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NEST360°

Target Product Profile

Respiratory Rate Monitor / Apnea Monitor – Respiratory Support

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Table of Contents

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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].

Respiratory rate is a critical vital sign. The causes are many but are commonly due to respiratory pathology. Increased respiratory rate (> 60bpm) in newborns can indicate respiratory distress syndrome (RDS), but as with infants and children, a high respiratory rate can also indicate pneumonia, which is the primary infectious cause of childhood death worldwide.

A low respiratory rate or gaps in breathing in infants is likewise indicative of potentially severe health concerns. Apnea of prematurity is a condition in which newborns temporarily stop breathing. Many apneas resolve without intervention, but frequent apnea (often paired with bradycardia and low SpO2) can indicate an underlying condition such as sepsis, hypoglycemia, or anemia. Apnea of prematurity (AOP), a condition in which newborns temporarily stop breathing due to neurologic immaturity, affects nearly 50% of infants born earlier than 32 weeks gestational age and nearly 100% of those born at fewer than 28 weeks, and may last for several weeks [2]. AOP can be associated with dangerous decreases in heart rate and oxygenation, which, left unchecked, could lead to respiratory arrest, increased morbidity, or death.

In high-resource settings, respiratory rate is monitored using impedance pneumography, which requires expensive patient monitors and delicate electronic sensors. Alternatively in high-resource settings, AOP is monitored by using low nursing ratios (1:2) in conjunction with continuous heart rate and pulse oximetry monitoring. In this setting, a nurse or caregiver would provide a manual intervention in the event of an AOP event causing a low heart rate or oxygen saturation, in order to re-establish normal breathing. In low-resource settings, a nurse, normally faced with high nurse to patient ratios, must rely on limited continuous monitoring capability of heart rate and saturation with most infants only receiving intermittent manual monitoring. Additionally, they should observe the number of breaths a child takes in one minute, a procedure that is both time-consuming and inadequate for monitoring infants at risk of AOP.

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.

15 respondents participated in the Delphi-like survey for the Respiratory Rate Monitor / Apnea Monitor.

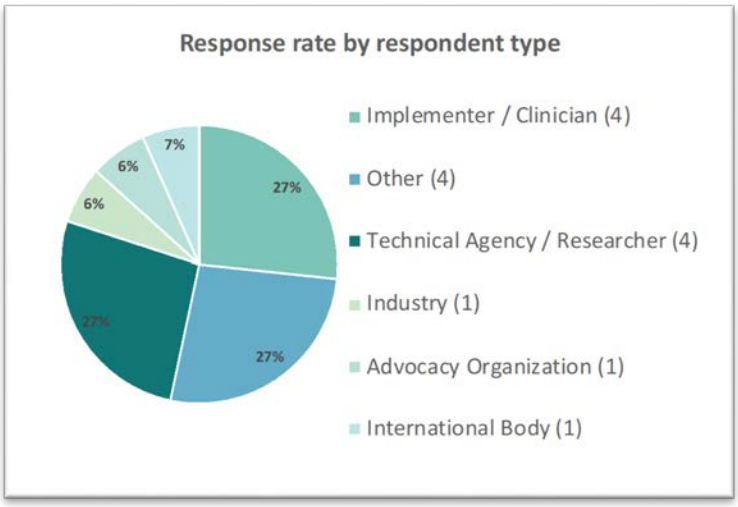
Survey respondents were requested to provide a statement on their level of agreement with each of the proposed characteristics for each TPP. Agreement was scored on a Likert scale ranging from 1 to 5 (1=disagree, 2=mostly disagree, 3= neither agree nor disagree, 4=mostly agree, 5=fully agree) with an 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.

