Development of the PREMature Infant Index (PREMII™), a clinician-reported outcome measure assessing functional status of extremely preterm infants

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Complete List of Authors:	Ward, Robert; University of Utah Turner, Mark; University of Liverpool Hansen-Pupp, Ingrid ; Lund University Higginson, Jason; Brody School of Medicine at East Carolina University, Pediatrics Vanya, Magdalena; ICON plc Flood, Emuella; ICON plc Schwartz, Ethan; ICON plc Doll, Helen; ICON plc Tocoian, Adina; Takeda Pharmaceutical Co Ltd Mangili, Alexandra; Takeda Pharmaceutical Co Ltd Barton, Norman; Takeda Pharmaceutical Co Ltd Sarda, Sujata; Takeda Pharmaceutical Co Ltd
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Robert M. Ward[a], Mark A. Turner[b], Ingrid Hansen-Pupp[c], Jason Higginson[d], Magdalena Vanya[e], Emuella Flood[f], Ethan J. Schwartz[f], Helen A. Doll[g], Adina Tocoian[h], Alexandra Mangili[h], Norman Barton[i] and Sujata P. Sarda[j*]

[a]Pediatrics, University of Utah, Salt Lake City, UT, USA; [b]Institute of Translational Medicine, University of Liverpool, Liverpool, UK; [c]Lund University, Skåne University Hospital, Department of Clinical Sciences Lund, Pediatrics, Lund, Sweden; [d]Department of Pediatrics, Brody School of Medicine, East Carolina University, Greenville, NC, USA; [e]Patient Centered Outcomes, ICON, South San Francisco, CA, USA; [f]Patient Centered Outcomes, ICON, Gaithersburg, MD, USA; [g]Patient Centered Outcomes, ICON, Oxford, UK; [h]Global Clinical Development, Rare Metabolic Diseases, Takeda, Zug, Switzerland; [i]Global Clinical Development, Rare Metabolic Diseases, Takeda, Lexington, MA, USA; [j]Global Outcomes Research and Epidemiology, Takeda, Lexington, MA, USA

*Corresponding author: Sujata P. Sarda, PhD, Global Outcomes Research and Epidemiology, Takeda, 300 Shire Way, Lexington, MA 02421; Tel: 1 (781) 266-3440; Cell: 1 (617) 893-3207; e-mail: sujata.sarda@takeda.com

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ABSTRACT

Background: Comprehensive measures to evaluate the effectiveness of medical interventions in extremely preterm infants are lacking. Although length of stay is used as an indicator of overall health among preterm infants in clinical studies, it is confounded by nonmedical factors (e.g., parental readiness and availability of home nursing support).

Objectives: To develop the PREMature Infant Index (PREMII™), an electronic content-valid clinician-reported outcome measure for assessing functional status of extremely preterm infants (<28 weeks gestational age) serially over time in the neonatal intensive care unit. We report the development stages of the PREMII, including suggestions for scoring.

Methods: We developed the PREMII according to US Food and Drug Administration regulatory standards. Development included five stages: (1) literature review, (2) clinical expert interviews, (3) Delphi panel survey, (4) development of items/levels, and (5) cognitive interviews/usability testing. Scoring approaches were explored via an online clinician survey.

Results: Key factors reflective of functional status were identified by physicians and nurses during development of the PREMII, as were levels within each factor to assess functional status. The resulting PREMII evaluates eight infant health factors: respiratory support, oxygen administration, apnea, bradycardia, desaturation, thermoregulation, feeding, and weight gain, each scored with three to six gradations. Factor levels are standardized on a 0–100 scale; resultant scores are 0–100. No usability issues were identified. The online clinician survey identified optimal scoring methods to capture functional status at a given time point.

Conclusions: Our findings support the content validity and usability of the PREMII as a multi-function outcome measure to assess functional status over time in extremely preterm infants. Psychometric validation is ongoing.

Key words (5–6): Clinician-reported outcome measure; extremely premature; functional status; infant; outcome assessment

PREMII Development

Introduction

Survival of infants born extremely preterm, defined as birth at <28 weeks gestational age (GA) by the World Health Organization, and used interchangeably with extremely low gestational age newborn (ELGAN), has improved over time [1,2]. The majority of extremely preterm infants require intensive care in the neonatal period [3], and survivors remain at risk of short- and long-term morbidities, such as intraventricular hemorrhage, necrotizing enterocolitis (NEC), chronic lung disease, and neurodevelopmental impairment [4-7].

A challenge for this patient population is the lack of outcome measures to evaluate treatment effects in clinical studies, and clinical assessment tools that monitor how the neonates grow and mature over time. While length of stay (LOS) is often used as an outcome measure in clinical studies, LOS can be influenced by nonmedical factors such as parental readiness and availability of home nursing support [8], and institutional variations in organization of care [9], thus limiting the appropriateness of LOS as a measure of infant health and development and as an endpoint in clinical trials. Existing neonatal illness measures, developed primarily to predict mortality and morbidity, combine neonatal data shortly after admission to the neonatal intensive care unit (NICU) and not over time. For example, the Score for Neonatal Acute Physiology (SNAP) [10] and SNAP Perinatal Extension Version II (SNAPPE-II) collect infant data within 24 h and 12 h of admission, respectively [11], while the Clinical Risk Index for Babies (CRIB) [12] and CRIB II collect data within 12 h and 1 h of admission, respectively, to evaluate risk for mortality [13].

The aim of this study was to develop a comprehensive content-valid clinician-reported outcome (ClinRO) measure, the PREMature Infant Index (PREMII^{TM}), to assess the functional status of extremely preterm infants (<28 weeks GA) over time in the NICU, for use in a phase 2 clinical trial. In the current article, we report on the development of the PREMII.

Materials and methods

Study design

Development of the PREMII followed US Food and Drug Administration regulatory guidance for patient-reported outcome instruments [14]—standards that apply to other clinical outcome assessment tools, including ClinROs. The PREMII development process (phase 1) consisted of five stages: (1) targeted literature review, (2) clinical expert interviews, (3) Delphi panel survey, (4) development of PREMII items and levels, and (5) cognitive interviews and usability testing of the electronic version. These stages were designed to provide evidence of content validity (i.e., relevance, clarity, and comprehensiveness) of the PREMII to measure accurately the clinical condition, specifically functional status as it changes over time, of the target population (i.e., extremely preterm infants). Additionally, an online clinician survey was conducted to explore potential approaches to scoring the PREMII.

Concept of interest

The concept of interest that the PREMII is designed to measure is functional status. Functional status is defined as an indicator of neonates' overall health and development encompassing physical, physiological, and clinical status—specifically, what an infant can do and what support the infant requires, on a day-to-day basis, as a reflection of their overall health and development, which can be also considered as maturation over time. Functional status can be assessed with respect to eight key functional areas included in the PREMII (feeding, weight gain, thermoregulation, respiratory support, apnea, bradycardia, desaturation [ABD] events, and oxygen administration). The PREMII can measure functional status as it changes over time with the baby's development.

PREMII Development

The original target concept for the study was discharge readiness. However, evidence gathered from the literature review and clinical expert interviews highlighted challenges to standardizing assessment of physical readiness for discharge. These included variability in standards of neonatal care, home medical support, and proximity and availability of outpatient support. Therefore, the target concept evolved to functional status, which is independent of the health care system or home situation.

Stage 1: targeted literature review

A targeted literature review was undertaken to identify relevant concepts for inclusion in the PREMII. We searched Embase, MEDLINE, and PubMed for English-language articles published from 2001 to 2015. The search strategy used search terms relevant to factors, attributes, and measures related to physical discharge readiness and LOS for extremely preterm infants (Supplementary Tables 1–2).

Stage 2: clinical expert interviews

Telephone semistructured qualitative interviews were conducted. Criteria for inclusion included specialized training in neonatology, with ≥10 years of experience caring for preterm infants (Table 1). The interviews were designed to obtain feedback from clinicians on the physical factors infants need to achieve to be considered ready for NICU discharge, as identified by the literature review. See Supplementary Table S3 for an overview of the interview questions.

Stage 3: Delphi panel survey

The Delphi method is a structured communication technique that involves participants (in this case, a panel of experts) who answer a questionnaire in an iterative manner after being

provided with an anonymized summary of group responses [15]. Participants were asked to rate the relative importance of factors, identified through the literature review and clinical expert interviews, for the assessment of functional status on a scale of 0 (not at all important) to 5 (extremely important). Additionally, participants were asked to provide feedback on the definitions of the levels for each factor, as well as other important aspects related to the factors and level definitions. The levels for each factor were intended to reflect a scale of functional status from very poor to very good. The purpose was to build consensus on the most important factors for evaluation of a preterm infant's functional status for inclusion in the PREMII, and to determine the importance of factors.

Stage 4: development of PREMII items and levels

This stage refers to the drafting of the instrument, namely, the formulation of instructions, items or questions capturing each of the identified factors relevant in assessing infant functional status, and response options.

Stage 5: cognitive interviews and usability testing of the electronic version

Note: cognitive interviews and the online clinician survey occurred in parallel.

Semistructured telephone interviews were conducted in two rounds. The purpose of the cognitive interviews was to assess the clarity of the instructions, items, and levels, as well as ease of completion of the instrument. Additionally, the interviews were designed to elicit any potential logistical difficulties with completing the instrument (e.g., due to nursing shift patterns, and differences in geographical or institutional NICU practices). Usability testing of the electronic version was undertaken via interviews to assess the ease of completion on an electronic device (e.g., a tablet device).

Online clinician survey

The online survey was developed to explore the most appropriate scoring method to capture accurately a preterm infant's functional status at a given time point during their NICU stay. ~~A detailed description of the online clinician survey is provided in Appendix 1.~~

The online survey included questions designed to explore the following: the best approach to calculate daily factor scores, the relative importance of each factor in rating an infant's overall functional status, and the best approach to calculate a weekly summary score. The questions were based on sample infant profiles that were presented to respondents.

Daily factor scores

Participants were presented with example individual factor ratings for each shift over a 24-h period and asked for their opinion on the optimal method to calculate a daily factor score from the shift ratings from the following options: the "most frequent" score across shift scores provided over the 24-h evaluation period, the "numerical average" score across shift scores provided over the 24-h evaluation period, the "worst" (or "best," as applicable) shift score during that period, the "most recent" shift score during that period, or "other" (with a request to provide details). Respondents were not asked for a preferred method for calculating a daily weight factor score, as weight is not measured repeatedly across shifts.

