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NEST360°

Target Product Profile

CPAP – Respiratory Support

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This report was prepared by Rebecca Kirby and Kara Palamountain from Northwestern University with input from UNICEF and other stakeholders. The document summarizes consensus achieved at a meeting on target product profiles for newborn care in low-resource settings, convened by NEST360°. This document was finalized following consideration of all comments and suggestions made by meeting participants at the Consensus Meeting.

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Note to the reader
Because of the richness of the discussion, and in an attempt to keep this report simple and readable, this report aims to convey the themes addressed in each session, rather than attempting to provide a chronological summary of the dialogue.

Disclaimer: The TPPs do not replace or supersede any existing UNICEF TPPs. The TPPs do not constitute tender specifications, nor is UNICEF bound to tender or procure products that arise as a result of these TPPs. UNICEF may require regulatory approval and proof of compliance to quality management and product-specific international standards for tendering purposes.

INTRODUCTION

At birth, a baby's lungs must transition from fetal to neonatal life in three key ways:

1. fluid in the lungs must be absorbed and replaced with air,
2. lungs must expand fully and regular breathing must be established, and
3. pulmonary blood flow is increased.

When these three things do not happen, a baby will have respiratory distress. Respiratory distress syndrome (RDS) is when there is deficiency of surfactant that is needed to prevent alveolar collapse; this is especially common in premature newborns.

Oxygen provision is important in the care of newborn infants because many conditions that affect babies in the first days of life can result in low levels of oxygen in the body. Hypoxemia, or low levels of oxygen in the blood, is a life-threatening condition that results in increased mortality and morbidity. Prematurity and respiratory distress syndrome (surfactant deficiency), pneumonia and other severe infections, asphyxia, and difficulties in the transition from fetal to neonatal life can all result in hypoxemia. Yet, despite its importance in acute severe illnesses, hypoxemia is often not well recognized or managed in settings where resources are limited. It is therefore important for health workers to know the clinical signs that suggest the presence of hypoxemia and how supplemental oxygen can appropriately be used as an essential lifesaving treatment [1].

In high-resource settings, a mother is given steroids before birth if a baby is anticipated to be born preterm to help prevent respiratory distress syndrome (RDS). If RDS still occurs, assisted breathing with continuous positive airway pressure (CPAP) is started. If CPAP is not sufficient, intubation, surfactant and/or ventilation may be needed.

In low-resource settings, many facilities lack the resources to implement CPAP. While many companies make newborn CPAP devices, only a few key players design their devices to work in low-resource settings.

Bubble Continuous Positive Airway Pressure (bCPAP) therapy is a common mode of treatment for RDS in premature neonates and for respiratory illness in young children. bCPAP provides a continuous flow of pressurized air into the patient's nostrils via nasal prongs or a mask; this pressure prevents alveolar collapse during exhalation. In high-income settings, early bCPAP is now preferred over mechanical ventilation as first line therapy for respiratory distress syndrome in preterm infants. bCPAP has been shown to promote production of endogenous surfactant [2] as well as dramatically decrease progression to intubation or death in both high [3-5] and low [6,7] income settings.

In low-resource settings, there is a need for CPAP that is designed for patients who weigh between 1 and 10 kg and that includes an oxygen blender which allows users to provide 21-90% oxygen to the patient when an external oxygen source is connected to the CPAP. The CPAP should ideally contain an integrated air-compressor, blender, and patient interface. Although there are short cuts for delivering positive airway pressure to a baby without an appropriate device, these generally rely on pure oxygen sources from oxygen cylinders or concentrators. Procurement officers should consider current evidence, target level of care, provision, and context when choosing between available CPAP devices. The ability of a CPAP device to deliver positive pressure at low fractional inspired oxygen concentrations (FiO2) is a critical feature for preventing retinopathy of prematurity and chronic lung disease associated with oxygen administration [8,9]. Some CPAP units use heated and humidified gas in the circuit, although the exact benefits of humidification in non-invasive

ventilation (i.e. CPAP) in terms of survival, complications from therapy and morbidity are not well established. Humidification, while a feature of some CPAP devices, remains a controversial feature of CPAP in low-resource settings, especially for CPAP devices utilizing compressed ambient air rather than gas cylinder sources.

DEVELOPING A TARGET PRODUCT PROFILE

Overview

Manufacturers need Target Product Profiles (TPPs) at an early stage in the medical device and diagnostic development process. These TPPs help inform the ideal targets and specifications and align with the needs of end users. TPPs outline the most important performance and operational characteristics as well as pricing. In the TPPs to follow, the term "Minimal" is used to refer to the lowest acceptable output for a characteristic and "Optimal" is used to refer to the ideal target for a characteristic. The Optimal and Minimal characteristics define a range. Products should meet at least all of the Minimal characteristics and preferably as many of the Optimal characteristics as possible. TPPs should also specify the goal to be met (e.g. to initiate treatment), the target population, the level of implementation in the healthcare system and the intended end users.

