some of these blood tests are done as part of standard care but some are done in addition to standard care to ensure your child's safety. The extra tests are called blood gases. These tests measure the oxygen and carbon dioxide levels in your child's blood, which helps doctors, monitor your child's health while they are receiving oxygen therapy. Other tests include oxygen monitoring, which is done via a tiny pain-free device attached to the skin; a physical exam, which includes simple tests like listening to their lungs and measuring their weight; and additional tests like heart rate, temperature, respiratory rate, and blood pressure.

Are there any risks or disadvantages to my child taking part?

There is a small possibility that the device may not deliver oxygen as well as the standard device. Your child will be monitored continuously during the study to detect any medical problems, such as a drop in the oxygen level. Your child will receive the same clinical care as children not enrolled in the study as well as additional physical and blood testing to ensure their safety. The nasal mask may be slightly uncomfortable for your child, but should not cause any pain. The additional physical tests like oxygen monitoring will not cause any pain. Your child may experience minor discomfort (like a finger prick) from the four blood draws (two at the beginning, one in the middle, one at the end). The total amount of blood drawn will be minimal (up to 1 teaspoon), and follows recommendations from medical experts, which are based on the weight of your child.

Are there any advantages to my child taking part?

The information we collect during this study will help us assess the novel nasal cannula's ability to safely and efficiently administer oxygen. For this study, the novel nasal cannula will be tested for 1 hour followed by the standard nasal cannula. Once this study is completed and the equipment is improved, a subsequent research study may help us learn if efficient oxygen helps patients have improved health outcomes or a shorter

hospital stay in the future. This may potentially help other children in Uganda and elsewhere in the future, for example, through access to better equipment and treatments.

Who will have access to my child's information?

We will not share individual information about your child with anyone beyond a few people who are closely concerned with the research. All of our documents are stored securely in locked cabinets and on password-protected computers. The knowledge gained from this research will be shared in summary form, without identifying any child by name.

What will happen if I refuse for my child to participate?

All participation in research is voluntary. You are free to decide if you want to take part or not. If you do agree you can change your mind at any time without any consequences.

Who pays for the study and what happens if my child is injured?

This investigation is covered by insurance policies that apply to this trial. If your child experiences harm or injury as a result of taking part, you may be eligible to claim compensation. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information, or if you wish to complain or have any worries about how your child has been treated, you should tell the Investigator, Dr. Hellen Aanyu-Tukamuhebwa, at the phone number below right away.

What if I have any questions?

You are free to ask me any question about this research. If you have any further questions about the study, you are free to contact the research team using the contacts below:

Dr. Hellen Aanyu-Tukamuhebwa, Mulago National Referral Hospital, P.O. Box 21846, Kampala, Uganda, +256 712 657096 / 759 969195

If you want to ask someone independent anything about this research please contact:
The Chairperson - Mulago Hospital Research and Ethics Committee, Dr. Fredrick Nelson Nakwagala, nakwagala@yahoo.com, +256-772-325-869/ 717-850-448

Consent Form for: A Feasibility Study Evaluating a Novel Mask (Nasal Reservoir Cannula) Plus Standard Nasal Cannula vs Standard Nasal Cannula Alone for Supplemental Oxygen Delivery in the Treatment of Hospitalized Pediatric Patients with Hypoxemia Due to Severe Pneumonia

I have had the study explained to me. I have understood all that has been read/explained and had my questions answered satisfactorily.

Yes *please tick* **I agree for my child to participate in this study**

I understand that I can change my mind at any stage and it will not affect my child or me in any way.

Signature: _____ **Date:** _____

Participant's Initials: _____ **Time:** _____
(Please print initials if parent can write)

I have explained the purpose of this study to the volunteer. To the best of my knowledge, he/she understands the purpose, procedures, risks and benefits of this study.

_____	_____	_____
Investigator/Designee Name *Type or print*	Investigator/Designee Signature	Date

Only necessary if the parent/guardian cannot read:

I* attest that the information concerning this research was accurately explained to and apparently understood by the parent/guardian and that informed consent was freely given by the parent/guardian.