Relative importance in rating overall functional status

Participants were asked to rate the relative importance (on a scale of 1 [most important] to 8 [least important]) of each factor in rating an infant's functional status; respondents were allowed to equally rate multiple factors. Respondents were presented with eight clinical examples of infants and their overall functional status scores over a seven-day period. The overall functional status scores were summarized as the infant's most frequent, worst (or best), average, and today's score, as well as the trend over the last three days ratings recorded over the seven-day evaluation period.

Weekly summary score

Respondents were asked to rate the weekly summary functional status of the infant (very poor, poor, moderate, good, very good). Additionally, they were asked to rate the importance of each rating approach.

The survey was developed in English and then translated into the following languages: Spanish (Spain, Latin America), French (France), German (Germany), Italian (Italy), Portuguese (Brazil), and Japanese (Japan). Translations met the requirements of the ISO 17100 standard.

Data analysis

Data are reported as descriptive statistics (*n* and percentage, mean, median). For the clinical expert interviews and cognitive interviews, data were analyzed using qualitative methods. For the online clinician survey, a linear regression analysis was performed to compare weekly summary PREMII scores ("most frequent," "worst," "average," "today," "trend [past three days]") with the actual weekly scores provided by the respondents ("weekly summary functional status") for the online infant profiles.

Results

Stage 1: targeted literature review

In total, 998 unique abstracts were identified, of which 48 duplicates were excluded. An additional 918 publications were excluded based on predefined exclusion criteria (Figure 1). A total of 32 full-text articles were assessed for eligibility, of which nine were excluded for lack of relevance. The remaining 23 articles were included in the analysis: 19 related to discharge readiness or LOS (original target concept) [9,16-33] (Table 2), three discussed instruments for assessing infant mortality/morbidity risk [11,17,34] (Supplementary Table 4;

one of these reported findings relevant to both LOS and instruments) [17], and two reported national guidelines on the care of preterm/high-risk infants [8,35] (Supplementary Table 5). No measures specifically assessing physical readiness for discharge were identified. From the included literature, over one-half of the articles noted the infant's cardiorespiratory stability and weight or ability to gain weight as key factors in determining discharge readiness or LOS (Table 2).

Stage 2: clinical expert interviews

Four expert neonatologists (RMW [United States], MAT [United Kingdom], IH-P [Sweden], JH [United States]) participated (Supplementary Table 6). The findings were similar to those identified in the literature, namely, oral feeding ability, consistent weight gain, physical/physiological stability, respiratory stability (e.g., absence of apnea), and thermostability (capacity to maintain normal temperature; Table 3). Additionally, two clinical experts noted retinopathy of prematurity (one each in relation to discharge readiness and LOS).

Stage 3: Delphi panel survey

In total, 17 neonatologists participated in the Delphi panel survey (Supplementary Table 6). In order of importance, participants endorsed respiratory status, ABD events, feeding ability, oxygen supplementation, thermoregulation, and weight gain (Figure 2). Retinopathy of prematurity was originally included but subsequently removed, as it was not considered to fall under the definition of functional status.

Feedback from the Delphi survey highlighted perceived differences in the relative importance of each ABD event in evaluating functional status, and underlined the need to

separate ABD events into individual factors due to potential different underlying physiologic causes of events.

Stage 4: development of the PREMII items and levels

The draft PREMII was developed based on the factors identified in the previous development stages, with further rounds of review by the four clinical experts to refine levels within each factor. Items included in the first version of the PREMII included weight gain, feeding ability, temperature, respiratory support, a single ABD item, and extent of oxygen supplementation.

Stage 5: cognitive interviews and usability testing of the electronic version

The first round of interviews was completed by 23 physicians and nurses; the second round was completed by nine nurses (Supplementary Table 6). Each of the PREMII items' levels underwent revisions based on findings from the interviews (Table 4). No issues relating to usability of the electronic version of the instrument were identified among the five nurses who participated in usability interviews.

Online clinician survey

The online survey was completed by 201 pediatricians and neonatologists (Supplementary Table 6). The "numerical average" score across the 24-h evaluation period was the most frequently reported preferred method for calculating daily factor scores for each of the seven applicable factors (respiratory support, oxygen administration, apnea, bradycardia, desaturation, thermoregulation, and feeding; weight gain was excluded from this analysis because weight is not measured repeatedly across nursing shifts; Supplementary Figure 1). In calculating a weekly summary score, the "trend" score over the past three days and "today's" score were most commonly reported to be most important in determining an infant's overall

functional status (53.0% and 34.7%, respectively), based on the previous seven-day period using hypothetical infant profiles. With regard to relative importance, on a scale of 1–8 (most to least important), respiratory support, apnea, and bradycardia were considered the most important of the eight factors (weight included in the assessment) in rating an infant's functional status (Supplementary Figure 2). However, there was variability among physicians in terms of relative importance of the factors.

Finalization of instrument

The resulting PREMII comprises eight items capturing each of the identified relevant factors (respiratory support, oxygen administration, apnea, bradycardia, desaturation, thermoregulation, feeding, and weight gain), each scored on three to six levels, representing a scale of functional status ranging from very poor to very good (Appendix). The assessment is intended to be repeated over the course of a study to capture change. The intended frequency of administration of the PREMII during a Takeda-sponsored clinical trial is described here. The PREMII assessment will start ≥48 h after birth on the day the infant reaches the next postmenstrual age (PMA) week. For example, if the infant is born at 23 weeks + 4 days, PREMII assessment will begin at 24 weeks PMA, but if an infant is born at 23 weeks + 5 days, PREMII assessment will begin the following PMA week at 25 weeks PMA. In the clinical trial, the PREMII will be administered weekly until 32 weeks PMA and then daily until discharge or 40 weeks PMA, whichever is the earliest. The nurse primarily responsible for the infants' care will score the PREMII on a tablet device near the end of each nursing shift. The PREMII captures a 24-h period and the number of PREMII assessments carried out during this time will depend on the duration of nursing shifts (e.g., 8 h or 12 h). Formal training will be provided for PREMII users before using the tool.

Discussion

We developed the PREMII, a ClinRO with evidence of content validity, designed to measure treatment benefit in clinical trials by assessing the functional status of extremely preterm infants in the NICU. To our knowledge, the PREMII is the first comprehensive multi-function outcome measure developed to capture and measure health and development repeatedly in extremely preterm infants over time from birth until discharge from the NICU.

While illness severity scores are available for the purpose of predicting mortality and morbidity [10-13], they primarily collect infant data within 24 h of admission to the NICU, and are not designed to assess the process of development and maturation over time. LOS is considered an important outcome measure in clinical studies; however, using LOS to assess treatment effect in neonatal studies can be challenging on account of factors not directly related to infant health that may influence time to discharge, such as parental readiness and organizational factors [8,9]. The PREMII includes eight infant health factors (respiratory support, oxygen administration, apnea, bradycardia, desaturation, thermoregulation, feeding, and weight gain), which will enable the assessment of functional status as an outcome measure in neonatal studies, thus providing a comprehensive approach to comparing groups of infants, for example, when examining the effects of treatments.

The development stages demonstrated that the PREMII adequately measures functional status in extremely preterm infants and therefore has good content validity, which is in accordance with US FDA regulatory standards for developing patient-reported outcome instruments [14]. Development of the PREMII was guided by neonatologists and NICU nurses, who provided their opinions based on clinical experience. Through the Delphi approach, expert neonatologists reached consensus agreement on the factors for inclusion in the PREMII, and the importance of factors. An example of this was the consensus that respiratory status and the level of support required would adequately measure the severity of

lung disease. Participants represented countries across a number of global regions, including North America, Europe, Latin America, and Asia-Pacific. This approach highlighted cultural differences in clinical practice across regions and aided the development of the PREMII to maximize applicability. Although designed for clinical trials, the PREMII could be used as a key performance indicator in NICUs, for benchmarking between sites/hospitals, or to adjust for illness severity as extremely preterm infants approach term equivalent age. The tool may even provide a structured approach to informing discharge readiness by providing the relevant data to inform discharge decision making. It should be noted, however, that the PREMII is not specifically intended to predict discharge readiness or LOS, but rather to assess functional status over time. Furthermore, although the PREMII was developed specifically for the population of extremely preterm infants (<28 weeks GA), it could be applied to infants born at other GA during their growth and development in the NICU as the factors for assessment will remain consistent.

There are limitations of the PREMII that should be considered. One is that local policies regarding neonatal care may differ (e.g., oxygen saturation limits), as well as definitions of what constitutes an event (e.g., apnea or bradycardia). The difficulty of controlling for differing standards of care and the potential for variability of practice across sites remain a challenge in clinical research. We standardized the factors and level ranges captured by PREMII items to the greatest extent by gaining consensus input from expert clinicians based on global considerations. Additionally, instructions and training are included in the PREMII instrument to minimize variation. A further consideration is the element of subjectivity in the clinician responses (e.g., “worst experience”). The development steps were designed to ensure appropriate and clear response options, to measure the abilities to respond using the response options, and consistency of interpretation across respondents. PREMII items and levels were developed with extensive clinical expert input and we expect a high

degree of consistency in item interpretation; there remains, however, the possibility that interpretation may vary among clinicians. We acknowledge that some factors (e.g. feeding and weight gain) can be affected by various comorbidities, such as NEC; this will be further explored in a separate study (outlined below).

A separate real-world, prospective, psychometric validation study is underway to ~~assess~~evaluate the ~~measurement~~psychometric properties of the PREMII~~, including~~ for clinical application. Specifically, we will evaluate inter- and intra-rater reliability, construct validity, ~~and~~ criterion (i.e. predictive) validity, sensitivity to change, and responder definition. Comorbidities, especially those that impact nutrition such as NEC, will be captured in the study, and outcomes will be categorized. Additionally, the psychometric validation study will further explore the scoring of the PREMII and evaluate the optimal frequency of administration of PREMII in real-world clinical practice. The PREMII is designed for use from shortly after birth through discharge from the NICU; longer term validation (e.g. at two years of age) is challenging owing to variation in clinical practice and patient attrition over time.

In conclusion, the PREMII represents a ClinRO measure with well-supported content validity and usability to assess the functional status of extremely preterm infants serially over time in the NICU. It is hoped this unique tool will be suitable for use in neonatal clinical studies.

