NEXT GENERATION PULSE OXIMETERS: TECHNOLOGY AND MARKET LANDSCAPE

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PATH

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ABBREVIATIONS

AC	alternating currents
AHA	automated haematology analyser
ALIMA	The Alliance for International Medical Action
ARIDA	Acute Respiratory Infection Diagnostic Aid
ChARM	Children's Automated Respiration Monitor
COVID-19	coronavirus disease 2019
DC	direct currents
ECG	electrocardiogram
EU	European Union
FDA	Food and Drug Administration
g/dL	grams per decilitre
Hb	haemoglobin
HCW	health care worker
IMCI	integrated management of childhood illness
IR	infrared
LMIC	low- and middle-income country
PO	pulse oximeter
PPG	photoplethysmography
PQ	prequalification
SpO2	blood oxygen saturation
TIMCI	Tools for Integrated Management of Childhood Illness
UNICEF	United Nations Children's Fund
US	United States
WHO	World Health Organization

EXECUTIVE SUMMARY

Background

Whilst progress has been made towards achieving Sustainable Development Goal 3, which aims to reduce the global maternal mortality rate and end preventable deaths of children under five years old, additional efforts are needed to achieve these targets. Most maternal deaths are caused by a range of complications that develop during pregnancy or exist before pregnancy but worsen during pregnancy. Infectious diseases such as pneumonia, diarrhoea, and malaria remain the leading causes of death globally for children under five years old. Although often these conditions are preventable or treatable with proven interventions, tools and integrated approaches that support diagnosis are not widely available.

Fever is the most common paediatric presenting symptom in primary care. Whilst fever is the main symptom of malaria, it is present with multiple other symptoms, such as cough, difficulty breathing, and diarrhoea. Pneumonia—along with hypoxaemia, a potentially fatal complication of severe pneumonia—is the leading infectious cause of death for children under five years old. When using clinical signs, pneumonia is diagnosed by the presence of either fast breathing or lower chest wall indrawing. Hypoxaemia is diagnosed using a pulse oximeter (PO) device, which measures blood oxygen saturation (SpO2) and pulse rate, and is treated with oxygen therapy. The critical link between these two lifesaving interventions has been highlighted in the wake of the COVID-19 pandemic. Anaemia is a significant health problem, with higher prevalence rates in children under five years old and pregnant women, especially in malaria-endemic areas. Anaemia is multifactorial clinical condition that has many causes, with iron deficiency, malaria, and hereditary haemoglobin (Hb) disorders being the main causes. Anaemia can be diagnosed by using diagnostic technologies that measure Hb levels or by looking at palmar pallor if using clinical signs.

Febrile illness, pneumonia, and anaemia each have multiple etiological origins, present with overlapping symptoms, and often are diagnosed by low-skilled frontline health care workers (HCWs) with insufficient or inadequate tools and high patient loads. Furthermore, HCWs in low-resource settings rely on clinical signs to triage these conditions, despite known issues with the accuracy and reliability of these methods, which results in patients being misdiagnosed and not receiving appropriate care. Providing HCWs with tools to help them identify the signs of severe illness could help overcome these challenges.

Multimodal (or next generation) PO devices —noninvasive handheld devices that expand the features of standard handheld POs by additionally measuring respiratory rate, temperature, and/or Hb—are a promising technology that can provide objective measurements to HCWs in low-resource settings to support clinical decision-making. Combining more than one clinical measurement into a multimodal PO device has the potential to improve the accuracy and efficiency of, as well as adherence to, consultations that facilitate more appropriate diagnosis and integrated management of illnesses, including application of the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) protocols. In addition to reducing mortality, multimodal PO devices could further optimise efficient use of resources and reduce the overall strain on the health system by minimising the need for costly testing, strengthening referral decisions, and reducing unnecessary hospitalisations, intensive therapy, and overuse of antibiotic treatments.

Multimodal PO devices are applicable in a broad range of settings; however, this report aims to assess the potential of multimodal PO devices to improve the integrated diagnosis and treatment of illnesses for patients presenting at health facilities in low- and middle-income

countries (LMICs), with a focus on maternal and child health applications. Understanding technological challenges, existing and pipeline products, and market challenges is key for facilitating equitable access to these tools through market-based interventions.

Technology challenges

There are devices that noninvasively measure SpO2, pulse rate, respiratory rate, temperature, and Hb. These devices can be simple (e.g., thermometers) or complex and costly multiparameter devices that integrate these clinical measurements. However, there are many factors—such as accuracy, usability, affordability, and quality—to consider when integrating multiple clinical measurements into one device that is appropriate for use in low-resource settings. Furthermore, the value of integrating these devices versus using inexpensive, existing methods and stand-alone technologies should be considered.

SpO2 and pulse rate

Many POs available on the market are not durable and do not provide accurate measurements due to inadequate device testing standards and fraudulent/misleading claims by some manufacturers. The accuracy of POs is also affected by specific patient conditions or characteristics, such as movement, skin pigmentation, low Hb levels, and poor perfusion.

Respiratory rate

There are various automated respiratory rate technologies that use different methods to measure respiratory rate. These technologies are sensitive to movement, affecting their accuracy, which can be problematic for use in young children who have difficulty remaining still. Accuracy is further challenged by the lack of an agreed upon reference standard in low-resource settings. Limited data on health impact and cost-effectiveness, especially relative to inexpensive substitute tools and methods, further contributes to the lack of consensus on the benefits of these devices.

Temperature

Accuracy of contact digital and infrared (IR) thermometers varies depending on site location and environmental factors that impact the skin measurement site. Ambient temperatures can lead to prolonged measurement times for contact digital thermometers. Additionally, contact digital thermometers require an additional probe when integrated into a PO device. Unlike contact digital thermometers, IR thermometers offer advantages, such as limited to no contact and faster readings, which are beneficial for use in young children. However, components for IR thermometers are more expensive and require hardware redesign when integrated into existing PO devices, which can lead to higher prices.

Hb

Several noninvasive Hb screening technologies are on the market, and more are under development. Compared to invasive and minimally invasive methods, these technologies may increase acceptability amongst patients, especially in children, as they do not require a blood sample. There may also be cost and supply chain benefits as these technologies do not require consumables. However, existing evidence indicates that the diagnostic accuracy of noninvasive devices is not well established for spot-check use in children and pregnant women, especially in rugged settings. Further validation and operational evidence with larger and more diverse populations across different environments are needed before normative bodies would recommend them.

Summary of technology landscape

There are multiple existing and pipeline multimodal PO and stand-alone noninvasive Hb devices, which are a more nascent technology, that could improve primary health care for women and children in LMICs. Development of multimodal handheld PO devices that are designed for low-resource settings has progressed since 2017 due to various global health investments, including coronavirus disease 2019 (COVID-19) investments. At the time this report was written, there were at least seven commercially available multimodal devices and five additional multimodal or stand-alone noninvasive Hb devices designed for low-resource settings in the pipeline, one of which was a smartphone application.

Summary of market barriers and opportunities

Whilst a range of products is in the development pipeline and commercially available, various market challenges limit the accessibility and scale-up of high-quality multimodal PO devices designed for low-resource settings. These include the challenges outlined below.

There is limited investment in research and development and accuracy verification processes that ensure affordable, high-quality products designed for diverse use settings and patient populations are available in LMICs. From a manufacturers' perspective, the case for investment in research and development is limited by three factors: (1) uncertain demand for new products in LMICs; (2) downward pressure on pricing for LMIC diagnostics, generally, which creates challenges for sustainable business models; and (3) required time-consuming and costly evidence generation across diverse populations and settings to support adoption.

Insufficient quality standards by stringent regulatory authorities and opaque verification and validation pathways by global normative bodies limit availability of high-quality and affordable multimodal PO devices. This is important given that many LMIC regulatory bodies lack capacity to regulate devices that enter their markets and thus rely on global normative bodies and stringent regulatory authorities. More specifically, (1) current stringent regulatory authority standards for some of the clinical measurements found in multimodal PO devices do not reflect the needs of key patient groups or the operating conditions at health facilities, including patients with dark skin pigmentation in high-income countries; (2) there is limited independent external validation of the performance and durability of diagnostic devices; (3) there is a lack of global alignment on standards required to verify and validate diagnostic tools in low-resource settings; and (4) there is limited endorsement of technology from normative bodies such as the WHO prequalification (PQ) programme, which does not currently include multimodal PO devices.

Lack of inclusion in global and national guidelines, lack of national-level champions, and limited awareness amongst HCWs limit adoption in LMICs. Evidence demonstrating health impact, operational fit, and cost-effectiveness is ideally needed by WHO and some national governments to update guidelines and recommend use of multimodal PO devices.

Demonstrating value-add (e.g., cost-effectiveness, total cost of ownership) of multimodal devices compared with inexpensive and often subpar existing tools is essential, especially in resource-constrained settings with competing priorities. Most multimodal PO devices cost more than the sum of the cost of individual tools, which is problematic as financing for multimodal PO devices, PO devices, and similar diagnostic tools rely primarily on domestic resources. In resource-constrained settings, lower-priced tools, even if less effective and/or

of lower quality, often are procured over multimodal PO devices. Evidence that establishes the value-add of multimodal PO devices is critical.

Similar to PO devices, supply chain markups, fragmented procurement, and lack of information on quality and suitability for frontline use in low-resource settings are gaps for multimodal PO devices.

Way forward and conclusion

There are various potential short-term (approximately one to three years), medium-term (three to five years), and longer-term (more than five years) opportunities for market intervention to address the challenges limiting progress of multimodal PO device use in low-resource settings. It is important to recognise that no single intervention will address all barriers and concerted efforts to address multiple challenges over time are required.

Short-term opportunities include leveraging ongoing global programmes aimed at scaling access to PO and multimodal PO devices to create sustainable local markets in early adopter countries. An example is the ongoing study being conducted by the Tools for Integrated Management of Childhood Illness TIMCI project, which is evaluating multimodal PO devices and their acceptability amongst primary health care providers. Additional opportunities include supporting procurement and supply chain–strengthening interventions, implementing coordinated awareness and introduction campaigns, integrating PO and multimodal PO devices into HCW training programmes, and improving market transparency for PO and multimodal PO devices.

In parallel, medium-term interventions include unlocking financial resources and pricing mechanisms for multimodal PO devices to accelerate uptake and improve affordability, as well as advancing noninvasive Hb technologies by defining and evaluating technical specifications. Furthermore, evidence specific to multimodal PO devices for low-resource settings is needed to revise global and national guidelines that enable adoption at scale. This will involve defining evidence requirements and coordinating the review and revisions of policy recommendations and guidelines. Efforts to improve quality standards are essential, which may include aligning on quality and standardisation thresholds at the global level, expanding the WHO PQ programme to include the multimodal PO device, and/or leveraging reputable third-party laboratories to define thresholds, test, and publish results for both PO and multimodal PO devices.

Long-term interventions should also be pursued to ensure sustainability. This involves strengthening national and/or regional regulatory systems to regulate and monitor products entering markets, as well as building the capacity of public health research institutions to define and generate nationally and/or regionally required evidence that reflects local contexts, which enables the adoption of emerging multimodal PO devices. Furthermore, it will be important to advance efforts that encourage stringent regulatory authorities to improve required standards for clinical measurements found in multimodal PO devices.

Without addressing these challenges, affordable, high-quality multimodal PO devices that are appropriate for use in low-resource settings in maternal and child health will likely not advance through the development pipeline or achieve meaningful scale and impact. This would be a missed opportunity in availing promising technologies that aim to address Sustainable Development Goal 3.

1. INTRODUCTION

1.1. Background

Since the launch of the Sustainable Development Goals, there has been significant global progress towards achieving Sustainable Development Goal 3, which aims to reduce the global maternal mortality rate and end preventable deaths of children under five years old. Whilst progress has been made, additional efforts are needed to achieve these targets. Approximately 75% of all maternal deaths are caused by the following complications that develop during pregnancy or exist before pregnancy but worsen during pregnancy: severe bleeding (mostly after childbirth), infections, high blood pressure, and complications from delivery.[1] For children under five years old, infectious diseases—including pneumonia, diarrhoea, and malaria—as well as preterm birth complications, birth asphyxia, and trauma remain the leading causes of death globally,[2] with malnutrition being an underlying factor associated with nearly half of these deaths.[3]

Although most of these conditions are preventable or treatable with proven, cost-effective interventions, tools and integrated approaches that can help diagnose these conditions are not widely available, especially to frontline health workers (primary health care workers [HCWs], nurses, community health workers, and pharmacists). These tools and approaches may have varying quality and/or may not be adapted for use in rugged settings. Additionally, HCWs in low-resource settings rely on clinical signs, such as respiratory rate or palmar pallor, for triaging and treatment. There are known issues with the accuracy and reliability of relying on clinical signs; these issues result in many patients being misdiagnosed and not receiving appropriate care.[4,5]

There is a wide range of available and emerging point-of-care technologies and tools that can provide objective measurements and data to HCWs in low-resource settings to support clinical decision-making. Of key interest and the focus of this report are integrated or multimodal pulse oximeter (PO) devices (also referred to as next generation pulse oximeters), which are defined as noninvasive handheld devices that expand the features of standard POs, in that standard POs measure blood oxygen saturation (SpO2) and pulse rate and multimodal PO devices collect additional clinical measurements, such as respiratory rate, temperature, and/or haemoglobin (Hb). Multimodal PO devices can be used to spot-check the indicated clinical measurements for use in triage. Ideally, they can also be used to continuously monitor the indicated clinical measurements in settings where multiparameter monitors are unavailable. Multimodal PO devices have potential to improve care across broad use settings and populations; this report, however, focuses on their use within the context of maternal, newborn, and child health, with a focus on febrile illness, pneumonia, and anaemia.

Fever is the most common paediatric presenting symptom in primary care.[6] Measuring body temperature accurately and rapidly is the first step in diagnosing and treating febrile illnesses and neonatal hypothermia, both of which contribute to substantial morbidity and death, particularly amongst children. Studies have shown that individuals in low- and middle-income countries (LMICs) are especially susceptible to febrile illnesses, where an average of 2 to 9 febrile episodes occur per year in children under five years of age in malaria-endemic areas and between 0.5 and 4 instances occur in adults, with the higher end of the range more likely in rural areas.[6] Febrile illnesses often present with multiple symptoms beyond increased body temperature, such as cough, difficulty breathing, and diarrhoea. Fever is the main symptom of malaria.

Pneumonia—along with hypoxaemia, a potentially fatal complication of severe pneumonia—is the leading infectious cause of death for children under five years old. It accounts for 14% of all deaths in children younger than five years and 22% of deaths in children aged one to five years, with the highest mortality in South Asia and sub-Saharan Africa.[7] Pneumonia can be caused by bacteria, viruses, or fungi. When using clinical signs, it is diagnosed by the presence of either fast breathing or lower chest wall indrawing. Hypoxaemia is when oxygen levels in the blood are lower than normal and can be caused by various conditions, including pneumonia, complications from pregnancy and premature birth, and COVID-19. Hypoxaemia is treated with oxygen therapy, and diagnosing it requires further assessment of SpO2 using a PO.[7] The World Health Organization's (WHO's) Integrated Management of Childhood Illness (IMCI) protocols recommend that IMCI-trained HCWs manually count respiratory rate in children with a cough or difficulty breathing to assess whether respiratory rate is higher than what is considered normal per age-specific cutoffs.[8] As part of IMCI, WHO recommends the use of POs to identify hypoxaemia in children aged 2 to 59 months who present with cough and/or difficult breathing at the primary care level, where available, and at secondary and tertiary health care levels.[8,9]

Anaemia is a common condition that affects 1.6 billion people. WHO estimates that, globally, anaemia is prevalent in one-quarter of the world's population,[10] with the highest prevalence in children (42.6%) and pregnant women (38.2%).[11] Maternal anaemia increases perinatal risks for mothers and infants, such as premature labour, gestational diabetes, preeclampsia, acute heart failure, postpartum haemorrhage, postpartum infection, and increased morbidity and mortality. For infants, anaemia can contribute to low birth weight and impaired growth and cognitive development, with potential for lifelong impact.[10] Whilst a global condition, the highest concentration of individuals with anaemia are found in Southeast Asia, in the Eastern Mediterranean, and across all of Africa.[11] Anaemia can result from multiple underlying factors, ranging from nutritional deficiencies, infections (e.g., malaria and HIV), chronic medical conditions (e.g., autoimmune disorders), inherited Hb disorders (e.g., sickle cell anaemia), and pharmaceutical treatments (e.g., chemotherapy). Iron deficiency, malaria, and Hb disorders are the leading causes of anaemia.[12] In fact, given that malaria is an important contributor to anaemia, WHO has identified anaemia as a priority area in the management of malaria cases. To diagnose anaemia in young children, WHO recommends in the IMCI protocols to look for palmar pallor.[8]

Given that pneumonia, febrile illness, and anaemia each have multiple etiological origins, present with overlapping symptoms, and often are diagnosed by frontline HCWs with insufficient or inadequate tools and high patient loads, there is potential for integrated tools and approaches to improve case management. Combining more than one clinical measurement into a multimodal PO device has the potential to improve the accuracy and efficiency of, as well as adherence to, consultations that facilitate more appropriate diagnosis and integrated management of illnesses, including application of IMCI protocols in LMICs. In addition to reducing mortality, multimodal PO devices could further optimise efficient use of resources and reduce the overall strain on the health system by minimising the need for costly testing, strengthening referral decisions, and reducing unnecessary hospitalisations, intensive therapy, and inappropriate use of antibiotic treatments.[13] Ensuring that these potentially lifesaving tools are accessible and appropriate for use in low-resource settings is important for achieving health equity.

1.2. Scope and methods

This report aims to assess the potential of multimodal PO devices to improve diagnosis and treatment of illnesses for patients presenting at health facilities in LMICs. This report provides

an overview of (1) multimodal technology and its challenges, (2) commercially available and emerging technologies, (3) anticipated product development and market barriers, and (4) opportunities for market interventions for multimodal PO devices in LMICs. Understanding these is key for facilitating access to these tools through market-based interventions.

The material in this report was gathered from a non-exhaustive review of publicly available and unpublished information, and discussions with a wide range of stakeholders and technology developers (see Annex 1). The technologies in the pipeline were identified primarily through a review of reports and targeted discussions with experts. The characteristics of the technology and devices were generally provided by the developers or gathered through publicly available information. The market barriers and opportunities were uncovered through targeted discussions with manufacturers and subject matter experts.