For the NEST360° Newborn Care in Low-Resource Settings Target Product Profiles, an initial set of TPPs were developed listing a proposed set of performance and operational characteristics for 16 product categories. The development timeline envisioned in the TPPs was four years, although some commercially available technologies may fit some of the criteria already. For several of the characteristics, only limited evidence was available and further expert advice was sought from additional stakeholders.

Delphi-Like Process

To obtain this expert advice and to further develop the TPPs, a Delphi-like process was used to facilitate consensus building among stakeholders. The initial TPPs were sent to a more comprehensive set of stakeholders including clinicians, implementers, representatives from Ministry of Health, advocacy organizations, international agencies, academic and technical researchers and members of industry. In total, 103 stakeholders from 22 countries participated in the TPP development process via survey.

44 respondents participated in the Delphi-like survey for CPAP.

Survey respondents were requested to provide a statement on their level of agreement with each of the proposed characteristics for each TPP. Agreement was scored on a Likert scale ranging from 1 to 5 (1=disagree, 2=mostly disagree, 3= neither agree nor disagree, 4=mostly agree, 5=fully agree) with an option to opt out with the selection of "Other - Do not have the expertise to comment". If participants did not agree with the characteristic (i.e., selected 3 or below) they were asked to provide an explanation with comments. Participants who agreed with the statements could also provide comments however were not explicitly asked. In total, over 1,780 comments were reviewed and summarized in this report.

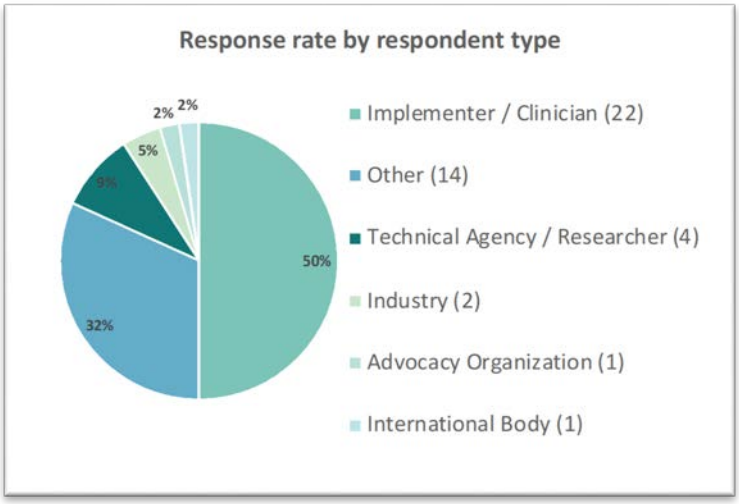
For each characteristic in each product category, a percentage agreement was calculated for both the Minimal and Optimal requirements. The percentage agreement was calculated as the ratio of the sum of number of

respondents who selected 4 and 5, to the sum of numbers of respondents who gave any score (from 1 to 5 where 5=fully agree, 4=mostly agree, 3=neither agree nor disagree, 2=mostly disagree and 1=disagree). Consensus for the survey characteristics was pre-specified at greater than 50% of respondents providing a score of at least 4 on the Likert scale.

A classic Delphi process requires at least two rounds of survey ahead of an in-person meeting. Initially, two rounds of the survey were planned, but since 50% consensus for most characteristics was reached after the first round survey, a second round survey was not initiated. Survey results are detailed by characteristic in the individual product category sections.

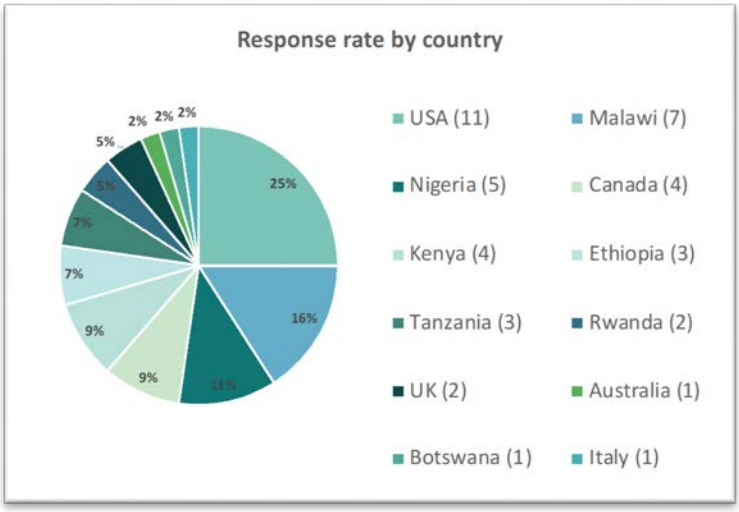
In total, over 180 organizations/individuals were asked to participate in this Delphi-like survey process, of whom 103 (see Appendix A) responded (response rate, 56%). Survey respondents were asked to self-disclose their affiliation.