PREMII Development

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Declaration of interest statement

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Disclosure statement

Robert M. Ward, Mark A. Turner, Ingrid Hansen-Pupp, and Jason Higginson were paid consultants to Takeda in connection with this study (Mark A. Turner's payment was received by his institution). Ingrid Hansen-Pupp also owns stock/stock options in Premalux AB. Magdalena Vanya, Emuella Flood, Ethan J. Schwartz, and Helen A. Doll are, or were, employees of ICON, who were paid consultants to Takeda in connection with this study. Adina Tocoian was an employee of Takeda at the time of the study. Alexandra Mangili, Norman Barton, and Sujata P. Sarta are employees of and own stock/stock options in Takeda. Robert M. Ward, Mark A. Turner, Ingrid Hansen-Pupp, and Jason Higginson participated as clinical experts in the clinical expert interviews.

Data Availability Statement

All relevant data are within the paper and its Supporting Information files.

Statement of ethics

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The authors have no ethical conflicts to disclose. Ethical approval was not required by the institutional review board because the study did not involve direct patient involvement or personal health information.

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PREMII Development

Table 1. Participant inclusion criteria for the PREMII development stages.

PREMII development stage	Participant inclusion criteria
Clinical expert interviews	• General medical license or registration, plus a specialty license or registration in neonatology, as applicable in country of origin • Practicing neonatologist with ≥10 years of experience in the care of preterm infants • Coauthored hospital management guidelines on the care of preterm infants or a neonatology-related textbook • Oral and written fluency in English • Availability for a 1-h interview and periodic consulting and/or review of short documents via email or telephone call throughout the duration of the study (~10 months)
Delphi panel survey	• General medical license or registration, plus a specialty license or registration in neonatology, as applicable in country of origin • Practicing neonatologist with ≥5 years of experience in the care of preterm infants • Coauthored peer-reviewed publications, hospital management guidelines on the care of preterm infants, or neonatology-related textbook; was a speaker at conferences or neonatology clinical meetings; or acted as a principal investigator/sub-principal investigator in any past or present neonatology-related trials • Oral and written fluency in English • Availability to complete up to three brief (10- to 15-min) online surveys
Cognitive interviews and usability testing	• Practicing neonatologist with >5 years of experience in the care of preterm infants, *or* neonatal nurse with >5 years of experience working in the NICU • Oral and written fluency in English
Online survey	• General medical license or registration • Specialist training in pediatrics or neonatology

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- Practicing neonatologist or pediatrician, with responsibilities that include the care of preterm infants
- ≥5 years of experience in the care of preterm infants
- Agreement to complete a 35- to 40-min online survey in English or native language of country of origin

NICU: neonatal intensive care unit; PREMII: PREMature Infant Index.

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Table 2. The number of articles reporting physical and nonphysical factors related to discharge readiness or length of stay in the included studies (n = 19).

Factor	Number of articles	Author(s)
Physical		
Weight or weight gain	13	Barone 2014 [16]; Bender 2013 [17]; Eichenwald 2001 [18]; Gaal 2008 [19]; Hintz 2010 [20]; Jeremic 2008 [21]; Lee 2013 [22]; Manktelow 2010 [23]; Merritt 2003 [24]; Picone 2011 [25]; Seki 2011 [26]; Temple 2015 [27]; Ye 2011 [28]
Cardiorespiratory stability	11	Barone 2014 [16]; Berry 2008 [29]; Eichenwald 2001 [18]; Gaal 2008 [19]; Hintz 2010 [20]; Jeremic 2008 [21]; Manktelow 2010 [23]; Merritt 2003 [24]; Nankervis 2010 [30]; Seki 2011 [26]; Ye 2011 [28]
Oral feeding to support growth	7	Barone 2014 [16]; Eichenwald 2001 [18]; Gaal 2008 [19]; McGrath 2004 [31]; Merritt 2003 [24]; Temple 2015 [27]; Ye 2011 [28]
Ability to maintain normal body temperature or thermoregulation	5	Barone 2014 [16]; Eichenwald 2001 [18]; Merritt 2003 [24]; Seki 2011 [26]; Ye 2011 [28]
Nonphysical		
Organizational	5	Eichenwald 2001 [18]; Manktelow 2010 [23]; Altman 2006 [32]; Altman 2009 [9]; Cotten 2005 [33]

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Adequate home environment	2	Merritt 2003 [24]; Seki 2011 [26]
Parental readiness	1	Picone 2011 [25]

Searches were conducted using databases including Embase, MEDLINE, and PubMed for English-language articles published between 2001 and 2015. Search terms included prematurity, newborn intensive care, gestational age, scoring systems, guideline, and hospital discharge (Supplementary Tables 1–2).

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Table 3. Key factors influencing discharge from NICU identified by clinical expert interviews.

Factor	Description
Feeding	Ability to feed orally to maintain consistent weight gain
Breathing	Stable respirations without positive airway pressure support
Thermostability	Ability to maintain normal temperature in open crib/bassinet
Physical/physiological stability	Includes *absence* of the following: apnea, oxygen desaturation, and gastrointestinal disturbances, such as severe reflux
Retinopathy of prematurity	Stable or regressing disease
Nonphysical factors	Parental readiness, parental interaction with infant, social network support, transportation, home situation, fluency in national language/access to translation services for communication during follow-up

NICU: neonatal intensive care unit.

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Table 4. Participant feedback from rounds 1 and 2 of the cognitive interviews, and the subsequent revisions made to the PREMII following consultation with the clinical experts.

Item		Participant feedback	Revisions to the PREMII
Respiratory support	Round 1	• Suggest clarifying "no supplemental oxygen" in last level	• Inclusion of a reference to negative pressure or positive pressure • Definition of high-flow and low-flow oxygen included
	Round 2	• "Intratracheal" not a familiar term • "Negative pressure support" isn't commonly used	• Both terms removed
		• "Only" doesn't fit with instructions	• Removal of "only" (to ensure that the worst level during the shift is selected)
		—	• "Supplemental oxygen continuously" and "low-flow nasal cannula" split into separate levels • Selection of "low-flow nasal cannula" prompts an answer on air source and greatest L/min setting
Oxygen administration	Round 1	• Levels are clearer if explicit ranges are reported • Distinction between >50% and <50% is important to capture	• Incorporation of additional ranges of percentage concentrations • Inclusion of instruction "report the highest concentration during each shift" (to ensure consistent and clear interpretation and completion of the item)

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	Round 2	• Uncertainty on how to rate the item for infants on low-flow nasal cannula	• Item skipped for infants rated as being on continuous low-flow nasal cannula
Apnea	Round 1	• ABD (as one item) should be separated	• ABD (as one item) revised to three separate items
	Round 2	• Important to clarify if infant needed intervention or not	• Inclusion of "requiring intervention"
Bradycardia	Round 1	• ABD (as one item) should be separated	• ABD (as one item) revised to three separate items
	Round 2	• Definition may change based on gestational age of the infant	• No revision made
		• "Clinically relevant" may cause confusion	• Definitions revised
Desaturation	Round 1	• ABD (as one item) should be separated	• ABD (as one item) revised to three separate items
	Round 2	• Important to clarify if event requires intervention or is self-resolving	• Inclusion of "requiring intervention"
		• Definition should include "≤"	• Inclusion of "≤"
Feeding	Round 1	• Need to define "oral feeds" and add/clarify regarding enteral feeding	• Oral feeds defined as feeds via breast or bottle
		• Suggest including reference to feeds via catheter	• Inclusion of reference to enteral feeding and catheter
	Round 2	• "Catheter" may cause confusion	• "Catheter" removed from feeding levels
		• Need to clarify "no feeds occurred"	• "No feed occurred" (originally intended to represent a "not applicable" option) removed

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			• Revised to include question on whether feeds (including IV or enteral tube feeding) occurred during the shift; if "no," item skipped
Weight gain	Round 1	• Infants may not be weighed every day	• Revised to account for the possibility of no weight recorded on a given day
	Round 2	—	—
Temperature	Round 1	• "Bundled" not a clear or familiar term	• Examples provided to define "bundled"
		• Need to better highlight differences between levels • Some words redundant	• Reference to radiant warmer included
	Round 2	• Statements wordy and too specific	• No revision made

ABD: apnea, bradycardia, desaturation; IV: intravenous; PREMII: PREMature Infant Index.

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Figure 1. Literature identification and study selection process for publications included in the targeted literature review.

Figure 2. Factors important in the assessment of functional status in order of importance rating during Delphi panel survey.

[a]Factors were rated on a scale of 0 (not at all important) to 5 (extremely important) and are listed in order of strength of endorsement (i.e., from highest mean importance rating to lowest). ABD: apnea, bradycardia, desaturation.

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Development of the PREMature Infant Index (PREMII™), a clinician-reported outcome measure assessing functional status of extremely preterm infants

Robert M. Ward[a], Mark A. Turner[b], Ingrid Hansen-Pupp[c], Jason Higginson[d], Magdalena Vanya[e], Emuella Flood[f], Ethan J. Schwartz[f], Helen A. Doll[g], Adina Tocoian[h], Alexandra Mangili[h], Norman Barton[i] and Sujata P. Sarda[j*]

[a]Pediatrics, University of Utah, Salt Lake City, UT, USA; [b]Institute of Translational Medicine, University of Liverpool, Liverpool, UK; [c]Lund University, Skåne University Hospital, Department of Clinical Sciences Lund, Pediatrics, Lund, Sweden; [d]Department of Pediatrics, Brody School of Medicine, East Carolina University, Greenville, NC, USA; [e]Patient Centered Outcomes, ICON, South San Francisco, CA, USA; [f]Patient Centered Outcomes, ICON, Gaithersburg, MD, USA; [g]Patient Centered Outcomes, ICON, Oxford, UK; [h]Global Clinical Development, Rare Metabolic Diseases, Takeda, Zug, Switzerland; [i]Global Clinical Development, Rare Metabolic Diseases, Takeda, Lexington, MA, USA; [j]Global Outcomes Research and Epidemiology, Takeda, Lexington, MA, USA

*Corresponding author: Sujata P. Sarda, PhD, Global Outcomes Research and Epidemiology, Takeda, 300 Shire Way, Lexington, MA 02421; Tel: 1 (781) 266-3440; Cell: 1 (617) 893-3207; e-mail: sujata.sarda@takeda.com

Category of study: Original article

Development of the PREMature Infant Index (PREMII™), a clinician-reported outcome measure assessing functional status of extremely preterm infants

ABSTRACT

Background: Comprehensive measures to evaluate the effectiveness of medical interventions in extremely preterm infants are lacking. Although length of stay is used as an indicator of overall health among preterm infants in clinical studies, it is confounded by nonmedical factors (e.g., parental readiness and availability of home nursing support).

