Target Product Profile

For Retinopathy of Prematurity (ROP) Imaging Device

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

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INTRODUCTION

BACKGROUND ON NEWBORN TPPS

Globally, 2.5 million children die in the first month of life and more than half of these deaths are due to conditions that could be prevented or treated with access to simple, affordable interventions [1]**.**

The first 28 days of life – the neonatal period – represent the most vulnerable time for a child's survival. Globally, more children than ever before are being born in facilities and there are well-described, low-cost, evidence-based practices to address neonatal mortality. However, three quarters of neonatal deaths (nearly 2 million) happen in the first week of life when a child is still at or near a health facility [2]. Health interventions are needed that can provide comprehensive neonatal care at facilities to address the major causes of neonatal deaths. Many of these health interventions are known and can be cost-effective. These interventions though may be different from other interventions needed to address broader under-5 deaths [3].

For the first time ever in 2015 the world pledged to end preventable newborn deaths by 2030 (Sustainable Development Goal 3.2) [4]. On current trends, more than 60 countries will miss the Sustainable Development Goal (SDG) target of reducing neonatal mortality to at or below 12 deaths per 1,000 live births by 2030. About half will still not reach the target by 2050. These countries carry about 80 per cent of the burden of neonatal deaths in 2016 [3]. Focused efforts to strengthen the ability of health systems to deliver neonatal care are still needed in sub-Saharan Africa and South East Asia so as to prevent 80 per cent of these deaths [1].

To address neonatal mortality, the World Health Organization (WHO) is working with Ministries of Health and partners to expand quality services for sick and small newborns in the first week of life [5]. Critical to the sustainable implementation of quality facility-based services will be equipping not only people, but facilities with neonatal equipment that is high quality, affordable, robust, and appropriate for comprehensive care delivery in low-resource settings.

Globally, the largest contributors to neonatal mortality are preterm birth, intrapartum complications, and infection. Many deaths attributable to these causes are preventable through six categories of care:

1. HYDRATION, NUTRITION, AND DRUG DELIVERY
2. JAUNDICE MANAGEMENT
3. POINT-OF-CARE DIAGNOSTICS
4. INFECTION PREVENTION AND CONTROL
5. RESPIRATORY SUPPORT
6. THERMAL MANAGEMENT

Most neonatal healthcare technologies that support these pathways of care are designed for high-resource settings and are either unavailable or unsuitable for use in low-resource settings. As a result, providers resource limited settings lack the tools needed to deliver quality, comprehensive, newborn care.

There is an urgent need for neonatal healthcare technologies that are affordable, rugged, effective, simple to use and maintain, and able to operate from various power supplies.

The Newborn Target Profiles outline sixteen product categories within these six categories of care and define the product requirements for these technologies. These technologies have the potential to save the lives of infants globally and reduce preventable newborn deaths. As these technologies become more widespread and available, the increased survival rate of low birth weight infants will lead to a population of infants at risk of developing Retinopathy of Prematurity (ROP) [6].

The Every Newborn Action Plan (ENAP) published by the World Health Organization (WHO) and UNICEF sets out a vision of "a world in which there are no preventable deaths of newborns or stillbirths" and where "babies and children survive, thrive and reach their full potential." As neonatal care improves, the quality of care is critical in order to reduce risks of disabilities or impairments, for example, for preterm infants vulnerable to eye complications [7]. As outlined in WHO/UNICEF's Survive and Thrive: Transforming care for small and sick newborns, ROP is directly related to the quality of inpatient care [8]. Blindness from retinopathy of prematurity can largely be prevented by improving the quality of neonatal care, including safer use of oxygen, and by screening to detect sight-threatening ROP early, followed by urgent treatment.

The launch of the Every Newborn Action Plan: 2025 Coverage Targets and Milestones intends to move faster to end preventable newborn deaths and stillbirths by 2030. The goal is to providing screening for and treatment for ROP at Level 3: Tertiary Care facilities [9]. In countries, such as India, where there has been an ambitious scale up of newborn care, ROP screening has become a more prominent issue, emphasizing the growing importance of ROP screening as newborn care continues to improve globally [10].

BACKGROUND ON RETINOPATHY OF PREMATURITY (ROP)

Overview

Why is ROP important?

ROP is a potentially blinding condition of infants born preterm who have received intensive neonatal care. The visual loss in ROP is usually total, bilateral and irreversible. As so much early learning is through vision, early onset blindness can have a major impact on all aspects of a child's development, which can have life-long consequences.

In 2010, it was estimated that 32,200 preterm infants became blind or visually impaired every year from ROP [11]. Most countries are now affected, due to the development or expansion of intensive neonatal care, apart from the least developed countries in Asia and Africa. In many middle income countries, ROP is the most common cause of blindness in children. The emerging epidemic of ROP blindness in many of these countries can be attributed to high preterm birth rates, suboptimal neonatal care which puts more mature infants at risk, and a lack of high quality screening and treatment programs for those at risk [12].

What is ROP?

Preterm infants are at risk of ROP as the blood vessels in their retinas are not fully developed at birth. In ROP the retinal blood vessels initially stop growing, and then proliferate abnormally. The end result can be total retinal detachment or scarring and distortion of the retina.

The international classification of ROP describes the severity (Stages) and site (Zones) in the retina of ROP, and signs of active disease [13]. There are 5 Stages; Stage 1 is mild disease and Stage 5 is total retinal detachment. There are 3 Zones; Zone 1 is an area around the optic disc and Zone 3 is the peripheral retina on the temporal side. Signs of active disease, "plus" disease, are characterized by abnormal dilation and tortuosity of the retinal blood vessels.

ROP is not present at birth, as it usually develops after the first few weeks. The condition then progresses over the following few weeks, with spontaneous regression in most infants. However, in 5-15% of preterm infants the signs progress to the "sight-threatening" stages; without treatment progression to retinal detachment occurs in approximately one in six of these infants.

What causes ROP?

The most important risk factor for ROP is prematurity and low birth weight; [14] the more preterm the infant the greater the risk. Modifiable risk factors at birth include early cord clamping, resuscitation with supplemental oxygen and mechanical ventilation when not required, and low body temperature. During the neonatal period, modifiable risk factors include [14]

- inadequately regulated supplemental oxygen leading to hyperoxia
- sepsis
- failure to gain weight
- lack of supportive care such as kangaroo care
- blood transfusions
- thrombocytopenia [15]

Indeed, ROP can be thought of as an indicator of the overall quality of neonatal care infants receive.

How can we prevent blindness from ROP?

Blindness from ROP can largely be prevented by implementing strategies for primordial and primary prevention (preventing preterm birth and reducing the risk of ROP in infants born preterm), secondary prevention (early detection and treatment of infants with sight-threatening ROP) and tertiary prevention (surgery for retinal detachment and vision rehabilitation)

Primordial prevention entails reducing preterm birth rates. Although this is challenging, preventing teenage pregnancies, better regulation of assisted fertilization and smoking cessation during pregnancy can be effective strategies [16].

Primary prevention entails a course of antenatal steroids to women threatening preterm delivery, as recommended by WHO, [17] followed by high quality neonatal care from immediately after birth.

Secondary prevention entails detecting infants who develop sight-threatening ROP, though routine examination / screening, followed by urgent treatment with laser or intravitreal injection of an anti-vascular endothelial growth factor (VEGF) agent [18]. Long-term follow up is essential to detect and manage other ocular complications of ROP.

Tertiary prevention entails complex vitreoretinal surgery for infants with partial retinal detachment (Stage 4) which can be effective [19]. Surgery for Stage 5 disease carries a very poor prognosis even after surgery. Tertiary prevention also entails vision rehabilitation to reduce developmental delay in infants and young children with vision loss from ROP.

1. Preventing ROP in preterm infants

High quality neonatal care from immediately after birth (the “first golden hour”) and during the inpatient stay can largely prevent sight-threatening ROP [20, 21].

Antenatal care

A course of antenatal steroids to women threatening preterm delivery.