Figure 1: Summary of organizational affiliation for CPAP TPP from Delphi-like Survey prior to Consensus Meeting (data as of Oct 25, 2019)



Respondent type	Percentage
Implementer / Clinician (22)	50%
Other (14)	32%
Technical Agency / Researcher (4)	9%
Industry (2)	5%
Advocacy Organization (1)	2%
International Body (1)	2%

Figure 2: Summary of response rate by country for CPAP TPP from Delphi-like Survey prior to Consensus Meeting (data as of Oct 25, 2019)



Country	Percentage
USA (11)	25%
Malawi (7)	16%
Nigeria (5)	11%
Canada (4)	9%
Kenya (4)	9%
Ethiopia (3)	7%
Tanzania (3)	7%
Rwanda (2)	5%
UK (2)	5%
Australia (1)	2%
Botswana (1)	2%
Italy (1)	2%

Consensus Meeting

On November 20 - 22, 2019 over 69 stakeholders gathered in Stellenbosch, South Africa to focus on building further consensus on areas of discrepancy in opinion within the 16 TPPs. More specifically, characteristics on which fewer than 75% of the respondents agreed, or on which a distinct subgroup disagreed, were discussed. Consensus Meeting moderators presented the results and comments from characteristics with <75% agreement from the Delphi-like survey, the moderators then solicited additional feedback on each characteristic with <75% agreement from the Consensus Meeting participants, and then a proposed change to the TPP characteristic was discussed amongst Consensus Meeting participants. In some cases, Consensus Meeting participants nearly universally agreed on proposed changes. In other cases, Consensus Meeting participants failed to reach 75% consensus on proposed changes. If consensus was not achieved after two votes on proposed changes, meeting participants agreed to move forward and the disagreement is noted in this report.

Methodology for Mentimeter Voting Results: Certain proposed changes to TPP characteristics, for which a distinct subgroup disagreed, were anonymously voted on using Mentimeter.com to determine the overall level of agreement and disagreement amongst the Consensus Meeting participants. The Mentimeter Voting Results are presented throughout this report in three distinct categories:

I. Overall vote – Includes all Consensus Meeting participants who voted on Mentimeter.com. To eliminate the possibility of duplicate votes, all respondents were asked to enter their name (to be viewed only by the report authors) and blank (potentially duplicate votes) were eliminated from the overall vote.
II. Clinicians – Includes all Consensus Meeting participants who voted on Mentimeter.com and who designated themselves as a Clinician on Mentimeter.com.
III. Excluding involvement with product development - Includes all Consensus Meeting participants who voted on Mentimeter.com minus those who indicated on a Declaration of Interest form that they are 'currently or have been involved in the development of a candidate technology or product' specific to the Product Category being voted on.

Of the 133 stakeholders that were invited to the meeting, 69 participants were able to attend. Participants comprised country representatives, stakeholders from technical and funding agencies, researchers, implementers and civil society organizations, and representatives from companies working on newborn care technologies (see Appendix B for the Consensus Meeting Participant List). An overview of the discussion for CPAP and final consensus achieved is included in this report. Most characteristics discussed are presented in this report, however, overarching characteristics that applied to all product categories were discussed in unison and are included in the NEST360° Newborn Care in Low-Resource Settings Target Product Profiles. These characteristics are: Target Operator; Target Population; Target Setting; Quality Management; Regulation; User Manual/Instructions; Warranty; Power Source; Battery; Voltage; Power Consumption.

FINAL TPP - CPAP

Final Target product profile for CPAP		
Characteristic	**Optimal**	**Minimal**
SCOPE		
Intended Use	To treat respiratory distress and other forms of respiratory illness in infants up to one year of age	
Target Operator	For use in low- and middle-income countries by a wide variety of clinicians, including nurses, clinical officers, and pediatricians	
Target Population	Neonates (born at any gestational age and require ongoing care)	
Target Setting	Hospitals in low-resource settings	
SAFETY AND STANDARDS		
Quality Management [1]	ISO 13485:2016 Medical devices – Quality management systems -- Requirements for regulatory purposes	
Regulation	At least one of: CE marking, approved by US FDA or another stringent regulatory body of a founding member of IMDRF (e.g., Japan or Australia or Canada)	
TECHNICAL CHARACTERISTICS		
Flow Driver	Integrated (on-board air compressor)	
Oxygen Flow Capacity	0-10 L/min	
Pressure	5-8 cm H20	
Total (blended) Flow	0-10 L/min	
Humidification	Yes, Heated Humidification	None [2]
Alarms	Audio and Visual: Power, low-flow, low-pressure	Audio Power
PURCHASING CONSIDERATIONS		
Accessories	Non-proprietary	Proprietary [3]
Consumables	Reusable	Available
Instrument Pricing	<$1,000 ex-works	<$2,000 ex-works
Consumable Pricing	<$10 / patient ex-works	<$15 per patient ex-works
UTILITY REQUIREMENTS		
Power Source	Mains with battery backup	Mains Power
Battery	Rechargeable integrated battery, >6 hours on a single charge	None [4]
Voltage	Model must match the voltage and frequency of the purchasing country's local power grid (e.g., 110-120 VAC at 60 Hz or 220-240 VAC at 50 Hz)	
TRAINING AND MAINTENANCE		

