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The Developmental, Medical and Nutritional Outcomes of Children Discharged from the Neonatal Unit in Rural Rwanda: Supporting the development of medically at-risk infants through the Pediatric Development Clinic

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Summary of Study (Synopsis):

Neonatal health and improving neonatal mortality has become one of the top priorities globally. In Rwanda, hospital care has advanced significantly with the development of national neonatal care guidelines and widespread provider training. As advances in technology and resuscitation become more commonly available, many preterm, low birth weight and other high-risk infants are surviving the early neonatal period. However, upon discharge from the neonatal units, this at-risk population has little support for their health, nutrition and development in the community. To address this emerging need, Partners In Health in collaboration with the Ministry of Health and UNICEF, has created a pediatric developmental clinic (PDC) to follow the high-risk infants after discharge from hospitals and health centers. Prior to implementation, a community-based descriptive study assessing the baseline medical, nutritional and developmental needs of low-birth weight and preterm infants who are the target population of the pediatric development clinic was conducted (Baseline Phase One). Subsequently, after 1-2 years of implementation an evaluation of clinical, nutritional and developmental outcomes of children followed in PDC will be conducted in comparison with the baseline study outcomes (Post-PDC Phase Two). Ongoing research on PDC implementation will focus on research on patient and provider experiences, overall clinic processes, cost-effectiveness, expansion of the PDC model, decentralization to health centers, and longer term outcomes of children enrolled in the PDC to further help refine the PDC model (Post-PDC Phase Three).

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1. Background

Early childhood from birth to 5 years of age is crucial for brain development (Sices, 2007). This period of growth for children is enhanced through adequate nutritional and developmental support. Furthermore, early intervention has been demonstrated to have significant impact on long-term outcomes (Childers et al, 2011). For example, early intervention has been associated with improved IQ in the first five years of life and has decreased behavioral problems (Nordhov et al, 2010), (Nordhov et al, 2012). Furthermore, studies have demonstrated that early intervention improves educational progression, incidence of delinquency and crime, and economic success (Baker-Henningham et al, 2010). Unsurprisingly, early childhood development support has been associated with improved outcomes of children in resource-limited settings as well (Ertem et al, 2008).

This critical time is especially important for high-risk populations, such as low- birth weight and preterm infants. Infants born premature or low birth weight are at increased risk for early death, developmental delay and nutritional and medical comorbidities (Feldman et al, 2006). Even infants born in the late preterm period, after 32 weeks up until 37 weeks, are at risk for adverse effects on development and academic difficulties (McGowan et al, 2011). Therefore, routine neurodevelopmental follow-up has increasingly become the standard of care in the United States and Europe for these infants (McManus et al, 2012).

In 2010 there were an estimated 15 million preterm (<37 weeks) births worldwide (Biencowe et al, 2013). It has been estimated that approximately 1 million of these infants have some degree of developmental delay. Some estimate that 200 million children in developing countries are not reaching their full developmental potential (Grantham-McGregor et al, 2007).

Improved quality of care can help reduce this burden. In Rwanda, up to 40% of under- five deaths occur within the first 28 days (Rwanda DHS 2010), and approximately 6% of all neonates born are low birth weight (WHO-ECDD 2012) with prematurity ranking among the top causes of under-five mortality (Rwanda Health Statistics, 2012). Currently, these infants are discharged from hospitals with little support out in the community.

To address this gap, Partners In Health, in close partnership with the Rwanda Ministry of Health and technical support from Boston Children's Hospital and UNICEF, is designing and implementing a Pediatric Development Clinic (PDC) specifically dedicated to the nutritional, medical and developmental concerns of this high-risk population, with the goal of improving the quality of life for affected infants and children. However, there is a lack of data regarding the current outcomes of these vulnerable newborns in resource-limited settings (Ballot et al, 2012).

The proposed study aims to assess the baseline needs and disease burden of low birth weight and preterm infants, whom will routinely be evaluated in this clinic and will comprise a large majority of the clinic patients. These data will be used to inform the development and implementation of a pediatric developmental clinic (PDC) to follow these infants long-term, with the goal of improving overall pediatric health especially for those high-risk children. Following 1-2 years of implementation, an evaluation of clinical, nutritional and developmental outcomes of children followed in PDC will be conducted in comparison with the baseline study outcomes. Additionally, the evaluation of PDC will continue after initial post-assessments focusing on research on patient and provider experiences, overall clinic processes, quality of care, cost of the PDC model, PDC training and mentorship, expansion of the PDC model, and longer term outcomes to further help refine the PDC model.