First golden hour [22]

- delayed cord clamping to 60-90 seconds after delivery
- keeping infants warm
- gentle resuscitation, avoiding supplemental oxygen and mechanical ventilation unless absolutely necessary

Care throughout the neonatal inpatient stay [23]

During the inpatient stay, the following can reduce the risk of sight-threatening ROP:

- careful monitoring of supplemental oxygen
- infection control

- avoiding blood transfusions
- ensuring adequate nutrition including early introduction of breast milk feeds
- supportive care, such as nesting and kangaroo mother care.

Regarding oxygen, ROP is associated with exposure to high levels of oxygen during the newborn period. According to the WHO/UNICEF's *Survive and Thrive: Transforming care for small and sick newborns*, while many LMIC settings offer oxygen to preterm newborns, they are not able to provide blended oxygen (i.e., less than 100%) which is a potent risk factor for ROP. [8] The World Health Organization (WHO) recommends that oxygen saturations should not be lower than 89% or higher than 94% for preterm babies with a gestational age of less than 32 weeks. This means that the lower alarm should be set at 88% and the upper at 95% [24, 25].

Regular, small doses of oral caffeine reduce the risk of ROP [21].

Preventing ROP requires neonatal teams who are adequately trained and equipped to deliver high quality care, and the active involvement of parents in their child's care [20, 22].

2. Detecting and treating sight-threatening ROP

Why is screening important?

The indications for treating ROP are a combination of the severity (Stage) and site (Zone) of the ROP, and whether plus disease is present. The current indications arise from the Early Treatment Trial of ROP [23], and the combination of signs is called Type 1 ROP. For example, an infant with Stage 3 ROP in Zone 1 with plus disease should be treated.

The purpose of screening is to detect Type 1 ROP early, when the disease can be effectively treated. If the condition progresses to Stage 4 or 5, treatment is far less effective.

Which infants should be screened?

This is a difficult question to answer, as which babies develop ROP depends on the level of neonatal care they have received [24]. In neonatal units providing excellent care, only very preterm, low birth weight babies develop sight-threatening ROP (i.e., born at less than 32 week's gestation, or with a birthweight of less than 1,500g). In units providing poorer care, more mature, heavier infants are also at risk. Each country needs to develop their own evidence-based screening criteria [25].

Who is responsible for identifying which infants should be screened?

This is the responsibility of neonatologists / pediatricians. A nurse or assistant can generate the list of infants eligible for screening and counsel the parents.

When should screening start?

Screening usually starts at around 4 weeks of age; this can be brought forward to 2 weeks in very sick infants.

How is Type 1 ROP detected?

A detailed examination of the retina in both eyes of all infants listed as requiring screening is required, after dilating the pupils. All infants who are still inpatients at the time of the first and subsequent screening should be examined in the neonatal unit. Discharged infants can be examined in the unit when they come back for follow up, or in an eye department / clinic.
There are several different approaches to screening:

- An ophthalmologist visits the unit once or twice a week on a fixed day and time to examine infants who have been listed. The examination can be undertaken using an indirect ophthalmoscope or a wide field imaging system.
- A trained nurse or technician takes images of the retina using a wide-field imaging system. The images are either sent via the internet to an ophthalmologist for grading, or the technician, if skilled enough, grades the images and sends images of infants where sight-threatening ROP is suspected to an ophthalmologist for confirmation [26].

A nurse must be present during screening, to monitor vital signs.

When can screening stop?

Screening should be repeated at one or two weekly intervals, depending on the clinical findings.

Screening can stop when one of the following occurs:

1. Early Treatment of Retinopathy of Prematurity (ETROP) Type 1 ROP is detected in one or both eyes. The infant must be treated within 48 hours.
2. Mild disease was present but has definitely regressed without treatment
3. ROP cannot develop as the retinal blood vessels have grown out normally i.e., to the periphery of the retina

How is sight-threatening ETROP Type 1 ROP treated

There are two approaches to treatment [18]

- Peripheral laser treatment by a skilled ophthalmologist
- Injections of an antiVEGF agent into the back of the eye (intravitreal) by a skilled ophthalmologist

Laser treatment is the gold standard method. Because the long-term systemic safety of antVEGF agents is not yet known, this treatment should only be used when laser is not technically possible, or when very severe disease is present. Written informed consent must be obtained from parents.

Laser treatment is painful and antiVEGF injections are stressful. The procedures should be carried out under sedation or general anesthetic. Vital signs must be monitored, and a neonatologist should be present in case resuscitation is required. The infants must be carefully observed for at least 24 hours after treatment.

When should babies be examined again after treatment?

An ophthalmologist should examine the babies one week after treatment, to look for signs of regression or complications. The timing of further follow up depends on the findings.

Infants treated with antiVEGF agents need frequent follow up during the first year, as the ROP can reactivate many months later.

Can the treatment be repeated?

Retreatment is sometimes indicated.

3. Follow up care

Why is follow up care important?

All children born preterm are at higher risk of short-sightedness (myopia) and squint than children born at term [27]. The risk is higher in infants who developed mild or moderate ROP, and is far higher in infants treated for ROP who can also develop other complications (see table below)

Eye condition	No ROP	Mild to moderate ROP	Treated for ROP
Short sightedness	+	++	+++++
Squint	+	+	++++
Retinal scarring/ distortion	-	+	++
Cataract	-	-	+
Late retinal detachment	-	-	+

Infants should be examined by a pediatric ophthalmologist. The examination should include

1. An assessment of whether the child can see or not (e.g., do they smile in response to a silent smile?)
2. Alignment of the eyes to detect squint
3. Detailed examination of the retina in both eyes
4. Refraction to detect short-sightedness or other refractive errors

If short-sightedness is detected, this must be treated with spectacles to prevent lazy eyes (amblyopia).

WHY IS A TARGET PRODUCT PROFILE (TPP) FOR ROP NEEDED?

Blindness from ROP has been categorized in three 'epidemics'. The 'first epidemic' occurred in the United States of America and Western Europe in the 1940s and 1950s and was due to the use of unmonitored 100% supplemental oxygen. Subsequently, with advances in neonatal care and increased survival of smaller and less mature infants in the 1970s and 1980s, another wave of visual loss from ROP began, leading to the 'second epidemic'. The world is currently experiencing the 'third epidemic' of ROP, where the majority of cases are appearing in middle-income countries. As these countries experience financial, social and medical progress and care is expanded for neonates, including those born preterm, relevant policies and guidelines on the complications of preterm birth, including ROP, are often not yet in place. Therefore, high preterm birth rates paired with suboptimal neonatal care and inadequate coverage of high quality programs for detection and treatment of sight threatening ROP all contribute to the 'third epidemic' [28].

Target Product Profiles (TPPs) are necessary to spur innovation for the development of low-cost technologies that can be used for the screening and treatment of ROP, especially in low-and middle-income countries where these technologies are not affordable or widely available. This TPP defines the product requirements for a low-cost imaging camera which can be used for screening.

Of the 36 respondents to the TPP survey, Figure 1 highlights that 34% or respondents are not currently screening for ROP. Figure 2 captures some of the barriers to screening that were cited, including affordability (44%), training (17%), image quality (16%), ease of use (10%), and internet connectivity (7%).