Objectives: To develop the PREMature Infant Index (PREMII™), an electronic content-valid clinician-reported outcome measure for assessing functional status of extremely preterm infants (<28 weeks gestational age) serially over time in the neonatal intensive care unit. We report the development stages of the PREMII, including suggestions for scoring.

Methods: We developed the PREMII according to US Food and Drug Administration regulatory standards. Development included five stages: (1) literature review, (2) clinical expert interviews, (3) Delphi panel survey, (4) development of items/levels, and (5) cognitive interviews/usability testing. Scoring approaches were explored via an online clinician survey.

Results: Key factors reflective of functional status were identified by physicians and nurses during development of the PREMII, as were levels within each factor to assess functional status. The resulting PREMII evaluates eight infant health factors: respiratory support, oxygen administration, apnea, bradycardia, desaturation, thermoregulation, feeding, and weight gain, each scored with three to six gradations. Factor levels are standardized on a 0–100 scale; resultant scores are 0–100. No usability issues were identified. The online clinician survey identified optimal scoring methods to capture functional status at a given time point.

Conclusions: Our findings support the content validity and usability of the PREMII as a multi-function outcome measure to assess functional status over time in extremely preterm infants. Psychometric validation is ongoing.

Key words (5–6): Clinician-reported outcome measure; extremely premature; functional status; infant; outcome assessment

Introduction

Survival of infants born extremely preterm, defined as birth at <28 weeks gestational age (GA) by the World Health Organization, and used interchangeably with extremely low gestational age newborn (ELGAN), has improved over time [1,2]. The majority of extremely preterm infants require intensive care in the neonatal period [3], and survivors remain at risk of short- and long-term morbidities, such as intraventricular hemorrhage, necrotizing enterocolitis (NEC), chronic lung disease, and neurodevelopmental impairment [4-7].

A challenge for this patient population is the lack of outcome measures to evaluate treatment effects in clinical studies, and clinical assessment tools that monitor how the neonates grow and mature over time. While length of stay (LOS) is often used as an outcome measure in clinical studies, LOS can be influenced by nonmedical factors such as parental readiness and availability of home nursing support [8], and institutional variations in organization of care [9], thus limiting the appropriateness of LOS as a measure of infant health and development and as an endpoint in clinical trials. Existing neonatal illness measures, developed primarily to predict mortality and morbidity, combine neonatal data shortly after admission to the neonatal intensive care unit (NICU) and not over time. For example, the Score for Neonatal Acute Physiology (SNAP) [10] and SNAP Perinatal Extension Version II (SNAPPE-II) collect infant data within 24 h and 12 h of admission, respectively [11], while the Clinical Risk Index for Babies (CRIB) [12] and CRIB II collect data within 12 h and 1 h of admission, respectively, to evaluate risk for mortality [13].

The aim of this study was to develop a comprehensive content-valid clinician-reported outcome (ClinRO) measure, the PREMature Infant Index (PREMII^{TM}), to assess the functional status of extremely preterm infants (<28 weeks GA) over time in the NICU, for use in a phase 2 clinical trial. In the current article, we report on the development of the PREMII.

Materials and methods

Study design

Development of the PREMII followed US Food and Drug Administration regulatory guidance for patient-reported outcome instruments [14]—standards that apply to other clinical outcome assessment tools, including ClinROs. The PREMII development process (phase 1) consisted of five stages: (1) targeted literature review, (2) clinical expert interviews, (3) Delphi panel survey, (4) development of PREMII items and levels, and (5) cognitive interviews and usability testing of the electronic version. These stages were designed to provide evidence of content validity (i.e., relevance, clarity, and comprehensiveness) of the PREMII to measure accurately the clinical condition, specifically functional status as it changes over time, of the target population (i.e., extremely preterm infants). Additionally, an online clinician survey was conducted to explore potential approaches to scoring the PREMII.

Concept of interest

The concept of interest that the PREMII is designed to measure is functional status. Functional status is defined as an indicator of neonates' overall health and development encompassing physical, physiological, and clinical status—specifically, what an infant can do and what support the infant requires, on a day-to-day basis, as a reflection of their overall health and development, which can be also considered as maturation over time. Functional status can be assessed with respect to eight key functional areas included in the PREMII (feeding, weight gain, thermoregulation, respiratory support, apnea, bradycardia, desaturation [ABD] events, and oxygen administration). The PREMII can measure functional status as it changes over time with the baby's development.

The original target concept for the study was discharge readiness. However, evidence gathered from the literature review and clinical expert interviews highlighted challenges to standardizing assessment of physical readiness for discharge. These included variability in standards of neonatal care, home medical support, and proximity and availability of outpatient support. Therefore, the target concept evolved to functional status, which is independent of the health care system or home situation.

Stage 1: targeted literature review

A targeted literature review was undertaken to identify relevant concepts for inclusion in the PREMII. We searched Embase, MEDLINE, and PubMed for English-language articles published from 2001 to 2015. The search strategy used search terms relevant to factors, attributes, and measures related to physical discharge readiness and LOS for extremely preterm infants (Supplementary Tables 1–2).

Stage 2: clinical expert interviews

Telephone semistructured qualitative interviews were conducted. Criteria for inclusion included specialized training in neonatology, with ≥10 years of experience caring for preterm infants (Table 1). The interviews were designed to obtain feedback from clinicians on the physical factors infants need to achieve to be considered ready for NICU discharge, as identified by the literature review. See Supplementary Table S3 for an overview of the interview questions.

Stage 3: Delphi panel survey

The Delphi method is a structured communication technique that involves participants (in this case, a panel of experts) who answer a questionnaire in an iterative manner after being

provided with an anonymized summary of group responses [15]. Participants were asked to rate the relative importance of factors, identified through the literature review and clinical expert interviews, for the assessment of functional status on a scale of 0 (not at all important) to 5 (extremely important). Additionally, participants were asked to provide feedback on the definitions of the levels for each factor, as well as other important aspects related to the factors and level definitions. The levels for each factor were intended to reflect a scale of functional status from very poor to very good. The purpose was to build consensus on the most important factors for evaluation of a preterm infant's functional status for inclusion in the PREMII, and to determine the importance of factors.

Stage 4: development of PREMII items and levels

This stage refers to the drafting of the instrument, namely, the formulation of instructions, items or questions capturing each of the identified factors relevant in assessing infant functional status, and response options.

Stage 5: cognitive interviews and usability testing of the electronic version

Note: cognitive interviews and the online clinician survey occurred in parallel.

Semistructured telephone interviews were conducted in two rounds. The purpose of the cognitive interviews was to assess the clarity of the instructions, items, and levels, as well as ease of completion of the instrument. Additionally, the interviews were designed to elicit any potential logistical difficulties with completing the instrument (e.g., due to nursing shift patterns, and differences in geographical or institutional NICU practices). Usability testing of the electronic version was undertaken via interviews to assess the ease of completion on an electronic device (e.g., a tablet device).

Online clinician survey

The online survey was developed to explore the most appropriate scoring method to capture accurately a preterm infant's functional status at a given time point during their NICU stay. The online survey included questions designed to explore the following: the best approach to calculate daily factor scores, the relative importance of each factor in rating an infant's overall functional status, and the best approach to calculate a weekly summary score. The questions were based on sample infant profiles that were presented to respondents.

Daily factor scores

Participants were presented with example individual factor ratings for each shift over a 24-h period and asked for their opinion on the optimal method to calculate a daily factor score from the shift ratings from the following options: the "most frequent" score across shift scores provided over the 24-h evaluation period, the "numerical average" score across shift scores provided over the 24-h evaluation period, the "worst" (or "best," as applicable) shift score during that period, the "most recent" shift score during that period, or "other" (with a request to provide details). Respondents were not asked for a preferred method for calculating a daily weight factor score, as weight is not measured repeatedly across shifts.

Relative importance in rating overall functional status

Participants were asked to rate the relative importance (on a scale of 1 [most important] to 8 [least important]) of each factor in rating an infant's functional status; respondents were allowed to equally rate multiple factors. Respondents were presented with eight clinical examples of infants and their overall functional status scores over a seven-day period. The overall functional status scores were summarized as the infant's most frequent, worst (or best), average, and today's score, as well as the trend over the last three days ratings recorded over the seven-day evaluation period.

Weekly summary score

Respondents were asked to rate the weekly summary functional status of the infant (very poor, poor, moderate, good, very good). Additionally, they were asked to rate the importance of each rating approach.

The survey was developed in English and then translated into the following languages: Spanish (Spain, Latin America), French (France), German (Germany), Italian (Italy), Portuguese (Brazil), and Japanese (Japan). Translations met the requirements of the ISO 17100 standard.

Data analysis

Data are reported as descriptive statistics (*n* and percentage, mean, median). For the clinical expert interviews and cognitive interviews, data were analyzed using qualitative methods. For the online clinician survey, a linear regression analysis was performed to compare weekly summary PREMII scores ("most frequent," "worst," "average," "today," "trend [past three days]") with the actual weekly scores provided by the respondents ("weekly summary functional status") for the online infant profiles.

Results

Stage 1: targeted literature review

In total, 998 unique abstracts were identified, of which 48 duplicates were excluded. An additional 918 publications were excluded based on predefined exclusion criteria (Figure 1). A total of 32 full-text articles were assessed for eligibility, of which nine were excluded for lack of relevance. The remaining 23 articles were included in the analysis: 19 related to discharge readiness or LOS (original target concept) [9,16-33] (Table 2), three discussed instruments for assessing infant mortality/morbidity risk [11,17,34] (Supplementary Table 4; one of these reported findings relevant to both LOS and instruments) [17], and two reported

national guidelines on the care of preterm/high-risk infants [8,35] (Supplementary Table 5). No measures specifically assessing physical readiness for discharge were identified. From the included literature, over one-half of the articles noted the infant's cardiorespiratory stability and weight or ability to gain weight as key factors in determining discharge readiness or LOS (Table 2).

Stage 2: clinical expert interviews

Four expert neonatologists (RMW [United States], MAT [United Kingdom], IH-P [Sweden], JH [United States]) participated (Supplementary Table 6). The findings were similar to those identified in the literature, namely, oral feeding ability, consistent weight gain, physical/physiological stability, respiratory stability (e.g., absence of apnea), and thermostability (capacity to maintain normal temperature; Table 3). Additionally, two clinical experts noted retinopathy of prematurity (one each in relation to discharge readiness and LOS).

Stage 3: Delphi panel survey

In total, 17 neonatologists participated in the Delphi panel survey (Supplementary Table 6). In order of importance, participants endorsed respiratory status, ABD events, feeding ability, oxygen supplementation, thermoregulation, and weight gain (Figure 2). Retinopathy of prematurity was originally included but subsequently removed, as it was not considered to fall under the definition of functional status.