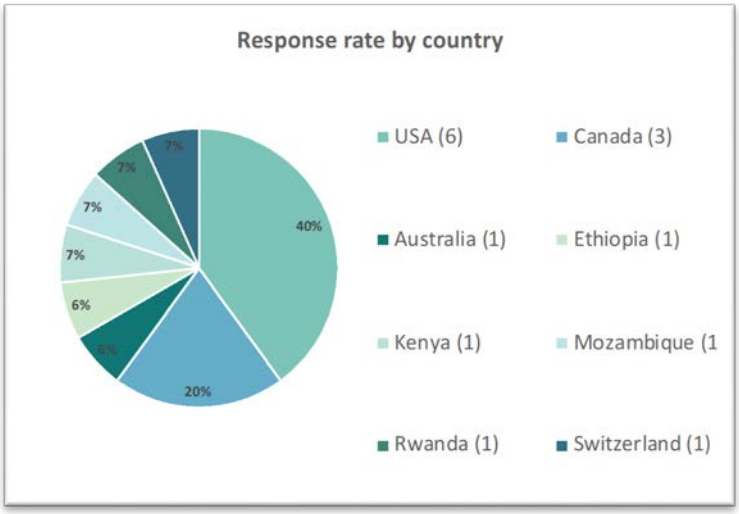
In total, over 180 organizations/individuals were asked to participate in this Delphi-like survey process, of whom 103 (see Appendix A) responded (response rate, 56%). Survey respondents were asked to self-disclose their affiliation.

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



Respondent type	Percentage
Implementer / Clinician (4)	27%
Other (4)	27%
Technical Agency / Researcher (4)	27%
Industry (1)	6%
Advocacy Organization (1)	6%
International Body (1)	7%

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



Country	Percentage
USA (6)	40%
Canada (3)	20%
Australia (1)	7%
Ethiopia (1)	7%
Kenya (1)	7%
Mozambique (1)	7%
Rwanda (1)	7%
Switzerland (1)	7%

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 Respiratory Rate Monitor / Apnea Monitor 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 - RESPIRATORY RATE MONITOR / APNEA MONITOR

Final target product profile for Respiratory Rate Monitor / Apnea Monitor		
Characteristic	**Optimal**	**Minimal**
SCOPE		
Intended Use	To provide continuous monitoring of respiratory rate	
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, but, may be used in health facilities based on country guidelines	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		
Apnea Detection	Detect periods of central apnea exceeding 20s duration (at 0)	
Respiratory Rate Accuracy	± 2 bpm	± 5 bpm
Respiratory Rate Range	0-100 bpm	
Alarm	Visual and auditory	An alarm (visual or auditory)
Patient Interface	Interface is biocompatible and reusable	Interface is biocompatible
Respiratory Rate Alarm Limits	Automatically adjust based on patient age	30-60 bpm
Apnea Intervention	Yes	No
PURCHASING CONSIDERATIONS		
Instrument Pricing	<$100 ex-works	<$250 ex-works
UTILITY REQUIREMENTS		
Power Source	Mains with rechargeable battery	Mains with rechargeable battery
Battery	Rechargeable battery, >24hrs on a single charge	Rechargeable battery, >6hrs on a single charge
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
Decontamination	Easy to clean with common disinfecting agents	

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

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Consensus Meeting Summary: Respiratory Rate Monitor / Apnea Monitor

To arrive at the final TPP for Respiratory Rate Monitor / Apnea Monitor, 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.