User Instructions	User manual and additional training materials (checklists, videos, guides) in at least one national official language for the country of intended use. Attached to device with labels and markings where possible	User manual provided in at least one national official language
Warranty	5 years	1 year

[1] There was not 75% voting agreement on the Minimal characteristic. Please refer to the TPP Report discussion for additional detail.
[2] There was not 75% voting agreement on this characteristic. Please refer to the TPP Report discussion for additional detail.
[3] There was not 75% voting agreement on this characteristic. Please refer to the TPP Report discussion for additional detail.
[4] There was not 75% voting agreement on this characteristic. Please refer to the TPP Report discussion for additional detail.

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Consensus Meeting Summary: CPAP

To arrive at the final TPP for CPAP, we conducted a pre-meeting survey to prioritize the items for discussion at the Consensus Meeting for characteristics that achieved below 75% agreement in the survey results. An overview of the discussion at the Consensus Meeting of these characteristics is included below.

- **Humidification**
  - There was disagreement in the group on whether heated humidification was required as a Minimal characteristic.
  - Proponents of heated humidification argued that some of the advantages of heated humidification include:
    - Better outcomes
    - Reduced risk of infection (with heated humidification)
    - Increased comfort and adherence
    - Decreased upper airway mucosal injury
    - Decreased convective heat losses which may lead to hypothermia and more challenging weight gain in infants
    - Decreased lung inflammation from aspirated secretions which has unknown impact on morbidity and mortality of very low birthweight infants.
  - Some potential drawback to heated humidification include:
    - Iatrogenic infection, especially in settings where clean water may not be readily available and humidifiers, which are typically meant for one time use, are being cleaned and re-used between patients
    - High financial cost of adding heated humidified gas
    - High cost of additional consumable required and ongoing maintenance
    - High human resource costs in terms of repair and preparation of non-invasive ventilation units which may limit not only their use, but availability of this life saving technology within our setting
  - Clinicians commented that humidification helps with the avoidance of hypothermia which is becoming increasingly important. These clinicians claimed that it is likely that heated and humidified air is most important for the smallest newborns less than 1-1.25kg. Other clinicians responded that the mortality impact has never been explicitly studied.
  - A research question was created to further explore outcomes and effects with and without heated humidification.
  - *Minimal: No heated humidification*

        - Overall Vote - 58% Agree (n = 31)
        - Clinicians - 61% Agree (n = 23)
        - Excluding involvement with product development - 58% Agree (n = 24)
- **Accessories**
    - There was a discussion surrounding the number of cannulas and hats included with each machine purchased – currently a standard does not exist and therefore it is dependent on the manufacturer. A research question was created to further explore the impact of reusable accessories. An existing JHPIEGO paper "Infection Prevention and Control - Module 6. Processing Surgical Instruments and Medical Devices" was referenced in providing recommendations on how to develop guidelines on the reprocessing of single-use device [11, p. 77-81].
    - *Minimal: Proprietary*
        - Overall Vote - 74% Agree (n = 31)
        - Clinicians - 79% Agree (n = 19)
        - Excluding involvement with product development - 75% Agree (n = 24)
- **Battery**
    - Participants noted the importance of a back-up power supply. Other participants noted the impact on price if the back-up power is needed for both heated humidification and an on-board air compressor. Product developers explained the negative impact that power outages have on the product and the importance of strong utility infrastructure to withstand power outages, including the principle of grounding [10].
    - There was agreement in the room that all characteristics relating to Utility Requirements (e.g., Back-up Battery; Battery Power; Batteries; Voltage; Power Requirement; Maximum Power Consumption; Response During Power Outage; Surge Protection, Electrical Plug) be reviewed and harmonized following the TPP meeting. In this specific case, the language used in the Optimal characteristic was adjusted during this harmonization review following the vote.
    - *Optimal: Built-in rechargeable battery, autonomy >6 hours, automatic switch to battery in case of power failure, automatic recharge on connection to mains (only applicable to the electric CPAP generator model)-*
        - Overall Vote - 95% Agree (n = 12)
        - Clinicians - 100% Agree (n = 27)
        - Excluding involvement with product development - 94% Agree (n = 16)
    - *Minimal: None (but assumption that facility has back up power for 6 hours)*
        - Overall Vote - 47% Agree (n = 30)
        - Clinicians - 38% Agree (n = 18)
        - Excluding involvement with product development - 43% Agree (n = 23)
    - *Final post Utility Harmonization - Optimal: Rechargeable integrated battery, >6 hours on a single charge*
    - *Final post Utility Harmonization - Minimal: None*
- **Instrument Pricing**
    - One participant mentioned that the pricing for commercially available products that meet this draft specification range from $1,000 - $3,000. Consensus achieved via voting.
    - *Minimal: <$2,000 ex-works*
        - Overall Vote - 71% Agree (n = 21)
        - Clinicians - 92% Agree (n = 12)
        - Excluding involvement with product development - 80% Agree (n = 15)
- **Consumable Pricing**
    - Participants commented that the minimum price was too high for single-use products, especially for certain markets where consumers may be paying out of pocket and the cost is prohibitively high.
    - *Minimal: <$15 per set ex-works*
        - Overall Vote - 79% Agree (n = 24)
        - Clinicians - 86% Agree (n = 14)
        - Excluding involvement with product development - 88% Agree (n = 17)