2. Aims of the study:

Phase One: Baseline/Pre-PDC

Aim 1: To describe the baseline outcomes of a selected sample of infants discharged from a rural hospital neonatal unit. This aim has been completed.

Aim 2: To identify specific patient-level predictors of developmental delay (if we have sufficient power based on prevalence of developmental delay in the sample population). This aim will not be completed due to the small sample size.

Phase Two: Post-PDC

Aim 3: To describe the pediatric development clinic (PDC) implementation process after approximately 24 months of implementation in terms of: services provided, referral system, patient population served and clinical, nutritional, and developmental status. This aim has been completed.

Aim 4: To describe the clinical, nutritional, and developmental outcomes of vulnerable patients enrolled in PDC in comparison with:

a) Medically vulnerable infants who did not receive PDC support from Phase One of this study. This comparison will be made using a cohort of preterm/LBW children who were born in Rwinkwavu District Hospital (RDH) before PDC started with medical, nutritional and developmental outcomes assessed at 12-36 months of age. under way
b) The general population of rural Rwandan children. This comparison will be looking at developmental outcomes of children followed in PDC compared to the same age children from the general population using UNICEF data that was collected in under 5 children.[1]

Phase Three: Expanding PDC

Aim 5: To evaluate the implementation of PDC during expansion, including patient characteristics, provider experiences, quality of care, impact of quality improvement interventions, cost-effectiveness, patient experiences, and patient outcomes. Findings from this aim will be used for continuous quality improvement of the PDC and informing scale-up.

Aim 5. 1. To evaluate the implementation of interventions that promote breastfeeding from as early as day one of life among newborns in the referring hospital neonatal units.

[1] The UNICEF data was conducted as part of an evaluation for UNICEF and Imbuto Foundation's ECD&F Baseline. PI of this study Hema Magge and Co-I Catherine Kirk were both on the UNICEF ECD&F study team and have access to the study data. The ECD&F study was approved by RNEC (PIs Theresa Betancourt and Vincent Sezibera).

3. Methods

3.1. Study description

This study has three phases. In the first phase, descriptive study will investigate at the community level the developmental, medical and nutritional outcomes of infants discharged from the neonatal unit, aged between 12 to 36 months at the time of data collection. In the second phase, the study will assess the services provided to children enrolled in the PDC and compare their outcomes to children from the first phase as well as to an existing random sample of children from an existing database. In the third phase, research will focus on answering questions raised from the initial PDC study aims – including patient and provider experiences, expansion of the PDC model, overall clinic processes, enrolment rates and retention, cost-effectiveness, and longer term outcomes of children enrolled in the PDC to further help refine the PDC model and maximize benefits for children.

3.2. Study design

Pre-PDC Phase One:

The first phase is a **cross-sectional study** of infants discharged from a district hospital unit using caregiver report of medical and developmental outcomes as well as relying on measured growth parameters for nutritional status. This study will serve as a baseline of developmental, medical, and nutritional outcomes for comparison to similar children who received services from the PDC.

Post-PDC Phase Two:

All under 5 years of age, high risk (preterm, LBW) children enrolled in PDC since April, 2014 when PDC was initiated. The second phase will be a second cross-section of children who have been receiving services from the PDC from April 2014 when the clinic launched until present. The study will describe PDC implementation, demographic characteristics, and clinical, nutritional and developmental outcomes of all children from zero to five years of age enrolled in PDC from April 2014 to the time of study.

Post-PDC Phase Three:

This phase will use mixed methods, with data sources including routinely collected data, chart review, household data collection, focus groups and interviews to evaluate the PDC as it expands to new areas. The study will provide essential information of the feasibility of the PDC model at larger scale. The study will describe barriers to care, retention, long-term patient outcomes, and provider and patient experiences, quality of care delivered in the PDC especially on growth monitoring and developmental screening and costing of the PDC.