- **Apnea Detection**
  - Consensus was achieved in the room (without a Mentimeter vote) for both the Optimal and Minimal characteristics. Clinicians confirmed that they definitely wanted the monitor to alarm for apnea and that, additionally, it would be helpful to have the ability to adjust the interval detection frequency based on the baby. Product developers noted that this technology was not fully mature yet and challenging to improve. They explained that from a technical perspective, the rate was retrospective and therefore more complex to technically calculate the average over a historical period of time and produce a read out based on the determined algorithm. One clinician suggested that the algorithm be built so that when a period of apnea was detected, a side countdown begins and if it hits 20 seconds, an alarm would sound. Both clinicians and technical developers agreed on the importance of two separate counters: one for historical averages of respiratory rate and a second for when a baby experiences apnea, upon which a prompt warning alarm would sound. One international NGO participant mentioned an interest in better understanding 'normal' apnea patterns/trends in newborns prior to agreeing on alarm levels since desaturation could happen quite quickly.
  - *Optimal: Detect periods of central apnea exceeding 20s duration (at 0).*
  - *Minimal: Same as Optimal.*
- **Respiratory Rate Accuracy**
  - Consensus was achieved in the room (without a Mentimeter vote) for the Minimal characteristic. Product developers noted that it can be challenging to conduct validation on accuracy for ±2 bpm since a gold standard does not currently exist to measure respiratory rate accuracy. A research question was developed emphasizing the need for an improved way to measure accuracy since international standards for respiratory rate accuracy do not currently exist. There is therefore a need to define gold standard for respiratory rate accuracy and standardize experimental conditions. Ethical considerations are important in evaluating and validating these standards at upper and lower ranges on neonates. One participant recommended that both SpO2 and respiratory rate accuracy thresholds be based on real clinical data (typical variability). In the Pre-Meeting report survey, one individual commented that given there was not a 'gold standard' measurement for respiratory rate, they specified a reasonable reference standard with human experts and video recordings and specifying an acceptable degree of agreement with that standard, using the 95% Limits of Agreement and the Bland-Altman plot. However, an international NGO responded that using humans as a 'reasonable reference standard' can be troublesome since

they can often be inconsistent or incorrect. Furthermore, they noted that "regulators will likely not see [human experts] as a means to validate".
  - *Minimal: ±5bpm*
- **Respiratory Rate Range**
  - Consensus was achieved in the room (without a Mentimeter vote) for the Optimal characteristic to be 0-100 bpm. Clinicians confirmed that 100 bpm was sufficient at the higher end and would not impact their treatment decision. Rather, they confirmed that it is helpful to view the trend (i.e., if a baby is at 85bpm and moving up to 95bpm).
  - *Optimal: 0-100 bpm*
  - *Minimal: Same as Optimal*
- **Respiratory Rate Resolution**
  - This characteristic was not discussed as it was determined to remove from the TPP. It was noted that the characteristic was too specific for early stage development.
- **Alarm**
  - Consensus was achieved in the room (without a Mentimeter vote) that an alarm should exist for the Minimal requirement, however, flexibility could be left to the developer on the type of alarm. Some participants voiced a preference for a sound alarm while others noted that in a hospital environment where there are already a lot of sound alarms, it was important to have a visual alarm.
  - *Minimal: Yes (an alarm)*
- **Apnea Alarm Limits**
  - This characteristic was not discussed as it was determined to remove from the TPP. It was noted that the characteristic was too specific for early stage development.
- **Consumables**
  - This characteristic was not discussed as it was determined to remove from the TPP. It was noted that the characteristic was too specific for early stage development.
- **Voltage**
  - 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.
  - *Optimal and Minimal: 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)*
- **Battery (previously titled 'Battery Powered')**
  - Clinicians noted that the intention is to leave the device on for 24 hours, hence the time period. Discussion in the room encouraged product developers to be creative (e.g., device could plug into wall, connect with other devices, etc.). Clinicians noted a preference to avoid wired connections to mains and emphasized that "there are already too many wires". There was agreement in the room that if the device was not connected to a mains power source, constant power for 24 hours would be required, however, if it was connected to a mains power source, then 12 hours back-up for power shedding would be sufficient for the Optimal characteristic. For the Minimal characteristic, if the device was not connected to a mains power source, constant power for 24 hours would be required, however, if the device was connected to a mains power source, then at least 6 hours of back-up for power shedding should be required. Product developers noted that the battery was more complex than a "watch battery" since certification was required for each part and supplier used in development.
  - A research question was established to review existing literature on power cuts to determine how long power supply should last. One meeting participant subsequently sent the following recommendations providing data on power cuts to share with the broader group in this report: 1) Limited electricity access in health facilities of sub-Saharan Africa: a systematic review of data on electricity access, sources, and reliability [3] 2) Oxygen insecurity and mortality in resource-constrained healthcare facilities in rural Kenya [4] and 3) Assessment of Power Availability and Development of a Low-Cost Battery-Powered Medical Oxygen Delivery System: For Use in Low-Resource Health Facilities in Developing Countries [5].