Figure 1: Summary of screening practices for ROP Imaging TPP

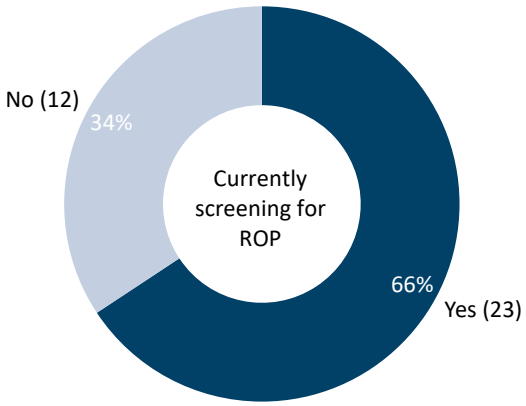
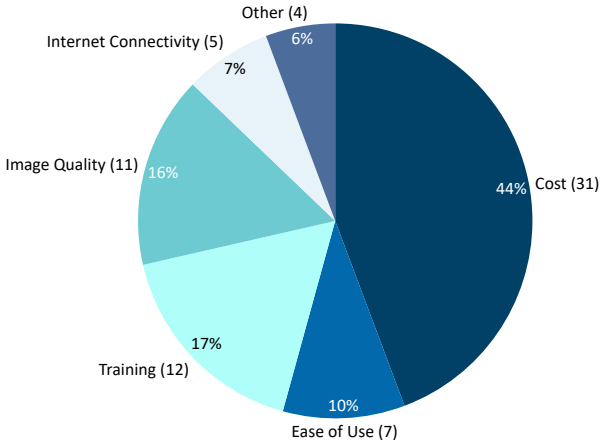
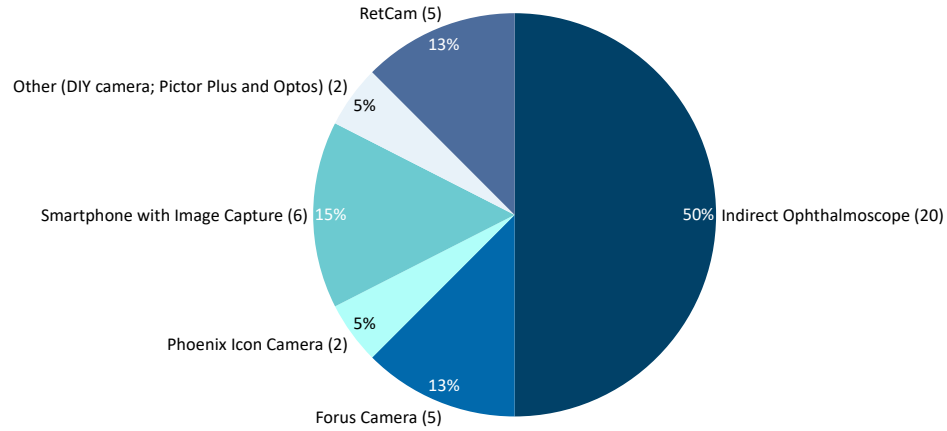


Figure 2: Summary of barriers to access screening for ROP Imaging TPP



Of the respondents who were currently screening for ROP (66%), Figure 3 highlights the different devices used for screening including indirect ophthalmoscope (50%), smartphone with image capture (15%), RetCam (13%), Forus Camera (13%), Phoenix Icon (5%), and Other (5%).

Figure 3: Summary of devices used for screening for ROP Imaging TPP



In a survey conducted by the Indian ROP (IROP) society, attitudes, access, and availability of widefield imaging in screening and documenting treatment were analyzed. 67% or respondents did not have access to a RetCam (Clarity MSI, USA) or the Indian-made wide-field ROP camera (Neo, Forus Health, India). Of those who did not have either device, over 50% were interested in incorporating imaging as part of their current practice [29].

DEVELOPING TARGET PRODUCT PROFILES

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 product requirements while aligning with the needs of end users. TPPs outline the most important performance and operational characteristics or product requirements (PR). In the TPP to follow, the term "Minimal" is used to refer to the lowest acceptable output or bare minimum for a product requirement and "Optimal" is used to refer to the ideal target for a product requirement. The Optimal and Minimal product requirements define a range. Products should meet at least all of the Minimal requirements and preferably as many of the Optimal requirements as possible. TPPs should also specify the goal to be met, the target population, the level of implementation in the healthcare system and the intended end users.

An initial TPP for an ROP imaging device was developed with leading global ROP experts which listed a proposed set of performance and operational product requirements. The development timeline envisioned is four years, although some commercially available technologies may meet the established criteria already.

DELPHI-LIKE SURVEY PROCESS

To obtain expert advice and to further develop the TPP, a Delphi-like process was used to facilitate consensus building among stakeholders.

As mentioned above, an initial draft TPP for an ROP imaging device was developed with leading global ROP experts. The initial draft TPP was translated into a survey. Prior to distribution of the survey, an open global Webinar was held on Wednesday, September 22, 2021. The title of the Webinar was "Imaging for Retinopathy of Prematurity (ROP): Challenges and Innovations" and it featured leading global experts from Asia, Africa, and Latin America along with innovative product developers. Panelists discussed the challenges with existing technologies as well as opportunities for innovation to improve access to reliable, quality ROP screening in resource-limited settings. Over 300 participants registered and 98 people were in attendance. A recording of the session is available here.

Following the Webinar, the survey link was distributed to attendees and session registrants to review the draft TPP outlining the product requirements for the imaging device TPP. This comprised a 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, 36 stakeholders from 17 countries participated in the TPP development process via an online survey.

Survey respondents were requested to provide a statement on their level of agreement with each of the proposed product requirements. 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

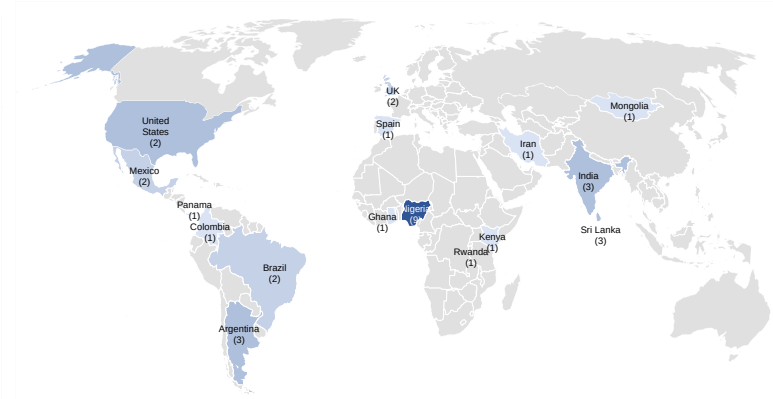
with the selection of “Other - Do not have the expertise to comment”. If participants did not agree with the product requirement (i.e., they selected 1, 2 or 3) they were asked to provide an explanation with comments. Participants who agreed with the statements could also provide comments, but these were not explicitly requested. Over 200 comments were reviewed and are summarized in this report.

For each product requirement, 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 was reached for nearly every product requirement after the first round survey, a second round survey was not initiated.

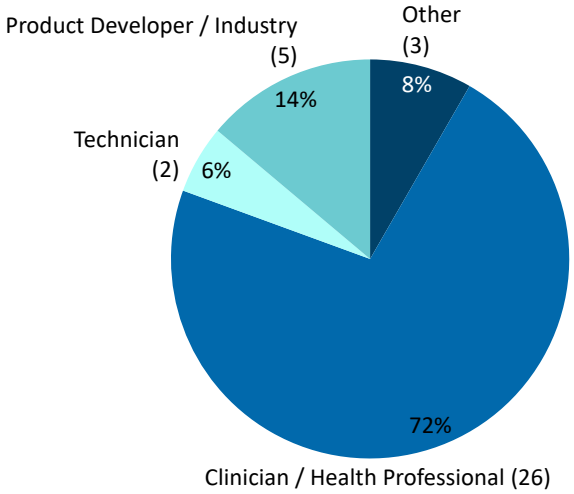
In total, over 300 individuals who registered for the Webinar were invited to participate in the Delphi-like survey process, of whom 36 (see Appendix A) responded (response rate, 12%) from 17 different countries (Figure 4). In summary, the majority of respondents were clinicians or health professionals (72%), with representation from product developers / industry (14%) and technicians (6%) (summarized in Figure 5 below).