3.3. Study sites

Pre-PDC Phase One:

Phase One data collection took place in the Rwinkwavu District Hospital catchment area: Nyamirama, Mukarange, Mwili, Murama, Rwinkwavu, Kabarondo, Ndego, Kabare, and Ruramira sectors.

Post-PDC Phase Two:

Phase Two data collection will take place in the PDC clinics in the Rwinkwavu District Hospital catchment area: Rwinkwavu, Kabarondo, Ndego, Cyarubare and Ruramira Health Centers. Additional data collection on patient outcomes will be collected during household interviews at the homes of PDC patients.

Expanding -PDC Phase Three:

Data collection will take place in all PDC clinics in the Rwinkwavu and Kirehe District Hospital catchment areas. Household data collection will be conducted in the communities of Kirehe District.

3.4. Study population

Pre-PDC Phase One:

All infants discharged from the Rwinkwavu District Hospital neonatal unit during the designated time period fulfilling the inclusion criteria: children were included if they were discharged between October 2011-October 2013 (prior to PDC implementation).

Post-PDC Phase Two:

All children enrolled in the PDC are eligible. PDC serves children up to age five years with prematurity, low birth weight, birth asphyxia, other perinatal risks, and other developmental delays.

Expanding-PDC Phase Three:

All children and their caregivers enrolled in the PDC clinics in S. Kayonza and Kirehe Districts are eligible. PDC serves children up to age five years with prematurity, low birth weight, birth asphyxia, other perinatal risks such as post CNS infections_cerebral malaria and meningitis, and other developmental delays.

3.5. Selection of study population

3.5.1. Inclusion criteria

Baseline Phase One:

All infants discharged from Rwinkwavu hospital neonatal unit and born at less than 37 weeks and infants born less than 2 kilograms during the designated study period.

Post-PDC Phase Two:

All children under five years of age enrolled in PDC in Rwinkwavu District Hospital catchment area PDC clinics, will be included in Aim 3 and Aim 4b. Aim 4a will include only preterm and/or LBW (<2000g) infants for comparison with the baseline population of similar infants.

Expanding-PDC Phase Three:

All children under five years of age and their caregivers referred to or enrolled in PDC in Rwinkwavu and Kirehe District Hospital catchment areas. In addition, newborns and their caregivers from Rwinkwavu and Kirehe District Hospital catchment areas will be included as the primary referral patient population to PDC. PDC providers will also be included in some components of the evaluation.

3.5.2. Exclusion and Stop Criteria

Pre-PDC Phase One:

1. Any infant whose family is unwilling to consent to study or decides to stop the home visit at any time.
2. Congenital heart disease per neonatal register
3. Genetic dysmorphology per neonatal register
4. Birth asphyxia per neonatal register

Post-PDC Phase Two:

1. For Aim 4a, exclusion criteria will match the Baseline Phase One exclusion criteria listed above.

Expanding-PDC Phase Three:

1. Children who do not meet inclusion criteria will be excluded.

3.5.3 Sampling

Pre-PDC Phase One:

Potential participants will be identified and sampling will be conducted in the following manner. The study coordinator will use the Rwinkwavu neonatal registry after obtaining consent from the medical director to identify potential study participants based on the inclusion criteria outlined above. The following identifiers will be extracted from the registry: name, sex, date of birth, discharge date and mother's name. After the identification of potential participants, the patient files will be located and examined to compile the demographic information of the infants: sector, cell, village, and health center.

Post-PDC Phase Two:

All children enrolled in the PDC are eligible and no new data will be collected for Aim 3. Children will be identified through PDC patient records, which include patient registers, patient enrollment forms, routine program forms, and the electronic medical record (EMR). To complete Aim 4, additional assessments of children's growth, development, and home environment including parenting practices will be conducted through household interviews with the primary

caregivers of PDC patients. Patient names and household location will be extracted from the EMR of patients who enrolled in the PDC at least 12 months prior to data collection.

Expanding-PDC Phase Three:
All children enrolled in the neonatal units or PDC, their caregivers, and PDC providers are eligible for participation in this aim. Children will be identified through neonatal unit and PDC patient records, which include patient registers/charts, patient enrollment forms, routine program forms, and the electronic medical record (EMR).