- 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.
- *Optimal: Rechargeable battery, >24hrs on a single charge*
- *Minimal: Rechargeable battery, >6hrs on a single charge*

- **Size**
  - This characteristic was not discussed as it was determined to remove from the TPP. It was noted that the characteristic was too specific for early stage development.
- **Weight**
  - This characteristic was not discussed as it was determined to remove from the TPP. It was noted that the characteristic was too specific for early stage development.
- **Consumable Pricing**
  - This characteristic was not discussed as it was determined to remove from the TPP. It was noted that the characteristic was too specific for early stage development.

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 is "110-240V 50-60hz" 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: Respiratory Rate Monitor / Apnea Monitor

Delphi-like survey results for Respiratory Rate Monitor / Apnea Monitor 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 provide continuous monitoring of respiratory rate.	**79% n = 14**	Minimal: Same as Optimal.	**77% n = 13**	4 comments as summarized below • Theme: Continuous not needed in all situations • Theme: Clinical value o "Respiratory rate monitors my experience are finicky, alarm a lot, and are only useful if there is someone there that was confident to respond to them. Theoretically you could try to get mothers to do this (respond to an alarm) if the ward is set up for them to stay with the babies (not usually the case). But I think even if the moms CAN be w/the babies 24/7 that is unrealistic expectation of them (we have trouble getting moms in the US to do this)." o "Optimally: In my mind the only useful respiratory rate

	Optimal		Minimal		
					monitor is one that could alarm AND respond (stimulate the baby) in the event of an apnea. Otherwise, this is something I would consider more for a ICU/level 3 care technology versus comprehensive/level 2 care technology." "Not accurate and of very limited immediate need in a SCN or NICU in limited resource not enough staffing…just use sat"
Target Operator	Optimal: For use in low- and middle-income countries by a wide variety of clinicians, including nurses, clinical officers, and pediatricians.	**100%** **n = 12**	Minimal: Same as Optimal	**100%** **n = 11**	1 comment • "I agree that this is the population that should be able to apply and trouble shoot a respiratory monitor - but it's not realistic in my opinion that the nurse:patient ratio will be such that they can respond to all the alarms."
Target Population	Optimal: Neonates (<28 days)	**83%** **n = 12**	Minimal: Same as Optimal.	**73%** **n = 11**	6 comments as summarized below • Theme: Broaden age range or specify weight range
Target Setting	Optimal: Hospitals in low-resource settings	**67%** **n = 12**	Minimal: Same as Optimal.	**64%** **n = 11**	8 comments as summarized below • Theme: Optimal would include high-functioning health centres (primary) or home-use o "Could be useful in diagnoses of pneumonia (would impact Intended Use)" o "How far into the periphery of the health service we can push oxygen for neonates? On the one hand the mortality tends to be at the village level or first-contact health facility, so we should aim for the smallest health facilities that care for in-patients. On the other hand, the level of skill, training and other resources needed to care for neonates may make it impractical to go beyond the largest sub-district health centres. Whatever level we choose, it is worthwhile thinking about some technology to help stabilise and transport a neonate who