Feedback from the Delphi survey highlighted perceived differences in the relative importance of each ABD event in evaluating functional status, and underlined the need to separate ABD events into individual factors due to potential different underlying physiologic causes of events.

Stage 4: development of the PREMII items and levels

The draft PREMII was developed based on the factors identified in the previous development stages, with further rounds of review by the four clinical experts to refine levels within each factor. Items included in the first version of the PREMII included weight gain, feeding ability, temperature, respiratory support, a single ABD item, and extent of oxygen supplementation.

Stage 5: cognitive interviews and usability testing of the electronic version

The first round of interviews was completed by 23 physicians and nurses; the second round was completed by nine nurses (Supplementary Table 6). Each of the PREMII items' levels underwent revisions based on findings from the interviews (Table 4). No issues relating to usability of the electronic version of the instrument were identified among the five nurses who participated in usability interviews.

Online clinician survey

The online survey was completed by 201 pediatricians and neonatologists (Supplementary Table 6). The "numerical average" score across the 24-h evaluation period was the most frequently reported preferred method for calculating daily factor scores for each of the seven applicable factors (respiratory support, oxygen administration, apnea, bradycardia, desaturation, thermoregulation, and feeding; weight gain was excluded from this analysis because weight is not measured repeatedly across nursing shifts; Supplementary Figure 1). In calculating a weekly summary score, the "trend" score over the past three days and "today's" score were most commonly reported to be most important in determining an infant's overall functional status (53.0% and 34.7%, respectively), based on the previous seven-day period using hypothetical infant profiles. With regard to relative importance, on a scale of 1–8 (most

to least important), respiratory support, apnea, and bradycardia were considered the most important of the eight factors (weight included in the assessment) in rating an infant's functional status (Supplementary Figure 2). However, there was variability among physicians in terms of relative importance of the factors.

Finalization of instrument

The resulting PREMII comprises eight items capturing each of the identified relevant factors (respiratory support, oxygen administration, apnea, bradycardia, desaturation, thermoregulation, feeding, and weight gain), each scored on three to six levels, representing a scale of functional status ranging from very poor to very good (Appendix). The assessment is intended to be repeated over the course of a study to capture change. The intended frequency of administration of the PREMII during a Takeda-sponsored clinical trial is described here. The PREMII assessment will start ≥48 h after birth on the day the infant reaches the next postmenstrual age (PMA) week. For example, if the infant is born at 23 weeks + 4 days, PREMII assessment will begin at 24 weeks PMA, but if an infant is born at 23 weeks + 5 days, PREMII assessment will begin the following PMA week at 25 weeks PMA. In the clinical trial, the PREMII will be administered weekly until 32 weeks PMA and then daily until discharge or 40 weeks PMA, whichever is the earliest. The nurse primarily responsible for the infants' care will score the PREMII on a tablet device near the end of each nursing shift. The PREMII captures a 24-h period and the number of PREMII assessments carried out during this time will depend on the duration of nursing shifts (e.g., 8 h or 12 h). Formal training will be provided for PREMII users before using the tool.

Discussion

We developed the PREMII, a ClinRO with evidence of content validity, designed to measure treatment benefit in clinical trials by assessing the functional status of extremely preterm infants in the NICU. To our knowledge, the PREMII is the first comprehensive multi-function outcome measure developed to capture and measure health and development repeatedly in extremely preterm infants over time from birth until discharge from the NICU.

While illness severity scores are available for the purpose of predicting mortality and morbidity [10-13], they primarily collect infant data within 24 h of admission to the NICU, and are not designed to assess the process of development and maturation over time. LOS is considered an important outcome measure in clinical studies; however, using LOS to assess treatment effect in neonatal studies can be challenging on account of factors not directly related to infant health that may influence time to discharge, such as parental readiness and organizational factors [8,9]. The PREMII includes eight infant health factors (respiratory support, oxygen administration, apnea, bradycardia, desaturation, thermoregulation, feeding, and weight gain), which will enable the assessment of functional status as an outcome measure in neonatal studies, thus providing a comprehensive approach to comparing groups of infants, for example, when examining the effects of treatments.

The development stages demonstrated that the PREMII adequately measures functional status in extremely preterm infants and therefore has good content validity, which is in accordance with US FDA regulatory standards for developing patient-reported outcome instruments [14]. Development of the PREMII was guided by neonatologists and NICU nurses, who provided their opinions based on clinical experience. Through the Delphi approach, expert neonatologists reached consensus agreement on the factors for inclusion in the PREMII, and the importance of factors. An example of this was the consensus that respiratory status and the level of support required would adequately measure the severity of

lung disease. Participants represented countries across a number of global regions, including North America, Europe, Latin America, and Asia-Pacific. This approach highlighted cultural differences in clinical practice across regions and aided the development of the PREMII to maximize applicability. Although designed for clinical trials, the PREMII could be used as a key performance indicator in NICUs, for benchmarking between sites/hospitals, or to adjust for illness severity as extremely preterm infants approach term equivalent age. The tool may even provide a structured approach to informing discharge readiness by providing the relevant data to inform discharge decision making. It should be noted, however, that the PREMII is not specifically intended to predict discharge readiness or LOS, but rather to assess functional status over time. Furthermore, although the PREMII was developed specifically for the population of extremely preterm infants (<28 weeks GA), it could be applied to infants born at other GA during their growth and development in the NICU as the factors for assessment will remain consistent.

There are limitations of the PREMII that should be considered. One is that local policies regarding neonatal care may differ (e.g., oxygen saturation limits), as well as definitions of what constitutes an event (e.g., apnea or bradycardia). The difficulty of controlling for differing standards of care and the potential for variability of practice across sites remain a challenge in clinical research. We standardized the factors and level ranges captured by PREMII items to the greatest extent by gaining consensus input from expert clinicians based on global considerations. Additionally, instructions and training are included in the PREMII instrument to minimize variation. A further consideration is the element of subjectivity in the clinician responses (e.g., “worst experience”). The development steps were designed to ensure appropriate and clear response options, to measure the abilities to respond using the response options, and consistency of interpretation across respondents. PREMII items and levels were developed with extensive clinical expert input and we expect a high

degree of consistency in item interpretation; there remains, however, the possibility that interpretation may vary among clinicians. We acknowledge that some factors (e.g. feeding and weight gain) can be affected by various comorbidities, such as NEC; this will be further explored in a separate study (outlined below).

A separate real-world, prospective, psychometric validation study is underway to evaluate the psychometric properties of the PREMII for clinical application. Specifically, we will evaluate inter- and intra-rater reliability, construct validity, criterion (i.e. predictive) validity, sensitivity to change, and responder definition. Comorbidities, especially those that impact nutrition such as NEC, will be captured in the study, and outcomes will be categorized. Additionally, the psychometric validation study will further explore the scoring of the PREMII and evaluate the optimal frequency of administration of PREMII in real-world clinical practice. The PREMII is designed for use from shortly after birth through discharge from the NICU; longer term validation (e.g. at two years of age) is challenging owing to variation in clinical practice and patient attrition over time.

In conclusion, the PREMII represents a ClinRO measure with well-supported content validity and usability to assess the functional status of extremely preterm infants serially over time in the NICU. It is hoped this unique tool will be suitable for use in neonatal clinical studies.

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Declaration of interest statement

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Disclosure statement

Robert M. Ward, Mark A. Turner, Ingrid Hansen-Pupp, and Jason Higginson were paid consultants to Takeda in connection with this study (Mark A. Turner's payment was received by his institution). Ingrid Hansen-Pupp also owns stock/stock options in Premalux AB. Magdalena Vanya, Emuella Flood, Ethan J. Schwartz, and Helen A. Doll are, or were, employees of ICON, who were paid consultants to Takeda in connection with this study. Adina Tocoian was an employee of Takeda at the time of the study. Alexandra Mangili, Norman Barton, and Sujata P. Sarta are employees of and own stock/stock options in Takeda. Robert M. Ward, Mark A. Turner, Ingrid Hansen-Pupp, and Jason Higginson participated as clinical experts in the clinical expert interviews.

Data Availability Statement

All relevant data are within the paper and its Supporting Information files.

Statement of ethics

The authors have no ethical conflicts to disclose. Ethical approval was not required by the institutional review board because the study did not involve direct patient involvement or personal health information.

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Table 1. Participant inclusion criteria for the PREMII development stages.

PREMII development stage	Participant inclusion criteria
Clinical expert interviews	• General medical license or registration, plus a specialty license or registration in neonatology, as applicable in country of origin • Practicing neonatologist with ≥10 years of experience in the care of preterm infants • Coauthored hospital management guidelines on the care of preterm infants or a neonatology-related textbook • Oral and written fluency in English • Availability for a 1-h interview and periodic consulting and/or review of short documents via email or telephone call throughout the duration of the study (~10 months)
Delphi panel survey	• General medical license or registration, plus a specialty license or registration in neonatology, as applicable in country of origin • Practicing neonatologist with ≥5 years of experience in the care of preterm infants • Coauthored peer-reviewed publications, hospital management guidelines on the care of preterm infants, or neonatology-related textbook; was a speaker at conferences or neonatology clinical meetings; or acted as a principal investigator/sub-principal investigator in any past or present neonatology-related trials • Oral and written fluency in English • Availability to complete up to three brief (10- to 15-min) online surveys
Cognitive interviews and usability testing	• Practicing neonatologist with >5 years of experience in the care of preterm infants, *or* neonatal nurse with >5 years of experience working in the NICU • Oral and written fluency in English
Online survey	• General medical license or registration • Specialist training in pediatrics or neonatology

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	• Practicing neonatologist or pediatrician, with responsibilities that include the care of preterm infants • ≥5 years of experience in the care of preterm infants • Agreement to complete a 35- to 40-min online survey in English or native language of country of origin

NICU: neonatal intensive care unit; PREMII: PREMature Infant Index.

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Table 2. The number of articles reporting physical and nonphysical factors related to discharge readiness or length of stay in the included studies (n = 19).