Figure 4: Summary of response rate by country for ROP Imaging TPP



Country Primarily Work	Respondents	Percentage
Argentina	3	8%
Brazil	2	6%
Colombia	1	3%
Ghana	1	3%
India	3	8%
Iran	1	3%
Kenya	1	3%
Mexico	2	6%
Mongolia	1	3%
N/A	1	3%
Nigeria	9	25%
Panama	1	3%
Rwanda	1	3%
Spain	1	3%
Sri Lanka	3	8%
United Kingdom	2	6%
United States of America	3	8%

Figure 5: Summary of participant affiliation for ROP Imaging TPP



Respondent type	Percentage
Clinician / Health Professional (26)	72%
Product Developer / Industry (5)	14%
Technician (2)	6%
Other (3)	8%

CONSENSUS MEETING

On November 10, 2021 a virtual Consensus Meeting was held via Zoom with 56 participants. The purpose was to focus on building further consensus on areas where opinions differed. More specifically, product requirements on which fewer than 75% of the respondents agreed, or on which a distinct subgroup disagreed, were discussed. In total, there were 64 product requirements included in the survey, of which, 53 (83%) achieved consensus. Consensus Meeting moderators presented the results and comments from the 11 product requirements (17%) 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 product requirement was discussed. Zoom polling was then used to assess the level of consensus on the changes proposed. In some cases, Consensus Meeting participants nearly universally agreed on proposed changes. In one case, Consensus Meeting participants failed to reach 75% consensus on proposed changes, however, meeting participants agreed to move forward and the disagreement is noted in this report.

RESEARCH QUESTIONS

Due to time constraints, some discussion topics were not covered. There are included here as Research Questions which require further investigation.

- How does COVID-19 impact the future of ROP screening? Does this change the value of contact vs. non-contact imaging devices with small and sick newborns? For pieces of the equipment that touch the newborn's face, how are these parts disinfected and how frequently?
- How does artificial intelligence influence the development of ROP technology?

- Will a device which fulfils the Minimal product requirements be of value compared with an indirect ophthalmoscope?
- What is currently considered the Gold Standard? See below for responses collected in the ROP TPP survey
    - Indirect Ophthalmoscope
    - RetCam, Forus, ICON GO: "The portable products as RetCam Portable and 3nethra NEO (Forus Health) ultrawidefield in mosaic or optos image" // "Something that is portable - currently the ICON GO, FORUS, and RetCam have good portable systems with adequate image quality."
    - Portability: "Portable, handheld, point-of-care device" // "Gold standard will be a portable device, non contact, ultra wide field up to 200 degree, no need for pupil dilatation and with image storage and transfer (tele screening) facility."
    - Non Mydriatic Camera: "Small/portable non mydriatic camera."

FINAL TARGET PRODUCT PROFILE (TPP) FOR ROP IMAGING DEVICE

Table 1: Final TPP for Retinopathy of Prematurity (ROP) Imaging Device

	Final target product profile for ROP Imaging Device		
	Product Requirement (PR)	**Optimal** *Refers to the ideal target*	**Minimal** *Refers to the lowest acceptable or bare minimum*
	USE CASE		
PR1	**Intended Use**	Screening / diagnosis of retinopathy of prematurity (ROP) in neonates	
PR2	**Target Operator**	For use in low- and middle-income countries by a wide variety of health care professionals including ophthalmologists, neonatal nurses, clinical officers and pediatricians, as well as technicians and non-clinicians	
PR3	**Target Population**	Neonates (primarily premature and/or low birth weight, at risk for ROP)	
PR4	**Target Setting**	Neonatal units and/or eye department in hospitals in low-resource settings	
	SAFETY AND STANDARDS		
PR5	**Manufacturers' Quality Management System**	ISO 13485:2016 Medical devices – Quality management systems -- Requirements for regulatory purposes	
PR6	**Device Regulatory Status**	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		
PR7	**Field of View (FoV)**	170 degrees	36 degrees used with an appropriate condensing lens to be able to view the peripheral retina (into Zone 3)
PR8	**Image Resolution**	2048 X 2048 pixels, 24-bit colors	750 x 1334 pixels
PR9	**Imaging**	All three modes available: still, burst mode, video	Still images captured from video
PR10	**Wavelength**	Color fundus - white LED (wavelength range 400 nm - 750 nm with a peak near 600nm) FFA - blue LED (dominant wavelength @480nm)	
PR11	**Illumination**	Integrated bright light, 100-6000 lux	
PR12	**Adjustment of Images**	Intensity, gain, balance, brightness, contrast, red free, gamma, and focus	Smartphone image editing services

PR13	**Dilation Needs**	No dilation required	Yes, dilation required
PR14	**Time to Result for Imaging**	3-4 minutes	10 minutes
PR15	**Image Output Format**	JPEG, PNG, DICOM, MPEG, HEIC, PACS support	MPEG, HEIC, DICOM
PR16	**System Integration** [1]	Ability to output to cloud based support system	Standalone device with ability to output and share images
PR17	**Clinical Accuracy**	100% sensitivity and 99.8% specificity (for ROP needing treatment)	100% sensitivity and 95% specificity (for ROP needing treatment)
PR18	**Accessibility**	Portable - handheld or mobile	Portable
PR19	**Device Weight (for Imaging Capture Component)**	Less than 720g	No more than 720g
PR20	**Patient Interface**	Non-contact	Non-invasive contact
	TRAINING AND MAINTENANCE		
PR21	**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
PR22	**Preventive Maintenance**	Preventive maintenance included with additional training materials (checklists, videos, guides)	Manual for preventive maintenance included
PR23	**Decontamination**	Easy to clean surfaces, compatible with common disinfecting agents	
	POWER REQUIREMENTS		
PR24	**Power Source**	Mains with rechargeable battery or solar powered without mains power	Mains power
PR25	**Battery**	Provides battery backup, autonomy >5 hours, automatic switch to battery in case of power failure, automatic recharge on connection to mains	Battery or power-pack back-up
PR26	**Voltage**	Output spike, surge and transient protection (including lightning), with availability of Type I and Type II IEC rating lightning surge protection. Voltage and power input and output metering	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)
	DURABILITY AND LIFETIME REQUIREMENTS		
PR27	**Consumables**	None	Pupil dilation drops

	PURCHASING CONSIDERATIONS		
PR28	**Price** [2]	<$500 ex-works	<$25,000 ex-works
PR29	**Warranty**	5 years	1 year

[1] This is a new product requirement that was developed following the Consensus Meeting due to the consolidation of various product requirements included in the initial TPP Survey. Please refer to the TPP Report discussion of PR16: System Integration for additional detail and further context.

[2] There was not 75% voting agreement on both the Optimal and Minimal product requirement. Please refer to the TPP Report discussion of PR28: Price for additional detail.

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

CONSENSUS MEETING SUMMARY

To arrive at the final TPP for Retinopathy of Prematurity (ROP) Imaging Device (Table 1), we conducted a pre-meeting survey to prioritize the items for discussion at the Consensus Meeting for product requirements that achieved below 75% agreement in the survey results (Table 2). An overview of the discussion at the Consensus Meeting of these characteristics is included below.

TECHNICAL CHARACTERISTICS

PR13: DILATION NEEDS

Optimal	**Minimal**
No dilation required *86% voting agreement (n=22)*	Yes, dilation required *100% voting agreement (n=19)*

Notes about this requirement:
In current practice, dilation drops are used to dilate an infants' eyes before screening. Dilation is used whether screening is being conducted with an indirect ophthalmoscope or with a more sophisticated imaging device. However, dilation can pose challenges from the additional cost of the consumables to the skill and time required to dilate the pupils.

A discussion ensued on whether technology might be on the horizon where pupil dilation was not needed (e.g., non-mydriatic systems, or transillumination through the sclera). Participants noted that in resource-limited settings, a non-mydriatic widefield imaging product would be highly desirable as the exam would be cheaper and drug reactions would not be a concern. Non-mydriatic imaging could also be helpful in advanced ROP with poor pupillary reaction.

Industry, however, commented that while technically possible, this technology was not feasible for development in the near-term. A variety of concerns and challenges were cited including the ability to develop a wide-field system in a handheld modality which gives reproducible and validated imaging. Additionally, in order to achieve a wide angle, the working distance becomes very close and contact may be necessary for stabilization. Contact could cause harm or irritation to the baby and poses a new challenge when working with

infants who may not be able to be still. Ultimately, industry agreed that it was not realistic in the near-term to develop a handheld device that was non-contact and where pupil dilation was not required.

Therefore, consensus was achieved through voting that the Optimal requirement would still strive for technology where dilation would not be required, however, the Minimal requirement would accept that dilation could be required for use.