	Optimal		Minimal		
					needs referral to a more central level."
International Standard	Optimal: ISO 13485:2016 Medical devices – Quality management systems -- Requirements for regulatory purposes.	**78%** **n = 9**	Minimal: Same as Optimal.	**63%** **n = 8**	4 comments as summarized below • The standard does not define specific testing requirements for respiratory monitors. Something similar to standard of pulse oximetry would be desirable • Requiring ISO may limit innovation and is not based on what is needed for low-resource settings
Regulation	Optimal: CE marking or US FDA Clearance	**73%** **n = 11**	Minimal: Same as Optimal.	**60%** **n = 10**	5 comments as summarized below • Theme: Add more flexibility v. irrelevance of characteristic • Consider additional 'or' options: o Other Stringent Regulatory Authorities – Japan or Australia or Canada o Consider regulatory bodies of Low- and Middle-Income Countries o Some respondents did not think that regulatory approval necessarily translated to good performance.
Apnea Detection	Optimal: Detect periods of central apnea exceeding 20s duration.	**70%** **n = 10**	Minimal: None.	**60%** **n = 10**	8 comments as summarized below • Theme: Recommend removing "central" to make implicit this is for premature infants • Theme: An accurate count of respiratory rate may alone be useful • Consider shorter periods
Respiratory Rate Accuracy	Optimal: +- 2 bpm	**75%** **n = 12**	Minimal: +- 10 bpm	**30%** **n = 10**	9 comments as summarized below • Theme: Wide variation in what is required vs. what might be technically achievable o Minimal needs to be less than +- 5 bpm o Optimal needs to be +- 5 bpm o Impossible to achieve o 10 bpm is not clinically useful / would alarm too often? o WHO has indicated absolute breathing rate deviance ±2 breaths/min in measuring RR. I believe what is stated here

	Optimal		Minimal		
					as Optimal is actually also minimal. o There is not a 'gold standard' measurement of respiratory rate that allows the calculation of accuracy for a new method. On the other hand, we did manage to specify a reasonable reference standard (the best being human experts with video recordings), and we can specify an acceptable degree of agreement with that standard, using the 95% Limits of Agreement and the Bland-Altman plot
Respiratory Rate Range *(corrected from 'Pressure')*	Optimal: 0-120 bpm	**73%** **n = 11**	Minimal: 0-100 bpm	**78%** **n = 9**	4 comments as summarized below • Theme: Other suggested ranges were provided o May be able to lower Minimal window to 0-90 bpm o Change Optimal to 0-100 bpm o Limit of 80 bpm is fine • For a neonate, anything above 60 is a cause for concern, and PALS indicate that even in HEALTHY premies and neonates, breath rate can climb to 70 and 55 respectively. So long as there is clinical rational for such a high end on the range, then one can only ask! However, given other 'asks' in this questionnaire, I am only aware of products whose algorithms can manage an upper bound of 90
Respiratory Rate Resolution	Optimal: 1 bpm	**100%** **n = 11**	Minimal: 2 bpm	**67%** **n = 9**	5 comments as summarized below • Need clarity on accuracy rate versus respiratory rate resolution • No technical reason to do this • Minimal should be same as Optimal
Alarm	Optimal: Visual and auditory	**100%** **n = 13**	Minimal: Visual only	**67%** **n = 12**	7 comments as summarized below • Theme: Auditory Only preferred over Visual Only • Depends on Continuous Monitoring vs. Spot Check • Minimal should be same as Optimal

	Optimal		Minimal		
Apnea Alarm Limits	Optimal: Adjustable	**82%** **n = 11**	Minimal: None	**70%** **n = 10**	6 comments as summarized below • "If the system has a built in apnea alert for pauses > 20 seconds, then there shouldn't be room to adjust it, possibly to silence the alarm but not to change the limits" • "What does it mean to have an "adjustable" apnea alarm? Like it only alarms if it's associated with a decrease in heart rate as well? Or do you mean that you can adjust the length of the apnea period for which it alarms? That also wouldn't really make sense to me as it seems like this would be a parameter internally set to optimize sensitivity/specificity of alarms" • "What about alarms for battery, error, etc."
Consumables	Optimal: >12 months before required	**82%** **n = 11**	Minimal: >6 months before required	**60%** **n = 10**	4 comments as summarized below • Theme: Need clarity on what consumables are required; prefer reusable probes or sensors
Decontamination	Optimal: Easy to clean with common disinfecting agents	**100%** **n = 12**	Minimal: Same as Optimal.	**100%** **n = 11**	2 comments as summarized below • Provide guidance • Needs to withstand chlorine and bleach
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.	**83%** **n = 12**	Minimal: User manual provided.	**82%** **n = 11**	5 comments as summarized below • Electronic copy is highly preferred o 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 (take India, for example) and so this is simply not a reasonable ask of manufacturers. "User language preference prioritized, English is mandatory." Also, any manufacturer should be encouraged to use