Factor	Number of articles	Author(s)
Physical		
Weight or weight gain	13	Barone 2014 [16]; Bender 2013 [17]; Eichenwald 2001 [18]; Gaal 2008 [19]; Hintz 2010 [20]; Jeremic 2008 [21]; Lee 2013 [22]; Manktelow 2010 [23]; Merritt 2003 [24]; Picone 2011 [25]; Seki 2011 [26]; Temple 2015 [27]; Ye 2011 [28]
Cardiorespiratory stability	11	Barone 2014 [16]; Berry 2008 [29]; Eichenwald 2001 [18]; Gaal 2008 [19]; Hintz 2010 [20]; Jeremic 2008 [21]; Manktelow 2010 [23]; Merritt 2003 [24]; Nankervis 2010 [30]; Seki 2011 [26]; Ye 2011 [28]
Oral feeding to support growth	7	Barone 2014 [16]; Eichenwald 2001 [18]; Gaal 2008 [19]; McGrath 2004 [31]; Merritt 2003 [24]; Temple 2015 [27]; Ye 2011 [28]
Ability to maintain normal body temperature or thermoregulation	5	Barone 2014 [16]; Eichenwald 2001 [18]; Merritt 2003 [24]; Seki 2011 [26]; Ye 2011 [28]
Nonphysical		
Organizational	5	Eichenwald 2001 [18]; Manktelow 2010 [23]; Altman 2006 [32]; Altman 2009 [9]; Cotten 2005 [33]

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Adequate home environment	2	Merritt 2003 [24]; Seki 2011 [26]
Parental readiness	1	Picone 2011 [25]

Searches were conducted using databases including Embase, MEDLINE, and PubMed for English-language articles published between 2001 and 2015. Search terms included prematurity, newborn intensive care, gestational age, scoring systems, guideline, and hospital discharge (Supplementary Tables 1–2).

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Table 3. Key factors influencing discharge from NICU identified by clinical expert interviews.

Factor	Description
Feeding	Ability to feed orally to maintain consistent weight gain
Breathing	Stable respirations without positive airway pressure support
Thermostability	Ability to maintain normal temperature in open crib/bassinet
Physical/physiological stability	Includes *absence* of the following: apnea, oxygen desaturation, and gastrointestinal disturbances, such as severe reflux
Retinopathy of prematurity	Stable or regressing disease
Nonphysical factors	Parental readiness, parental interaction with infant, social network support, transportation, home situation, fluency in national language/access to translation services for communication during follow-up

NICU: neonatal intensive care unit.

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Table 4. Participant feedback from rounds 1 and 2 of the cognitive interviews, and the subsequent revisions made to the PREMII following consultation with the clinical experts.

Item		Participant feedback	Revisions to the PREMII
Respiratory support	Round 1	• Suggest clarifying "no supplemental oxygen" in last level	• Inclusion of a reference to negative pressure or positive pressure • Definition of high-flow and low-flow oxygen included
	Round 2	• "Intratracheal" not a familiar term • "Negative pressure support" isn't commonly used	• Both terms removed
		• "Only" doesn't fit with instructions	• Removal of "only" (to ensure that the worst level during the shift is selected)
		—	• "Supplemental oxygen continuously" and "low-flow nasal cannula" split into separate levels • Selection of "low-flow nasal cannula" prompts an answer on air source and greatest L/min setting
Oxygen administration	Round 1	• Levels are clearer if explicit ranges are reported • Distinction between >50% and <50% is important to capture	• Incorporation of additional ranges of percentage concentrations • Inclusion of instruction "report the highest concentration during each shift" (to ensure consistent and clear interpretation and completion of the item)

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PREMII Development Clean Version

	Round 2	• Uncertainty on how to rate the item for infants on low-flow nasal cannula	• Item skipped for infants rated as being on continuous low-flow nasal cannula
Apnea	Round 1	• ABD (as one item) should be separated	• ABD (as one item) revised to three separate items
	Round 2	• Important to clarify if infant needed intervention or not	• Inclusion of "requiring intervention"
Bradycardia	Round 1	• ABD (as one item) should be separated	• ABD (as one item) revised to three separate items
	Round 2	• Definition may change based on gestational age of the infant	• No revision made
		• "Clinically relevant" may cause confusion	• Definitions revised
Desaturation	Round 1	• ABD (as one item) should be separated	• ABD (as one item) revised to three separate items
	Round 2	• Important to clarify if event requires intervention or is self-resolving	• Inclusion of "requiring intervention"
		• Definition should include "≤"	• Inclusion of "≤"
Feeding	Round 1	• Need to define "oral feeds" and add/clarify regarding enteral feeding	• Oral feeds defined as feeds via breast or bottle
		• Suggest including reference to feeds via catheter	• Inclusion of reference to enteral feeding and catheter
	Round 2	• "Catheter" may cause confusion	• "Catheter" removed from feeding levels
		• Need to clarify "no feeds occurred"	• "No feed occurred" (originally intended to represent a "not applicable" option) removed

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PREMII Development			Clean Version
			• Revised to include question on whether feeds (including IV or enteral tube feeding) occurred during the shift; if "no," item skipped
Weight gain	Round 1	• Infants may not be weighed every day	• Revised to account for the possibility of no weight recorded on a given day
	Round 2	—	—
Temperature	Round 1	• "Bundled" not a clear or familiar term	• Examples provided to define "bundled"
		• Need to better highlight differences between levels • Some words redundant	• Reference to radiant warmer included
	Round 2	• Statements wordy and too specific	• No revision made

ABD: apnea, bradycardia, desaturation; IV: intravenous; PREMII: PREMature Infant Index.

Figure 1. Literature identification and study selection process for publications included in the targeted literature review.

Figure 2. Factors important in the assessment of functional status in order of importance rating during Delphi panel survey.

[a]Factors were rated on a scale of 0 (not at all important) to 5 (extremely important) and are listed in order of strength of endorsement (i.e., from highest mean importance rating to lowest). ABD: apnea, bradycardia, desaturation.

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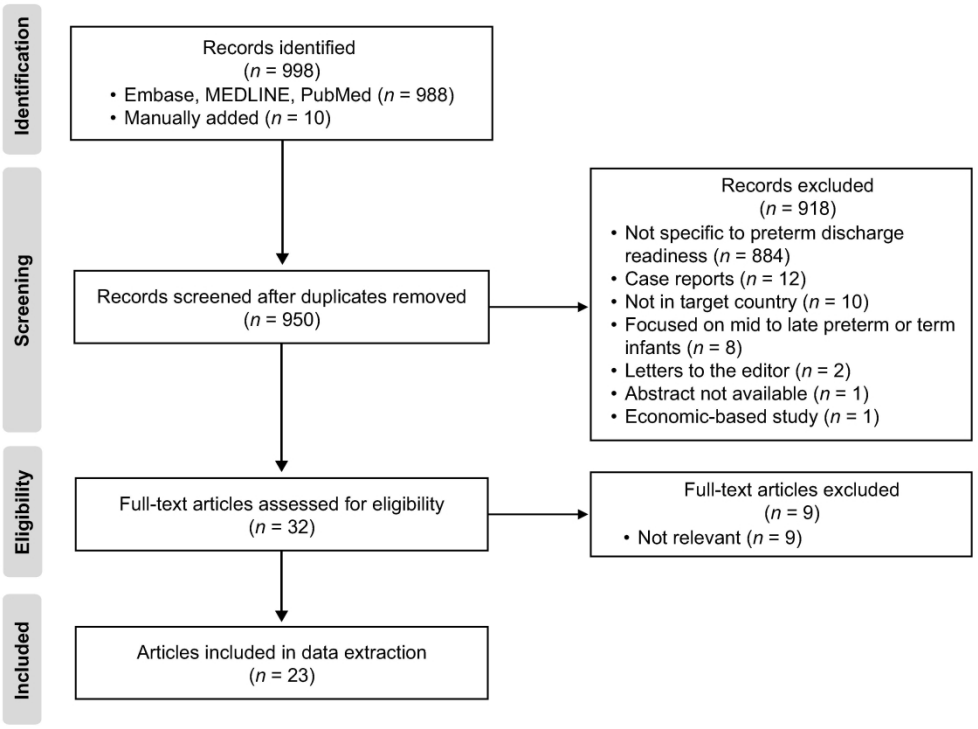

Figure 1. Literature identification and study selection process for publications included in the targeted literature review.

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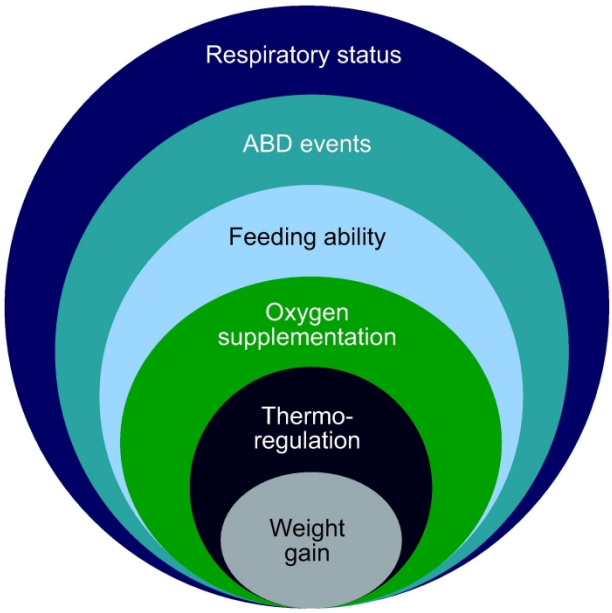

	Importance rating[a]	
	Median	**Mean**
Respiratory status	5.0	5.0
ABD events	5.0	4.8
Feeding ability	5.0	4.6
Oxygen supplementation	4.0	4.2
Thermo-regulation	4.0	3.9
Weight gain	4.0	3.8

Figure 2. Factors important in the assessment of functional status in order of importance rating during Delphi panel survey. [a]Factors were rated on a scale of 0 (not at all important) to 5 (extremely important) and are listed in order of strength of endorsement (i.e., from highest mean importance rating to lowest). ABD: apnea, bradycardia, desaturation.