Given the exceptionally broad application of multimodal PO devices and the dynamic nature of the technology pipeline, this report is targeted and intentionally highlights several areas. For example, whilst multimodal PO devices can have broad benefits to many patients presenting at health facilities globally, this report focuses on the relevance of these devices for use in maternal, newborn, and child health in low-resource settings. Additionally, the product landscape focuses only on identifying multimodal PO devices as defined above; only a few stand-alone noninvasive Hb measurement technologies are included as they are a more nascent technology compared with stand-alone POs and thermometers.

2. TECHNOLOGY OVERVIEW

2.1. Background

Measurement of vital signs (such as SpO2, pulse rate, respiratory rate, and temperature) as well as clinical measurements (such as Hb) are fundamental to assessing presence or absence of disease and determining disease severity and appropriate course of treatment. Integration of these measurements into a single device has great potential to ensure they are correctly and routinely taken in primary care consultations in low-resource settings. However, existing technologies that measure each of these clinical signs have limitations in terms of accuracy and quality. The following section provides an overview of how each of these clinical measurements is assessed with existing technologies, limitations, and important considerations when integrating multiple clinical measurements into a single device.

2.2. Key clinical measurements

2.2.1 SpO2 and pulse rate

SpO2 and pulse rate are standard vital signs that are measured to screen for a wide range of health conditions, including pneumonia. In 2016, WHO issued guidance on the management of hypoxaemia in children in low-resource settings.[14] Hypoxaemia—a severe lack of oxygen in the blood—is a potentially fatal complication of pneumonia and other conditions. Hypoxaemia is treated with oxygen therapy. Recent estimates report a hypoxaemia prevalence of 31% amongst children under five years old with WHO-classified pneumonia, 41% amongst those with very severe or severe pneumonia, and 8% amongst those with nonsevere pneumonia.[15] PO devices, which measure SpO2 and pulse rate, have been shown to detect hypoxaemia in 20% to 30% more children than clinical signs alone.[16,17] As such, WHO IMCI protocols recommend the use of POs to identify hypoxaemia in combination with screening for other danger signs at the primary care level, where available, and at secondary and tertiary health care levels.[8]

Pulse oximetry noninvasively collects data to determine both pulse rate and the SpO2 of Hb in arterial blood (recorded as peripheral SpO2 due to the measurement location) by employing the principles of spectrophotometry.[18] In their simplest form, POs consist of two LEDs, a light sensor, and a processor unit. The position of the light sensor determines if the PO relies on reflectance spectrometry (the light sensor is on the same side as the LEDs) or transmission spectrometry (the light sensor is across from the LEDs).[19] Oxygenated Hb and deoxygenated Hb absorb infrared (IR) and red light differently. The processor measures the ratio of transmitted red light to IR light and converts that to an oxygen saturation percentage. Photoplethysmography (PPG) is an optical method to detect volumetric changes in blood in peripheral circulation and can noninvasively provide information related to the cardiovascular system. Based on light absorption or reflection, changes in blood flow can be detected as changes in light intensity through the blood and tissues. In addition to oxygen saturation, several clinical measurements for other circulatory conditions can be derived from PPG, such as pulse rate and respiration, as well as Hb and blood glucose levels.

POs have been available for over 30 years, are widely used in both high- and low-income settings, and have numerous comparators available on the market. This is beneficial because there are options that meet different needs, such as cost, size, durability, and accuracy. However, it is also a challenge because not all PO devices are equal in terms of quality and accuracy,[20] with many consumers unaware of these discrepancies. There are several reasons for these discrepancies, including inadequate device testing standards, limited public access to device testing data, as well as fraudulent or misleading claims by some manufacturers.

Additionally, multiple factors—such as poor circulation, skin pigmentation, movement, skin thickness, skin temperature, Hb levels, current tobacco use, and use of fingernail polish—can affect the accuracy of these methods. In fact, due to the increased use of POs during the COVID-19 pandemic, the US Food and Drug Administration (FDA) issued a safety communication alert around the accuracy and limitations of POs.[20] These accuracy limitations exist due to how the technology works. Extremities—such as finger, toe, or earlobe—are ideal probe locations because it is difficult to shine light through other body parts; however, a weak pulse and low blood pressure can lead to poor data collection at these extremities (coldness and many other factors also can restrict blood flow to extremities). Additionally, low Hb values caused by anaemia, which is extremely prevalent in women and children in LMICs, can compromise PO readings. Movement artefacts and ambient light interference are also potential causes of variability in these devices.[21]

Generally, POs provide a reliable and rapid screening of SpO2 and pulse rate for patients all over the world, but there is still a need for improved systems that minimise the challenges mentioned above, which are more likely to be barriers to access for populations across LMICs. Furthermore, there is limited evidence demonstrating that pulse oximetry can reduce the cognitive burden on HCWs and assist in accurate diagnostics at primary health care levels. As such, current IMCI protocols recommend using pulse oximetry only "if available."[9]

2.2.2 Respiratory rate

Respiratory rate (defined as the number of times a person breathes in one minute) is a critical vital sign encompassing multiple clinical conditions. It is amongst the first vital signs to change in patients with deteriorating health.[22] Respiratory rate is also a key vital sign in the diagnosis of pneumonia in children under five years old. The WHO IMCI protocols recommend HCWs manually count respiratory rate in children with a cough or difficulty breathing to assess whether respiratory rate is higher than normal. However, manually counting breaths for 60 seconds is a difficult exercise, even for trained HCWs. Many studies have found that health care providers do not adhere to measuring respiratory rate due to factors such as educational level of the health care provider, length of time since last IMCI training, a belief that not all protocol steps need to be followed, time pressure, cognitive overload, and motivation.[4,5] Failure to measure respiratory rate can lead to an incorrect diagnosis and, consequently, inappropriate treatment (and associated morbidity and/or mortality).

Various automated respiratory rate technologies are available on the market, including several designed specifically for low-resource settings. These devices use different methods to measure respiratory rate, including measuring changes in exhaled gases (capnography), chest movement (accelerometer or strain sensor), changes in pulsatile blood flow (derived from PPG waveform changes), shifts in electrocardiogram (ECG) tracing, and changes in electrical signals passed through the chest (impedance), as well as listening to breathing sounds (acoustic sensors to detect breathing noises). The following section describes the gold standard method and the most common methods found in multimodal PO devices, and their respective limitations.

2.2.3 Capnography

Capnography uses spectography to measure carbon dioxide concentration in respiratory gases expelled during breathing. Capnometers typically require a nasal cannula across the nasal airways or a face mask in extubated patients. They are frequently used by anaesthesiologists to monitor respiratory rate during surgeries and in intensive care units. Many publications use capnography as the gold standard reference method for judging performance of newer devices and technologies,[23] but it is not a feasible option for use in low-resource settings due to the

high price of the equipment and consumable cannulas and masks. Challenges of this system centre around the nasal cannula or face mask dislodging or clogging, patients removing the nasal cannula or face mask due to discomfort, and the need for a high breath flow rate of 150 to 200 mL/min, which can be unrealistic for paediatric and neonatal patients.[24,25]

2.2.4 Chest movement

There are two methods to measure chest movement: accelerometers and respiratory inductive plethysmography. Accelerometers are worn on chests and convert chest movements into breath counts using advanced signal processing and algorithms. This method is used by the Philips Children's Automated Respiration Monitor (ChARM). Accelerometers are designed to allow measurement in any direction regardless of posture and positioning of the patient. However, studies have shown that supine posture demonstrates higher accuracy than seated posture.[26,27] Movement of any kind is also a challenge with this technique and can lead to unreliable data and results, which can be problematic for its use in young children who have difficulty remaining still.

Respiratory inductive plethysmography uses two transducer bands placed below the nipples and above the umbilicus to measure the movement of the thoracic muscles, abdominal muscles, and diaphragm.[28] An algorithm then uses this information to calculate respiratory rate. A major limitation of this method is that the device must be recalibrated any time position is changed—for example, from standing to lying down—which makes it less useful as a continuous monitoring device and challenging for use in young children. Additional risk is introduced from improper size/fit of the bands (e.g., stretching a band too tight to fit a larger patient) or the band slipping out of place during measurement.[29]

2.2.5 Derivatives from PPG and ECG measurements

Algorithms have been developed to measure changes in pulsatile blood flow derived from PPG waveforms, which are found in all POs, as well as from ECG patterns. These algorithms are used to estimate respiratory rate. Both PPG and ECG readings rely on the physiological mechanisms of respiration.[30] These methods are advantageous because they do not require additional sensors, as the measurements are derived from the same sensors used in a PO or ECG. These techniques are used by various commercially available and pipeline products (described in the "Product landscape" section), most notably by Masimo's Rad-G™ (Masimo Corporation, Irvine, California, United States).

Despite automated respiratory rate devices being commercially available, challenges remain before they can be fully accepted and implemented within the global health community. The accuracy of automated respiratory rate devices is challenged by the lack of an agreed upon gold standard for studies in low-resource settings. In a controlled setting, capnography is an ideal gold standard. However, capnography is not a feasible reference when testing devices on children under five years old outside of a lab or hospital in low-resource settings. Currently, manual counting is the only established reference standard for respiratory rate measurement in these settings, but manual counting is known to be imperfect and error prone.[31] As a result of the lack of a gold standard, measurement differences observed in the Acute Respiratory Infection Diagnostic Aid (ARIDA) project, which compared the Rad-G and ChARM's performance to human manual counting, have created uncertainty amongst some researchers in the global health community on the accuracy of automated respiratory rate devices. Additionally, data on the health impact and cost-effectiveness of automated respiratory rate devices are limited, especially relative to substitute products and methods (e.g., manual counting), which further contributes to the lack of consensus on the benefits of these devices.

Devices that have acquired regulatory approval, such as the Rad-G, have been validated in high-resource clinical and laboratory settings. Manufacturers with pipeline products experience difficulties obtaining regulatory approval due to the lack of standardised testing methods and predicate devices, without which regulatory approvals require additional clinical data and therefore higher costs and longer timelines. Furthermore, establishing accuracy of these devices in agitated young children and infants is challenging.[31–33] Whilst more studies in children in primary health care settings across LMICs have been conducted[32,34,35] or are underway[a] to generate evidence on the performance and usability of automated respiratory rate devices, building confidence in these technologies is still needed.

2.2.6 Temperature

Measurement of body temperature is a standard practice in the clinical field. Body temperature has proven to be an invaluable vital sign, regularly measured at the point of intake across all levels of care. The "normal" body temperature is on average 37°C (98.6°F) but can vary based on factors such as time of day, individual activity level, and age.[36] There are known discrepancies between core body temperature and peripheral temperature, with core body temperature being a more significant representation of physiological status. Invasive medical procedures are needed to accurately measure a patient's core body temperature, such as the gold standard pulmonary artery catheter temperature.[37,38] In general, core and peripheral body temperature measurements can vary as much as 1°C to 2°C, depending on the site of measurement.[39,40] This inherent difference, along with the normal fluctuations of body temperature, makes it difficult to validate temperature measurement technologies accurately and reproducibly.

The following summarises the most common methods used to measure temperature, which can be integrated into PO devices.

2.2.7 Contact digital thermometers

Contact digital thermometers rely on the heat transfer principle of conduction and require direct physical contact with the surface of the site being measured. Digital thermometers that use contact sensors can be used rectally, orally, or in the axillary location. Site selection can impact accuracy, with axillary temperature averaging −0.67°C lower than rectal measurements, which are accepted as the closest representation of core body temperatures.[41] Advantages of digital contact thermometers include the ability to select site location based on the specific patient's situation and the ability for continuous or dual monitoring using certain probes. Although inexpensive (priced as low as approximately US$2[42]), limitations of these thermometers include the variable accuracy depending on site location, environmental factors impacting temperature of the skin measurement site, direct contact with patient requiring proper disinfection method or disposable covers, and large ambient temperature differences leading to prolonged measurement times.[43]

2.2.8 IR thermometers

IR thermometers use the level of IR emissions to determine the temperature of an object or surface from a distance. IR thermometers have become widely available over the past few years. As alternatives to contact digital thermometers, IR thermometers provide advantages—

[a] As part of Unitaid's Tools for Integrated Management of Childhood Illness (TIMCI) project, various commercially available and pipeline multimodal PO devices will be evaluated in children under five years old at primary health care settings in Kenya, India, Senegal, and Tanzania. Specifically, a hybrid type 2 study will assess multimodal PO devices' performance and feasibility of use by primary care providers. The reference standard for respiratory rate used in this study will include standardised manual counting through use of video recordings, which is an accepted approach that minimises variability and invasive procedures on children, whilst generating meaningful comparison. The TIMCI project will also model the potential cost-effectiveness of use of multimodal PO plus respiratory rate devices in this context.

for example, they require limited to no contact and provide readings more quickly. There are various versions of body temperature IR thermometers that are meant to be used at specific body locations to measure the temperature of the subcutaneous blood supply. In general, these devices are more expensive than contact digital thermometers; prices vary by model, with some available for approximately $25 through the UNICEF Supply Catalogue.[44] IR thermometers have variable accuracy depending on site location, model used, and environmental factors, such as perspiration, humidity, and ambient temperature.

- **IR temporal artery thermometer:** Temporal artery thermometers require the user to slowly move the device from the centre of the forehead to the lateral hairline whilst the device measures IR radiation emitted over the superficial temporal artery. These devices require direct probe-to-skin contact, requiring disinfection.
- **IR tympanic thermometer:** Tympanic thermometers require the user to gently place the probe into the patient's ear until the ear canal is sealed off, press a button to initiate measurement, remove the device from the patient's ear, and read the measured value. Advantages of these devices include fast measurement speed, easily accessed measurement location, and simple use procedure. However, body contact requires cleaning of the device between patients or disposable probe covers.
- **Noncontact IR thermometers:** IR thermal imaging cameras and IR forehead thermometers use the same technology as the other IR models, but they do not require direct contact with the patient to obtain a measurement. Advantages of noncontact IR thermometers include their ability to reduce the risks of cross-contamination and disease spread, rapidly measure and display a temperature reading, and retake a measurement quickly if needed.[45] Limitations include the risks of user error if the proper distance between the device and measurement site is not used, of the patient's forehead temperature increasing or decreasing due to excessive clothing or head covers, and of sensors collecting dirt if not cleaned properly. While the COVID-19 pandemic increased the demand for IR thermometers, challenges related to varying quality and price remain.

Since core body temperature cannot be accurately measured through the finger, most multimodal PO devices that integrate temperature obtain a reading from a different body location. Contact-based methods may be an inexpensive way to integrate temperature, but they require an additional probe. IR-based thermometers are potential options for integrating this measurement into existing devices without the use of an additional probe. However, IR sensors are more expensive than contact sensors and require hardware redesign. For example, Masimo increased the price of the Rad-G by $50, from $250 to $300, when it added a temperature feature to the device. As such, the value of an integrated device that measures temperature compared with inexpensive stand-alone thermometers may need to be demonstrated.

2.2.9 Haemoglobin

Anaemia is a significant public health problem and is the second-leading cause of disability.[12] WHO estimates the global prevalence of anaemia to be highest amongst children aged 6 to 59 months (42.6%) and pregnant women (38.2%).[11] Anaemia can result from multiple underlying factors, ranging from nutritional deficiencies, infections (e.g., malaria and HIV), chronic medical conditions (e.g., autoimmune disorders), inherited Hb disorders (e.g., sickle cell anaemia), and pharmaceutical treatments (e.g., chemotherapy).[12] As such, diagnosis of anaemia involves assessing anaemia through clinical signs or measurements of Hb levels and detecting the type and/or cause of anaemia through biomarkers and other diagnostic tests. This report only discusses methods to assess anaemia, with a focus on noninvasive technologies.

Hb is a protein within red blood cells that is responsible for the transport of oxygen from the lungs to the tissues. To maintain sufficiently oxygenated tissues, an adequate Hb level must be sustained.[46] Hb amounts are measured in grams per decilitre (g/dL), with normal levels varying based on a person's age, gender, residential altitude, smoking behaviour, and pregnancy status.[47] As such, WHO's detailed definition of anaemia is based on Hb thresholds by different population groups: children in different age groups, adult nonpregnant women of reproductive age, adult pregnant women, and adult men. Table 1 provides WHO's Hb levels per group.

TABLE 1. Haemoglobin levels to diagnose anaemia at sea level.

Population	Non-Anaemia (g/dL)	Anaemia		
		Mild*	Moderate	Severe
Children, 6-59 month	≥11.0	10.0–10.9	7.0–9.9	<7.0
Children, 5-11 years	≥11.5	11.0–11.4	8.0–10.9	<8.0
Children, 12-14 years	≥12.0	11.0–11.9	8.0–10.9	<8.0
Nonpregnant women (>15 years)	≥12.0	11.0–11.9	8.0–10.9	<8.0
Pregnant women	≥11.0	10.0–10.9	7.0–9.9	<7.0
Men (>15 years)	≥13.0	11.0–12.9	8.0–10.9	<8.0

Adapted from World Health Organization (WHO). *Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity*. Geneva: WHO; 2011. https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf?sequence=22&isAllowed=y.

*"Mild" does not mean anaemia is not yet advanced; by the time it is clinically apparent, the deficiency has consequences.

The following sections focus on various measurement methods and their respective challenges.

2.2.10 Invasive and minimally invasive methods

Invasive and minimally invasive methods are defined as any that require a blood sample to measure Hb concentrations. The current recommended methods include automated haematology analysers (AHAs), manual-based laboratory processes, haemoglobinometers, and quantitative colour scales, which use principles of colourimetry as their primary measurement and vary in how they prepare and process a blood sample. All of these methods are appropriate for use in patients of all ages; however, the least invasive methods have higher acceptability and usability, especially amongst paediatric populations.

- **AHAs** are laboratory-based devices that measure, count, and characterise blood cells and provide complete blood count assessments that include additional parameters to identify anaemia subtypes. AHAs are the current gold standard (e.g., Sysmex Kn21) for clinical Hb level measurement. Although this method is currently considered the most accurate way to measure clinical Hb levels, its use is limited because it requires the use of expensive laboratory equipment, trained staff, access to a laboratory within

a reasonable distance, and lengthy turnaround time from sample collection to results. As such, AHAs are often unavailable in low-resource settings, especially in rural areas.