Ophthalmologists noted that while the task of dilation is a relatively mundane affair given their expertise, it can be more challenging to neonatologists and other clinicians with less experience. While the risk of dilation is relatively low when the guidelines are carefully followed, there may be some lingering concerns with unexperienced, unsupervised, or unmonitored clinicians using dilation drops incorrectly.

For the Minimal product requirement, consensus was achieved through voting that prescribing a diameter of pupil dilation was not necessary. Specifically, caution was advised against defining a set diameter as it would not be particularly helpful given the wide variation based on different sizes of babies (e.g., geometry of the eye, lens power, refractive power of the eye). Therefore, through a vote it was agreed that while it was reasonable to require dilation for the Minimal product requirement, it should not be prescribed to a specific mm diameter.

PR14: TIME TO RESULT FOR IMAGING

Optimal	**Minimal**
3-4 minutes *Voting not needed*	10 minutes *95% voting agreement (n=19)*

Notes about this requirement:
This product requirement focused on the time to result for image capture and output from the device. However, the discussion highlighted that for this product requirement, technology was not the limiting factor but rather the skill and experience of the user. For example, there were comments that experienced technicians could have a result for imaging in two minutes for each eye using the RetCam and 3Nethra Neo. Technology such as Optos, which provides 200 degrees visibility, can even be completed in less than a minute for both eyes by a skilled technician. Ultimately, consensus was achieved that this product requirement was highly dependent on the individual taking the images. Through a vote, consensus was achieved to keep the Minimal product requirement at 10 minutes.

PR16: SYSTEM INTEGRATION

Optimal	**Minimal**
Ability to output to cloud based support system	Standalone device with ability to output and share images

Notes about this requirement:
This new product requirement was developed following the Consensus Meeting due to the vibrant nature of the discussion. Various product requirements that were included in the initial TPP Survey (Table 2) were consolidated into this new requirement including Results Output, Storage, Connectivity, and Support System.

The discussion highlighted that extraction was a critical component for an imaging device (i.e., the device was not useful for screening unless the images could be saved and viewed again in the future). Participants noted that at a minimum, the device should be able to export images externally in some capacity (i.e., whether via a USB port, internet, etc.). Some participants preferred cloud based images for use with artificial intelligence and noted the importance of integration of information with Electronic Medical Records (EMR). Image extraction from the device was determined to be non-negotiable and critical for clinical management. Specifically, storage is required for long term care and follow-up, for legal reasons as well as for educational and research purposes. A device that can capture images for review must allow for the images to be stored, otherwise, there is limited value beyond examination with an indirect ophthalmoscope. Participants noted that the images must be compatible in an agnostic way so that they could be uploaded to different systems or platforms for review. Many participants commented that it was important to ensure that images could be extracted seamlessly, and avoid making the user a "prisoner of the product" where they are bound to a particular proprietary device or format.

It was noted that an ideal solution would have the capacity to track image progression over time, at a patient level (i.e., essentially image registration on the device). However, participants responded that this specification would go beyond an imaging camera as it would require integration with a larger system. Specifically, while an imaging device would not have the ability to store and catalogue images, an integrated platform which the camera connects to would, such as a Picture Archiving and Communications Systems (PACS). The value of the PACS is that it can provide clinical care management and potential ability for telemedicine diagnosis. For existing technologies (e.g., ICON, RETCAM), the imaging device connects to a computer which enables the storage component. Industry representatives highlighted that adding computing power for image storage to the physical device would impact other product requirements (e.g., size, weight, price).

It was highlighted that from an industry perspective, it would be in their best interest to integrate the imaging camera and system together in a proprietary fashion. However, from a clinician and public health perspective, the preference would be for an imaging camera to be system agnostic so that it would be easier to use ("we don't want to be bound or held captive by a specific industry partner"). Given there are other solutions for

managing medical images, as long as the device has the ability to export to such a system, the requirement to track within the camera itself was not deemed critical for an imaging camera.

However, a vibrant discussion at the Consensus Meeting was devoted to clarifying the difference between an imaging device and a screening device. In particular, participants emphasized the distinction between an imaging camera (which provides photo documentation) and a more comprehensive screening device (which would require storage, PACS integration, and connectivity). *Since the initial TPP survey set out to define the product requirements for an imaging device for ROP, the summary below highlights the importance of developing a meaningful ROP screening program without specifying the product requirements for such a system*.

Participants commented that a better imaging camera alone will not improve ROP screening. They noted that screening is a public health program, not just an isolated activity. Many participants commented that in order to effectively conduct screening, a better device requires not only the ability to capture images, but also a repository for storage and retrieval for clinical management. *Clinicians in India, Africa, and South America emphasized the importance of developing a screening device rather than simply a low-cost standalone imaging device*. In order to implement an effective screening program, certain attributes are important for a device, including the ability to track images on a patient level over time; ultimately, policies and programs for ROP at a national level need to be established. There are many logistical difficulties in setting up screening programs and government programs often lack the necessary monitoring and evaluation systems to track progress and identify problems as they occur [30]. Specifically, standard criteria are required to help health-care providers identify which newborns are eligible so that potential cases are not missed. It is also critical that health systems have the capacity to provide follow-up care and a skilled workforce with trained ophthalmologists [31]. Furthermore, it requires significant effort and substantial funding for a national screening program to be effective. In a Letter to the Editor titled “Screening of Retinopathy of Prematurity: A Neglected Public Health Issue”, it was proposed to integrate awareness of ROP into existing national programs dealing with maternal and child heath [32].

Product developers highlighted the cost implications of creating a system for screening. One idea proposed was designing a modular product suite which would involve users purchasing the standalone device at a certain price-point but provide the ability to “upgrade” or add-on the system integration or telemedicine for an additional cost. However, other participants strongly disagreed with the idea of offering a menu of options with the rationale being that this would ultimately increase the price if certain features were not included as part of the minimum product requirements or basic expectation.

POWER REQUIREMENTS

PR25: BATTERY

Optimal	Minimal
Provides battery backup, autonomy >5 hours, automatic switch to battery in case of power failure, automatic recharge on connection to mains *Voting not needed*	Battery or power-pack back-up *75% voting agreement (n=16)*

Notes about this requirement:
While 75% agreement was achieved through voting for the Minimal product requirement for a battery or power-pack back up, the discussion at the Consensus Meeting highlighted that a battery or power-pack back-up in the device would make the device heavier and more expensive (ranging from additional maintenance costs to regulatory costs). However, participants discussed whether the Minimal product requirement should simply be for the device to be connected to a small, uninterrupted power supply which would be a separate, stand-alone device. Ultimately, participants agreed that this would pose new challenges and that given the circumstances of use for an imaging camera, a battery or power-pack back-up was critical.

PURCHASING CONSIDERATIONS

PR28: PRICE

Optimal	Minimal
<$500 ex-works	<$25,000 ex-works

Notes about this requirement:
Consensus was not achieved on this product requirement. A summary of the discussion is captured below and please refer to Figure 2 where cost was listed as a major barrier to accessing screening for ROP.

There was disagreement on Price for both the Optimal and Minimal product requirements. From a clinician's perspective, the Optimal would be a price point that each neonatal unit could afford, thereby allowing each unit to purchase their own device. This would provide a continuous service to be available, allowing infants to

be screened at a time that is convenient and when infants return for follow-up after discharge regardless of the day of the week [30].

Some participants felt that the Optimal price should be increased to $2,000 as "anything cheaper might compromise on the quality". However, geographical differences emerged as representatives from Latin America and Africa felt that the suggested minimal requirement price of $2,5000 was not reasonable. In fact, they suggested anything more than $2,000 was unreasonable and highlighted that "eye screening is not a priority at this point for the NICU…no hospital will pay that". A nother participant commented that while equipment for the NICU can range in price, $25,000 was well above even the most expensive pieces of equipment being purchased for newborns in resource-limited settings.

In India, a cost-sharing model is being implemented whereby a screening device can be "shared" across many units through the deployment of mobile screening teams [33]. This method is likely to be more cost-effective as the price of the device can be split across multiple facilities. However, this approach requires a significant amount of coordination (e.g., which day each site will be visited and communication with families of babies requiring screening after discharge) and financial support for transport etc. Furthermore, this model may not be feasible in locations with low population density where transporting the device to remote facilities may not be practical.