Broad Themes and Considerations

At the Consensus Meeting, the following additional themes emerged and are summarized below:

Instrument Pricing
In order to provide a consistent measure of pricing, the ex-works price is included in the TPPs. Participants highlighted that ex-works pricing is not a true measure of landed cost and is often vastly understated to what a procurement agent will pay. One participant from an international NGO noted that there is a "minimum 30% mark-up on the ex-works price." The rationale for using the ex-works price is that it is a reliable measure that can be used for consistent comparison across geographies since distributor markups vary by country and geography.

Utility Requirements
A significant portion of the discussion was devoted to deliberating on how equipment can be designed to work in health facilities with limited electrical infrastructure. Designing the equipment for low-resource conditions often requires back-up batteries which adds to the expense of the technology, as well as the size of the equipment which can pose a challenge in crowded newborn wards. Some participants noted that rather than designing equipment for these facilities with limited electrical infrastructure, to consider whether a broader investment in electrical infrastructure would be a better use of funds. This inherent tradeoff was discussed multiple times when electrical characteristics were discussed.

Additionally, there were a variety of characteristics in the initial survey that related to Utility Requirements (i.e., electricity and power) that varied slightly in title across the TPPs. During the TPP Consensus Meeting, participants agreed that all characteristics relating to Utility Requirements (includes Back-up Battery; Battery Power; Batteries; Voltage; Power Requirement; Maximum Power Consumption; Response During Power Outage; Surge Protection, Electrical Plug) be reviewed and harmonized following the TPP meeting across the product categories. These characteristics have since been reviewed and harmonized into four distinct characteristics (Power Source, Battery, Voltage, and Power Consumption) in the final TPPs.

- **Power Source** - This defines the desired power source for the device and can be broken down into the following categories:
    - *Mains power* - device must be plugged into a mains power source for use
    - *Mains with battery backup* - device must be plugged into a mains power source for use, however, in the case of a power failure, the device has a battery backup that can last a specified period of time
    - *Mains with rechargeable battery* - device has a rechargeable battery that operates both when the device is charged by a mains power source, or, when the device is plugged in (e.g., a mobile phone)
    - *Battery is disposable and replaceable*
    - *No power required (i.e., disposable device)*
- **Battery** - This includes the length of time the rechargeable or disposable battery should function
- **Voltage** - This specifies the preferred voltage conversion if the Power Source utilizes Mains Power. Note that for certain technologies (i.e., Bilirubinometer, Glucometer, Hemoglobinometer, pH monitor, and Pulse Oximeter), the Voltage characteristic is included in reference to the rechargeable battery charger requirements. For example, while the Optimal Voltage characteristic is "None" (i.e., no charging is necessary), the Minimal Voltage characteristic should conform to "the voltage and frequency of the purchasing country's local power grid (e.g., 110-120 VAC at 60 Hz or 220-240 VAC at 50 Hz)" to ensure that the charger for the battery is compliant.

- **Power Consumption** - This specifies the maximum Watts of electricity that the device should consume

Ideally, all devices should be developed to withstand power surges and voltage spikes.

Note that comments received in the Pre-Meeting survey report highlighted the importance of the correct frequency in electrical plugs. It was noted that a universal adaptor would not safely support the conversion of 60Hz equipment to 50Hz and that a machine relying on this method could fail in a short period of time (applicable to Oxygen Concentrator, Warming Crib, Radiant Warmer).

Delphi-like Survey: CPAP

Delphi-like survey results for CPAP TPP prior to Consensus Meeting (data as of Oct 25, 2019)

	Optimal		Minimal		
Characteristic	**Optimal requirement**	**% agreement (n size)**	**Minimal requirement**	**% agreement (n size)**	**Collated comments from Delphi-like survey**
Intended Use	Optimal: To treat respiratory distress and other forms of respiratory illness in infants up to one year of age.	**95% n = 42**	Minimal: Same as Optimal.	**95% n = 37**	12 comments summarized below • Theme: Narrow vs. Broaden Age Range • Target Population is defined as neonates, but Intended Use defined as infants up to one year of age. Need to synch and/or clarify age of patient
Target Operator	Optimal: For use in low- and middle-income countries by a wide variety of clinicians, including nurses, clinical officers, and pediatricians.	**93% n = 42**	Minimal: Same as Optimal	**90% n = 39**	7 comments summarized below • Theme: Training and Supervision should accompany Bubble CPAP • Requires training and supervision when introducing to new clinical and nursing professionals
Target Population	Optimal: Neonates (<28 days)	**88% n = 42**	Minimal: Same as Optimal.	**85% n = 39**	16 comments summarized below • Theme: Narrow vs. Broaden Age Range • Target Population is neonates but Intended Use infants up to one year of age. Need to synch and/or clarify age of patient • Bubble CPAP is very effective in neonatal population but also evidence suggests that has a role in respiratory illness of other causes in infants and children <5 yrs, such as pneumonia and bronchiolitis