- **Manual laboratory assessments** are based on the cyanmethaemoglobin (Drabkin's) method; WHO has considered this to be a reliable quantitative reference method since the 1950s.[48] It requires whole blood to be mixed with reagents that form methaemoglobin and cyanmethaemoglobin, which are stable colour pigments read photometrically at a wavelength of 540 nm with the use of a spectrophotometer. A standard curve is used to estimate the concentration of Hb in a sample based on the absorbance, which is then compared with a standard control. Drabkin's method requires potassium cyanide as a reagent, but manual reagent-based colourimetry methods that use safer reagents are available. These include the alkaline hematin and Sahli's methods; the latter is currently recommended by the government of India.[49] These methods are generally simple, fast, and inexpensive. However, they have limitations, such as significant measurement errors, lower sensitivity and reliability (which may vary by type of reagent), high instance of observer bias (for Sahli's method specifically), variability depending on environmental factors, and lack of quality control.[50]
- **Haemoglobinometers** are minimally invasive point-of-care methods that are more commonly found in field settings. These devices rely on principles of colourimetry—the measurement of the wavelength and intensity of electromagnetic radiation in the visible region of the spectrum—to quantitatively measure the amount of Hb in a small capillary sample of blood. Portable haemoglobinometers require minimal training and provide instant digital readings. HemoCue® systems (HemoCue AB, Ängelholm, Sweden) are the reference standard for these types of devices. They function using reagent-coated microcuvettes that are filled with a capillary blood sample, allowing Hb to be converted to haemoglobinazide and then loaded into the photometer reader.[51] Although HemoCue devices have been shown to have accuracy rates of greater than 90% of measurements within 1 g/dL when compared with laboratory complete blood count measurements,[52] higher variability has been noted in field settings. Errors and variation in measurements can be caused by improper cleaning of the device and incorrect capillary blood–collection practices[53] (e.g., collecting inadequate or excess blood volumes in the microcuvettes, measuring blood long after collection, diluting Hb concentration due to excess plasma in sample). Furthermore, haemoglobinometers are expensive and require the use of microcuvettes, which can be difficult to have in stock due to limited funding and/or supply chain and logistics challenges that are common in low-resource settings.
- **Hb colour scales** are inexpensive, minimally invasive point-of-care tools that WHO developed for low-resource settings to offer an improved method of diagnosing anaemia in comparison with assessment of clinical signs and symptoms (e.g., assessment of pallor). Hb colour scales are currently used by frontline HCWs. A capillary blood sample is placed onto a chromatography paper test strip, allowed to rest for 30 seconds, and then compared with the hues on the scale card, which represent Hb levels at 4, 6, 8, 10, 12, and 14 g/dL. Whilst more accurate than clinical assessments alone[54] and one-tenth of the cost of haemoglobinometers,[48] these methods have accuracy issues as they can only estimate Hb in 2 g/L increments. Furthermore, studies have reported issues with inaccurate readings due to inadequate or excess blood volume in the sample, results being read too soon or too late, poor lighting, or the scale being held at the wrong angle.[48]

2.2.11 Noninvasive methods

Noninvasive Hb devices are promising screening tools. Unlike minimally invasive methods, these technologies do not require a blood sample to produce results; thus, they reduce the risk of preanalytical errors, minimise risk of infection, and increase acceptability amongst patients and caregivers. They also do not require additional material inputs for each test administered. A lack of required consumables favourably impacts the costing structure of these products and reduces the burden on supply and distribution.[55] Various noninvasive devices are commercially available that have improved their technology over the years, and emerging technologies are in the pipeline. However, to date, the evidence on the diagnostic accuracy of noninvasive devices for spot-check use indicates the need for further improvements prior to reliable use in clinical decision-making.[48,50,53] Prior to wider adoption of noninvasive tools, advancements are needed to improve sensitivity and specificity, especially for use in low-resource settings.[53] Specifically, Parker et al. conducted a study in 2018 that evaluated the accuracy of a minimally invasive device and a noninvasive device as compared with a standard reference haematology analyser for measuring Hb levels amongst children aged 6 to 59 months in Rwanda. Results indicated that the noninvasive device was less accurate and that the failures were associated with lower measurement of the mid-upper arm circumference and SpO2 values. These conditions are more commonly found in low-resource settings due to higher rates of malnutrition and comorbidities.[53]

The following sections summarise methods used by available and emerging noninvasive Hb devices, highlighting key limitations that will be important to overcome for any noninvasive Hb technology, including multimodal PO devices that incorporate noninvasive Hb measurements.

2.2.12 Spectrophotometry and PPG

Most commercially available noninvasive devices rely on spectrophotometry or PPG to determine Hb levels. Spectrophotometry and PPG are methods used in POs, which is why some noninvasive Hb devices can also measure SpO2, pulse rate, and other clinical parameters common in standard POs. These methods operate by identifying Hb's spectral patterns in underlying blood vessels in the finger and using this information along with other known values—such as output light intensity, incident light intensity, light absorption coefficient, and light path—to quantify Hb level. Spectrophotometry methods transmit near-IR light through, or reflect from, tissue and blood; this enables measurement of their absorption properties, which vary based on specific characteristics of a living tissue.[50] PPG systems use alternating currents (AC) and direct currents (DC) to quantify the light absorption from changes of the pulsatile component of artery blood and from tissues and continuous venous blood, respectively. Light absorption or reflection can be measured by placing photosensors from the light source (e.g., sensor found in a PO probe) on the same or opposite sides of tissue.

The most well-known commercially available noninvasive Hb devices include the Pronto®, Radical-7®, and Rad-67™, which use spectrophotometry; NBM 200, developed by OrSense, which uses occlusion spectroscopy; and Haemospect®, developed by MBR Optical Systems, which uses transcutaneous reflection spectroscopy. A 2021 review of published studies comparing these devices with both the gold standard (AHAs) and various reference standards suggested taking general caution on making clinical decisions based on these measurements alone.[50] The accuracy of noninvasive methods in diverse populations compared with both AHAs and haemoglobinometers is not well established. For example, studies evaluating Masimo's Pronto and haemoglobinometers found the Masimo devices had lower precision

and wider 95% limits of agreement compared with haemoglobinometers.[56] Another study that evaluated the performance of two haemoglobinometers and Masimo's Pronto device against a standard AHA (e.g., Sysmex Kn21) in a Rwandan paediatric clinic found that the Masimo Pronto device required further improvements in sensitivity and specificity before wider adoption, especially amongst children under 18 months of age. Most relevant, this study determined that only 65% of the Pronto Hb readings fell within 1 g/dL of the AHA estimate, whereas 77% to 91% of the haemoglobinometer Hb readings fell within 1 g/dL of the AHA.[53] Another issue with these methods, which is also an issue with POs, is creating accurate algorithms in a patient who is moving, has low perfusion, or has more skin pigmentation.[48] Furthermore, these devices are expensive (ranging between $500 and $2,000) and remain largely unaffordable for low-resource settings.

What are the different uses for spectrophotometry and PPG?

Spectrophotometry

Spectrophotometry is a quantitative measurement of the colour or optical properties of an object in the form of absorbed light intensity. A wide range of materials can be quantified using varying spectrophotometer devices, such as liquids, textiles, solid surfaces, and skin or tissues. Tools that measure colour change reactions or clinical signs such as pallor leverage integrated spectrophotometers to quantify colour measurement.

Photoplethysmography

Photoplethysmography (PPG) monitors changes in the blood flow based on light absorption through the blood and tissues, in the form of light intensity. By detecting volumetric changes in blood in peripheral circulation, PPG noninvasively collects clinical measurements that provide information related to the cardiovascular system. Medical devices and consumer products using PPG have been in development for a wide range of use cases, including measuring pulse rate, respiration, blood pressure, haemoglobin levels, and glucose levels. Integrating additional clinical measurements derived from PPG may have the potential to accelerate the introduction of more robust clinical measurement tools. However, an early research and development challenge in this space is access to PPG measurements across diverse populations and settings to build, refine, and validate new algorithms to detect additional physiologic conditions.

2.2.13 Other methods

Another method for measuring Hb noninvasively uses a photo of the conjunctiva of the eye, including the thin inner surface of the eyelid, to estimate Hb concentrations based on the pallor in the colour of the conjunctiva. ToucHb, which was launched in India in 2019 by Biosense Technologies, uses this method. However, accuracy and usability challenges have been reported with this product. Other limitations specific to this method stem from the sensitivity of the image processing algorithm, which can be further exacerbated by a low-quality photo. Environmental factors, such as inadequate ambient light or artificial light sources, can result in a poor image exposure, thus impacting the performance and accuracy of this method. Furthermore, this method may not be suitable for use in young children as it requires patients to keep eyes still and focused to obtain the image.

Various smartphone-based applications that use a similar photography method are available or in development. These applications aim to make Hb screening easily accessible at low cost.

These methods generally use the high-performance photographic sensors built into most smartphones to capture images from the conjunctiva, fingertip, nail bed, or retinal fundus. These images are then analysed using complex algorithms and machine learning to determine Hb values, similar to clinical assessment of pallor to determine anaemia.[50] To date, these smartphone applications are for consumer use and not considered medical-grade devices.

2.2.14 Challenges for noninvasive Hb devices

One challenge for developers and researchers is ensuring the accuracy, precision, validity, and reliability of noninvasive Hb devices. This is also an issue in studies that assess accepted invasive methods, as discussed previously in this report. Published studies have compared methods against comparators in a variety of settings (e.g., varying altitudes) and populations (e.g., varying age, gender, pregnancy, and health status), using varying reference methods. As each reference standard, discussed above, has its own limitations, it is challenging to determine if discrepancies in accuracy are due to varying reference standards or the noninvasive device. Other factors that add variability to study results include the use of different protocols, equipment and devices, training material, type of blood collected (capillary versus venous), and blood-collection methods and techniques.[48] There is a need for studies that evaluate these new technologies to use and publish results following harmonised protocols to compare emerging noninvasive Hb technologies more easily with established methods.

Noninvasive Hb devices are promising; however, they still require further validation before they are recommended by normative bodies, such as WHO. Additionally, operational evidence with larger and more diverse populations across different environments is important to better understand how noninvasive Hb measurement devices will be used, their impact on clinical care, and the feasibility of integration into current public health programmes in LMICs.

2.3. Other considerations for integrated clinical measurements

As described in the preceding sections, individual measurement technologies have their own requirements to achieve acceptable levels of accuracy, usability, and cost (see Table 2 for a summary). When integrating many clinical measurements into a single device, there are additional requirements that may have pricing and usability implications for end users. Additionally, the length of time needed to produce an accurate measurement value varies based on clinical measurement and sensor type and method. Whilst SpO2 and pulse rate values can be determined very quickly, time to result for respiratory rate, temperature, and Hb may be longer. For example, devices that use contact sensors to determine temperature can take anywhere from 1 to 15 minutes to adjust from ambient temperatures to skin temperature, or a respiratory rate result may take several minutes on an agitated child. This may create challenges for HCWs with high workloads. Overall, the value of using integrated devices versus inexpensive, existing methods and stand-alone technologies should be considered.

TABLE 2. Summary of technology challenges by clinical measurement and interventions.

Clinical measurement	Potential benefits	Challenges with technology	Potential interventions
SpO2/pulse rate	POs measure SpO2 and pulse rate, which are used to determine if a patient is hypoxemic. Identifying hypoxaemia in combination with other danger signs may help in the diagnosis of pneumonia in the IMCI guidelines at primary care levels	Performance limited by motion, low perfusion, skin pigmentation, and extreme measurement ranges Insufficient standards for testing devices on patients with more skin pigmentation, low perfusion, and motion	Improvements to sensors, processing, or algorithms Regulatory authorities to (a) improve standards for measuring accuracy and precision of oximeter performance, (b) require more diversity in study subject pools, (c) more clearly define skin pigmentation, and (d) require more transparency in reporting data
Respiratory rate	Key vital sign encompassing multiple clinical conditions, including in the diagnosis of pneumonia in children under five years old per IMCI guidelines. Currently typically measured manually, which is challenging. Automated respiratory rate devices may help improve adherence and accuracy	Difficult to measure on children and infants due to movement and fast breathing Lack of gold standard reference method in low- and middle-income countries (currently compared to manual counting)	Improved algorithms for mitigating motion artifacts and detecting fast breathing rates Development of standardized test procedures for comparing device accuracy in low- and middle-income countries
Temperature	Measured as standard practice across all levels of care and clinical settings. Various types of thermometers available, with varying pros and cons in terms of usability and accuracy	Difference between core and peripheral body temperatures Variable accuracy depending on site location and environmental factors that impact the skin measurement site Large ambient temperature differences can lead to prolonged measurement times for contact sensors	Further development of algorithms for scaling between core and peripheral body temperatures Improved sensor performance
Haemoglobin	Anaemia is significant health problem, with higher prevalence rates in children under five years old and pregnant women, especially in malaria-endemic areas. Considered a priority in the case management of malaria by WHO.	Difficult to compare emerging non-invasive haemoglobin technologies with established methods Accuracy of noninvasive technologies is not well established	Enforcement of study procedures and transparency of methods Further development of sensor, processing, and/or algorithm systems to improve accuracy. More studies in diverse populations and environments

Abbreviations: IMCI, integrated management of childhood illness; PO, pulse oximeter; SpO2, blood oxygen saturation; WHO, World Health Organization.

3. PRODUCT LANDSCAPE

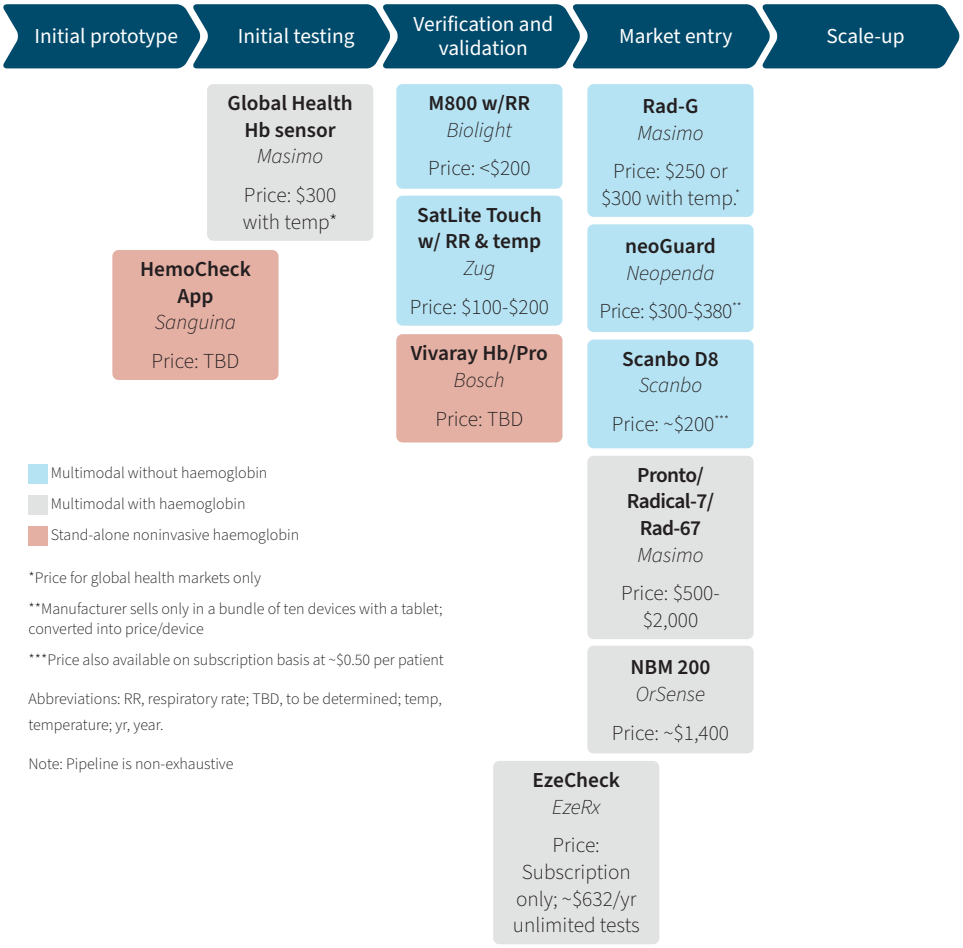
3.1. Background

Multimodal PO devices are defined in this report as noninvasive handheld devices that expand the features of standard POs by collecting additional clinical measurements, such as respiratory rate, temperature, and/or Hb. These devices can be used to spot-check the indicated clinical measurements for use in triage. Ideally, they can also be used to continuously monitor all clinical measurements in settings where multiparameter monitors are unavailable. These devices have the potential to improve diagnosis of various illnesses that affect maternal and child health in low-resource settings. Several of these products are on the market, whereas others are in later stages of product development (Figure 1).[b] Their individual product profiles, with detailed product specifications, can be found in Annex 2.

This product landscape focuses on multimodal PO devices; it includes only a few promising stand-alone noninvasive technologies to diagnose anaemia as these technologies are more nascent compared with POs, thermometers, and automated respiratory rate devices. Additionally, with the advancement of telemedicine and in-home care during the COVID-19 pandemic, there has been a surge in consumer-based health products that use smartphone applications and wristwatches (e.g., Apple Watch) to measure many of the clinical measurements that POs measure. Because this report focuses on devices for clinical use, most of these consumer-focused products are excluded. However, this report does include one promising anaemia-screening smartphone application that may be launched as a medical device in the future. Additionally, there is a need to evaluate the potential role of consumer-based health products as screening tools in primary health care settings. The potential benefit of more competitive price points and existing distribution channels requires further exploration along with potential challenges of submedical device performance standards.

[b] The technologies in the pipeline were identified primarily through a review of reports and targeted discussions with experts; the list included in this report is not exhaustive. The characteristics of the technology and devices were generally provided by the developers or gathered through publicly available information. Lastly, the technology landscape focused only on identifying multimodal PO devices as defined in this report as well as stand-alone non-invasive Hb measurement technologies, as the latter are a more nascent technology compared with stand-alone POs and thermometers.

FIGURE 1. Product pipeline and prices.