3.5.4. Randomization

None

3.5.5. Proposed Intervention

Children in Phases Two and Three of this study have participated in the PDC program as described previously, unless they are in a comparison group. The PDC provides medical, nutritional and developmental supportive programs to at-risk children under age five using trained nurses and social workers in addition to overall clinic supervision by a general practitioner. Children are referred to the PDC from the hospital (neonatal unit, maternity, inpatient pediatrics, and the outpatient or emergency departments), health centers, and from the community. Children are eligible to enroll in the PDC if they meet the following program eligibility criteria: prematurity, low birth weight (<2000grams), hypoxic ischemic encephalopathy, hydrocephalus, cleft lip and palate, trisomy 21, post central nervous system infections (meningitis and cerebral malaria) severely malnourished children requiring hospitalization post-discharge, as well as children presenting with other developmental delays. Children come in for routine visits, on a timeline determined by their specific condition. On each PDC clinic day, social workers facilitate a group counseling session focused on topics relevant to children's growth and development. After group sessions, children undergo a clinical screening and growth monitoring by a nurse as well as one-on-one sessions with a social worker to identify needs for additional social support whether financial, emotional, nutritional, or a home visit. PDC social support groups are formed to engage father's in the care of their children. Health

center PDC clinics receive mentorship visits from the hospital PDC supervision team; mentors use structured observation checklists for monitoring quality of care delivery and data-feedback. An application to aid decision making using tablets has been designed to address challenges with growth monitoring especially for preterm infants and identification of feeding difficulties, which has limited the PDC's ability to successfully provide early intervention in cases of growth failure. The mHealth tool supports providers in calculating z-scores, interval growth, and adjusted age as well as providing counseling that is tailored to the individual child's needs. Also, in an effort to optimize nutritional outcomes of babies discharged from Rwinkwavu and Kirehe Neonatal Units, as part of phase 3 of the project, we will also be implementing interventions to promote breastfeeding from as early as day one of life. This will primarily be done through early, individualized counseling and education on the importance and best techniques for breastfeeding and expressing breast milk, but will also employ visual aids such as posters and videos, and the institution of a policy to restrict use of artificial milk to clinically indicated situations, such as growth failure that requires breast milk supplementation to provide additional calories, or within the first two weeks of life if the mother has insufficient breast milk production, to avoid negative effects on growth. By targeting mothers and infants in the Neonatal Unit to establish strong breastfeeding during admission, growth of high-risk infants will be optimized from day one of life, and babies will also experience additional benefits of breast milk such as reduced infections and improved neurodevelopmental outcomes before they are discharged for follow-up in PDC. Future, planned interventions are to promote maternal nutrition by providing supplementary meals and involving our maternity department in counseling mothers on early initiation of breastfeeding for all babies, and expressing breast milk for babies who are unable to breastfeed due to prematurity or their clinical status.

3.5.6. Recruitment Methods

Pre-PDC Phase One:

Our data collection is based on the use of independent data collectors. Data collection officers will be identified from the Family Strengthening Intervention Study staff (through coordination with their study coordinator) and will be trained on the use of the Ages and Stages Questionnaire as well as weight, length and head circumference measurements. Training sessions will take place at Rwinkwavu Center for Training and Operational Research. After completion of training, the data collection officers will be given a list of potential study participants. The data officers

will then contact the family's community health worker prior to making home visits and approaching the family for study participation.

Post-PDC Phase Two: All children enrolled in the PDC are eligible and the study will use routinely collected data from patient charts and EMR. In addition, patients who have been seen in the PDC clinic for 12 or more months will be contacted to participate in a household interview to be conducted by trained, independent data collectors. Patients will be identified from PDC enrollment records, and information will be extracted from patient charts for follow-p in the community (this includes caregiver name, geographic location of the household, and any relevant contact information for the household such as a phone number). Data officers will then contact the family's community health worker prior to making home visits and approaching the family for study participation.