Product developers noted that most of the product requirements outlined in the TPP add to the cost of the device. Product developers also need to consider the regulatory costs for each country of production as well as the long sales cycle requiring upfront capital. Interestingly, one product developer highlighted that when they brought the price of their camera five times lower, sales stagnated which wasn't sustainable.

Several studies have assessed the cost-effectiveness and value of ROP screening and treatment, with the number of healthy life years lost as the outcome. Given the high lifetime costs of early-onset severe visual impairment, screening and treatment provide significant long-term cost savings and benefit. For example, one study found that the cost-effectiveness of early intervention to prevent severe visual impairment was $14,200 per eye , which was more cost effective for severe ROP ($6,200 per eye) [34].

Another study in Brazil estimated that each examination using indirect ophthalmoscopy cost $18 per newborn. The budgetary implications for a ROP screening programme were that the addition of ROP screening would increase the overall neonatal care budget by less than 2% [35].

PR29: WARRANTY

Optimal	**Minimal**
5 years *Voting not needed*	1 year *94% voting agreement (n=16)*

Notes about this requirement:
Clinicians preferred longer warranty times and more favorable terms (e.g., in the event a device was stolen). Product developers explained that extended warranty times are very achievable, however, come with an

added cost. Ultimately consensus was achieved for the Minimal product requirement via voting that a 1-year warranty was acceptable as standard practice.

DELPHI-LIKE SURVEY RESULTS

Table 2: Delphi-like survey results for ROP Imaging Device TPP prior to Consensus Meeting (data as of Oct 11, 2021)

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS					
Characteristic	**Optimal requirements**	**Agree (all)**		**Agree (excluding product developer)**		**Minimal requirements**	**Agree (all)**		**Agree (excluding product developer)**		**Collated comments from Delphi-like survey**
		%	**n**	**%**	**n**		**%**	**n**		**n**	
Intended Use	Screening / diagnosis of retinopathy of prematurity (ROP) in neonates	100%	n=35	100%	n=28	Screening / diagnosis of retinopathy of prematurity (ROP) in neonates	91%	n=34	93%	n=27	-"For Cameras" -"I think that transillumination accessories will give opportunities of training more health teams. Easier learning curve. Also integration of images to EHR is important"
Target Operator	For use in low- and middle-income countries by a wide variety of clinicians, including ophthalmologists, neonatal nurses, clinical officers, technicians, non-clinicians and pediatricians	100%	n=35	100%	n=28	For use in low- and middle-income countries by a wide variety of clinicians, including ophthalmologists, neonatal nurses, clinical officers, technicians, non-clinicians and pediatricians	91%	n=34	89%	n=27	-"Training programs with simple techniques avoiding reflexes and artifacts of current images devices developed now. Open source cloud based AI and EHR projects to support images networks in integrated data projects"
Target Population	Neonates (primarily premature and/or low birth weight, at risk for ROP)	94%	n=35	93%	n=28	Neonates (primarily premature and/or low birth weight, at risk for ROP)	91%	n=35	89%	n=28	***Proposed Adjustments****: "Remove "primarily" // "Optimal should also include other neonates and infants with suspected vitreo-retinal diseases"* -"Can have universal screening for all babies" -"Premature babies born at 32 weeks or less and bigger babies with risk factors" -"Prematurity and follow up useful data integrated."

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS				
Characteristic	Optimal requirements	Agree (all)		Agree (excluding product developer)		Minimal requirements	Agree (all)		Agree (excluding product developer)		Collated comments from Delphi-like survey
		%	n	%	n		%	n		n	
Target Setting	Neonatal units and/or eye department in hospitals in low-resource settings	97%	n=35	96%	n=28	Neonatal units and/or eye department in hospitals in low-resource settings	91%	n=34	89%	n=27	-"If only one equipment is at the institution, the operating room would be the better place. We are a third level Hospital and manage premature infants and also retinoblastoma cases. For oncology, the operation room is a must. For premature babies, the ophthalmologist do the screening in our hospital. Nurse screening has never been done. Second level hospitals would benefit from telemedicine programs. -"All neonatal units should be screened." -"Connecting healthcare points with opensource EHR and EPR networks. Integrated data for better decision making. Importance of long term follow up prematurity projects" -"Question; do ROP screening tools have applications in adult populations (increased market need)?"
Manufacturers' Quality Management System	ISO 13485:2016 Medical devices – Quality management systems -- Requirements for regulatory purposes	93%	n=27	90%	n=21	ISO 13485:2016 Medical devices – Quality management systems -- Requirements for regulatory purposes	93%	n=27	90%	n=21	-"Workforces to build policies for data security confidentiality and big data management. Telehealth projects. International standards. Use of AI tools." -'"Minimal should be all sort of equipment that permits adequate screening of babies at risk of ROP and other vitreo-retinal diseases."
Device Regulatory Status	At least one of: CE marking, approved by US FDA or another stringent regulatory body of a founding member of IMDRF (e.g., Japan, Australia or Canada)	97%	n=30	96%	n=25	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)	87%	n=30	84%	n=25	-'"Validation works over the devices"
Field of View (FoV)	170 degrees	97%	n=30	96%	n=26	36 degrees used with an appropriate condensing lens to be able to view the peripheral retina (into Zone 3)	81%	n=27	87%	n=23	**Less than 170 FoV:** "110 or 120 field would be OK as long as the device could be used to image the retinal periphery." // "Widest field camera is 150 foV…one can take montage images with that" **Negative of too small FoV:** "Viewing systems with too short field of view are not ideal for screening"

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS					
Characteristic	Optimal requirements	Agree (all)		Agree (excluding product developer)		Minimal requirements	Agree (all)		Agree (excluding product developer)		Collated comments from Delphi-like survey
		%	n	%	n		%	n		n	
											// "A smaller field of view may not allow unskilled nurses to do the ROP screening" **Quality and Market Size:** "The high price of high quality devices [is impacted by] market size. [The market size is] limited by users (nurses; opticians; neonatologist) in some countries, [and if] the market was bigger, the price could be more affordable" **AI:** "Note that AI systems ultimately may be able to predict activity in periphery" -"170 degree" -"Yes I Agree but eighth smartphone videos processes by AI big data clouds you can have the same "Zone assessment""
Image Resolution	2048 X 2048 pixels, 24-bit colors	100%	n=24	100%	n=21	750 x 1334 pixels	83%	n=23	90%	n=20	-"Not enough resolution to provide crisp visualization of fine details, especially when enlarging the image taken from a video capture. -"Yet to be validated." -"The quality of images of portable devices" -"With better picture resolution screening for all newborn would develop the Artificial intelligence for Neurology and Ophthalmology at least. It means a big step science and non-invasive. Of course under data protection GDPR"
Imaging	All three modes available: Still, burst mode, video	97%	n=30	100%	n=25	Still images captured from video	80%	n=30	80%	n=25	***Proposed Adjustments**: "Minimal - add ..."video taken with Smartphone" and "Provided a super high resolution and quality of video is available."* **Video Sufficiency:** "Video will not give the level of clarity required" // "Video mode is essential to keep records of the full screening" -"At least still images and video " -"All kind of images for a complete evaluation" -"The process must need the minimum time and store size possible"
Wavelength	Color fundus - white LED (wavelength range 400-750 nm with a peak near	91%	n=22	89%	n=19	Color fundus - white LED (wavelength range 400 nm - 750 nm with a peak near 600nm). FFA - blue LED	90%	n=20	94%	n=17	-"I do not know enough to comment: blue light is damaging to the retina... for debate!"