	Optimal		Minimal		
Target Setting	Optimal: Hospitals in low-resource settings	**93%** **n = 41**	Minimal: Same as Optimal.	**86%** **n = 37**	11 comments summarized below • Theme: Need to define what is meant by hospital • Bubble CPAP can be used in hospitals in low-resource settings but ideally also high-functioning health centres • Requires training and supervision when introducing to new clinical and nursing professionals • May also need to define what is needed at setting: electricity, sterilization capabilities, etc.
International Standard	Optimal: ISO 13485:2016 Medical devices – Quality management systems -- Requirements for regulatory purposes.	**86%** **n = 22**	Minimal: Same as Optimal.	**85%** **n = 20**	7 comments • Theme: Low familiarity on what ISO 13485 means
Regulation	Optimal: CE marking or US FDA Clearance	**69%** **n = 26**	Minimal: Same as Optimal.	**68%** **n = 25**	14 comments summarized below • Theme: Reduce regulatory options or add more flexibility • CE Mark alone is sufficient • Consider additional 'or' options: o Other Stringent Regulatory Authorities – Japan or Australia or Canada o Consider regulatory bodies of Low- and Middle-Income Countries
Flow Driver	Optimal: Integrated (on-board air compressor)	**90%** **n = 29**	Minimal: Same as Optimal.	**86%** **n = 28**	9 comments summarized below • Need to clarify what is meant by flow driver and on-board air compressor and whether this impacts the Accessories or Consumables characteristics (e.g., does an integrated on-board air compressor require proprietary)

	Optimal		Minimal		
Oxygen Flow Capability	Optimal: 0-10 L/min	**86%** **n = 37**	Minimal: Same as Optimal.	**79%** **n = 33**	15 comments summarized below • If the Intended Use is up to 1 year of age (or more), then flows higher than 10 L/min may be required • Instead of Oxygen Flow Capability, perhaps Fio2 range or Peep range should be considered
Pressure	Optimal: 5-8 cm H20	**84%** **n = 38**	Minimal: Same as Optimal.	**80%** **n = 35**	12 comments summarized below • Additional ranges to consider: o Weaning o Older babies o Extreme cases
Total (blended) Flow	Optimal: 0-10 L/min	**86%** **n = 37**	Minimal: Same as Optimal.	**85%** **n = 34**	10 comments summarized below • If the Intended Use is up to 1 year of age (or more), then flows higher than 10 L/min may be required • Instead of Oxygen Flow Capability, perhaps Fio2 range or Peep range should be considered
Humidification	Optimal: Yes, Heated Humidification	**95%** **n = 38**	Minimal: None	**62%** **n = 34**	17 comments summarized below Some bCPAP units use heated and humidified gas in the circuit, although the exact benefits of humidification in non-invasive ventilation (i.e. bCPAP) in terms of survival, complications from therapy and morbidity are not well established. Potential benefits of heating and humidification could include: • Increased comfort and adherence • Decreased upper airway mucosal injury • Decreased convective heat losses which may lead to hypothermia and more challenging weight gain in infants • Decreased lung inflammation from aspirated secretions which has unknown impact on morbidity and mortality of very low birthweight infants. Potential drawbacks to heated humidification include:

	Optimal		Minimal		
					• Iatrogenic infection, especially in settings where clean water may not be readily available and humidifiers, which are typically meant for one time use, are being cleaned and re-used between patients • High financial cost of adding heated humidified gas • High human resource costs in terms of repair and preparation of non-invasive ventilation units which may limit not only their use, but availability of this life saving technology within our setting It is likely that heated and humidified air is most important for the smallest newborns less than 1-1.25kg although this has never been explicitly studied.
Alarms	Optimal: Audio/Visual Power, low-flow, low-pressure	**90%** **n = 39**	Minimal: Audio Power	**85%** **n = 39**	10 comments summarized below • FiO2 alarms and not necessarily flow-rate alarms may be more critical • Need to clarify Audio/Visual. Is this Audio and/or Visual or Audio or Visual
Consumables	Optimal: Reusable	**88%** **n = 41**	Minimal: Available	**82%** **n = 39**	15 comments summarized below • Clarify what is meant by consumable and reusable: o Bottle o Tubing o Nasal Cannulas o Hat • Potential benefits of reusable consumables: o Lower cost o Reduces supply chain delays • Potential drawbacks of reusable consumables: o Infection risk (perhaps mitigated with instructions / guidance for decontamination; specify autoclavable or disinfectable