Expanding-PDC Phase Three:
All children enrolled in the hospital neonatal units or PDC, and their caregivers, are eligible. The study will use routinely collected data from patient registers, patient charts and EMR in addition to qualitative methods. In addition, a list of PDC-eligible children prior to the opening of PDC in Kirehe (i.e., before May 2016) will be identified for household data collection to establish baseline status of high-risk infants prior to PDC. PDC providers (nurses, doctors, social workers, other parahealth professionals, volunteers) will be eligible to participate if they have been working in the PDC for at least 3 months.

3.5.7. Subjects enrollment

Pre-PDC Phase One:
After consent obtained from the caregiver by the data collector, the study participant will be enrolled and data collection will begin. All patient data will be stored in a password-protected access database.

Post-PDC Phase Two:

All children enrolled in the PDC are eligible and the study will use routinely collected data. Informed consent will be obtained for all participants who enrolled in PDC at least 12 months prior to data collection that willing to participate in household data collection.

Expanding-PDC Phase Three:
All children enrolled in the neonatal unit or PDC, and their caregivers, are eligible and the study will use routinely collected data. When routinely collected data is being used, we will not conduct additional informed consent. For any additional data collection with caregivers using qualitative methods or household data collection, caregivers will provide written informed consent for themselves and their child. Any PDC provider who participates in the study will provide written informed consent.

3.6. Study Procedures

3.6.1. Procedures at enrollment and data collection.

Pre-PDC Phase One:
After consent is obtained, data will be collected using a data collection form and the ASQs from 12 to 36 months of age on an Android tablet. The ASQ is a validated screening tool for child development that has also been translated to Kinyarwanda and validated for local use. The Ages and Stages questionnaire went through a validation process with the publisher to adapt the screening tool to Rwanda. The questionnaire was first translated from English to Kinyarwanda. After translation the questionnaire was field-tested. The questionnaire was then adapted to Rwandan cultural context and underwent field-testing again. The ASQ went through a final adaptation to Rwandan culture and was translated to English. It was then back translated to Kinyarwanda and finally submitted to the publisher for approval. Questions will be in a simple yes/no format and growth parameters of weight, height, head circumference and MUAC will be measured. Questions will be asked about the medical complications and developmental milestones will be assessed using the ASQs per age group. Upon data collection completion, the growth parameters and medical comorbidities will first be entered into the database and then the ASQ will be scored by a study staff. The scoring of the ASQ will be based on the answers of the caregivers. A score will be given to each answer. The ASQ has three possible answers: yes, not yet, or sometimes. At the end of the questionnaire the total score will be tabulated for each of the

five subsections based on a standard scoring methodology. Depending on the score, the questionnaire will be counted as normal or abnormal (developmental delay present). Developmental delay will be defined as any single domain score that falls within the limits of concern or delay according to the ASQ scoring table at the end of the questionnaire.

Post-PDC Phase Two:

The majority of phase two data comes from existing program records, both paper-based and electronic as well as pre-existing de-identified data. The procedure is as follows for using routinely collected program data: After RNEC and MOH approvals are obtained, data will be collected from electronic medical records (EMR) and paper forms that are part of routine programmatic record keeping (See Appendix F for complete list of PDC routine data collection forms approved; new routine forms are contained in Appendix B). Demographic characteristics, anthropometric measurements, clinical, nutritional and developmental outcomes information will be extracted from the PDC EMR dataset and patient files. After extraction from the original dataset, data will be transferred into STATA (Stata Corp, College station, Texas, USA) for data cleaning and further statistical analysis. Patient identifiers will be removed and unique identification numbers will be assigned to the working dataset to respect patient confidentiality. As Aim 3 is a secondary dataset analysis of de-identified patient records, no individual patient consent procedure will be needed.

Aim 4 will include household interviews with caregivers of children who enrolled in PDC at least 12 months prior to data collection (see study tools for household data collection in in Appendix A). These patients will be identified using EMR records and will be asked if they are willing to be contacted by the study team by PDC staff. If a caregiver is willing to participate, he/she will be contacted by the study team and complete informed consent prior to data collection. Consenting participants will complete an interview about the child's development, nutrition, parenting, and the home environment (see Appendix A for household data collection tool). Child development will be measured using the Ages and Stages Questionnaire, as has been previously approved for use in this study protocol. Appendix A contains all 20 age-specific forms of the Ages and Stages Questionnaires, however each caregiver will be asked only the 30 age-specific questions that are appropriate for their child; all questions for children of different ages will be skipped. Data will be collected on Android tablets using the software platform

KoboCollect.