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SUPPLEMENTAL MATERIAL

Development of the PREMature Infant Index (PREMII™), a clinician-reported outcome measure assessing functional status of extremely preterm infants

Robert M. Ward[a], Mark A. Turner[b], Ingrid Hansen-Pupp[c], Jason Higginson[d], Magdalena Vanya[e], Emuella Flood[f], Ethan J. Schwartz[f], Helen A. Doll[g], Adina Tocoian[h], Alexandra Mangili[h], Norman Barton[i] and Sujata P. Sarda[j*]

[a]Pediatrics, University of Utah, Salt Lake City, UT, USA; [b]Institute of Translational Medicine, University of Liverpool, Liverpool, UK; [c]Lund University, Skåne University Hospital, Department of Clinical Sciences Lund, Pediatrics, Lund, Sweden; [d]Department of Pediatrics, Brody School of Medicine, East Carolina University, Greenville, NC, USA; [e]Patient Centered Outcomes, ICON, South San Francisco, CA, USA; [f]Patient Centered Outcomes, ICON, Gaithersburg, MD, USA; [g]Patient Centered Outcomes, ICON, Oxford, UK; [h]Global Clinical Development, Rare Metabolic Diseases, Takeda, Zug, Switzerland; [i]Global Clinical Development, Rare Metabolic Diseases, Takeda, Lexington, MA, USA; [j]Global Outcomes Research and Epidemiology, Takeda, Lexington, MA, USA

*Corresponding author: Sujata P. Sarda, PhD, Global Outcomes Research and Epidemiology, Takeda, 300 Shire Way, Lexington, MA 02421; Tel: 1 (781) 266-3440; Cell: 1 (617) 893-3207; e-mail: sujata.sarda@takeda.com

PREMII Development

Supplementary Table 1. Embase search strategy.

Search number	Query	Number of results
1	exp prematurity/ or exp newborn intensive care/ or exp gestational age/	174,535
2	exp scoring system/ or exp gestational age/ or exp newborn intensive care/ or *mortality/ or Score for Neonatal Acute Physiology.mp. or exp prematurity/ or exp very low birth weight/	433,189
3	(SNAP or SNAP-II or SNAPPE-II).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	11,262
4	exp hospital discharge/	75,321
5	(guideline$ or factor$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	4,378,844
6	(Benchmarking or Quality Control).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	165,380
7	(Projection$ or Prediction$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	526,088
8	(Neonate or Preterm Infant or Premature Infant).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	42,190
9	or/5–7	4,901,511
10	4 and 9	20,122
11	2 and 3 and 10	4
12	4 and 7 and 8	13
13	3 and 8	33
14	1 and 2 and 3	246
15	4 and 5 and 8	168
16	1 and 2 and 4 and 9	835
17	or/11–16	1133

PREMII Development

18	limit 17 to (human and english language and yr="2001 -Current")	917
19	conference.so.	2,063,092
20	limit 19 to yr="1902 - 2013"	1,554,910
21	18 not 20	846

PREMII Development

Supplementary Table 2. MEDLINE search strategy.

Search number	Query	Number of results
1	newborn intensive care unit.mp. or exp Intensive Care Units, Neonatal/	10,996
2	exp Infant, Premature/ or extreme$ preterm infant.mp. or exp Gestational Age/ or exp Infant, Low Birth Weight/	122,948
3	*"Severity of Illness Index"/ or exp Infant, Premature/ or *Infant, Newborn/ or Score for Neonatal Acute Physiology.mp. or exp Intensive Care Units, Neonatal/	94,251
4	(SNAP or SNAP-II or SNAPPE-II).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7732
5	exp Patient Discharge/mt, og, st, sn, td [Methods, Organization & Administration, Standards, Statistics & Numerical Data, Trends]	5921
6	(guideline$ or factor$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	4,479,794
7	(Benchmarking or Quality Control).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	75,144
8	(Projection$ or Prediction$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	253,412
9	or/6–8	4,724,286
10	5 and 9	2631
11	2 and 5 and 6	54
12	1 and 2 and 4	38
13	2 and 10	54

PREMII Development

14	1 and 5 and 6	33
15	3 and 5	142
16	or/11–15	190
17	limit 16 to (English language and humans and yr="2001 -Current")	144

Supplementary Table 3. Overview of clinical expert interview questions.

Question 1	What is the average length of stay in your NICU for extremely premature infants? Near their due date? Or after their due date?
	• What percentage of premature infants treated at your NICU are discharged home? To other departments in the hospital? Other?
	• What are the readmission rates of these babies?
	• What are the factors that affect the length of stay for extremely premature infants?
	  ○ Infant related?
	  ○ Parent/caregiver related?
	  ○ Institution related?
	  ○ Other?

Question 2	How do you determine when an extremely premature infant can be discharged from the NICU? • What physical factors are considered in the decision? • What other nonphysical factors are considered in the decision? • Do you rely on any guidelines when assessing an extremely premature infant's readiness for NICU discharge?
Question 3	Do factors considered vary when assessing the physical readiness of an extremely premature infant versus mid or late preterm infant? If yes, how so?
Question 4	Based on your own individual practice, what are the FIVE most important criteria of those you listed used to determine if an infant is physically ready to be discharged from the NICU?
Question 5	Do you use any assessment tools in making the decision? Please describe each.
Question 6	Is there anything else important for us to know in designing a measure to assess physical readiness for discharge?
Question 7	Do you think physical readiness is an important outcome to measure? Do you think physical readiness is predictive of length of stay?

NICU: neonatal intensive care unit.

PREMII Development

Supplementary Table 4. Measures assessing infant morbidity and mortality risk (n = 3).

Author	Instrument	Primary outcome	Relevant factors
Richardson 2001 [1]	Score for Neonatal Acute Physiology (SNAP-II) and SNAP-Perinatal Extension Version II (SNAPPE-II)	In-hospital mortality	Birth weight; Apgar score at birth; 5-min Apgar score; GA; size for GA
	Clinical Risk Index for Babies (CRIB)	Mortality and morbidity	—
	Pediatric Risk of Mortality (PRISM)	Mortality	—
Robison 2000[a] [2]	Neonatal Discharge Assessment Tool (N-DAT)	Identification of areas of need	Medical need: postoperative care, nutritional issues, medications, and behavioral and developmental implications
Bender 2013 [3]	Morbidity Assessment Index for Newborns (MAIN)	Morbidity	—

[a]Study published before 2001 cutoff date, but included due to the high relevance to the subject of inquiry.

GA: gestational age.

PREMII Development

Supplementary Table 5. Country-specific guidelines (n = 2) and clinical expert opinion (n = 3) on assessment of physical discharge readiness from the NICU, by country.

	Physical factors				
Country	Weight or weight gain	Cardiorespiratory stability	Oral feeding to support growth	Thermoregulation	Additional factors
United States [4]	Yes	Yes	Yes	Yes	Immunizations; metabolic screening; hematologic status; nutritional risk assessment; hearing evaluation; funduscopic exam; neurodevelopmental/neurobehavioral status; car seat evaluation; environmental factors
Canada [5]	Yes	Yes	Yes	Yes	Immunizations; provincial newborn screening; assessment for RSV prophylaxis and administration; cranial imagining at near term; ROP screening; hearing evaluation; car seat evaluation; predischarge physical exam
Argentina[a]	Yes	Yes	Yes	Yes	Nutritional risk assessment; inguinal hernia assessment
Europe[b]	Yes	Yes	Yes	Yes	Stable laboratory parameters (e.g., SaO2, acid/base/electrolyte balance); gestational age

PREMII Development

Germany[b]	NR	NR	NR	NR	No official guideline on discharge of preterm neonates; only specific guidelines addressing specific topics (e.g., necrotizing enterocolitis, primary care after delivery)

[a]Translated by ICON. ICON is a contract research organization providing a range of drug development services globally to the pharmaceutical, biotechnology, and medical device industries. The company specializes in the strategic development, management, and analysis of programs that support clinical development from compound selection to phase 1–4 clinical studies. The headquarters are in Dublin, Ireland, and ICON currently operates from 93 locations in 37 countries and has ~13,675 employees.

[b]Per communication with ICON Clinical Research.

NICU: neonatal intensive care unit; NR: not reported; ROP: retinopathy of prematurity; RSV: respiratory syncytial virus; SaO2: oxygen saturation.

PREMII Development

Supplementary Table 6. Participant characteristics for the clinical expert review, Delphi panel survey, and cognitive interview development stages of the PREMII and the online survey for scoring.

Clinical expert interviews (n = 4)		Delphi panel survey (n = 17)		Cognitive interviews, round 1 (n = 23)		Cognitive interviews, round 2 (n = 9)		Online clinician survey (n = 201)	
Characteristic									
Specialty, n		Specialty, n		Specialty, n		Specialty, n		Specialty, n	
Neonatologist	4	Neonatologist	17	NICU nurse	18	NICU nurse	9	Pediatrics	136
				Neonatologist	5			Neonatologist	65
Country, n		Country, n		Country, n		Country, n		Country, n	
Sweden	1	United States	3	Australia	3	United States	5	United States	37
United Kingdom	1	Germany	2	Canada	3	United Kingdom	4	Japan	31
United States	2	Australia	1	Japan	3			Mexico	16
		Brazil	1	United Kingdom	3			Australia	13
		Canada	1	United States	3			Brazil	13
		France	1	Brazil	2			Canada	13
		Israel	1	Germany	2			Colombia	12
		Japan	1	The Netherlands	2			United Kingdom	12

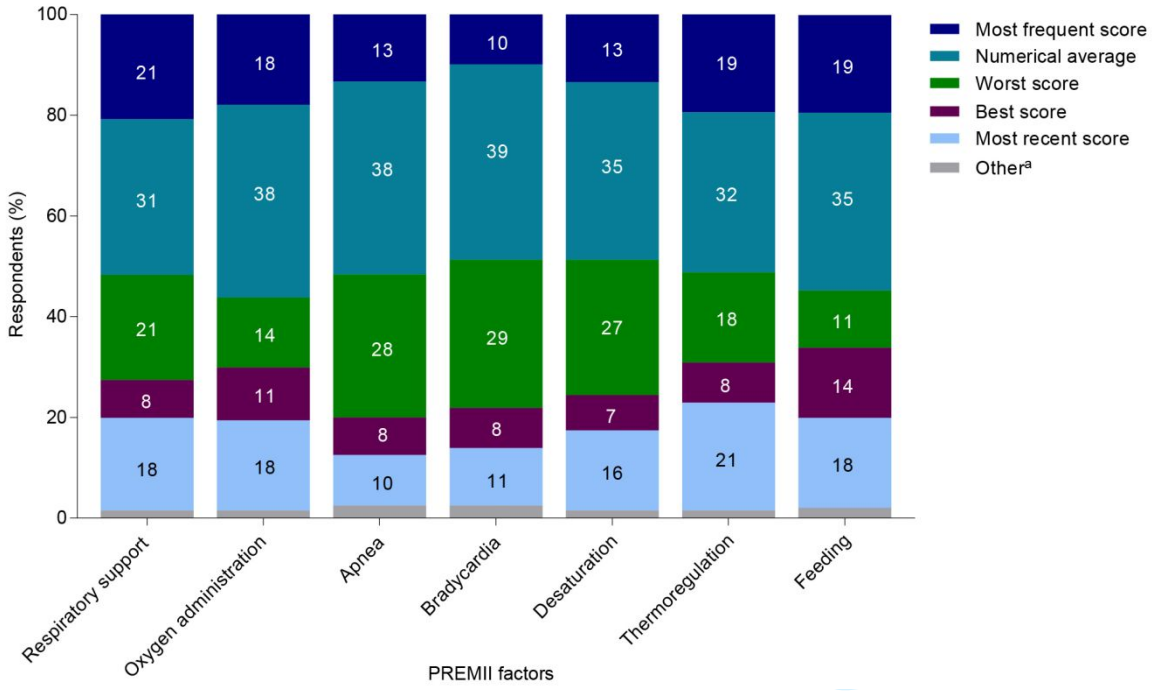
PREMII Development

	The Netherlands	1	Poland	1	France	10
	Mexico	1	Spain	1	Germany	10
	Poland	1			Italy	10
	Spain	1			Argentina	9
	Sweden	1			Spain	9
	United Kingdom	1			Singapore	4
					New Zealand	2

NICU: neonatal intensive care unit; PREMII: PREMature Infant Index.