	Optimal		Minimal		
					with specific cleaning agent) o May not allow for approval by Stringent Regulatory Authority
Accessories	Optimal: Non-proprietary	**84%** **n = 31**	Minimal: Proprietary	**64%** **n = 28**	13 comments • Clarify what is meant by accessories: o Bottle o Tubing o Nasal Cannulas o Hat • Potential benefits of proprietary accessories: o Designed to reduce user errors • Potential drawbacks of proprietary accessories: o Often cost more o Introduces delays due to supply chain o May not allow for approval by Stringent Regulatory Authority
Back-up Battery	Optimal: Built-in rechargeable battery, autonomy >1 hour, automatic switch to battery in case of power failure, automatic recharge on connection to mains (only applicable to the electric CPAP generator model)	**89%** **n = 38**	Minimal: None	**52%** **n = 33**	21 comments summarized below • Potential benefits of back-up battery: o Allows for use in between power outage and when the generator turns on • Potential drawbacks of back-up battery: o Increases the cost of device; may be best to resolve with back-up UPS
Voltage	Optimal: 110-240V 50-60hz	**82%** **n = 28**	Minimal: 220-240V 50-60hz	**83%** **n = 29**	13 comments as summarized below • Voltage can always be corrected with step-up / step-down transformers; however, these come at an added cost. So whether the cost be borne by the purchaser (Caribbean, Central- or South-American countries w/ 120V) or the manufacturer who makes

	Optimal		Minimal		
					devices that can work across all contexts • Frequency needs to be appropriate for frequency rating of specific country, as this is something that cannot be corrected and though 50 Hz can be used in a 60 Hz system, it is hard on the device and it will be compromised • Voltage stabilizers and surge suppressors are important to consider
User Manual	Optimal: User manual and additional training materials (checklists, videos, guides) in English and local language. Attached to device with labels and markings where possible.	**95%** **n = 41**	Minimal: User manual provided.	**77%** **n = 39**	12 comments as summarized below • A variety of hard and soft copy materials mentioned with particular mentions of difficulty in reading a user manual and preference for videos so people can see vs. read • All claims must be filed with the regulatory dossier, so this is not as straight forward as a simple translation. Appropriate, professional translations are a must and are costly to the manufacturer. Additionally, local language varies greatly across a country and is often-times not even the official language of the country and so this may not be a reasonable ask of manufacturers
Warranty	Optimal: 5 years	**79%** **n = 39**	Minimal: 1 year	**68%** **n = 38**	19 comments as summarized below • Desire to increase Minimal (1 year) but acknowledgement that this may come at a cost that donors or procurement agencies may not be ready for
Instrument Pricing	Optimal: <$1,000 ex-works	**82%** **n = 33**	Minimal: <$2,500 ex-works	**52%** **n = 31**	21 comments as summarized below • Extremely price-sensitive geography and even $1,000 was viewed as too expensive by some respondents • Ex-works not likely a true measure of landed costs

	Optimal		Minimal		
					• Devices below $2,000 ex-works would encounter some sort of other trade-off (no air compressor, no humidification, 1 year warranty, etc.)
Consumable Pricing	Optimal: <$10 / patient ex-works	**83%** **n = 29**	Minimal: <$50 per patient ex-works	**42%** **n = 31**	19 comments as summarized below • Extremely price-sensitive geography and even $10 was viewed as too expensive by some respondents, especially for countries where patient pays out of pocket for consumables (e.g. Nigeria) • Ex-works not likely a true measure of landed costs • If consumables were reusable, then price point slightly higher than $10 is more realistic • "$10 is too low for effective circuits"

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APPENDICES

Appendix A: Delphi-like Survey Respondent Organizational Designation

3rd Stone Design
Abuja University Teaching Hospital
Alex Ekwueme Federal University Teaching Hospital Abakaliki
Baylor College of Medicine
BC Children's Hospital
Burnet Institute
CCBRT Dar es Salaam
CENETEC-Salud
Center for Public Health and Development (CPHD)
Children's Hospital of Philadelphia
Christian Medical College, Vellore
Clinton Health Access Initiative
College of Medicine, University of Lagos
College of Medicine, University of Malawi
Dartmouth
Day One Health
Diamedica UK Ltd
D-Rev
Egerton University - Nakuru County Referral Hospital
ETH Zurich
Fishtail Consulting
FREO2 Foundation Australia
Global Strategies
Hawassa University
Independent Biomedical Engineer
Institute for Healthcare Improvement
intelms.com
Kamuzu Central Hospital
Kamuzu College of Nursing
Kemri-Wellcome Trust
Kenya Paediatric Association
Komfo Anokye Teaching Hospital
Malawi-Liverpool Wellcome Trust
Mama Lucy Hospital
Masimo
Mbarara University of Science and Technology
McGill University Health Centre
McMaster University
Medecins Sans Frontieres
Mediquip Global Limited
Ministry of Health, Senegal
mOm Incubators
MRC Gambia at LSHTM
Muhimbili National Hospital
Muhimbili University of Health and Allied Sciences (MUHAS)
Neopenda
No designation listed (10)
Pediatric and Child Health Association in Malawi