Expanding-PDC Phase Three:
The majority of phase three data comes from existing program records, both paper-based and electronic as well as pre-existing de-identified data (see Appendix B for new tools being used in the PDC; Appendix F contains all the tools previously approved by RNEC). Additional data will be collected through household data collection and qualitative methods (new tools contained in Appendix B).

The procedure is as follows for using routinely collected program data: Data will be collected from electronic medical records (EMR) and paper forms that are part of routine programmatic record keeping (See Appendices B and F for all PDC data collection forms). Demographic characteristics, anthropometric measurements, clinical, counseling assessments, nutritional and developmental outcomes information will be extracted from the PDC EMR dataset and patient files. After extraction from the original dataset, data will be transferred into STATA (Stata Corp, College station, Texas, USA) for data cleaning and further statistical analysis. Patient identifiers will be removed and unique identification numbers will be assigned to the working dataset to respect patient confidentiality.

For household data collection, the procedure is as follows: neonatal unit registers will be reviewed for patients who would have been eligible for the PDC prior to the opening of the PDC in May 2015. Eligible caregivers of patients who were discharged alive will be contacted in the community to ask if they are willing to participate in the study. If caregivers provide written informed consent, they will be interviewed by trained data collectors using Android tablets about the current health, nutritional, and developmental status of their child as well as questions on the family environment. Household data collection tools are contained in Appendix A.

For qualitative data collection with PDC providers and patient caregivers, they will be invited by study staff (not PDC providers) to participate in focus groups and/or individual interviews. Only those who provide written informed consent will participate and interviews and/or focus groups

will be conducted at Partners In Health offices or other private spaces away from the PDC clinics.

When evaluating cost data, we will also access routine financial reports from Partners In Health and the Ministry of Health to assess program costs such as supplies, equipment, staffing, patient costs, supervision costs, and other inputs required for the PDC program.

3.6.2. Outcomes, exposures, and confounders to be measured

Pre-PDC Phase One:

Aim 1: Describe the baseline outcomes of a selected sample of infants discharged from a rural hospital neonatal unit.

1. ***Primary Outcome*:**

The primary outcome is the proportion of study participants alive with developmental delay.

Developmental delay is defined as one domain that is scored as an area of concern or presence of delay using the Ages and Stages Questionnaire (ASQ-3).

2. ***Secondary Outcomes:***
    1. Proportion of study subjects deceased
    2. Proportion of study subjects with malnutrition
    3. Proportion of study subjects with medical co-morbidities, further broken down into the four categories: hydrocephalus, anemia, feeding difficulty, and respiratory disease.
    4. Proportion of the study subjects with developmental delay and malnutrition
    5. Proportion of study subjects with developmental delay and medical comorbidities

Aim 2: Identify specific patient-level predictors of developmental delay. Main exposures of developmental delay include prematurity, low birth weight and malnutrition. Potential

confounders include but not limited to sector of residence, sex, ubudehe category (measure of economic status), household size, and education level.

Post-PDC Phase Two:

Aim 3: Describe the PDC. This aim is to describe the pediatric development clinic (PDC) after 24 months of implementation in terms of the following main outcomes: services provided, referral system, patient population served and clinical, nutritional, and developmental status after support and follow-up in the clinic.

Other Variables to be measured include (See Appendix F for data source forms)

Characteristics of Clinic Patients

Proportion of study participants per age category and per medical condition. Broken down by:

- Proportion of infants
- Proportion of children from one year to five years
- Proportion of children born premature
- Proportion of ELBW/ VLBW
- Proportion of infants born at term with HIE or cerebral infection

Proportion of children with developmental delays, trisomy 21, hydrocephalus, cleft lip/palate, and developmental delay

- Proportion of children deceased
- Proportion of children lost to follow-up
- Proportion of children with malnutrition per age category or per medical condition

Clinic activities will be described

Patient flow: Group education, individual social worker screening, clinical evaluation including danger sign assessment, nutritional assessment/classification/treatment, developmental screening/therapy, and condition-specific screening and treatment.