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS					
Characteristic	Optimal requirements	Agree (all)		Agree (excluding product developer)		Minimal requirements	Agree (all)		Agree (excluding product developer)		Collated comments from Delphi-like survey
		%	n	%	n		%	n		n	
	600nm). FFA - blue LED (dominant wavelength @480nm)					(dominant wavelength @480nm)					-"This is evolving. We may be able to do screening with wavelengths outside those suggested."
Illumination	Integrated bright light, 100-6000 lux	90%	n=21	89%	n=18	Integrated bright light, 100-6000 lux	89%	n=18	93%	n=15	-"We need luxes enough to perform FA also"
Adjustments of Images	Intensity, Gain, Balance, Brightness, Contrast, Red Free, Gamma, and Focus	93%	n=30	92%	n=25	Smartphone image editing services	77%	n=30	80%	n=25	**Original image must be saved:** "Some times color corrections can help but keeping the original picture stored" // "The pictures must be stored with the parameters fixed by user and no edited to avoid errors for color corrections" -"Usability issues" -"The smartphone option still has many challenges."
Dilation Needs	Pupil dilation is not required	67%	n=33	71%	n=28	4mm	71%	n=31	78%	n=27	**Dilation required**: "Good dilatation is must. Then only image quantity And Image diagnosis is perfect" // "If pupils are not dilated will miss the Rop. If pupils are not dilating after instilling the drops need urgent referral for treatment" // "Pupil dilation is needed specially in incoming countries where we may have atypical cases where it is essential to evaluate the retinal periphery to define treatments. Small pupils let us see only posterior zone I -where we diagnose plus disease, but sometimes we need to do treatments in cases with fibrovascular proliferation that doesn´t have plus disease." // "I don't see a logic in having un-dilated pupil. In adults, wherein they will have to carry on work immediately after imaging is required. In babies who are any dependent on their mothers, dilation should not matter. If that allows taking a good picture , then it should be the realistic requirement. Also since the intervention is time bound taking the best picture/video at a given single instance is very important non mydriatic camera is preferred"" **Image quality concerns**: "Dilation is currently required due to limitation of the optics used in the

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS				
Characteristic	Optimal requirements	Agree (all)		Agree (excluding product developer)		Minimal requirements	Agree (all)		Agree (excluding product developer)		Collated comments from Delphi-like survey
		%	n	%	n		%	n		n	
											cameras" // "If image quality is suboptimal, pupil dilation should be a must." // "Quality of image in not dilated pupils are not good" // "Full dilation provides better quality of image and illumination" // "Best to dilate in order to have good view of fundus" "4mm or more" "A nonmydriatic system would be great but difficult to develop. We are also looking at this option."
Time to Result for Imaging	3-4 minutes	94%	n=32	92%	n=26	10 minutes	74%	n=31	76%	n=25	**Faster**: "I am not sure how easy it is to get images faster, I would something like something faster, less than a minute" **Impact based on quantity:** "Amount of screenings"
Image Output	.JPEG, .PNG, DICOM, MPEG, HEIC, PACS support	97%	n=29	95%	n=22	MPEG, HEIC, DICOM	89%	n=28	90%	n=21	***Proposed Adjustments:*** *"Need JPEG [for Minimal]"* -"Any kind of image available should be generated for any device. Image extension should not be a limitation these days." -"Importance of integration to EHR / EPR"
Results Output	Ability to output to cloud based support system	94%	n=34	93%	n=27	No exporting required	53%	n=34	56%	n=27	**Exporting required:** "Exporting must to save data as a rule in telemedicine the export of images is very important" // "Export must for tele screening" // "Export is a must for my setting" // "Exporting images and videos is essential for Telemedicine" // "One major limitation of some of the systems is the inability to export the images. Exporting the images from the hardware is necessary and in my opinion it is a requirement." // "It would be better if there was some way to export the image." **Ability to work with other systems:** "Through interoperability between open source and paid services, depending on the network built" // "The data must be exported at least to corporative network cloud-based systems are the new reality.

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS					
Characteristic	Optimal requirements	Agree (all)		Agree (excluding product developer)		Minimal requirements	Agree (all)		Agree (excluding product developer)		Collated comments from Delphi-like survey
		%	n	%	n		%	n		n	
											A wide range of API's are available and cannot be easily developed to assure information ubiquity."
Storage	Track image progression over time at a patient level	100%	n=33	100%	n=27	No storage required for clinical management	45%	n=31	46%	n=26	**Storage required for legal reasons:** "Storage must for record purpose - Medicolegal record" // ”According to legal aspect it is very important” // "Having storage in some way is important. These are part of the clinical record." **Storage required for long-term care:** "I strongly feel the device should have some means of image storage. Storage is crucial since ROP is a condition which needs long term care” // "Storage is essential for follow up and comparison” // "Images belong to family and later to the premature adult. Long term Follow up is extremely important” // "Is necessary to be able to track changes” // "Storage is must for comparison and monitoring" ”One of the richnesses of obtaining images is to provide documented evidences of possible modifications over time” // "For appropriate digitalization, there is need for data storage over time"" "Full traceability should be a feature of every system and device."
Clinical Accuracy	100% sensitivity and 99.8% specificity (for ROP needing treatment)	97%	n=31	96%	n=26	100% sensitivity and 95% specificity (for ROP needing treatment)	94%	n=31	92%	n=26	***Proposed Adjustment:*** *Clarify whether Clinical Accuracy is referring to camera or AI system //* *"Optimal: could be more lenient on the specificity - say 97%"* -"Especially if the method would not be used by ophthalmologists experts in ROP."

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS					
Characteristic	Optimal requirements	Agree (all)		Agree (excluding product developer)		Minimal requirements	Agree (all)		Agree (excluding product developer)		Collated comments from Delphi-like survey
		%	n	%	n		%	n		n	
											-"Validation required" -"Highest accuracy possible. The Human also fail"
Accessibility	Portable - Handheld or mobile	97%	n=34	96%	n=27	Portable	91%	n=34	93%	n=27	***Proposed Adjustments:*** *Add to Minimal handheld or mobile: "Any device should be handheld or mobile. Procedures should not be restricted to healthcare facilities."* **Regulatory / Legal considerations:** "Taking care of legal issues , like HIPAA" -"Portability is a very good feature but with a good screen the auxiliar is keeping more attention helping to the main user. It happens also in surgery room with monitors around the auxiliar is focused in the process and can follow up and learn how is going." -"Portable devices are user friendly"
Device Weight for Imaging Capture Component	Less than 720g	97%	n=31	96%	n=26	No more than 720g	97%	n=31	96%	n=26	-"Most of our operators are women and more than 1000 grams [too] heavy for them" -"Similar weight (or slightly more) than a cell phone seems appropriate" -"Must be portable"
Connectivity	LAN, Multiple USBs, Cellular messaging, File sharing	100%	n=30	100%	n=25	No connectivity required	38%	n=32	46%	n=26	**Connectivity required:** "Connection needed" // "Connectivity to other digital devices is an essential tool" // "Absolutely necessary to have connectivity during the screening" // "Connectivity is must for tele screening" // "Connectivity would be preferred" // "Connectivity is not a problem these days. If the device is portable, data should be exportable whenever and wherever needed." // "Must have all the possibilities to connect depending on the network you are working" // "Needed for a second opinion if required" // "Connectivity to other digital devices is an essential tool" // "Absolutely necessary to have connectivity during the screening" // "Connectivity is must for tele

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS				
Characteristic	Optimal requirements	Agree (all)		Agree (excluding product developer)		Minimal requirements	Agree (all)		Agree (excluding product developer)		Collated comments from Delphi-like survey
		%	n	%	n		%	n		n	
											screening" // "Connectivity would be preferred" // "Connectivity is not a problem these days. If the device is portable, data should be exportable whenever and wherever needed." **File sharing is a must:** "The images must be exported" // "Should have at least a way for file sharing" // "At least WIFI connectivity should be available for files' sharing" Privacy/confidentiality concerns with sharing: "Will there be concern about the sharing of PIH?" // "Some of our NICUS are very wide spread and they need to transfer the images very soon and safe"
Patient Interface	Non-contact	82%	n=34	81%	n=27	Non-invasive contact	94%	n=35	96%	n=28	**Technical feasibility:** "Technically it is not currently possible to take a non-contact picture with wide FOV. Even if [we were able to develop it], it will be expensive. Given that only indirect & Retcam are the only options which the industry has lived with for decades, and given that better affordable options are available now, it is important that more widespread imaging should take place. Trying to create the most idealistic product - Low cost, non-contact, low weight, imaging+ video , 150+ FOV , connectivity - can be a non-starter" **Challenges with Non-Contact: "**Difficult to get to peripheral retina without some kind of contact, so it's okay as long as non-invasive." // "I think non-contact Images will be poor quality" // "It's difficult to image a baby through a noncontact system" **Patient comfort:** "Less contact is always better for the patient." // "Maybe my personal experience makes me think contact is better" -"Integration of family and patient is key"