3.2. Multimodal PO devices

Development of multimodal handheld PO devices that are designed for low-resource settings has progressed since 2017 due to various global health investments, most notably the UNICEF ARIDA project, Bill & Melinda Gates Foundation's research and development product investments, Clinton Health Access Initiative's PO and respiratory rate dual device target product profile, and Unitaid's ongoing Tools for Integrated Management of Childhood Illness (TIMCI) project, which is led by PATH. The COVID-19 pandemic has also helped to accelerate the deployment of these devices in LMICs, specifically Masimo's Rad-G device.

The following provides an overview of multimodal PO devices by manufacturer, noting which are appropriate for use in paediatric and neonatal populations. Table 3 below provides an overview of select attributes, features, and the regulatory status of each product.

3.2.1 EzeRx (Odisha, India)

EzeRx is an Indian medical technology start-up founded in 2018 that aims to develop affordable devices for remote and low-resource settings. Its device, EzeCheck, is a noninvasive technology that connects to smartphones via Bluetooth and measures SpO2, Hb, bilirubin, creatine, and blood sugar. This screening device is currently approved for use in India for patients aged four years and older at primary health care settings. It has been purchased by the government for use in community health centres and primary health

centres in the state of Odisha. The product is available to public-sector customers in India on a subscription model at approximately $632 per year for unlimited tests. The product is under review by the US FDA and European Union (EU) CE marking regulatory bodies, and it is being piloted in Myanmar, Nigeria, and Mauritius. EzeRx has plans to expand its use cases to children aged 30 months and older as well as to add other clinical measurements, such as temperature, respiratory rate, and HbA1c for a more specific glucose reading. A device for use in neonates is also under development.

3.2.2 Guangdong Biolight Meditech (Zhuhai, China)

Biolight is a global manufacturer of a wide range of medical devices and consumables, including POs and patient monitors. In response to a target product profile developed by the Clinton Health Access Initiative in 2019, Biolight enhanced its M800 handheld PO device to include respiratory rate measurement derived from the PPG. The M800 handheld PO without respiratory rate measurement has been approved by the US FDA. It is indicated for use in adult, paediatric, and neonatal patients. The M800 device with respiratory rate measurement has not yet been validated. Biolight intends to secure EU CE marking for the product. It also has indicated that the ex-works price will be less than $200, so this device may be an affordable multimodal PO device option.

3.2.3 Masimo Corporation (Irvine, California, United States)

With funding support ($5 million grant) from the Bill & Melinda Gates Foundation, Masimo developed the Rad-G, an affordable multimodal PO device for low-resource settings that measures SpO2, pulse rate, and respiratory rate in adult, paediatric, and neonatal populations as a spot-check device. Since the Rad-G's launch in 2017, Masimo has adapted[c] and enhanced the device in response to LMIC user preferences. For example, a version of the Rad-G has added alarms, so it can be converted into a continuous monitoring device in situations where multiparameter monitors are not available. Masimo also expanded the device to include functionality to measure body temperature. In September 2020, the Rad-G received US FDA approval to enter the US market, and the Rad-G with Temperature received the EU CE marking in March 2021. The global health price is $250 for the Rad-G (with one sensor) and $300 for the Rad-G with Temperature.

Masimo is also a leading manufacturer of noninvasive handheld devices that measure SpO2, pulse rate, and Hb (SpHb®). The Pronto, Radical-7, and Rad-67 are handheld devices that provide spot-checking or continuous monitoring capabilities. The Pronto model, which is a spot-checking device, is indicated for use in adult and paediatric populations, but not neonates. The SpHb measurement in the Rad-67, which is also a spot-checking device, is currently not intended for use on paediatric patients, pregnant patients, and patients with renal disease. The prices for these products vary by market, mode of distribution and procurement, and payment model (for spot-check SpHb). Global health discounted pricing for these products is available but varies depending on volumes, programme, and preferred payment model. Non-global health prices from online third-party distributors in the United State are approximately $979 for the Pronto (including 200 SpHb tests, or approximately $5 per test) and $2,000 for the Rad-67 and Radical-7.

Building on Masimo's noninvasive Hb technology, the Bill & Melinda Gates Foundation is partnering with Masimo again in the development and validation of an affordable global health SpHb sensor that can be connected into the Rad-G and smartphone/tablet for use at community and/or primary care levels. This sensor will enable the Rad-G to provide

[c] The adapted version also no longer has the clinical decision support feature.

SpO2, pulse rate, respiratory rate, temperature, and Hb measurements for use on adult and paediatric patients. Product development and validation, including regulatory clearance, are expected to be completed by the end of 2023. Pricing model and structures for the global health SpHb platform are yet to be determined.

3.2.4 Neopenda (Chicago, Illinois, United States)

Developed by Neopenda, neoGuard™ is an affordable wearable device designed for low-resource settings that continuously monitors SpO2, pulse rate, respiratory rate, and temperature from the patient's forehead. Originally designed for use in neonatal and paediatric populations, neoGuard was adapted in response to the COVID-19 pandemic to work on adults as well. The device has EU CE marking, and it is currently available in Kenya; the company aims to expand to more LMICs beginning in 2022. Currently operating as a continuous monitoring device, Neopenda has indicated plans to adapt the product for spot-check measurements. Neopenda offers neoGuard in a bundle of ten devices at $3,000 to $3,800, inclusive of the operating tablet.

3.2.5 Scanbo (British Columbia, Canada/Chennai, India)

Scanbo's Scanbo D8 is a smart, noninvasive, portable, handheld device that conducts spot checks and remote patient monitoring and measurement for eight vital signs: SpO2, respiratory rate, pulse rate, temperature, ECG, glucose, pulse rate variability, and blood pressure. The device connects to a smartphone via Bluetooth, and it is nearly consumable free (requiring glucose disposable strips and blood pressure cuffs). Scanbo D8 captures patient data for integration into health information management systems. Scanbo D8 offers flexible pricing structures, either a per patient and subscription model (approximately $0.50 per patient) or device ownership model (approximately $200).

The product has Japan CE marking, with the ECG and respiratory rate measurements still under review. It is commercially available in India. As of 2021, Scanbo has begun to expand to other LMICs—namely, Kenya and Nigeria. Although the device is not currently validated for use in paediatric patients, the manufacturer has plans to validate the product's performance in paediatric populations.

3.2.6 OrSense (Tel Aviv-Yafo, Israel)

Developed by OrSense, NBM 200 is a commercially available noninvasive device that spot-check measures SpO2, pulse rate, and Hb by using occlusion spectroscopy, which estimates Hb concentration in the blood. The NBM 200 places a ring-shaped probe around the finger and temporarily applies pressure to restrict blood flow, which creates an optical signal and results in a measurement. Although the device uses minimal probes and is battery operated, it is not indicated for use in paediatric populations and remains largely unaffordable (priced at approximately £1,100[57]) to LMICs.

3.2.7 Zug Medical Systems (Brignoles, France/China)

Part of a broader group, Zug Medical Systems owns a range of technologies and patents in the fields of algorithms for ECG diagnosis, PO, respiration and gas monitoring, electronics phygmomanometer, oxygen monitoring, pacing, and defibrillation. Zug Medical Systems offer a range of products for use in ambulances, intensive care units, neonatal care units, operating theatres, and home care. Zug's SatLite Touch is a handheld spot-check and continuous monitoring device that can include respiratory rate measurement derived from the PPG, as well as temperature and ECG measurements. The manufacturer has indicated that the price ranges between $100 and $200.

SatLite Touch with SpO2 and pulse rate measurements have EU CE marking for use in adult, paediatric, and neonatal populations. It is under review for US FDA approval. Enhanced versions with respiratory rate, temperature, and ECG measurements have not yet been validated. Zug Medical Systems is considering securing EU CE marking for all the clinical measurements.

3.3. Stand-alone noninvasive anaemia devices

3.3.1 Bosch (Stuttgart, Germany/Bengaluru, India)

Developed in 2021 by Bosch India, a subsidiary of the German multinational engineering and technology company, Vivaray Hb and Vivaray Hb Pro are new portable and noninvasive Hb devices intended for use in low-resource settings. Without the use of any probes, the device determines Hb levels through a finger scanner using multiwavelength spectrophotometry to measure PPG signals. Vivaray Hb is specifically intended for unskilled HCWs as it provides clinical decision support features, whereas Vivaray Hb Pro provides numeric Hb levels as a result. Both products capture patient data for integration into health information management systems. The products' regulatory status and pricing information are not yet publicly available.

3.3.2 Sanguina (Peachtree Corners, Georgia, United States)

Developed through a multi-institution collaboration with the Georgia Institute of Technology, Children's Healthcare of Atlanta, and Emory University, AnemoCheck Mobile is a smartphone application that estimates Hb levels by processing patient-sourced smartphone pictures to analyse nail-bed paleness. Launched in December 2021 by Sanguina, AnemoCheck Mobile is currently available for free through the App Store and Google Play in the United States. Whilst AnemoCheck Mobile is currently a consumer product intended as a health and wellness tool for the management of nutritional deficiencies, Sanguina has plans to add personalised functionality to the app and launch the product as a medical device with equal or better performance to current reference standard products, such as blood haemoglobinometers. Sanguina also is planning to release a minimally invasive, over-the-counter anaemia-screening test called AnemoCheck Home.

Although the AnemoCheck Mobile health and wellness application is free of charge, the algorithm is continually enhanced, and the user interface is continually updated to incorporate user preferences, Sanguina notes that it may require payment in the future. Pricing structures are still to be determined. Sanguina remains committed to making this product accessible and affordable.

TABLE 3. Features of available and pipeline products.

Product (manufacturer)	Clinical measurements	Measurement mode	Target population	Regulatory	Consumables	Power requirements
Rad-G (Masimo)	SpO2, pulse rate, respiratory rate, temperature	Spot-check and continuous monitoring	Adult, paediatric, and neonatal populations; however, neonatal probe for respiratory rate not cleared by US FDA	US FDA (without temperature) EU CE mark (with temperature)	Reusable probe for children/ adults; neonatal probe requires disposable wrap	Rechargeable battery with adapter
Pronto (Masimo)	SpO2, pulse rate, Hb	Spot-check	Adult and paediatric populations	US FDA	Reusable probe for adult and paediatric populations	AA alkaline batteries
Radical-7 (Masimo)	SpO2, pulse rate, Hb	Continuous monitoring	Adult, paediatric, and neonatal populations	US FDA	Reusable probe for adult, paediatric, and neonatal populations	Rechargeable battery with adapter
Rad-67 (Masimo)	SpO2, pulse rate, Hb	Spot-check	The SpO2 and pulse rate measurements are indicated for use in adult, paediatric, and infant populations, but the total Hb measurement is not intended for use on paediatric patients, pregnant patients, and patients with renal disease	US FDA	Reusable probe for adult, paediatric, and neonatal populations	Rechargeable battery with adapter
SatLite Touch (Zug Medical Systems)	SpO2, pulse rate, respiratory rate, temperature, ECG	Spot-check and continuous monitoring	Device without respiratory rate, temperature, and ECG features has EU CE mark and pending US FDA approval for adult, paediatric, and neonatal populations	Device without respiratory rate, temperature, and ECG features has EU CE mark and pending US FDA approval for adult, paediatric, and neonatal populations Manufacturer has plans to secure EU CE mark approval for device with additional clinical measurements	Reusable probe for children/ adults; neonatal probe requires disposable wrap	Rechargeable battery with adapter

Scanbo D8 (Scanbo)	SpO2, pulse rate, respiratory rate, temperature, glucose, blood pressure, ECG, pulse rate variability	Spot-check	Adult populations Performance validation in paediatric and neonatal populations underway	Japan CE mark for all measurements except respiratory rate and ECG, which are currently under review	Reusable blood pressure cuff and disposable blood test strips	Rechargeable battery with adapter
M800 Respiratory Rate (BioLight)	SpO2, pulse rate, respiratory rate	Spot-check and continuous monitoring	M800 without respiratory rate feature for adult, paediatric, and neonatal populations	M800 without respiratory rate feature has US FDA approval for adult, paediatric, and neonatal populations Manufacturer has plans to secure EU CE mark approval for device with respiratory rate feature	Reusable probes for adult, paediatric, and neonatal populations	Rechargeable battery with adapter
neoGuard (Neopenda)	SpO2, pulse rate, respiratory rate, temperature	Continuous monitoring Manufacturer has plans to adapt product for spot-check measurements	Adult, paediatric, and neonatal populations	EU CE mark	None	Rechargeable battery with adapter
EzeCheck (EzeRx)	SpO2, Hb, creatine, glucose	Spot-check	Approved for use in patients aged four years and older Manufacturer has plans to validate product's use in children aged 30 months and older, as well as develop a device for neonatal populations	Approved by India's Central Drugs Standard Control Organization The device is also under review for US FDA approval and EU CE mark; approval expected by end of 2022/ early 2023	None	Rechargeable battery with adapter
NBM 200 (OrSense)	SpO2, pulse rate, Hb	Spot-check	Adults	Approved by US FDA, EU CE mark, Brazil Health Regulatory Agency (Anvisa), China FDA, Mexico Federal Committee for Protection From Sanitary Risks (COFEPRIS)	Reusable probe	AA alkaline batteries or rechargeable battery with adapter
Vivaray (Bosch)	Hb	Spot-check	Not publicly available	Not publicly available	None	Rechargeable
AnemoCheck Mobile app (Sanguina)	Hb	Spot-check	N/A	N/A; currently a consumer health and wellness-tracking tool	None	Rechargeable

Abbreviations: Anvisa, Agência Nacional de Vigilância Sanitária; COFEPRIS, Comisión Federal para la Protección contra Riesgos Sanitario; ECG, electrocardiogram; EU, European Union; FDA, Food and Drug Administration; Hb, haemoglobin; N/A, not applicable; SpO2, blood oxygen saturation.

4. MARKET BARRIERS AND OPPORTUNITIES FOR MULTIMODAL PO DEVICES

In addition to technical product development challenges, other barriers limit access to and scale-up of multimodal PO devices in LMICs, including issues related to innovation and availability, quality, affordability, demand and adoption, and supply and delivery. These are discussed below and are summarised in Annex 3. Whilst this report is specific to multimodal PO devices, these barriers apply to many types of medical devices.

4.1. Barriers and opportunities

4.1.1 Innovation and availability

Advancement in multimodal PO device innovation has resulted in the development and commercialisation of multiple products (see previous section). However, uncertain demand, competition from single-indication devices, and insufficient financial incentives are slowing additional high-quality products that are suitable for use in diverse settings and across patient populations (adults, children, neonates) from being developed and entering the market. Multimodal devices often compete within a highly fragmented market for low-cost single-indication devices (e.g., thermometers and POs). With constrained budgets, significant product analogues, varying user requirements, limited familiarity with the benefits of multimodal technology, and the tendency to verticalise decisions to focus on one illness/indication at a time, procurement decision-makers anecdotally often opt to purchase lower-cost single-indication devices. This competition from single-indication devices puts downward pressure on pricing for multimodal devices, which limits incentives for innovation.

Manufacturers have stated that given the high cost of developing and validating high-quality clinical measurement technology (e.g., respiratory rate and noninvasive Hb devices) across diverse populations and environmental settings, and the lack of alignment on product thresholds (discussed further in the following section), they lack financial incentives to develop and/or integrate their capabilities into one device. Developing and validating new products or algorithms for diverse populations and settings—in particular children, pregnant women, and anaemic patients—are challenging and expensive. Manufacturers often do not have access to these populations and health settings. In many cases, manufacturers must adapt product design or functions to accommodate specific patient populations, such as developing neonatal-specific probes. In integrating clinical measurements, these manufacturers take on additional challenges and potentially cannibalise sales of their other stand-alone devices. This is further complicated by the various user preferences, requirements, and use cases that fragment the market and make it unlikely for any one device to capture the entire market. Given the price-sensitive market for diagnostic tools in LMICs, these challenges limit innovation of multimodal PO devices that are simultaneously low cost and designed for low-resource settings.

Despite these challenges, several products have been developed for use in low-resource settings and commercialised, some with financial support from global health donors to offset research and development costs. However, many of the manufacturers have stated that they struggle to find a sustainable business model for these products. This is especially true for those manufacturers that only have products intended for low-resource settings and do not have a wide range of products to support losses in other areas. This warrants consideration of other interventions to incentivise innovation and accelerate early research and development efforts. Such interventions could include using subscription-based pricing models, assessing the potential

value of consumer-based health products as screening tools in health facilities, validating tools across diverse settings and populations, and creating open-access data repositories, such as on video or PPG waveform–based/artificial intelligence–derived technologies.

Consistent with findings from the 2018 *Fever Diagnostic Technology Landscape*, uncertain demand for new products in LMICs, downward pressure on pricing for LMIC diagnostics generally, and time-consuming and costly validation and evidence requirements to support adoption limit innovation of high-quality and affordable multimodal PO devices.[6]

Where do smartphone-based technologies fit in?

Smartphone- and smartwatch-based applications that measure clinical conditions, such as pulse rate or blood oxygen saturation, have been in development and on the market as wellness products for many years. During the COVID-19 pandemic, quarantine and home health management practices highlighted an opportunity for medical devices to leverage data connectivity for remote monitoring of vital sign measurements. Various manufacturers are exploring product designs that integrate medical device functionality with smartphone-enabled data connectivity to better address self-care and continuous monitoring product categories. Form factors that move beyond the stand-alone handheld or finger-clip medical device are handheld or finger-clip sensor medical device components that connect to a smartphone for primary or secondary functionality and consumer-focused smartwatch- or smartphone-based applications that use internal sensors.

Smartphones have evolved since they were first introduced, with current versions having enhanced processing power, high-quality cameras, and an array of continuously improving sensors. As more health information is collected through integrated or stand-alone tools, the aggregated data allow investigation of health patterns that may be associated with important outcomes, such as severe disease or rapid deterioration of health. If identified early by using machine learning– and artificial intelligence–based tools to predict or stratify risks, action could be taken, such as further diagnostics or earlier referral for care.

Whilst consumer products are not suited to replace medical devices, they may have a role and value as screening tools that digitise health data, enable risk-based stratification of patients, and more rapidly inform decision-making on patient- and population-based care. Below are some implications of smartphone-based tools.