PREMII Development

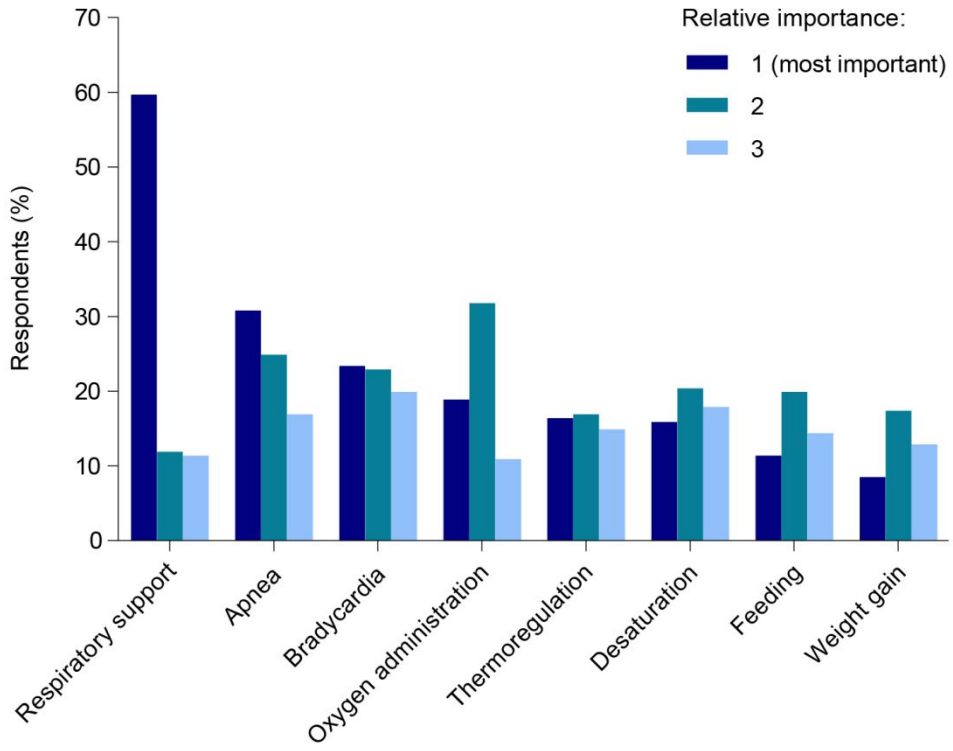
Supplementary Figure 1. Respondent preferences for calculating daily individual factor scores for use in the PREMII: findings from the online clinician survey (n = 201). Respondents were presented with example individual factor ratings for each shift over a 24-h period and then asked to indicate the most appropriate method (most frequent, numerical average, worst [or best, as applicable], most recent, or other) to calculate a daily factor score from the shift ratings to accurately capture functional status. [a]All ≤2.5%. Note: weight gain was excluded from this measurement due to weight not being measured repeatedly across shifts. PREMII: PREMature Infant Index.



PREMII Development

Supplementary Figure 2. Relative importance of PREMII factors in rating overall functional status: findings from the online clinician survey (n = 201).

Respondents rated the importance of each factor on a scale from 1 (most important) to 8 (least important) when rating overall functional status and were allowed to provide the same rating for multiple factors. Results for relative importance rated ≤4 are not shown. PREMII: PREMature Infant Index.



PREMII Development

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3. Bender GJ, Koestler D, Ombao H, et al. Neonatal intensive care unit: predictive models for length of stay. J Perinatol. 2013;33(2):147–153.
4. Committee on Fetus and Newborn. Hospital discharge of the high-risk neonate. Pediatrics. 2008;122(5):1119–1126.
5. Jefferies AL; Canadian Paediatric Society; Fetus and Newborn Committee. Going home: facilitating discharge of the preterm infant. Paediatr Child Health. 2014;19(1):31–36.

Appendix

PREMII™

PREMature Infant Index Questionnaire

Instructions:

- To be completed by the NICU nurse near the end of his or her shift, for each infant during the study period, in accordance with the study schedule.
- For each question, select one response that reflects the **WORST** experience observed for the infant during your shift.

Factors	Levels	SHIFT 1 Start: ____ (e.g., 12:00) End: ____ (e.g., 24:00)	SHIFT 2 Start: ____ (e.g., 12:00) End: ____ (e.g., 24:00)	SHIFT 3 Start: ____ (e.g., 12:00) End: ____ (e.g., 24:00)	SHIFT 4 Start: ____ (e.g., 12:00) End: ____ (e.g., 24:00)
RESPIRATORY SUPPORT	Report the **GREATEST** level of support during your shift				
	Mechanical ventilation with endotracheal or tracheostomy tube or mask	□	□	□	□
	Respiratory pressure support [for example: high flow (≥2 L/min or ≥2000 cc/min) nasal cannula, nCPAP]	□	□	□	□
	Supplemental oxygen continuously not through a nasal cannula	□	□	□	□
	Continuous low flow (<2 L/min or <2000 cc/min) nasal cannula	□	□	□	□
	[If "Continuous low flow (<2 L/min or <2000 cc/min) nasal cannula" selected, complete the following, otherwise skip to Oxygen Administration] Please select source:	□ Air flow meter	□ Air flow meter	□ Air flow meter	□ Air flow meter

	Please select unit of measurement: *[If L/min selected above]* Please enter the greatest setting: *[If cc/min selected above]* Please enter the greatest setting:	□ Oxygen flow meter □ L/min □ cc/min _____ L/min _____ cc/min	□ Oxygen flow meter □ L/min □ cc/min _____ L/min _____ cc/min	□ Oxygen flow meter □ L/min □ cc/min _____ L/min _____ cc/min	□ Oxygen flow meter □ L/min □ cc/min _____ L/min _____ cc/min
	Supplemental oxygen but not continuously OR pulmonary medication administered (for example: diuretics, inhaled steroids, or inhaled bronchodilators)	□	□	□	□
	No supplemental oxygen AND no pulmonary medication administered (for example: diuretics, inhaled steroids, or inhaled bronchodilators)	□	□	□	□

OXYGEN ADMINISTRATION	Report the **HIGHEST** concentration during your shift *[Skip if "Continuous low flow (<2 L/min or <2000 cc/min) nasal cannula" selected for Respiratory Support]*				
	61% or greater	☐	☐	☐	☐
	51–60%	☐	☐	☐	☐
	41–50%	☐	☐	☐	☐
	31–40%	☐	☐	☐	☐
	22–30%	☐	☐	☐	☐
	21% (room air or no additional oxygen administered)	☐	☐	☐	☐
APNEA, BRADYCARDIA, DESATURATION	***For this shift, a bradycardia event is defined as ≤:***	_____ beats/min	_____ beats/min	_____ beats/min	_____ beats/min
	For this shift, a desaturation event is defined as ≤:	____%	____%	____%	____%
	Enter the total number of the following events, if any, that occurred during your shift: Apnea • Event(s) that required intervention (for example: increasing oxygen, physical or mechanical stimulation, initiating compressions, bag mask ventilation) • Event(s) that did NOT require intervention	_____ _____	_____ _____	_____ _____	_____ _____

	Bradycardia • Event(s) that required intervention (for example: increasing oxygen, physical or mechanical stimulation, initiating compressions, bag mask ventilation) • Event(s) that did NOT require intervention Desaturation • Event(s) that required intervention (for example: increasing oxygen, physical or mechanical stimulation, initiating compressions, bag mask ventilation) • Event(s) that did NOT require intervention	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____
	Is the infant currently prescribed caffeine or other stimulant?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
THERMOREGULATION	Select one response that reflects the WORST experience for the infant during your shift				
	Infant was in a closed and heated incubator OR was under a radiant warmer	□	□	□	□
	Infant was in an open bassinet or cot and required additional support to stay warm (for example: multiple blankets, a heated mattress)	□	□	□	□

	Infant was in an open bassinet or cot and did NOT require additional support to stay warm	□	□	□	□
FEEDING	Did any feeds [including intravenous nutrition (solution containing amino acids or lipids) or enteral tube feeding] occur during your shift?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
	[If "Yes" selected above, complete below; if "No" selected above, skip to Weight]				
	Select one response that reflects the WORST experience for the infant during your shift				
	Any intravenous nutrition (solution containing amino acids or lipids) OR all feeds by enteral feeding tube (no breast or bottle)	□	□	□	□
	Some portion of feeds by enteral feeding tube AND some by breast or bottle but WITH a problem breathing or swallowing	□	□	□	□
	Some portion of feeds by enteral feeding tube AND some by breast or bottle but WITHOUT any problems breathing or swallowing	□	□	□	□
	All feeds by breast or bottle (no enteral feeding tube) but WITH a problem breathing or swallowing	□	□	□	□
	All feeds by breast or bottle (no enteral feeding tube) WITHOUT any problems breathing or swallowing but at least one feed took LONGER THAN 30 MINUTES	□	□	□	□

	All feeds by breast or bottle (no enteral feeding tube) WITHOUT any problems breathing or swallowing and all feeds took 30 MINUTES OR LESS	□	□	□	□
WEIGHT	*[Complete ONLY for first administration for a given infant]* Enter last recorded weight prior to your shift. Please round to the nearest whole number: Date (DD-MMM-YYYY; for example: 01-JAN-2017): Time (00:00 to 23:59):	_____ grams _____ _____			
	Was the infant weighed during your shift?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
	[If "Yes" selected above] Enter lowest recorded weight during your shift. Please round to the nearest whole number:	__ grams	__ grams	__ grams	__ grams