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS				
Characteristic	Optimal requirements	Agree (all)		Agree (excluding product developer)		Minimal requirements	Agree (all)		Agree (excluding product developer)		Collated comments from Delphi-like survey
		%	n	%	n		%	n		n	
Consumables	None	85%	n=33	85%	n=26	Pupil dilation drops	88%	n=33	88%	n=26	-"Contact will need gel, which is also okay." -"The images with undilated pupils don't have good quality" -"If one device can be developed and can work without consumables, all should follow the same principle."
Support System	Cloud platform for uploading, tracking, remote/telemedicine diagnosis via external clinicians	97%	n=33	96%	n=27	N/A - standalone device	58%	n=33	67%	n=27	**Transportability:** "Remote or Tele medicine diagnosis will save time Energy and Saves patient" Ability to work with other systems: "Interoperability does not depend on the device nowadays. Using standards should let any device interoperate. Standalone is the past. Open and interoperable is the future." // "Sharing info to other platforms is the best way to grow." **Standalone devices:** "Standalone device will not be helpful for tele screening" // "Both are okay as long as images are transferable uploading, tracking of images are paramount in managing ROP-like get opinion from colleagues, experts. Standalone system will not allow a connectivity to shared data which may affect the ROP grading" "Important tools for ROP and prematurity networking"
Instrument Pricing	<$500 ex-works	72%	n=32	73%	n=26	<$25,000 ex-works	58%	n=31	64%	n=25	**Too expensive**: "25,000 USD is still out of reach for may centers where it is intended for use." // "In middle income countries over 10,000US is too much money for a real program" // "25k is a big budget for under developed areas" // "Costs over $2000-3000 are extremely difficult to afford by Latin American health providers (ophthalmologists). Moreover, investing in ROP screening equipment is generally not a priority among government Health departments." // "Maybe change to $2,000 as this would still be an affordable device for most neonatal units" // "The price is very important for low and middle income countries" // "A cost of $25000 will not be affordable"

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS					
Characteristic	Optimal requirements	Agree (all)		Agree (excluding product developer)		Minimal requirements	Agree (all)		Agree (excluding product developer)		Collated comments from Delphi-like survey
		%	n	%	n		%	n		n	
											Quality should not be compromised: "A high quality device that does the job would be acceptable to purchasers if the price was a bit higher than this i.e., $2000US. I think rather than talking about price of the device, by screening more babies - the price per baby can be brought down given the device is in the 30000-40000 USD range" // "Low price will compromise quality of images" // "The price and the sustainability must have a good balance"
Power Source	Mains with rechargeable battery or solar powered without mains power	88%	n=34	89%	n=27	Mains Power	79%	n=34	78%	n=27	**Solar power:** "Solar power [is] great" // "Will need to be taken to different locations where obtaining a power source is difficult compatible with mains electricity is better than solar power in my set up" "the portable devices are very applicable" **Cost implications to adding a battery:** "Battery adds to cost and also it is expected that an NICU will have power for the baby to anyway survive. In the worst can have a simple UPS ,which can be standalone . By creating a battery based device, you are increasing the maintenance cost yearly which is not required" **Alternatives to mains:** "Avoid main power could be a good option in addition to the main power"
Battery	Provides battery backup, autonomy >5 hours, automatic switch to battery in case of power failure, automatic recharge on connection to mains	91%	n=34	96%	n=27	None	50%	n=32	50%	n=26	**Battery required**: "Battery is essential to screen outside clinics and hospitals" // "Needs a battery for areas where there are power issues. This has happened to me." // "Power outage is common occurrence in my set up" // "Power back up very helpful" // "The power in areas with electric problem as in my country is very important" **Minimal backup supply:** "Battery is need at least to change from bed to bed in addition to main power" // "Backup power supply is important to allow work to be concluded to a reasonable point after power outage" **12 hour backup supply:** "Device should be minimal power and therefore would be ideal if

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS					
Characteristic	Optimal requirements	Agree (all)		Agree (excluding product developer)		Minimal requirements	Agree (all)		Agree (excluding product developer)		Collated comments from Delphi-like survey
		%	n	%	n		%	n		n	
											could last 1 full clinical day (12 hours)" // "I believe a minimum battery specification requirement is necessary." -"Amount of premature in NICU and follow up office per hospital"
Voltage	Output spike, surge and transient protection (including lightning), with availability of Type I and Type II IEC rating lightning surge protection. Voltage and power input and output metering	96%	n=24	95%	n=20	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)	83%	n=23	84%	n=19	-"Good addition"
User Instructions	User manual and additional training materials (videos, checklists, guides) in at least one national official language for the country of intended use. Attached to device with labels and markings where possible	92%	n=36	93%	n=29	User manual provided in at least one national official language	81%	n=36	79%	n=29	-"Can have user manual online in different languages" -"Instructions in English will be adequate" -"Important point" -"Instructions are always crucial."
Warranty	5 years	89%	n=35	96%	n=28	1 year	71%	n=34	67%	n=27	**Longer warranty**: "One year warranty will not help remote places screening" // "At least 3 years cover for warranty if the pricing is in reasonable level" // "Devices are unpredictable need long warranty" **Extended warranty increases price:** "Warranty comes with a cost. people can demand 10 years also but then that cost gets added to product price. If the product is well maintained it does not need major servicing" "It is very important for countries such as us. we don't have much money."

	OPTIMAL PRODUCT REQUIREMENTS					MINIMAL PRODUCT REQUIREMENTS					
Characteristic	**Optimal requirements**	**Agree (all)**		**Agree (excluding product developer)**		**Minimal requirements**	**Agree (all)**		**Agree (excluding product developer)**		**Collated comments from Delphi-like survey**
		%	**n**	**%**	**n**		**%**	**n**		**n**	
											"Once tested/ validated: OK" "Technology becomes obsolete very quickly. One expects to replace equipment as soon as new tech arises"
Preventive Maintenance	Preventive maintenance included with additional training materials (checklists, videos, guides)	97%	n=35	96%	n=28	Manual for preventive maintenance included	86%	n=35	82%	n=28	**Sustainability:** "Can make preventive maintenance easier to sustain" // "Good point for sustainability of projects" -"I think it's important to have a maintenance backup, not only the manual" -"Additional training is better"
Decontamination	Easy to clean surfaces, compatible with common disinfecting agents	100%	n=35	100%	n=28	Easy to clean surfaces, compatible with common disinfecting agents	89%	n=35	86%	n=28	-"100% agree"

APPENDICES

APPENDIX A: COLLABORATORS (SURVEY & CONSENSUS MEETING PARTICIPANTS)

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- Antonio Castilla Bombín -
- Dr. Ashish N Holani - Aarambh ROP Screening Project
- Betsy Asma - Rice360 Institute for Global Health Technologies
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APPENDIX B: ABBREVIATIONS

°C	Degrees Celsius
CE Mark	Conformité Européenne – certification mark
cm	Centimeters
cm^2	Centimeter squared
DHS	Demographic and health survey
ETROP	Early Treatment of Retinopathy of Prematurity
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
mm	Millimeters
MCH	Maternal and Child Health
MDG	Millennium Development Goal
MMR	Maternal mortality rate
MNCH	Maternal, newborn, and child health
MNH	Maternal and neonatal health
NMR	Neonatal mortality rate
PR	Product requirement
ROP	Retinopathy of prematurity
SDG	Sustainable Development Goal
U5MR	Under-5 mortality rate
UNFPA	United Nations Population Fund
USAID	U.S. Agency for International Development
WHO	World Health Organization

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