- Smartphones' data connectivity and computer processing capabilities support machine learning methods that may enable artificial intelligence–derived risk stratification features in the future.
- Smartphone penetration in low- and middle-income countries is high, especially compared with that of many clinical measurement tools available to individuals, communities, or primary health care providers in low-resource settings.
- Software downloads and updates avoid traditional supply chain barriers with next-generation product introduction.
- Larger markets allow economies of scale, which result in lower costs of goods.
- Quality oversight is led by consumer demand rather than regulatory agencies.
- Use cases are restricted to screening tools without medical device approval.
- Market entry is easier for new developers and manufacturers and does not involve regulatory requirements.
- Potential benefits and challenges of use in low- and middle-income countries need to be better understood.

4.2. Quality

Improved regulatory practices and higher-quality standards are required to improve the accuracy of device performance in LMICs. The quality standards and regulation of many medical devices are limited and/or poorly enforced across many LMICs due to these countries' limited resources and capacity. In 2005, WHO found that only 7% of sub-Saharan African countries had national regulatory bodies; of the remaining countries, 63% had minimal regulation and 30% had no regulation at all.[58] In the absence of strong national regulatory bodies, many LMICs rely on products' stringent regulatory authority approval, especially EU CE marking and WHO endorsements, as signals of quality.[59,d] The reliance on EU CE marking presents its own unique challenges due to varying quality control measures with EU CE marking; however, the new Medical Device Regulation framework that came into effect in May 2021 aims to address these issues. Despite this, without national regulatory bodies to set context-specific standards, enforce these standards, and/or establish postmarket surveillance systems, and with limited registration processes for medical devices within LMICs, the ability to control the quality of multimodal PO devices within the market is severely limited. To support the development of a market for high-quality multimodal PO devices, there is need for more stringent evaluation standards as well as innovative interventions that can help reduce the burden on national systems.

4.2.1 Enhanced global quality standards

The current quality and accuracy standards imposed on some clinical measurement technologies by stringent regulatory authorities do not reflect the needs of key patient groups or the operating conditions at health facilities in high-, medium-, or low-income countries. For example, pulse oximetry has been found to be less accurate for patients with more skin pigmentation,[60] patients with poor circulation,[61] or patients with voluntary or involuntary movement.[21] Further, studies of both noninvasive and minimally invasive Hb technologies have found that even devices with regulatory approval yield inconsistent results when used in health facilities.[52,53] This can be explained, in part, by the minimal requirements for testing amongst diverse patient populations for EU CE marking or US FDA approval and a lack of testing requirements for approval in conditions with suboptimal climate control. For example, the US FDA acknowledges that medical devices that have been exposed to high levels of heat or humidity may not function properly.[62] Even when devices do not malfunction, sensitivities to temperature and humidity can lead to inaccurate results in quality-marked devices.[63,64] Expanding certification requirements to include diverse populations and operating conditions can facilitate improved performance across all settings, but it would be expensive and potentially not feasible for manufacturers without up-front incentives.

For medical devices that have received regulatory approval from an EU CE mark notified body or the US FDA, there is no clear process to expedite the certification of incremental device updates. Several manufacturers profiled in the previous section have added clinical measurements to existing products that have regulatory approval but have yet to validate and secure regulatory approval for the newer measurements, noting that this is lower priority due to the insufficient business case to undergo the full certification process. Furthermore, companies have mentioned that stand-alone PO products that already have stringent regulatory authority approval and then add new, unvalidated measurements can be sold to customers in countries without strict regulatory requirements.

[d] Stringent regulatory authorities include the national regulatory bodies in Australia, Canada, Japan, the European Union, and United States.

In addition to these challenges, most medical devices, including those with diagnostic capabilities like multimodal PO devices, are not currently eligible for the WHO prequalification (PQ) programme. The WHO PQ process is intended to review and recommend specific diagnostic devices that meet quality, efficacy, and safety standards needed for procurement via global health donors such as the United Nations and the Global Fund to Fight AIDS, Tuberculosis and Malaria. In practice, the lack of national regulatory processes for medical equipment and lack of stringent regulatory authority quality standards within many LMICs have resulted in national programmes and donors using the WHO PQ status to optimise use of health resources and ensure high-quality items are procured. The WHO PQ process involves defining criteria for and testing a product's performance across different settings and populations. Currently, the WHO PQ diagnostic programme focuses on cholera, glucose-6-phosphate dehydrogenase, hepatitis B and C, HIV, syphilis, human papillomavirus, and malaria.[65] These focus areas are chosen based on WHO-identified priorities and funding availability. At present, WHO is considering expanding the PQ process to include other medical devices—beginning with surgical masks, automated blood pressure devices with cuffs, and computer-aided diagnostics for tuberculosis. With these additions currently in the early stages and with limited funding, it is unlikely that the WHO PQ programme will extend to include multimodal PO devices soon. However, prior to the COVID-19 pandemic, WHO discussed expanding the PQ process to include point-of-care Hb tests, including noninvasive technologies. WHO may be revisiting these plans soon, which would involve convening various WHO global health programmatic areas (i.e., nutrition, malaria, child health, and maternal health) as well as consulting the Alliance for Anaemia Actions (a global effort that is forming and will represent community health worker perspectives) to agree on a product's technical specification across diverse settings. Although this effort would not benefit multimodal PO devices specifically, it might help advance accuracy specifications for noninvasive Hb technology, which is the most-nascent clinical measurement in multimodal PO devices.

For other medical devices, whilst there currently is no formal review process, WHO publishes the annual *Compendium of Innovative Health Technologies for Low-Resource Settings*. This document assesses products against a set of criteria to identify those that address health challenges and are well adapted for use in LMICs. However, the *Compendium* does not evaluate the devices' quality. Additionally, inclusion in the *Compendium* is not a WHO endorsement and further is not equivalent to the WHO PQ endorsement. To be included in the *Compendium*, manufacturers must apply to have their products reviewed. Various editions of the *Compendium* have included POs and patient monitors.[66-68] However, greater awareness and use of this resource by countries would be helpful.

To better define quality standards for medical devices, WHO is currently developing the Strategic and Technical Advisory Group on Medical Devices. This group will act as an advisory body to WHO on global policies and strategies related to medical devices. As part of this work, the group will develop the WHO priority medical devices list, which will include over 1,500 devices and could lay the groundwork for PQ prioritisations and qualifications.[69,70] Further, this list has the potential to support prioritisation of individual diagnostic technologies by supplementing existing resources such as the WHO Essential Diagnostic List and the Interagency List of Medical Devices for Essential Interventions for Reproductive, Maternal, Newborn and Child Health, which respectively encourage the prioritisation of Hb and PO devices.

In the absence of more stringent regulatory bodies, there have been discussions on innovative interventions to support LMICs in assessing and selecting high-quality devices suitable for use in low-resource settings. Following US FDA safety communication alerts on

the accuracy and limitations of POs during the COVID-19 pandemic, global health partners have been calling, in addition to more stringent regulatory standards, for independent external validation labs to validate the performance and durability of POs and make these results publicly available. This concept has been championed by the Hypoxia Lab at the University of California San Francisco.[e] The lab would both test POs and publish results on the existing OpenOximetry.org platform, which would inform decision-making by consumers, encourage transparency amongst manufacturers, and support regulatory bodies to enforce standards.

Overall, a lack of enhanced quality standards or WHO PQ makes it challenging for high-quality multimodal PO devices to differentiate themselves on the market. It may lead to the proliferation of devices that are of low quality and/or are not calibrated for their intended use case.

4.2.2 Alignment on standardisation thresholds

There is a need for alignment on appropriate reference standards to assess the performance of emerging technologies, such as automated respiratory rate or noninvasive Hb technologies. For example, the current clinical standard for measuring respiratory rate involves a trained health care provider using a timer to manually count breaths for 60 seconds. This is known to be challenging due to human variability and error, which produce inconsistent comparison with newer technologies.[31] For noninvasive Hb technologies, there is a need to differentiate performance standards based on the target use case. Within IMCI protocols, a screening tool to improve the subjective assessment of pallor may be valuable; however, tools to be used as diagnostic tests for Hb measurement may require higher accuracy. Classifying noninvasive Hb devices by use case is important to align accuracy requirements for diagnostic tests versus screening tools. Key to accelerating development of newer technologies is having clear consensus on accuracy requirements and appropriate reference standards.[31] Similar to pulse oximetry, manufacturers and consumers would benefit from an independent external validation lab that would systematically validate the performance and durability of newer automated respiratory rate and noninvasive Hb technologies. Alignment on reference standards in advance would allow developers to refine their technology to directly address validation requirements and facilitate acceptability amongst adopters.

As discussed in the “Technology overview” section, in addition to alignment on reference standards to further verify and validate diagnostic tools, studies that evaluate these new technologies should use and publish results following standard guidelines, such as the Standards for Reporting of Diagnostic Accuracy Studies checklist. This would enable easier comparison of emerging noninvasive Hb technologies with established methods. For example, commercialised minimally invasive and emerging noninvasive Hb measurement technologies both face significant challenges in reliably validating device accuracy across patient populations. This can be attributed, in part, to the different protocols followed in each study and various methods benchmarked against as a reference.

Without agreed upon reference standards for quality and verification, developers are unable to generate adequate evidence that clearly demonstrates their products’ performance. For emerging technologies to demonstrate value, it is essential that global governing bodies set clear reference standards for performance evaluation that can be replicated across large, diverse populations to support their quality endorsement.

[e] As presented on the Every Breath Counts Coalition COVID-19 coordination call on January 24, 2022.

4.3. Demand and adoption

4.3.1 Overview of the multimodal PO device market

Whilst the current market for multimodal pulse oximeter (PO) devices is nascent, modelled estimates indicate a significant potential total market for multimodal PO devices in low- and middle-income countries (LMICs)—estimated to range between 3.9 million and 7.6 million units of multimodal PO devices.[f] This estimated market size is based on current infrastructure need (i.e., number of beds at facilities and number of health care workers [HCWs]) in LMICs but does not factor in current willingness/ability to pay or demand. Further, it assumes there is no market saturation of devices as currently known demand for POs in LMICs accounts for less than 5% of the total market size. See Annex 4 for the full market sizing methodology and key assumptions.

The overall market size is driven by spot-check use in both inpatient and outpatient triage settings, which accounts for approximately 85% of the estimated market size, followed by continuous monitoring, which accounts for approximately 15%. Furthermore, the market size estimates differentiate between multimodal PO devices with and without Hb functionality because the latter has limited use in settings that require continuous monitoring. Given the various potential use cases and available substitute products for multimodal PO devices, the total market size is estimated across three scenarios—optimistic, base, and conservative—which are detailed in Table 4.

In the optimistic scenario, a key market segment—at approximately 10% of the total estimated market size or 30% of the spot-check market segment—is the use of multimodal PO devices by community HCWs (all of whom are assumed to have Hb-measuring capability). Whilst the value of community HCWs having diagnostic technologies has been questioned, in the wake of the COVID-19 pandemic, some national governments with robust community HCW programmes, such as India and Ethiopia, have begun equipping community HCWs with POs. Given this emerging trend, in an optimistic scenario, 60% of community HCWs would be equipped with multimodal PO devices. In a base scenario, only 40% of community HCWs would be equipped with multimodal PO devices. The conservative forecast assumes 20% of community HCWs would be equipped with multimodal PO devices.

Although multimodal PO devices are not considered to be direct substitutes for patient monitors, market trends and research have shown that users in LMICs use handheld POs with continuous monitoring functionality in critical care settings that lack more expensive patient monitors and/or in facilities with limited infrastructure. This market feedback led Masimo to adapt the Rad-G to include continuous monitoring functionality. As such, the optimistic scenario assumes that multimodal PO devices account for 70% of the total continuous monitoring need; the estimate is 50% in the base scenario and 30% in the conservative scenario.

[f] The total market size is based on the following assumptions: (a) accounts for anticipated need across all levels of care, based on an infrastructure approach, but does not factor in demand or ability to pay; (b) current market saturation of 0% by existing products as currently known procurement accounts for less than 5% of the total market; (c) additional annual, ongoing costs for maintenance and consumables are not factored into the market size; (d) underlying infrastructure assumptions are based on public bed count and HCW datasets gathered by WHO and the World Bank.

TABLE 4. Estimates of the total market for multimodal PO devices.

Market segment	Optimistic forecast	Base forecast	Conservative forecast
Inpatient continuous monitoring	1,200,000	900,000	500,000
Outpatient and inpatient spot checking	6,400,000	4,900,000	3,400,000
Facility-based spot checking	5,300,000	4,100,000	2,900,000
Community health care worker–based spot checking	700,000	500,000	200,000
Specialist doctors with need	400,000	300,000	200,000
Total multimodal PO units	**7,600,000**	**5,800,000**	**3,900,000**

Abbreviation: PO, pulse oximeter.

Whilst there is market potential, interventions are needed to catalyse demand for multimodal PO devices. For example, during the COVID-19 pandemic, there was an unprecedented demand for comprehensive oxygen delivery. Despite this clear need and available funding, which was allocated for procurement through COVID-19 grants, pulse oximetry did not see the same increases in demand as oxygen delivery systems through global procurement platforms. Available global procurement data through United Nations agencies show that LMICs have procured approximately 164,000 POs and approximately 14,000 patient monitors[g] since the start of the pandemic, filling only a fraction of the optimistic estimated market need. Limited demand may be explained partially by LMICs purchasing these devices locally and/or the demand for diagnostics lagging behind the demand for treatment. However, anecdotally, global nongovernmental organisations report that many LMIC governments did not prioritise high-quality handheld or tabletop POs. Instead, decision-makers opted to purchase inexpensive, low-quality fingertip POs. This could be due, in part, to the challenges national governments have in allocating and mobilising the requisite funds for recommended devices. When funding is available, such as through COVID-19 funds, opaque national procurement practices further prevent procurement of new, innovative items.

Although demand for POs has been higher than in previous years across LMICs due to the COVID-19 pandemic and has included some (around 25,000) uptake of available multimodal PO devices, the procured quantities do not meet the estimated need. Furthermore, it is unclear if elevated demand will be sustained after COVID-19 emergency response efforts.

Based on the PO market as an indicator, there is significant market potential for multimodal PO devices (see the text box on the "Overview of the multimodal PO device market"). However, interventions to generate sustainable demand for and catalyse adoption of multimodal PO devices, such as the following, will be required. Furthermore, the absence of a funded global coordination mechanism, such as the Global Fund, that would aggregate demand across multiple LMICs and alleviate domestic funding constraints (discussed below in the "Affordability" section) limits demand for and adoption of PO and multimodal PO devices. In contrast, items supported by global coordination mechanisms, such as vaccines, have a more transparent and direct pathway to scale as financing and demand are aligned from the onset.

[g] These data are from the World Health Emergency Dashboard, accessed on April 1, 2022. Data are inclusive of procurements managed by UNICEF on behalf of the Global Fund COVID-19 Response Mechanism.

4.3.2 Inclusion of multimodal PO devices in global guidelines

The role of global entities, such as WHO, in establishing, coordinating, monitoring, and enforcing global clinical norms and standards is becoming increasingly important as the pace of health innovation and discovery accelerates. WHO's endorsement of new diagnostics or treatment can rapidly catalyse change within the health care delivery system as public health programmes and global health donors often look to WHO for normative guidance.

More specifically, there is opportunity to streamline diagnostic testing protocols for a variety of disease areas. Febrile illnesses, pneumonia, and anaemia currently carry a high burden of disease, but the diagnostic criteria are unclear across guidelines. For example, to diagnose anaemia, WHO suggests in the IMCI protocols to look for palmar pallor as the primary check.[8] However, in other guidelines, WHO recommends measuring Hb levels to diagnose anaemia for the same patient populations, which would require the use of a diagnostic technology.[47] Whilst these recommendations do discreetly endorse the use of technology to increase diagnostic accuracy, there is a clear opportunity for WHO to adapt policy recommendations to directly reference specific classes of devices across diagnostic guidelines. This likely requires evidence generation across multiple areas—such as health impact, cost-effectiveness, and operational research—to inform policy change.

Similarly, in assessing and classifying sick children under five years old, the IMCI chart booklet instructs HCWs to assess difficulties breathing based on clinical signs, with a footnote recommending use of pulse oximetry only "if PO is available."[8] There is preliminary evidence that pulse oximetry can reduce the cognitive burden on HCWs and assist in accurate diagnostics,[16,17,71] but further evidence is required for WHO to include pulse oximetry within its standards and guidelines/protocols. The ongoing Unitaid-funded TIMCI and AIRE projects, led by PATH and The Alliance for International Medical Action (ALIMA), aim to generate evidence on the use of pulse oximetry and electronic decision-support algorithms to identify severe disease in children under five years old at the primary health care level. Additionally, the TIMCI project is implementing a range of activities to advance the market for multimodal PO devices. The project will conduct a study to evaluate the performance of several pipeline and commercially available multimodal PO devices and their feasibility of use by primary health care providers in children under five years old in Kenya, Tanzania, India, and Senegal. Furthermore, the project will model cost-effectiveness of multimodal PO devices that measure SpO2 and respiratory rate as well as conduct postmarket surveillance on Rad-G devices procured through COVID-19 funding to understand HCW experience with them. However, as the market for multimodal PO devices rapidly develops, there may be need for additional evidence generation to understand the operational fit and value of multimodal PO devices within current care pathways. The specific type of evidence required—whether it is impact, cost-effectiveness, operational, and/or other—remains to be defined and agreed upon by countries, WHO, global health donors, and partners.

4.3.3 Inclusion of multimodal PO devices in national guidelines

In addition to updating global guidance, national policies must be adapted to include multimodal PO devices. Given the broad range of use cases for multimodal PO devices—from continuous monitoring, to spot checking and triaging, to delivery of advanced care—it is important to ensure that national guidelines are updated to reflect the full potential of multimodal technology and to allow HCWs to integrate the technology into their local context and daily routine. However, national policy updates are often lengthy and costly

processes. These updates often start with global normative guidance, but they also include gathering insights from multiple perspectives (e.g., professional associations, regulators, practitioners, government stakeholders) and may require evidence that is specific to local context.[72] Whilst evidence-based decision-making is crucial, most multimodal PO device manufacturers and national governments are unable to fund evidence-generating studies on a country-by-country basis or even across geographic regions. Regional bodies, such as the Africa Centres for Disease Control and Prevention, are working to build the capacity of national-level public health institutions to generate this type of evidence on emerging technologies; however, these efforts will take time and, in the interim, require funding and technical assistance from global health donors and partners.