Witness' signature: _____ **Date** _____

Witness' name: _____ **Time** _____
(Please print name)

***A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.**

Thumbprint of the parent as named above if they cannot write: _____

NOTE: This consent form, with original signatures, must be retained on file by the Principal Investigator. A copy must be given to the participant.

Appendix F:
Serious Adverse Event Reporting Form

Protocol Title: A Feasibility Study Evaluating a Novel Mask (Nasal Reservoir Cannula) Plus Standard Nasal Cannula vs Standard Nasal Cannula Alone for Supplemental Oxygen Delivery in the Treatment of Hospitalized Pediatric Patients with Hypoxemia Due to Severe Pneumonia	
Pt_IP number: _____ **Study ID number:** _____	

1. SAE Onset Date: _____ (dd/mm/yyyy)
2. SAE Stop Date: _____(dd/mm/yyyy)
3. Location of serious adverse event: _____
4. Was this an unexpected adverse event? Yes ☐ No ☐
5. Brief description of participant(s) with no personal identifiers:
   Sex: F ☐ M ☐ Age: _____
6. Brief description of the nature of the serious adverse event (attach description if more space needed): _____
   _____
7. Category of the serious adverse event:

   ☐ death – date __/___/___(dd/mmm/yyyy)
   ☐ life-threatening
   ☐ hospitalization-initial or prolonged
   ☐ disability / incapacity
   ☐ congenital anomaly / birth defect
   ☐ required intervention to prevent permanent impairment
   ☐ other:_____
8. Intervention type:

   ☐ Medication or Nutritional Supplement: specify_____
   ☐ Device: Specify: _____
   ☐ Surgery: Specify: _____
   ☐ Behavioral/Life Style: Specify: _____

9. Relationship of event to intervention:

- ☐ Unrelated (clearly not related to the intervention)
- ☐ Possible (may be related to intervention)
- ☐ Definite (clearly related to intervention)

10. Was study intervention discontinued due to event? ☐ Yes ☐ No

11. What medications or other steps were taken to treat serious adverse event?

_____

_____

12. List any relevant tests, laboratory data, history, including preexisting medical conditions

_____

_____

13. Type of report:

- ☐ Initial
- ☐ Follow-up
- ☐ Final

Signature of Principal Investigator: _____ Date: _____

APPENDIX G
LABORATORY REFERENCE RANGES

iSTAT CG4 reportable ranges		
Lab Value	Reportable Range (units)	Lowest allowable values in data base
pH	6.5 – 8.2	6.4
BE	-30-+30mmol/L	-29
pCO_2	5 – 130 (mm Hg)	4.9
pO_2	5 – 800 (mm Hg)	4.9
HCO_3	1.0 – 85.0 (mmol/L)	0.9
Total CO_2	5 – 50 (mmol/L)	4.9
Lactate	0.30 – 20.0 (mmol/	0.2

iSTAT Chem8+ reportable ranges		
Lab Value	Reportable Range (Conventional Units)	Lowest Values allowed in data base
Sodium	100-180(mmol/L)	
Potassium	2.0-9.0(mmol/L)	
Chloride	65-140(mmol/L)	
Ionized Calcium	0.25-2.50(mmol/L)	0.2
Glucose	1.11-38.89(mmol/L)	1.0
BUN	1.07-49.98(mmol/L)	1.0
Creatinine	17.68-1768(µmol/L)	17
Anion Gap	-10-99(mmol/L)	-9.9
Total CO2	5-50(mmolL)	4.9
Hemoglobin	3.4-25.5(g/dL)	3.3
Hematocrit	10-75(% PCV)	9.9

AReportable Ranges for the ACutrend Lactometer, Glucometer and Haemocue

Lab Value	Point of Care Equipment	Reportable Range	Lowest value in data base
Lactate	ACutrend Lactometer	0.8 -22 Mmol/L	0.7
GLUCOSE	GLUCOMETER	1.1–33.3 Mmol/L	1.0
HAEMOGLOBIN	HAEMOCUE 301	0-25.6g/dl	1.0

APPENDIX H
Data and Safety Monitoring Plan

A. Confidentiality

1. Protection of Subject Privacy– During this study, a physical examination and blood tests will be performed. Data will be kept in strict confidence. No information will be given to anyone without permission from the parents of the participant. This statement guarantees confidentiality. Confidentiality is assured by use of study identification numbers. All clinical and laboratory data will be identified only by the study identification number unique to the subject. No participant specimens will be stored for future use.