	Optimal		Minimal		
					pictograms to support user manuals
Voltage	Optimal: 110-240V 50-60hz	**100%** **n = 10**	Minimal: 220-240V 50-60hz	**44%** **n = 9**	5 comments as summarized below • Theme: Lower Voltage should be considered o 12 Volt might be more appropriate for this size of device • This is a device with a very low power consumption so, like our laptops and our mobile phones, the Optimal should be the minimal
Battery Powered	Optimal: Yes, > 4 hr on a single charge	**85%** **n = 13**	Minimal: No	**42%** **n = 12**	9 comments as summarized below • Theme: Clarify what is meant by 'None': o Backup power is a must have o Optimal: rechargeable batteries with ability to swap out to standardly available batteries (e.g. AA) o Minimal: rechargeable batteries o Can device be used while charging? • Theme: Variation in length of battery backup o 1 hour o 4 hours
Patient Interface	Optimal: Interface is biocompatible and reusable.	**100%** **n = 12**	Minimal: Interface is biocompatible.	**80%** **n = 10**	4 comments as summarized below • Theme: Even low-cost consumables become a financial burden, and single-use items should be avoided wherever possible
Respiratory Rate Alarm Limits	Optimal: Automatically adjust based on patient age	**82%** **n = 11**	Minimal: 30-60 bpm	**100%** **n = 9**	6 comments as summarized below • Theme: Broaden the range: o Minimal needs to be 0-60 since the whole point is to detect apnea in neonates? o Consider some other method besides age (e.g., weight) Not really clinically useful
Size	Optimal: Small footprint; can be left at bedside.	**75%** **n = 12**	Minimal: Same as Optimal.	**73%** **n = 11**	4 comments as summarized below • Theme: Small size may need to consider additional insights o More easily displaced More easily used across patients without cleaning

	Optimal		Minimal		
Weight	Optimal: < 500 g	**73%** **n = 11**	Minimal: Same as Optimal.	**78%** **n = 9**	4 comments as summarized below • Theme: Varying opinions on the need to specify weight o Weight on baby? o Less portable is viewed as more robust o Portability may lead to disappearance of device WHO-UNICEF interagency spec is less than 400g for a handheld device (no weight maximum for tabletop device)
Apnea Intervention	Optimal: Yes	**88%** **n = 8**	Minimal: No	**75%** **n = 8**	6 comments as summarized below • Theme: Varying opinions on Apnea Intervention • Comment on Minimal: Apnea monitor without automated intervention is likely to be background noise in busy setting • No clinical evidence these interventions work This is important for neonates. If a device that monitors RR has an algorithm sensitive enough to generate RR but can also discern what is apnea and not simply loss of signal, that would be great!
Warranty	Optimal: 5 years	**80%** **n = 10**	Minimal: 1 year	**90%** **n = 10**	5 comments as summarized below • Theme: 5 years too long • Suggested Ranges: o 2 years To honor a 5 year warranty, you will have to have strong in-country representation. All an extended warranty is a degree of assurance of the above, and this will come at a cost. Manufactures of concentrators willing to extend a warranty from 2-5 do so at a cost. What might be more useful is that during any procurement, consideration be given to establishing a SLA with an in-country rep. In this case, you can take care of any major PPM requirements, as well as "swap out" in the event of a break-down, and there is no discussion of warranties and no need for spares and an in-country source for consumables.
Instrument Pricing	Optimal: <$100 ex-works	**90%** **n = 10**	Minimal: <$250 ex-works	**78%** **n = 9**	2 comments as summarized below Based on COGS, minimal should be <$150, but I am assuming RR derivation using a limited technologies (based on other questions in this survey)

	Optimal		Minimal		
Consumable Pricing	Optimal: <$50 per year ex-works	**80%** **n = 10**	Minimal: <$100 per year ex-works	**67%** **n = 9**	4 comments as summarized below • Single-use items not feasible Minimal, under $80, Optimal, under $40.

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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