4.3.4 Coordinated awareness and introduction campaigns

Multimodal PO devices can be used across multiple use cases. Like oxygen therapy, this crosscutting intervention creates unclear leadership for the devices' introduction and scale-up, often leading to a lack of ownership and nonintegrated approaches for device use and maintenance. A coordinated introduction and scale-up plan will be important for efficiency and cost saving. There is an opportunity for the global health community and governments to coordinate across programmes to identify key champions that can strengthen awareness, introduction, and scale-up of these devices.

4.3.5 Integration into HCW training programmes

Currently, HCWs rarely use multimodal PO devices because limited availability and relatively high cost prevent widespread access to the devices. When the devices are available, limited training and HCW knowledge of device capabilities limits use across the spectrum of use cases. Inclusion within clinical guidelines is important to enable adoption of multimodal PO devices, yet these updates alone are insufficient to generate demand. Successful examples have shown that integrating recommended devices into relevant clinical guidelines and clinical workflows, paired with knowledge and skills training to improve HCW understanding and acceptance, helps translate policy changes into practice.[72] Further, within the training package, there is opportunity to incorporate modules for HCWs and technicians on proper use and maintenance practices. This minimises the chances of unsafe device handling and potentially harmful patient outcomes (e.g., misdiagnosis due to miscalibration).[73]

Because they perform multiple clinical measurements, multimodal PO devices could be integrated into a wide range of services and thus improve quality of care. For example, including multimodal PO devices in the IMCI package of care and training programmes has the potential to reach service providers in over 100 countries that currently implement some form of IMCI programming.[74] Further, integration of multimodal PO devices into antenatal care has the potential to improve outcomes for the 87% of pregnant women globally who access at least one antenatal care visit.[75]

4.4. Affordability

Health care systems in LMICs face substantial resource constraints, requiring decision-makers to prioritise health interventions. Increasingly, these decisions are based on evidence-based frameworks, many of which include cost-effectiveness as a predominant decision-making factor.[76] Anecdotally, this cost-conscious mindset is further reiterated by suppliers, distributors, and country procurement agents, all of whom note that price is a key factor in making purchasing decisions. Further, multimodal PO devices primarily rely on domestic financing, which can be inconsistent since there is no clear global procurement or financing mechanism for these devices. Whilst there is ad hoc procurement of PO

devices through the UNICEF Supply Catalogue and funding support from multilateral and bilateral organisations through their existing vertical programmes, there is no clear funding champion for PO and multimodal PO devices akin to the Global Fund, which provides support for HIV, tuberculosis, and malaria. Despite this acknowledgment of price sensitivity and lack of clear financial support, multimodal PO devices may have high up-front costs because key market challenges limit uptake, such as those described in the following sections.

4.4.1 Price variability between products

Current diagnostic devices that perform one clinical measurement, or multimodal PO devices that perform multiple clinical measurements, have variable pricing for seemingly similar devices. For example, in LMIC markets, commercially available and pipeline multimodal PO devices without Hb measurement range in cost from approximately $100 to $300. In even more contrast, prices for handheld POs range between $80 and $600.[77] These price differences can be driven, in part, by quality differences as well as by small volume orders, with unclear total demand driving up the ex-works price to ensure manufacturer targets are met. As discussed above, without stronger quality standards and price transparency, it is challenging for procurement bodies to assess tangible differences across products. This often results in procurers choosing the most inexpensive products, which leads to proliferation of low-quality devices that may have a higher total cost of ownership due to replacement and/or repair needs.

Multimodal PO devices face another layer of added complexity to remain competitive. The addition of multiple clinical measurements can increase the price to consumers. For example, introducing temperature measurement into multimodal PO devices requires the inclusion of a new sensor as temperature cannot be accurately measured from a fingertip. This means manufacturers must then incorporate an additional contact-based temperature probe, which has a relatively lengthy time to measurement and requires additional user steps, or a more costly IR sensor. In the Masimo Rad-G, the inclusion of an additional IR thermometer increased the price of the device by $50, from $250 to $300. The inclusion of noninvasive Hb technology is expected to lead to further price increases. Furthermore, the different product offerings (e.g., clinical measurements, types of screen displays, etc.) and pricing structures make it challenging for buyers to compare and choose products.

Given the price sensitivity in LMIC markets, these incremental increases in price have significant potential to price the devices out of the markets' willingness and ability to pay. Data on total cost of ownership and demonstrated cost-effectiveness may help establish the potential value of devices that integrate multiple clinical measurements.

4.4.2 Accounting for full cost of device ownership

Whilst the up-front cost of diagnostic devices is a key factor in purchasing decisions, it is recommended that decision-makers consider the total cost of ownership as well. It is estimated that between 40% and 70% of medical equipment in LMICs are broken or unused.[73] The limited functionality is, in part, driven by incomplete costing considerations and lack of HCW training. Incomplete costing leads to insufficient budgets for maintenance and procurement of consumables. To accurately guide decision-making, decision-makers should consider a product's total life-cycle cost, which accounts for maintenance, consumables, HCW training, and decommissioning and disposal services.[73] For example, emerging technologies for noninvasive Hb measurement, as stand-alone devices or integrated into multimodal PO devices, may cost more up front but may have lower life-cycle costs. The noninvasive measurement technology relies on a reusable finger probe that

performs many tests before replacement is needed. This eliminates the need for single-use consumables and biohazardous waste.[53] Additionally, this technology eliminates the need for difficult blood draws or can shift the task to a lower cadre of HCW, reducing barriers associated with introducing the device and training HCWs. Last, multimodal PO devices may provide an opportunity to streamline HCW training and device maintenance requirements by introducing one device with multiple measurements rather than multiple single-use devices. This may improve use of limited financial resources as well as appropriate use of devices, leading to better patient care.

4.4.3 Demonstrating cost-effectiveness

By simultaneously assessing multiple clinical parameters (e.g., Sp02, pulse rate, respiratory rate, temperature, and Hb levels), multimodal PO devices have the potential to cost-effectively improve quality of care. Moving from assessment of clinical signs to diagnostic tools with objective measurements supports more accurate diagnosis and treatment. Combining multiple clinical measurements into one device supports more thorough assessments across a wide range of patients. For example, studies have shown that for children under five years old in LMICs, only 7% presented with a fever alone,[78] 5% presented with hypoxaemia,[79] and, in some cases, less than 20% of patients with anaemia received an accurate diagnosis.[80] Without multimodal technology, HCWs would need to know how to use, and have available, thermometers, POs, and Hb measurement technologies for patients presenting with each of these indications respectively. Multimodal PO devices may reduce the number of individual diagnostic equipment needed and could greatly assist HCWs in providing more complete and accurate triaging and diagnostic assessments. Evidence is needed to determine the cost-effectiveness of an integrated device on a per-test basis in comparison to current diagnostic methods and across various applications (e.g., triaging, continuous monitoring, spot checking) within clinical pathways. This evidence will be crucial for decision-makers to adopt new multimodal PO devices.

4.5. Supply and delivery

To ensure an adequate and consistent supply of multimodal PO devices, it is essential to strengthen national-level health regulatory and procurement systems. Creating efficiencies in procurement involves developing a healthy market where high-quality products are available at the right time and at affordable prices. This requires the cooperation and coordination of multiple national and international agencies, and enhanced market transparency for suppliers.

4.5.1 Increased registration of market competitors

Although competition between products has positive externalities, such as reduced markups that lead to improved affordability, maintaining a high-quality supply chain for a significant proliferation of devices is challenging and has the potential to fragment limited demand into small high-cost transactions. This currently describes the market for POs, but it could apply to multimodal PO devices as more enter the market. To limit market fragmentation and manage the quality and suitability of devices, when possible, it is important for national governments to reduce regulatory exemptions and clearly and transparently publish as well as enforce regulatory pathways. This would ensure higher-quality devices are on the market and consolidate demand into fewer devices, thereby increasing economies of scale and reducing transaction costs for devices and their consumables. It then becomes possible to ensure devices meet national standards and limit the strain on supply chains.

In countries that currently require registration of medical devices, low registration rates for similar products are often due to the need for locally generated evidence on product efficacy and high transaction costs of registration. One way to reduce these costs would be through leveraging regional regulatory harmonisation efforts. For example, the East African Community began to harmonise medicine registration across its five member states. The programme has resulted in significant reductions in national registrations, which has been enabled, in part, by the adoption of a modified application process that builds on the WHO PQ documents. Whilst the East African Community programme was intended to expand beyond medicines to include medical devices, the programme has not yet been able to identify a self-sustaining financing mechanism beyond the initial donor-led catalytic support.[81]

4.5.2 Inclusion in, and strengthening of, routine procurement systems

With a growing product pipeline, limited quality endorsements, and brand-agnostic inclusion in international procurement catalogues—whereby PO devices are listed generically within procurement catalogues and orders are filled with available devices and can contain multiple brands[82]—multimodal brands may proliferate within a single market, as was seen in the stand-alone PO market. To ensure consistent access to high-quality diagnostic technologies, inclusion of specific multimodal PO devices into local procurement systems is necessary. For many medical devices, particularly those that are donated, LMICs often lack the supply chains required to replace devices or provide consumable components and spare parts, such as replacement probes, batteries, or chargers.[83,84] This challenge is exacerbated by the lack of standardisation of consumables across manufacturers and the fragmented donation and procurement landscapes in LMICs. This fragmentation leads to small, low-value, repetitive procurements of individual devices to obtain compatible parts for each individual brand. Including multimodal PO devices and their consumables in routine public- and private-sector procurement systems and framework agreements increases the likelihood that facilities will have consistent access to replacement items as needed, without placing additional burden on the HCWs to source compatible products. This would further reduce the potential that the devices would lay dormant. For example, current minimally invasive Hb measurement technologies require consumables that are both costly and challenging to keep in stock; this inconsistent availability limits the devices' usability.[53] In addition to inclusion within procurement systems, it is important to work towards strengthening the routine supply chain systems. This includes strengthening quantification exercises, which can facilitate advanced planning, funding mobilisation, procurement processes, and distribution processes down to the last mile.

There are ongoing and new programmes led by PATH and other organisations that are building on COVID-19 response efforts to ensure long-term access to medical oxygen and resilient respiratory care systems. These programmes will focus on strengthening capacity-building and implementation support for respiratory care equipment, including POs and multimodal PO devices.

4.5.3 Increased market transparency

The underdeveloped market for multimodal PO devices limits funded demand and understanding of the total market size. Without evidence of affordability, as discussed above, domestic funds have yet to be allocated for large-scale multimodal device procurement. In many health areas, domestic funding often precedes extensive supplemental funding by programmatic donors. Although there are increasing amounts of funding support for

maternal, newborn, and child health (e.g., from the Global Financing Facility), funding remains limited, with no visible commitments to provide for procurement of multimodal PO devices. This unknown demand, coupled with high transaction costs of entering each market, disincentivises new suppliers from directly entering LMIC markets, limits their reach, leads to inconsistent and sometimes significant product markups, and/or makes it challenging to remain profitable. Market intelligence reports that include information on regulatory pathways, demand forecasts, and available financing are key resources that help increase transparency. In developing and sharing these reports with interested suppliers, the information gap on LMIC markets can be minimised. For example, improved demand forecasts illustrate the total need within a select market. This can help manufacturers ensure the availability of the appropriate volume of devices to meet the market needs. This also can minimise rushed procurement and thus support improved pricing through volume discounts and reduced margins. However, this transparency would not address the absence of funded demand. There are further opportunities to work with the private sector to evaluate the effectiveness of various business strategies—for example, use of subscription-based pricing models or regional distribution—to increase access to and affordability of multimodal PO devices.

Additionally, from the procurement agents' perspective the lack of quality endorsements and the highly proliferated market with a wide range of device costs lead to opaque pricing. For medical devices, particularly those with low-volume procurements, sales agents and distributors often add considerable margins to the price of individual devices. With the lack of price transparency, decision-makers then default to the cheapest list price despite any quality or usability considerations. Increasing pricing transparency by publishing reference pricing materials, akin to those described in the "Product landscape" section of this report, and sharing these with country partners may assist pricing negotiations to improve device affordability.

5. RECOMMENDATIONS ON A WAY FORWARD

The previous section discussed in depth the range of market barriers and potential interventions to address those barriers. Table 5 below summarises short-term (approximately one to three years), medium-term (three to five years), and longer-term (more than five years) opportunities that address multiple market barriers. These opportunities are not exhaustive, and many are interdependent. It is important to note that no single intervention will address all barriers, and concerted efforts to address multiple barriers over time are required.

TABLE 5. Summary of opportunities for market interventions.

Intervention	Examples of implementation activities	Addressed market barriers	Time frame
Create sustainable local markets in early adopter countries.	• Build on existing child health and COVID-19 response investments that have focused on scaling access to POs. • Leverage existing/upcoming evidence on multimodal PO devices (if positive) to mobilise financing (domestic and global donor) and aggregate funded demand in early adopter countries. • Implement coordinated awareness and introduction campaigns. • Integrate into HCW training programmes. • Integrate into and support national procurement and supply chain systems.	• Innovation and availability. • Demand and adoption. • Supply and delivery.	Short term
Increase market transparency for PO and multimodal PO devices.	• Improve completeness of procurement data in both public and private sectors. • Conduct analysis of demand (e.g., forecasting and quantification) and price sensitivity at country level across public and private sectors. • Explore opportunities to create and publish reference pricing resources. • Evaluate the effectiveness of different business strategies, such as subscription models.	• Supply and delivery. • Demand and adoption. • Affordability. • Innovation and availability.	Short to medium term
Unlock financial resources and pricing mechanisms for multimodal PO devices.	• Leverage generated evidence on PO and multimodal devices to secure new or continuation of domestic and donor funds (e.g., Global Fund to Fight AIDS, Tuberculosis and Malaria's COVID-19 Response Mechanism). • Reduce multimodal PO device prices through market-shaping interventions (e.g., pooled procurement mechanisms and volume guarantees).	• Demand and adoption. • Innovation and availability. • Affordability	Short to medium term

Advance noninvasive Hb technology.	• Leverage existing health programmes and efforts, such as the WHO PQ anaemia programme (which crosscuts malaria, child health, and maternal health programmes) and the Alliance for Anaemia Actions, to define and evaluate technical specifications for Hb technologies. • Generate evidence to establish the accuracy of noninvasive Hb technology across diverse populations and settings.	• Innovation and availability.	Short to medium term
Strengthen national systems.	• Strengthen regulatory capacity for PO and multimodal PO devices by standardising registration requirements, implementing postmarket surveillance systems, and leveraging regional harmonisation efforts. • Support public health research institutions' capacity to conduct studies that are adapted to the local context and that enable adoption of emerging multimodal PO technologies. • Support national and private-sector procurement and supply chain systems, including exploring role of the private sector (e.g., regional and national distributors) as a service provider.	• Quality. • Supply and delivery. • Demand and adoption.	Short to long term
Revise global and national guidelines to enable adoption and scale across multiple countries.	• Engage WHO to define the policy and guidance pathway, including evidence (e.g., health impact, cost-effectiveness, operational research) gaps for multimodal PO devices for use across PHC programmes. • Generate required evidence (e.g., product efficacy and others as identified by gap analysis) across multiple countries that are representative of various regions. • Work with national governments to update guidelines leveraging WHO guidance and evidence.	• Demand and adoption.	Medium term
Create more upstream interventions that define and establish quality standards for multimodal PO devices.	• Convene normative bodies for alignment on quality and standardisation thresholds. • Expand WHO PQ process to include multimodal PO devices. • Leverage third-party evaluators and laboratories, as well as open-access data repositories, to objectively define thresholds, test devices, and publish results for stand-alone and multimodal PO devices. • Advance efforts that encourage stringent regulatory authorities to improve required standards.	• Quality. • Innovation and availability.	Medium to long term

Abbreviations: Hb, haemoglobin; PHC, primary health care; PO, pulse oximeter; PQ, prequalification; WHO, World Health Organization.

6. CONCLUSION

Multimodal PO devices are a promising technology that has the potential to reduce maternal and child health mortality and strengthen the implementation of integrated delivery platforms by low-skilled frontline HCWs in low-resource settings. These devices may help improve the accuracy and efficiency of, and adherence to, consultations that facilitate more appropriate diagnosis and integrated management of illnesses—namely, fever, pneumonia, and anaemia. They also may minimise the burden on health systems by strengthening referral decisions and overuse of antibiotic treatments.

Due to various global health investments and the COVID-19 pandemic, the multimodal PO product landscape has progressed, with several devices currently commercially available or in the pipeline. There are also emerging stand-alone Hb devices, some which are derived from the PPG waveform. However, several technological and market challenges threaten the adoption and scale-up of high-quality and affordable multimodal PO devices. In particular, there is a need to define quality requirements and performance thresholds and evaluate efficacy across diverse settings and populations. There is also a need to define and align on required evidence for policy and guideline recommendations at both global and national levels. Additionally, unlocking financing and strengthening national systems to facilitate the implementation of integrated delivery platforms are essential to enabling uptake.

Continued engagement with manufacturers, specifically by communicating priorities and quality requirements as well as providing market intelligence, is key to strengthening the business case for multimodal PO devices. If challenges are addressed, multimodal PO devices that are affordable, high quality, and appropriately designed for use in rugged maternal and child health settings will advance through the development pipeline and achieve meaningful scale and impact.