2. Database Protection– The database is secured with password protection. The informatics manager receives only coded information, which is entered into the database under those identification codes. Electronic communication with outside collaborators involves only unidentifiable information.

3. Confidentiality during Adverse Event Reporting– Adverse event reports will not include subject-identifiable material. Each will include the study identification number only.

B. Adverse Event Information

1. Definitions- An adverse event (AE) will be defined as **any** new unfavorable or unintended sign, symptom, or disease or change of an existing condition, which occurs during or within 1 hour after treatment, whether or not considered treatment-related. If clinically significant laboratory values lead to or are associated with clinical symptom(s), the diagnosis should be reported as an AE. Lack of treatment effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish (or evaluate for) a treatment effect.

A serious adverse event (SAE) is defined as an AE that suggests a significant hazard or side effect, regardless of the relationship to study treatment. An SAE includes, but may not be limited to, any event that:

- Results in death.
- Is life-threatening. This definition implies that the subject, in the view of the investigator, is at immediate risk of death from the event. It does not include an event that, had it occurred in a more serious form, might have caused death.
- Requires inpatient hospitalization or prolongs existing hospitalization.
- Results in persistent or significant disability/incapacity.

2. Classification of AE Severity– AEs will be labeled according to severity, which is based on their impact on the patient, per this Event Grading Scale:

- Grade 1 Mild: Transient of mild discomfort; no limitation in activity; no medical intervention/therapy required.
- Grade 2 Moderate: Mild to moderate limitation in activity – some assistance may be needed; no medical intervention/therapy required.

- Grade 3 Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
- Grade 4 Life-threatening: Extreme limitation in activity, significant medical intervention/therapy required.

3. AE Attribution Scale– AEs will be categorized according to the likelihood that they are related to the study intervention. The relationship of an AE/SAE to the study treatment or procedure should be based on the judgment of the investigator and assessed using the following the guidelines:

- Definitely: Previously known toxicity of study treatment or procedure; or an event that follows a reasonable temporal sequence from administration of the study treatment or procedure; that follows a known or expected response pattern to the suspected study treatment or procedure; that is confirmed by stopping or reducing the dosage of the study treatment or procedure; and that is not explained by any other reasonable hypothesis.
- Probably: An event that follows a reasonable temporal sequence from administration of the study treatment or procedure; that follows a known or expected response pattern to the suspected study treatment or procedure; that is confirmed by stopping or reducing the dosage of the study treatment or procedure; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
- Possibly: An event that follows a reasonable temporal sequence from administration of the study treatment or procedure; that follows a known or expected response pattern to that suspected of study treatment or procedure; but that could readily have been produced by a number of other factors.
- Unrelated: An event that can be determined with certainty to have no relationship to the study treatment or procedure.

4. Expected Risks– Expected risks to the subjects are mild discomfort due to blood draws. These risks are considered to be minimal and are addressed in the protocol and consent form. There is minimal risk associated with the device.

This study involves a newly developed non-invasive investigational device, a nasal reservoir cannula that can significantly improve access to effective and safe oxygen therapy for children with respiratory distress. This device is an add on approach to be used in conjunction with a standard nasal cannula with prongs which will allow a more rational use of oxygen and in turn better adjustment of treatment to patient needs. The device does not replace the standard method of care of oxygen delivery via nasal cannula; therefore, it does not present any new or additional potential for serious risk to health, safety or welfare of subjects.

Potential risks might be that the subject develops a condition or begins a therapy that would have excluded entry into the study such as hypercapnia, requiring intubation or non-invasive or invasive positive–pressure ventilation, or suspected or known pneumothorax. It is important to note that these potential risks are independent of the investigational device

and might be a potential risk during any type of oxygen therapy. The study investigators have years of experience providing clinical care for children with respiratory problems and conducting clinical research in children.