Pumwani Hospital
Queen Elizabeth Central Hospital
Rice 360 Institute for Global Health
Royal Children's Hospital and Centre for International Child Health (University of Melbourne)
Save The Children
Texas Children's Hospital
The University of Queensland
UCSF and London School of Hygiene & Tropical Medicine
UNICEF
University of Alabama at Birmingham
University of British Columbia
University of Global Health Equity
University of Maiduguri Teaching Hospital, Maiduguri
University of Nairobi
UNTH, Enugu

Appendix B: Consensus Meeting Participation

Albert Manasyan (University of Alabama Birmingham)
Anna Worm
Antke Zuechner (CCBRT)
Audrey Chepkemoi (Moi Teaching and Referral Hospital)
Bentry Tembo (Kamuzu Central Hospital)
Bev Bradley (UNICEF)
Casey Trubo (D-Rev)
Chishamiso Mudenyanga (Clinton Health Access Initiative)
Danica Kumara (3rd Stone Design)
Daniel Wald (D-Rev)
Edith Gicheha (Kenya Pediatric Research Consortium)
Emily Ciccone (University of North Carolina - Chapel Hill)
Emmie Mbale (PACHA)
Grace Irimu (University of Nairobi)
Guy Dumont (The University of British Columbia)
Helga Naburi (Muhimbili National Hospital)
Jeffrey Pernica (McMaster University)
John Appiah (Kumfo Anokye Teaching Hospital)
Jonathan Strysko (Children's Hospital of Philidelphia/Princess Marina Hospital)
Joy Lawn (London School of Hygiene and Tropical Medicine)
Lincetto Ornella (WHO)
Liz Molyneux (College of Medicine, Malawi)
Lizel Lloyd (Stellenbosch University)
Mamiki Chise
Marc Myszkowski
Maria Oden (Rice University)
Martha Franklin Mkony (Muhimbili National Hospital)
Martha Gartley (Clinton Health Access Initiative)
Mary Waiyego (Pumwani Maternity Hospital)
Matthew Khoory (mOm Incubators)
Melissa Medvedev (University of California, San Francisco; London School of Hygiene and Tropical Medicine)
Msandeni Chiume (Kamuzu Central Hospital)
Naomi Spotswood (Burnet Institute)
Norman Lufesi (Ministry of Health Malawi)
Pascal Lavoie (University of British Columbia)
Queen Dube (College of Medicine, Malawi)
Rachel Mbuthia (GE Healthcare)
Rebecca Richards-Kortum (Rice University)
Rhoda Chifisi (Kamuzu Central Hospital)
Rita Owino (GE Healthcare)
Robert Moshiro (Muhimbili National Hospital)
Ronald Mbwasi (Kilimanjaro Christian Medical Centre)
Sam Akech (KEMRI-Wellcome Trust Research Programme)
Sara Liaghati-Mobarhan (Rice University)
Sona Shah (Neopenda)
Steffen Reschwamm (MTTS)

Steve Adudans (CPHD/MQG)
Thabiso Mogotsi (University of Botswana)
Walter Karlen (ETH Zurich)
Zelalem Demeke (Clinton Health Access Initiative)

Appendix C: Abbreviations

°C	Degrees Celsius
bCPAP	Bubble continuous positive airway pressure
bpm	Beats per minute / Breaths per minute
CE Mark	Conformité Européenne – certification mark
cm	Centimeters
cm^2	Centimeter squared
CRP	C-reactive protein
CPAP	Continuous positive airway pressure
DHS	Demographic and health survey
FDA	Food and Drug Administration
HIS	Health information system
Hz	Hertz
IMR	Infant mortality rate
ISO	International Standards Organization
IV	Intravenous
KMC	Kangaroo Mother Care
kg	Kilogram
LPM	Liters per minute
LRS	Low-resource settings
MCH	Maternal and child health
MDG	Millennium Development Goal
Mg/dL	Milligrams per deciliter
mL/hr	Milliliters per hour
mmol/L	Millimoles per liter
µmol/L	Micromoles per liter
MMR	Maternal mortality rate
MNCH	Maternal, newborn, and child health
MNH	Maternal and neonatal health
nm	Nanometer
NMR	Neonatal mortality rate
PCT	Procalcitonin
PEEP	Positive end-expiratory pressure
PR	Pulse rate
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SpO2	Peripheral saturation of oxygen
SDG	Sustainable Development Goal
TFR	Total fertility rate
U5MR	Under-5 mortality rate
UNFPA	United Nations Population Fund
USAID	U.S. Agency for International Development
uW	Micro Watts
W	Watt
WHO	World Health Organization