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ANNEX I
CONSULTED STAKEHOLDERS

- Africa Centres for Disease Control and Prevention: Dr. Raji Tajudeen
- Bill & Melinda Gates Foundation: Caeley Harihara, Douglas Call, Rasa Izadnegahdar
- Biosense Technologies: Yogesh Patil
- Bosch: Mihir Mehta
- Clinton Health Access Initiative: Audrey Battu
- EzeRx: Partha Pratim Das Mahapatra
- Guangdong Biolight Meditech: Tadson Tan, Shumail Mahmood
- Independent consultant: Jenn Daily
- Masimo Corporation: Grant Aaron
- Medtronic: Allie Sibole
- Muhimbili University of Health and Allied Sciences and Karolinska Institutet: Tim Baker
- Murdoch Children's Research Institute: Hamish Graham
- Nonin Medical, Inc.: Walter Holbein
- PATH: Mercy Mvundura, Shan Hsu, Manjari Quintanar Solares, Elizabeth Abu-Haydar, Raphael Kayambankadza, Megan Parker, Andolo Miheso, Kovid Sharma, Lisa Smith
- Sanguina: Erika Tyburski, Rob Mannino
- Save the Children: Rasheduzzaman Mohammad Shah, Tahlil Ahmed
- Scanbo: Ashissh Raichura
- United Nations Children's Fund (UNICEF): Noah Mataruse, Fiorella Polo, Florin Gheorghe
- United States Agency for International Development: Rahima Dosani, Nikki Tyler
- Vayu Global Health Innovations: Thomas Burke
- World Health Organization: Jane Cunningham, Francesco Ribolzi, Adriana Velazquez Berumen, Wilson Were, Yasir Bin Nisar
- Zug Medical Systems: Stephane Hollande

ANNEX 2[a]
PRODUCT PROFILES

Masimo Corporation	
Product name	Rad-G™
Source: Masimo	
Parameters measured	SpO2, PR, and RR; the Rad-G with Temperature version also measures temperature Hb sensor is under development
Measurement mode	Rad-G: Spot-check Rad-G Continuous version: Spot-check and continuous
Intended use and target population	Indicated for noninvasive spot-checking or continuous monitoring of SpO2, PR, and photoplethysmography, or pleth, RR. The SpO2 and PR features are indicated for use in adult, paediatric, infant, and neonatal patients during both no-motion and motion conditions, and in patients that are well or poorly perfused in hospitals, hospital-type facilities, transport, and home environments. The RR feature is indicated for use in adults and paediatric patients that are well or poorly perfused in hospitals, hospital-type facilities, transport, and home environments. The RR feature is indicated for use in adults and pediatric patients during no-motion conditions in hospitals, hospital-type facilities, transport, and home environments.
Description	The Rad-G Pulse Oximeter and accessories use the same principles of operation for functional oxygen saturation of arterial Hb, PR, and pleth RR as the Radical-7. The principles of operation of pulse oximetry are based on the fundamental principle that Hb bound to oxygen (oxyhaemoglobin) and Hb unbound to oxygen (deoxyhaemoglobin) absorb wavelengths of light differently; these absorptions can be used to estimate SpO2 and PR. RR from pleth relies on the principle that the cyclic variations in plethysmograph can be used to establish an RR measurement. The temperature reading integrated into the Rad-G device comes from a noncontact, infrared thermometry that does not require probes or other disposable accessories.
Availability	Commercially available
Development phase	Global health SpHb® sensor that can be connected to the Rad-G is under development. This sensor would enable users to measure adult and paediatric patients' SpO2, heart rate, RR, temperature, and Hb measurements through one platform.

[a] Product profiles for the Vivaray Hb and Vivaray Hb Pro are not included in this section per Bosch's request. Please see page 18 in the "Product landscape section" for an overview of the products. Further details are available at www.bosch-softwaretechnologies.com%2Fmedia%2Fdocuments%2Fdownloads%2Fhealthcare_1%2Fwhitepaper_mod_bosch_hemoglobin_monitor_solution.pdf&clen=1440828&chunk=true

Performance and accuracy	SpO2 (no motion, adults/paediatrics/infants): 70%–100% ± 2% SpO2 (no motion, neonates): 70%–100% ± 3% SpO2 (with motion, all patient populations): 70%–100% ± 3% SpO2 (low perfusion, all patient populations): 70%–100% ± 2% PR (no motion): 25–240 bpm ± 3 bpm PR (with motion): 25–240 bpm ± 5 bpm PR (low perfusion): 25–240 bpm ± 3 bpm RR (no motion, adults/paediatrics >2 years of age): 4–70 rpm ± 3 rpm ARMS, ± 1 rpm mean error Hb: To be determined
Time to result	<30 seconds for stabilized values
Consumables	Probes
Power	Rechargeable lithium-ion battery
Price	Global health pricing is $250 for the Rad-G with one sensor and $299 for the Rad-G with Temperature. Price for the Rad-G in non-global health markets varies by region, mode of distribution, and mode of procurement. Price from online third-party distributors in the United States is $594†–$659.‡ Pricing for the global health SpHb® Rad-G-compatible sensor is to be determined.
Regulatory	US FDA approved (2020), and EU CE marking received (2021). Development and validation of the global health SpHb® sensor, including regulatory clearance, are expected to be completed by the end of 2023.

Abbreviations: bpm, beats per minute; EU, European Union; FDA, Food and Drug Administration; Hb, hemoglobin; PR, pulse rate; rpm, respirations (breaths) per minute; RR, respiratory rate; SpO2, blood oxygen saturation.

* Source: US Food and Drug Administration 510(k) Premarket Notification Database website. Masimo Rad-G Pulse Oximeter and Accessories 510(k) summary page. https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201770.pdf. Accessed April 6, 2022.

† Source: Concord Health Supply website. Masimo Rad-G rechargeable oxygen saturation monitor page. https://www.concordhealthsupply.com/Masimo-Rad-G-Handheld-Pulse-Oximeter-p/mas-9847.htm?gclid=Cj0KCQiA95aRBhCsARIsAC2xvfzo9zet9T9gKCtaDT7iaENrvCqc1ZZoEvO8imPWVJm5S3UZHmYHu2MaAog6EALw_wcB&click=71. Accessed April 6, 2022.

‡ Source: Cascade Health Care website. Masimo Rad-G pulse oximeter with multisite & finger sensors page. https://cascadehealth.com/masimo-rad-g?gclid=Cj0KCQiA95aRBhCsARIsAC2xvfwfF4xOxZlDl98jGlEkey5v5J5swjehCTs_3-AYOTTRD-y9KEgNqH8aAjlEEALw_wcB. Accessed April 6, 2022.

Masimo Corporation	
Product name	Pronto®
Parameters measured	SpO2, PR, and Hb
Measurement mode	Spot-check
Intended use and target population	Indicated for use by trained personnel in adult and paediatric individuals in clinical and nonclinical settings (e.g., hospitals, hospital-type facilities, homes, clinics, physicians' offices, and ambulatory surgery centers).*
Description	Uses pulse CO-oximetry to monitor oxygen saturation in the blood. The device is used by placing a sensor that measures different wavelengths of light onto the tip of a patient's ring finger.
Availability	Commercially available
Development phase	N/A
Performance and accuracy	SpO2: 70%–100% ± 2% PR: 30–250 bpm +3 bpm Normal sensitivity mode: SpHb: 6–18 g/dL ± 1 g/dL Maximum sensitivity mode: SpHb: 4.5–20.0 g/dL ± 1.1 g/dL*
Time to result	N/A
Consumables	Probes and batteries
Power	Four AA alkaline batteries
Price	Price for these products varies by market, mode of distribution, mode of procurement, and payment model (for spot-check SpHb). Global health discounted pricing for these products is available but varies depending on volumes, programme, and preferred payment model. Non-global health price from online third-party distributors in the United States is approximately $979† (includes 200 SpHb tests; approximately $5 per test).
Regulatory	US FDA approved (2011)

Abbreviations: bpm, beats per minute; CO, carbon monoxide; FDA, Food and Drug Administration; Hb, haemoglobin; N/A, not applicable; PR, pulse rate; SpHb, total haemoglobin; SpO2, blood oxygen saturation.

* Source: US Food and Drug Administration 510(k) Premarket Notification Database website. Masimo Rainbow SET Pronto-7 Pulse CO-Oximeter and Accessories 510(k) summary page. https://www.accessdata.fda.gov/cdrh_docs/pdf11/K111403.pdf. Accessed April 6, 2022.

† Source: Concord Health Supply website. Masimo Pronto for spot checking Hemoglobin (SpHb), arterial oxygen saturation (SpO2), pulse rate (PR), and perfusion index (PI) page. https://www.concordhealthsupply.com/Masimo-Pronto-for-Spot-checking-hemoglobin-SpHb-p/mas-3580-3581-3584.htm?gclid=CjwKCAiAsYyRBhACEiwAkJFKops363qsPS7osFB1ewVnJlCVXmgGo5-uz3ZG1vHkRymeUu-ykB4uKxoC-msQAvD_BwE. Accessed April 6, 2022.

Masimo Corporation	
Product name	Radical-7®
Parameters measured	SpO2, PR, and Hb
Measurement mode	Continuous
Intended use and target population	Indicated for use in adult, paediatric, and neonatal patients during no-motion conditions, and for patients who are well or poorly perfused in hospitals, hospital-type facilities, and mobile and home environments.*
Description	Uses pulse CO-oximetry to monitor oxygen saturation in the blood. The device is used by placing a sensor that measures different wavelengths of light onto the tip of a patient's ring finger.
Availability	Commercially available
Development phase	N/A
Performance and accuracy	SpO2 (no motion): 60%–80% ± 3% SpO2 (with motion): 70%–100% ± 3% SpO2 (low perfusion): 70%–100% ± 2% HR (no motion): 25–240 bpm ± 3 bpm HR (with motion): 25–240 bpm ± 5 bpm HR (low perfusion): 25–240 bpm ± 3 bpm During no motion (SpHb was not validated with motion or low perfusion), SpHb: 7–17 g/dL ± 1 g/dL*
Time to result	N/A
Consumables	Probes
Power	Rechargeable nickel-metal hydride battery
Price	The price for these products varies by market, mode of distribution, and mode of procurement. Global health discounted pricing for these products is available but varies depending on volumes, programme, and preferred payment model. Non-global health price from online third-party distributors in the United States is approximately $2,115.†
Regulatory	US FDA approved (2008)

Abbreviations: bpm, beats per minute; CO, carbon monoxide; FDA, Food and Drug Administration; Hb, haemoglobin; HR, heart rate; N/A, not applicable; PR, pulse rate; SpHb, total haemoglobin; SpO2, blood oxygen saturation.

* Source: US Food and Drug Administration 510(k) Premarket Notification Database website. Masimo Rainbow SET® Radical 7 CO-Oximeter 510(k) summary page. https://www.accessdata.fda.gov/cdrh_docs/pdf8/K080238.pdf. Accessed April 4, 2022.

† Source: Medical Device Depot website. Masimo Radical-7 bedside pulse oximeter page. https://www.medicaldevicedepot.com/Masimo-Radical-7-Bedside-Pulse-Oximeter-p/9500-masimo.htm. Accessed April 6, 2022.

Masimo Corporation	
Product name	Rad-67™
Parameters measured	SpO2, PR, and Hb
Measurement mode	Spot-check
Intended use and target population	Indicated for use by trained personnel in adult, paediatric, and infant individuals in clinical and nonclinical settings (e.g., hospitals, hospital-type facilities, homes, clinics, physicians' offices, and ambulatory surgery centers).*
Description	Uses pulse CO-oximetry to monitor oxygen saturation in the blood. The device is used by placing a sensor that measures different wavelengths of light onto the tip of a patient's ring finger.
Availability	Commercially available
Development phase	N/A
Performance and accuracy	SpO2 (no motion): 10%–100% ± 2% SpO2 (with motion): 70%–100% ± 3% SpO2 (low perfusion): 70%–100% ± 2% PR (no motion): 25–240 bpm ± 3 bpm PR (with motion): 25–240 bpm ± 5 bpm PR (low perfusion): 25–240 bpm ± 3 bpm During no motion (SpHb was not validated with motion or low perfusion), SpHb: 8–17 g/dL ± 1.82–2.04 g/dL*
Time to result	30 seconds
Consumables	Probes
Power	Rechargeable nickel-metal hydride battery
Price	Price for these products varies by market, mode of distribution, mode of procurement, and payment model (for spot-check SpHb). Global health discounted pricing for these products is available but varies depending on volumes, programme, and preferred payment model. Non-global health price from online third-party distributors in the United States is approximately $1,949† (includes 200 SpHb tests; approximately $5 per test).
Regulatory	US FDA approved (2019)

Abbreviations: bpm, beats per minute; CO, carbon monoxide; FDA, Food and Drug Administration; Hb, haemoglobin; N/A, not applicable; PR, pulse rate; SpHb, total haemoglobin; SpO2, blood oxygen saturation.

* Source: US Food and Drug Administration 510(k) Premarket Notification Database website. Masimo Rad-67 Pulse CO-Oximeter and Accessories 510(k) summary page. https://www.accessdata.fda.gov/cdrh_docs/pdf18/K182887.pdf. Accessed April 6, 2022.

† Source: Cardiac Direct website. Masimo Rad-67 handheld pulse CO-oximeter page. https://www.cardiacdirect.com/product/masimo-rad-67-handheld-pulse-co-oximeter/. Accessed April 6, 2022.

Guangdong Biolight Meditech	
Product name	M800 with RR

Source: Guangdong Biolight Meditech

Parameters measured	SpO2, PR, and RR
Measurement mode	Spot-check
Intended use and target population	Indicated for spot-checking of functional arterial oxygen saturation (SpO2) and PR of adult, paediatric, and neonatal patients in hospitals, hospital-type facilities, as well as in the home care environment.*
Description	The M800 builds on the US FDA–approved pulse oximetry device, using the photoplethysmography, or pleth, waveform changes to measure RR. Measurements are taken through a finger clip.
Availability	M800 with RR is not yet commercially available.
Development phase	Product is under verification and validation, including for use in children under five years old at primary health care levels in low-resource settings.
Performance and accuracy	With BLT digital SpO2 sensor: SpO2: 70%–100% ± 2% SpO2: 0%–69% unspecified Resolution 1% PR: 25%–250% ± 2% or 1 bpm (whichever is greater) Resolution 1 bpm With Nellcor™ SpO2 sensor: SpO2 (adult/paediatric): 70%–100% ± 2% SpO2 (neonate): 70%–100% ± 3% SpO2 (low perfusion): 70%–100% ± 2% SpO2: 0%–69% unspecified Resolution 1% PR: 20–250 bpm ± 3 bpm PR: 251–300 bpm unspecified Resolution 1 bpm RR: Not yet validated
Time to result	Measurements with BLT digital sensor refresh every 13 seconds. Measurements with Nellcor sensor refresh every 7 seconds. RR time to result not yet validated
Consumables	Probes
Power	Rechargeable lithium-ion battery
Price	Manufacturer has indicated that the price will be <$200; price will vary by volume.
Regulatory	Planning for EU CE marking

Abbreviations: BLT, Biolight; bpm, beats per minute; EU, European Union; FDA, Food and Drug Administration; PR, pulse rate; RR, respiratory rate; SpO2, blood oxygen saturation.

* Source: US Food and Drug Administration 510(k) Premarket Notification Database website. M700 Handheld Pulse Oximeter 510(k) summary page. https://www.accessdata.fda.gov/cdrh_docs/pdf10/K101694.pdf. Accessed April 6, 2022.

Scanbo	
Product name	Scanbo D8

Source: Scanbo

Parameters measured	Scanbo D8
Measurement mode	SpO2, PR, RR, temperature, ECG, blood glucose, heart rate variability, blood pressure
Intended use and target population	Spot-check and remote patient monitoring
Description	Device connects via Bluetooth to a smartphone and is nearly consumable free (only requiring glucose disposable strips and a blood pressure cuff). Scanbo D8 captures patient data for integration into health information management systems.
Availability	Commercially available in India. As of 2021, Scanbo has begun to expand to other LMICs—namely, Indonesia, Kenya, and Nigeria.
Development phase	Whilst the device is not currently validated for use in paediatric patients, it will be evaluated at primary health care levels in children under five years old in low-resource settings.
Performance and accuracy	SpO2: 70%–80% ± 4% 80%–90% ± 2% 90%–100% ± 1% Temperature: 35°C–42°C ± 0.2°C <35°C ± 0.4°C ECG: ≤ ± 5% sensitivity error RR: Specificity: 93% Sensitivity: 95% Deviation: ± 2% Glucose: ± 0.83 mmol/L (± 15 mg/dL), for ≤5.55 mmol/L (≤100 mg/dL); ± 15%, for >5. 55 mmol/L (>100 mg/dL) PR: ± 5% error rate Blood pressure: ± 3 mmHg
Time to result	2 minutes for all measurements, plus additional time for repositioning in between
Consumables	Blood pressure cuff and disposable strips for glucose
Power	Rechargeable lithium-ion battery
Price	Flexible pricing structure: ~<$0.50 per patient for subscription model or ~$200 for device ownership.
Regulatory	Japan CE marking; ECG and RR measurements under review

Abbreviations: ECG, electrocardiogram; LMIC, low- and middle-income country; PR, pulse rate; RR, respiratory rate; SpO2, blood oxygen saturation.

Neopenda	
Product name	neoGuard™

Source: Neopenda

Parameters measured	SpO2, PR, RR, temperature
Measurement mode	Continuous monitoring; spot-check under development
Intended use and target population	Indicated for use by trained physicians or nurses in adult, paediatric, and neonatal populations during no-motion conditions in hospitals and hospital-type facilities.
Description	Device is worn on forehead and intended for prescription use only for continuous noninvasive monitoring of SpO2, HR, RR, and temperature. The device connects via Bluetooth to a software application installed on a tablet. The application includes a centralized patient dashboard, patient information, patient vital sign trends, and back-end data storage.
Availability	Commercially available in Kenya. Neopenda plans to expand to more LMICs in 2022.
Development phase	Product will be evaluated at primary health care levels in children under five years old in low-resource settings.
Performance and accuracy	SpO2 (no motion, normal perfusion): 70%–100% ± 4% (displayed range 0%–100%) Resolution 1% PR (no motion, normal perfusion, neonates): 75–205 bpm ± 3 bpm PR (no motion, normal perfusion, adults): 45–145 bpm ± 3 bpm (displayed range 0–250 bpm); resolution 1 bpm RR (no motion, normal perfusion): 5–30 rpm ± 5 rpm (displayed range 0–150 rpm); resolution 1 rpm Temperature: 30°C–40°C ± 0.3°C (display range 0°C–99.9°C); resolution 0.1°C
Time to result	<30 seconds for SpO2, PR, and RR Temperature varies from 10–30 minutes based on ambient temperature.
Consumables	None
Power	Rechargeable lithium-ion battery
Price	Neopenda offers the product in a package of ten, including a tablet, for $3,000–$3,800.
Regulatory	EU CE marking

Abbreviations: bpm, beats per minute; EU, European Union; HR, heart rate; LMIC, low- and middle-income country; PR, pulse rate; rpm, respirations (breaths) per minute; RR, respiratory rate; SpO2, blood oxygen saturation

Zug Medical Systems	
Product name	SatLite Touch

Source: Zug Medical Systems

Parameters measured	SpO2, HR, RR, temperature, ECG
Measurement mode	Spot-check and continuous monitoring
Intended use and target population	Indicated to measure SpO2, PR, perfusion index, RR, skin temperature, and one-channel ECG. The oximeter is intended to provide patient monitoring for medical use by health care workers in health care facilities and the home care environment.
Description	The SatLite Touch builds on the EU CE mark–approved pulse oximetry device, using photoplethysmography, or pleth, waveform changes to measure RR. Measurements are taken through a finger clip. The temperature is derived from the skin through a separate probe.
Availability	SatLite Touch with RR and temperature is not yet commercially available; target date of availability is by end of 2022 or the first quarter of 2023.
Development phase	Product with additional clinical measurements is under verification and validation.
Performance and accuracy	SpO2: 70%–100% ± 2% SpO2: 0%–69% unspecified Resolution 1% PR: 13–300 bpm ± 1 bpm Resolution 1 bpm RR: 5–150 rpm ± 2 rpm (to be validated) ECG range: 0.15–5.5 mV, accuracy 2.36 uV/LSB, resolution undefined (to be validated) Temperature accuracy is to be confirmed
Time to result	Depends on patient motion; typically 5 seconds
Consumables	Probes
Power	Rechargeable lithium-ion battery
Price	Manufacturer has indicated that the price may range between $100 and $200.
Regulatory	Product with SpO2, PR, and perfusion index measurement features already on market and have EU CE marking. Currently pending US FDA approval for those same parameters (expected summer 2022). Plans for EU CE marking for the product with additional parameters, such as RR, temperature, and ECG.