5. SAE Reporting- SAEs that are unanticipated, serious (grades 3 and 4), and/or possibly related to the study intervention must be reported to the sponsor by telephone within 24 hours of the investigator becoming aware of the event. In addition, a SAE reporting form must be completed by the site PI and faxed to the sponsor within 24 hours of the PI becoming aware of the event. In addition, the site PI must report SAEs to the Mulago Research and Ethics Committee (MREC) in accordance with the MREC's standard operating procedures and policies. Anticipated SAEs or those unrelated to the study intervention will be reported to the same individuals/entities in accordance with requirements.

Sponsor phone numbers include: David Bell: +1 4254672300 or Christine Bachman +1 2539702040 (United States-based).

Investigator phone numbers include: Hellen Aanyu-Tukamuhebwa +256 712 657096 / 759 969195 (Uganda-based.
If abnormal lab values are discovered during the study, the site PI will be notified and will address this issue as early as possible. Clinically significant laboratory abnormalities (see protocol Appendix F), which are new or worsen during the study period, will be recorded and reported as AEs or SAEs as appropriate based on the above definitions. Abnormal lab values will be reported as AEs only when the site PI deems them to be clinically significant. For clinically significant laboratory abnormalities, a member of the local research team (site PI, study pediatrician, or study nurse) will provide a brief report on how the abnormal value was managed.

C. Data Quality and Safety Monitoring and Review Plan

1. Data Quality and Management

a. Description of Plan for Data Quality and Management– The study coordinator will review all data collection forms on an ongoing basis for data completeness and accuracy. A statement reflecting the results of the review will be sent to the sponsor at 6-month intervals. Data quality will be assessed using measures such as time from study visit to data entry, time to resolution of data queries, number of missing forms, and proportion of all study variables queried. Guidelines for concern regarding these measures are outlined below:

Measure	Goal Value	Acceptable Value
Time from visit to data entry	<1 week	<2 weeks
Time to resolution of queries	<2 weeks	<3 weeks
Percentage of missing fields on data collection forms	0	<5%

b. Frequency of Review–The frequency of data review depends according to the type of data and is summarized in the following table.

Data Type	Frequency of review	Reviewer
Subject accrual (adherence to eligibility criteria)	Every 2 weeks	Study pediatrician/coordinator and site PI
Protocol adherence	Monthly	Study pediatrician/coordinator and site PI
Adverse event rates	Monthly	Study pediatrician/coordinator and site PI
Evaluation of data relevant to stopping rules	After 10 participants have been enrolled	Study pediatrician/coordinator, site PI, and UCSF PI

2. Subject Accrual and Protocol Adherence

a. Measurement and reporting of subject accrual, adherence to inclusion/exclusion criteria–Review of the rate of subject accrual and adherence to inclusion/exclusion criteria will occur every 2 weeks.
b. Measurement and reporting of protocol adherence– Data on protocol adherence will be reviewed monthly.

3. Safety Monitoring- Safety evaluations will include collection of AE, physical examination, vital sign, and clinical laboratory data. Safety evaluation will involve the collection of data from:

- Continuous transdermal end-tidal carbon dioxide (CO_2) monitoring
- Capillary blood gases (PO_2, PCO_2, pH, base excess, lactate)
- Peripheral blood oxygen saturation (SpO_2)

Additional laboratory tests at the time of screening will include rapid hemoglobin, malaria rapid test, blood glucose (point of care), and complete blood count (CBC), which may include hemoglobin, hematocrit, erythrocyte or red blood cell count (RBC), mean cell volume (MCV), segmented neutrophils, juvenile neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, cell morphology, reticulocyte count. The decision to obtain metabolic panel in subjects will be based on local standard of care for patients with respiratory distress, but may include evaluation of:

- Metabolic panel: Serum concentrations of sodium, potassium, chloride, total bilirubin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin.

4. Stopping Rules– An individual subject will be withdrawn from the study if he or she develops a condition or begins a therapy during the study period that would have excluded entry into the study (e.g., hypercapnia, acidosis, hemodynamic instability, requirement of intubation or positive pressure ventilation, $SpO_2 < 90\%$ on oxygen, SICK score > 2.4). In addition, a comprehensive evaluation of data relevant to stopping rules will occur after enrollment of the first 10 participants. This study will be stopped at this time if: (1) the majority of investigators find that the harm to study participants outweighs the benefit of the scientific evidence to be accrued by continuing the trial; (2) new information from sources outside the trial provides definitive information that the intervention is effective or

harmful; (3) any new information becomes available that necessitates stopping the trial; and (4) other situations occur that might warrant stopping the trial.