Abbreviations: bpm, beats per minute; ECG, electrocardiogram; EU, European Union; FDA, Food and Drug Administration; HR, heart rate; PR, pulse rate; rpm, respirations (breaths) per minute; RR, respiratory rate; SpO2, blood oxygen saturation.

EzeRx	
Product name	EzeCheck

Source: EzeRx

Parameters measured	SpO2, Hb, bilirubin, creatine, and blood sugar
Measurement mode	Spot-check
Intended use and target population	Approved for screening patients aged four years and older in medical settings.
Description	Device uses cool white LED light from the left-hand ring finger and transmits data to the mobile application via Bluetooth, which then transmits data to the patented cloud-based artificial intelligence algorithm that determines the different clinical parameters. The data can be accessed by an Android application or by the EzeCheck website.
Availability	Commercially available in India. Company has plans to expand to LMICs upon completion of pilots being conducted in Nigeria, Mauritius, and Myanmar.
Development phase	Product completed clinical and validation studies in two hospitals in India in October 2021 and November 2021, where the device's performance was assessed in comparison to automated haematology analysers. Study results are under review by medical journals and expected to be published by October 2022.
Performance and accuracy	Hb: 8–15 g/dL ± 1.5 g/dL All other values ± 3.0 g/dL SpO2: 0%–90% ± 12%–15% >90% defined as "LOW" variability
Time to result	Less than 1 minute
Consumables	None
Power	Rechargeable lithium-ion battery
Price	Company provides flexible pricing structures. Current prices in India: Public sector: 48,000 Indian rupees (~$632) for a one-year, unlimited subscription. Private sector: 40 Indian rupees (~$0.50) per test with a subscription.
Regulatory	Approved as a category A, low-risk product by India's Central Drugs Standard Control Organization. The device is also under review for US FDA approval and EU CE marking; approval expected by the end of 2022/early 2023.

Abbreviations: EU, European Union; FDA, Food and Drug Administration; Hb, haemoglobin; LMIC, low- and middle-income country; SpO2, blood oxygen saturation.

OrSense	
Product name	NBM 200
Parameters measured	SpO2, HR, and Hb
Measurement mode	Spot-check
Intended use and target population	Indicated for use by trained medical personnel in adult individuals in noncritical clinical and nonclinical settings (e.g., noncritical settings in hospitals, hospital-type facilities, mobile environments, clinics, physicians' offices, and ambulatory surgery centers).*
Description	Relies on occlusion spectroscopy, using spectrophotometry to estimate Hb concentration in the blood. The device uses a ring-shaped probe around the finger and temporarily applies pressure to restrict blood flow, which creates an optical signal and results in a measurement.
Availability	Commercially available
Development phase	N/A
Performance and accuracy	SpO2: 70%–100% ± 3% (below 70% unspecified) HR: 30–240 bpm ± 3 bpm Hb: 7–17 g/dL ± 1 g/dL (resolution of 0.1 g/dL)
Time to result	60 seconds
Consumables	Probe and battery
Power	Four standard AA batteries or a built-in rechargeable lithium-ion backup battery
Price	Approximately £1,100†
Regulatory	US FDA approved (2015), EU CE marking, China FDA approved, Brazilian Health Regulatory Agency (ANVISA) approved, Mexican Federal Committee for Protection from Sanitary Risks (COFEPRIS) approved

Abbreviations: ANVISA, Agência Nacional de Vigilância Sanitária; bpm, beats per minute; COFEPRIS, Comisión Federal para la Protección contra Riesgos Sanitarios; EU, European Union; FDA, Food and Drug Administration; Hb, haemoglobin; HR, heart rate; N/A, not applicable; SpO2, blood oxygen saturation.

* Source: US Food and Drug Administration 510(k) Premarket Notification Database website. NBM-200 Pulse Oximeter and Hemoglobin Monitor 510(k) summary page. https://www.accessdata.fda.gov/cdrh_docs/pdf14/K142209.pdf. Accessed April 6, 2022.

† Source: Ahankari AS, Dixit JV, Fogarty AW, Tata LJ, Myles PR. Comparison of the NBM 200 non-invasive haemoglobin sensor with Sahli's haemometer among adolescent girls in rural India. BMJ Innovations. 2016;2:144–148. https://innovations.bmj.com/content/2/4/144?panels_ajax_tab_tab=jnl_template_bmjj_cite_apa&panels_ajax_tab_trigger=

Sanguina	
Product name	AnemoCheck Mobile

Source: Sanguina

Parameters measured	Hb
Measurement mode	Spot-check
Intended use and target population	Currently, the device is intended for use as a health and wellness tool by individuals with iron-deficiency anaemia who are interested in tracking Hb and dietary/nutritional supplement/vitamin intake. Sanguina continues to develop versions of the application for clinical utility for broader use cases.
Description	Estimates blood Hb levels using a patient-sourced smartphone "selfie" by quantitatively assessing pallor of fingernail beds. Whilst differences in skin tones do not affect results, the application is incompatible with nail polish or fingernail abnormalities.
Availability	The AnemoCheck Mobile smartphone application is available for download through the App Store and Google Play in the United States. With subsequent algorithm updates and in accordance with local regulatory requirements, Sanguina will also launch AnemoCheck outside of the United States.
Development phase	The product has been evaluated against automated haematology analysers and other reference standards (i.e., haemoglobinometers and clinical methods) in several peer-reviewed, published studies.* It demonstrated high specificity and sensitivity results, making it a promising screening tool for use in low-resource settings. In 2021, Sanguina and AstraZeneca partnered on a collaborative study to verify the mobile application's accuracy and usability as well as to further enhance the accuracy of the application's algorithm. Results of this collaboration will be submitted for publication in a peer-reviewed medical journal in 2022 (manuscript in preparation). While currently a consumer product, Sanguina will launch the product as a medical device in the near future.

Abbreviations: Hb, haemoglobin.

*Sources: Mannino RG, Myers DR, Tyburski EA, et al. Smartphone app for non-invasive detection of anemia using only patient-sourced photos. *Nature Communications*. 2018;9(1):4924. https://doi.org/10.1038/s41467-018-07262-2.

Perez-Plazola MS, Tyburski EA, Smart LR, et al. AnemoCheck-LRS: an optimized, color-based point-of-care test to identify severe anemia in limited-resource settings. *BMC Medicine*. 2020;18(1):337. https://doi.org/10.1186/s12916-020-01793-6.

ANNEX 3
SUMMARY OF MARKET BARRIERS

Category	Barrier	Root cause
Innovation and availability	Limited incentives for development and accuracy verification of high-quality clinical measurements tailored for use with LMIC populations.	• Uncertain demand for new products. • Downward pressure on pricing for diagnostics in LMICs creates challenges for sustainable business models. • Lack of alignment on a defined product, including sensitivity and specificity requirements across diverse populations and settings, for emerging technologies. • High level of technical complexity creates significant costs for research and development and for verification of accuracy across diverse patient populations and operating conditions.
Quality	Global need for more stringent quality standards and clear verification and validation processes.	• Current quality and accuracy standards lack testing requirements inclusive of diverse populations and operating conditions. • Limited independent external validation of the performance and durability of diagnostic devices. • Lack of inclusion in World Health Organization prequalification programme or other LMIC-focused technology reviews. • Lack of global alignment on standards (e.g., gold standards, clinical benchmarks, methods) for verification and validation of diagnostic tools.
Demand and adoption	Lack of inclusion in global and national guidelines and recommendations.	• Clinical measurement technologies are referenced in guidelines, yet not directly recommended by normative bodies such as the World Health Organization. • Unclear standards for inclusion in global and national guidelines. • Additional evidence (e.g., impact, operational, cost-effectiveness) is needed for normative bodies and national governments to endorse technology, slowing national adoption. • Insufficient funding and capacity at global normative bodies to evaluate the quality and accuracy of multimodal PO devices.
Demand and adoption	Limited realised demand for multimodal technology in LMICs.	• High up-front costs for multimodal PO devices and competition from low-cost, stand-alone devices in LMICs cannibalises demand. • Funding gaps for diagnostic multimodal PO technology. • Lack of full endorsements of multimodal PO technology by global normative bodies • Limited inclusion in national guidelines driven by lack of coordination and further lack of national champions, limited local efficacy evidence, and limited funds for evidence generation. • Limited integration of multimodal PO devices into health care worker knowledge and skills trainings. • Low levels of health care worker awareness and bottoms-up demand by facility decision-makers.

Affordability	Significant price variability between competing products and substitutes leading to proliferation of low-quality devices.	• Inclusion of additional clinical measurements drives pricing increases. • Without enhanced quality standards, it is challenging for high-quality devices to differentiate from lower-quality competition.
Affordability	High up-front cost misaligned with the market's willingness to pay.	• Incomplete cost considerations (e.g., considerations for maintenance, consumables, training, disposal) for multimodal PO technology lead to prioritisation of lower-cost, single-measurement devices. • Further research is needed to determine the full cost-effectiveness of an integrated multimodal PO device on a per-test basis, and as a comparison to current diagnostic methods/ stand-alone devices.
Supply and delivery	Highly fragmented and inconsistent supply of multimodal devices in LMICs.	• Low level of regulation leads to market oversaturation of products, many of which are low quality. • Limited inclusion in routine procurement systems, leading to broken supply chains for consumables and spare parts. • Fragmenting demand necessitates small, low-value procurements of consumables and spare parts and prevents economies of scale. • There is limited transparency into the needs or market for multimodal PO devices, limiting suppliers' reach.

Abbreviations: LMIC, low- and middle-income country; PO, pulse oximeter.

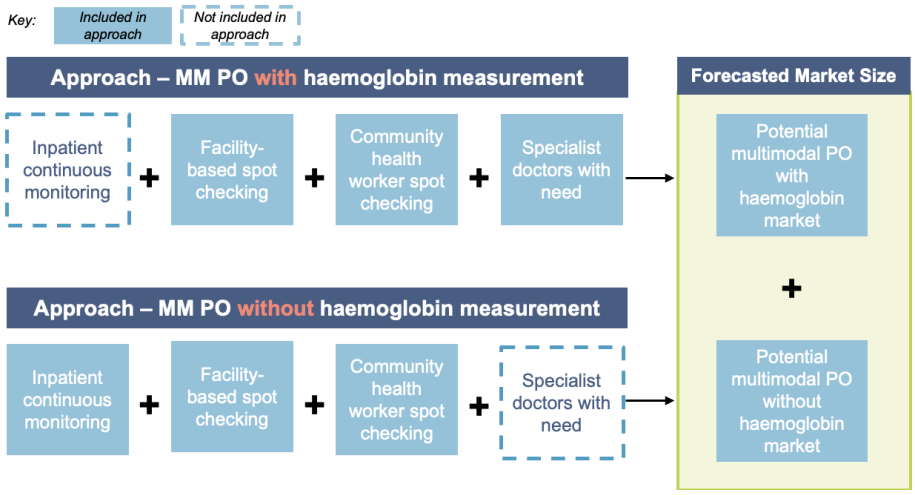
ANNEX 4
MULTIMODAL PULSE OXIMETER DEVICE MARKET SIZE FORECAST

This market size forecast estimates need for multimodal pulse oximeter (PO) devices in all 137 low- and middle-income countries (LMICs), as classified by the World Bank in 2021. The forecast quantifies relevant use cases across all patient groups in both inpatient and outpatient settings, built on the following methodology:

- The forecast is grounded in infrastructure need that leverages both the number of beds in health facilities and relevant on-duty health care workers to estimate use cases for continuous monitoring and spot-check respectively.
- The market size estimates differentiate between multimodal PO devices with and without hemoglobin (Hb) functionality due to the latter having limited use in settings requiring continuous monitoring.
- Uses scenarios to show range, based on various coverage rates due to the various potential use cases and existence of substitute products.

Figure A1 illustrates, at a high level, the components of the market size forecast.

FIGURE A1. Illustrative of market segments for multimodal PO devices with and without Hb measurement



Abbreviations: MM, multimodal; PO, pulse oximeter.

Assumptions

- Does not factor current willingness or ability to pay.
- Does not factor current demand for and saturation of devices currently in the market, as currently known demand for POs in LMICs accounts for less than 5% of the total forecasted market size.
- Infrastructure assumptions are based on public bed count datasets gathered by the World Bank.

- Available bed count data are disaggregated between general and critical care; assumes a ratio of one multimodal PO device to ten general beds and one multimodal PO device to one critical bed, based on expert opinion.
- Health care workforce data are from the World Health Organization Global Health Workforce Statistics database and based on expert opinion; assumes one-third of each relevant health workforce cadre would be working at any given time.
- Relevant health care workforce cadres (e.g., nurses, midwives) are assumed to be based at health facilities; each cadre's need is aggregated together to provide facility-based spot-checking estimates.
- For most health care workforce cadres, a one-to-one multimodal PO device ratio and varying ratios of use for the multimodal PO device with Hb measurement are assumed. Each scenario assumes a different level of coverage for relevant health workforce cadres.
- Given their decentralised patient interface and the emerging trend of some national governments equipping community health workers with POs, a ratio of one multimodal PO device to one community health worker is assumed, based on expert opinion. Each scenario assumes a different level of coverage for community health workers.
- Given the high prevalence of anaemia in LMICs and triaging implications, it is assumed that all community health workers would be relevant users of multimodal PO devices with Hb measurement.
- Additional annual, ongoing costs for maintenance and consumables are not factored into the market size.

Scenarios

Scenarios have been developed to show the potential market size for multimodal PO devices. The scenarios are intended to show range, based on various coverage rates due to the various potential use cases and existence of substitute products. More information is necessary to understand demand.

Optimistic forecast

- Accounts for 70% of total continuous monitoring needs at health facilities.
- Accounts for 60% of community health care worker needs.
- Accounts for 90% of facility-based spot-checking needs
- Accounts for 90% of specialist doctor needs.

Base forecast

- Accounts for 50% of total continuous monitoring needs at health facilities.
- Accounts for 40% of community health care worker needs.
- Accounts for 70% of facility-based spot-checking needs.
- Accounts for 70% of specialist doctor needs.

Conservative forecast

- Accounts for 30% of total continuous monitoring needs at health facilities.
- Accounts for 20% of community health care worker needs.
- Accounts for 50% of facility-based spot-checking needs.
- Accounts for 50% of specialist doctor needs.

TABLE AI. Estimates of the total market for multimodal PO devices

Market segment	Optimistic forecast	Base forecast	Conservative forecast
Inpatient, continuous monitoring	1,200,000	900,000	500,000
Outpatient and inpatient, spot checking	6,400,000	4,900,000	3,400,000
Facility-based spot checking	5,300,000	4,100,000	2,900,000
CHW-based spot checking	700,000	500,000	200,000
Specialist doctors with need	400,000	300,000	200,000
Total multimodal PO units:	**7,600,000**	**5,800,000**	**3,900,00**

Optimistic forecast			
Market segment	**# of multimodal PO devices without Hb**	**# of multimodal PO devices with Hb**	**Total # of multimodal PO devices**
Inpatient, continuous monitoring	1,200,000	—	1,200,000
Outpatient and inpatient, spot checking	4,100,000	2,300,000	6,400,000
Facility-based spot checking	4,100,000	1,200,000	5,300,000
CHW-based spot checking	—	700,000	700,000
Specialist doctors with need	—	400,000	400,000
Total multimodal PO units:	**5,300,000**	**2,300,000**	**7,600,000**

Base forecast			
Market segment	**# of multimodal PO devices without Hb**	**# of multimodal PO devices with Hb**	**Total # of multimodal PO devices**
Inpatient, continuous monitoring	900,000	—	900,000
Outpatient and inpatient, spot checking	3,200,000	1,700,000	4,900,000
Facility-based spot checking	3,200,000	900,000	4,100,000
CHW-based spot checking	—	500,000	500,000
Specialist doctors with need	—	300,000	300,000
Total multimodal PO units:	**4,100,000**	**1,700,000**	**5,800,000**

Conservative forecast			
Market segment	**# of multimodal PO devices without Hb**	**# of multimodal PO devices with Hb**	**Total # of multimodal PO devices**
Inpatient, continuous monitoring	500,000	—	500,000
Outpatient and inpatient, spot checking	2,300,000	1,100,000	3,400,000
Facility-based spot checking	2,300,000	600,000	2,900,000
CHW-based spot checking	—	300,000	300,000
Specialist doctors with need	—	200,000	200,000
Total multimodal PO units:	**2,800,000**	**1,100,000**	**3,900,000**

Abbreviations: CHW, community health worker; Hb, haemoglobin; PO, pulse oximeter.

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