D. Progress Reports

Progress reports summarizing data quality, protocol adherence, and AEs will be prepared by the study pediatrician/coordinator and provided to the PI and sponsor monthly for review. After 10 patients have been enrolled, an additional report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims; and (5) conditions whereby the study might be terminated prematurely. This report will be signed by the PIs and forwarded to the MREC and the sponsor.

APPENDIX I
DEVICE BROCHURE:
Global Good/ Intellectual Ventures Mask (Nasal Reservoir Cannula)

Rationale:
Used properly this oxygen conserving nasal reservoir cannula will provide the patient adequate oxygen support equal to that of with conventional nasal cannula with prongs and the following added benefits:

- It will take a lower oxygen flow rate (l/min) to provide the same level of oxygenation in the body, which can be as much as 50% less (depending on the actual flow rate) than that of with a standard nasal cannula
- In case of using an oxygen storage system (e.g. oxygen cylinder), it will last significantly longer and in turn increase treatment capacity, spare resources with the same level and quality of care

Directions:

The mask is recommended for patients aged ≥ 1 year and ≤ 6 years with body weight of ≥ 8 kg and ≤ 26 kg. The proper mask size should be selected based on the patient's body weight (see table 1). Patients with a body weight of 8-13 kg should receive treatment with the small 30 ml mask and patients with a body weight of 14-26 kg should receive treatment with the large 50 ml mask.
The duration of the treatment and the oxygen flow rate should be based on the clinical judgment of the physician. This mask should only be implemented when the patient is monitored by adequate pulse oximetry and blood gas analysis tools.

Table 1. Mask size selection should be made based on patient weight.

Mask size	Child weight
Small (30 mL)	8-13 kg
Large (50 mL)	14-26g

Application:

1. Connect the standard nasal cannula to the oxygen source.
2. Turn on the oxygen and set flow rate (l/min).
3. Insert the mask over the conventional nasal cannula with prongs by installing the prongs into the respective slots of the mask.
4. Place the mask over the nose of the patient. The nasal piece does not need to tightly cover the nose but should rest loosely on the nose and the philtrum (upper lip) of the patient with the prongs extending into the nostrils.
5. Place the nasal cannula flexible tubing over the ears of the patient and then under the chin (per manufacturer's instructions). Slide the bola of the standard nasal cannula up toward the chin.

Cleaning:
The mask is disposable and should be used on an individual basis. During the duration of the oxygen substitution treatment if the mask gets contaminated with body fluids or secretions of the patient it can be washed with a mild soap and warm water, and thereafter can be wiped and disinfected with 70% alcohol. After total evaporation of the alcohol the mask may be re-used on the same individual. The use of bleach may not be recommended since residual bleach may cause skin, eye or respiratory tract irritation.

Humidification:
The system may be used with conventional supplementary humidifiers attached via a standard nasal cannula.

APPENDIX J
Blood draw limits and anticipated blood draw volumes

Blood draw limits by weight

Weight in kg	Limit for single blood draw (mL) *Calculated as 2 mL/kg	Limit for 24 hour period (mL) *Calculated as 3 mL/kg
8	16	24
9	18	27
10	20	30
11 - 15	22 - 30	33 - 45
16 - 20	32 - 40	48 - 60
21 - 25	42 - 50	63 - 75
26	52	78

Blood draw volumes for this study (all in mL)

Laboratory test	Screening	Period 1	Period 2
Capillary blood gas (CBG) with lactate	0.095	0.095	0.095
Complete blood count (CBC)	1		
Hemoglobin (Hb) rapid test	0.01		
Malaria rapid test	0.05		
Blood glucose (point of care)	0.05		
Metabolic panel [a]	3		
Total each period (range)	1.19 - 4.21	0.095	0.095
Total overall (range)	1.38 - 4.40		

a. Metabolic panel done *only* if obtained as part of standard care.