Aim 4: Compare developmental, medical, and nutritional outcomes of children who were enrolled in the PDC to other children on the main outcomes of prevalence of developmental delay as measured using the Ages and Stages Questionnaires (ASQ-3) and the prevalence of undernutrition (stunting, wasting, underweight) using anthropometric assessments.

This aim is to describe the clinical, nutritional, and developmental outcomes of vulnerable patients enrolled in PDC in comparison with:

a. Medically vulnerable infants who did not receive PDC support. This comparison will be made using a cohort of preterm/LBW children who were born in Rwinkwavu District Hospital (RDH) before PDC started with medical, nutritional and developmental outcomes assessed at 12-36 months of age (the dataset from Aim 1).
b. The general population of rural Rwandan children.[2] This comparison will be looking at developmental outcomes of children followed in PDC compared to the similar age children from the general population using UNICEF data that was collected in children ages 0-11 months and 24-35 months randomly sampled from ten rural sectors of the country.

Additional variables to be measured include (See Appendix F for data source forms of routinely collected data and Appendix A for household interview forms. All measures used in the household interview were previously used in the two comparison datasets):

- Descriptive characteristics of caregivers.
- Proportion of visits where a nutritional screening was done, danger sign screening was done, and patient had a documented ASQ within the 6 months prior to visit date.

[2] This existing data set was collected by UNICEF, Harvard School of Public Health, Partners In Health, and the University of Rwanda. Dr. Hema Magge and Catherine Kirk were investigators on both study teams and have access to the data.

- Proportion of children who received nutrition supplement.
- Proportion of currently enrolled children with a visit in the reference quarter whose caregivers have had at least one documented ECD counseling session
- Proportion of children with moderate or severe chronic malnutrition (height/age Z score < 2 or height/age z score < 3) at the last visit.
- Proportion of children with moderate or severe acute malnutrition (weight/height Z score < 2 or weight/height z score<3) at the last visit.
- Proportion of children with a completed and documented ASQ in the reference quarter failing one or more domains on the ASQ.
- Mean/median scores on the overall ASQ
- Mortality rate in both groups
- Percentage of patients lost to follow-up
- Opportunities for learning and stimulation in the home, measured by the Rwanda-adapted HOME Inventory and the Rwanda DHS Early Childhood Development Index
- Caregiver mental health, measured by the Hopkin's Symptom Checklist which has been validated in Rwanda and used in Rwanda to assess symptoms of depression and anxiety for over twenty years
- Caregiver-child interactions and discipline practices, using the Kinyarwanda version of the Observations of Mother-Child Interactions (OMCI) as well as the Rwanda DHS Child Discipline Module
- Socioeconomic status of the household, using wealth index from the Rwanda DHS
- Expoure to daily hardships and household stressors

Expanding-PDC Phase Three:

Aim 5: To evaluate the implementation of PDC during expansion, including patient characteristics, provider experiences, quality of care, cost-effectiveness, patient experiences, and patient outcomes. Findings from this aim will be used for continuous quality improvement of the PDC and informing scale-up.

***Primary Outcome*:** The primary outcome is the proportion of study participants alive who are meeting developmental and growth milestones.

Secondary Outcomes:

- Cost-effectiveness of the PDC model
- Adherence to PDC care protocols by PDC providers
- Quality of care
- Enrollment rates, clinic retention, and barriers to care
- Patient and provider experiences
- Impact of training and mentorship in the PDC protocol
- Evaluation of improved exclusive breastfeeding prior to PDC referral
- Impact of PDC mHealth tool on protocol adherence and child growth
- Impact of PDC on child outcomes in Kirehe

3.6.3. Data Management

For all phases, patient identifiers will be removed and a separate linking file will be kept in a password-protected computer with access only by the study staff to allow for data quality assessments of the EMR. All data will be kept in a password-protected database.

Pre-PDC Phase One:

After collection of the completed data forms, all information will be uploaded into a password-protected database.

Post-PDC Phase Two:

Data will be extracted from the EMR system and exported into Stata for statistical analysis. All participants will be assigned a study ID. Any additional data that is not in the EMR will be entered from paper-based patient files into a database for data management and cleaning. Additional paper-based data extracted from patient charts and entered into KoboCollect will be merged into the EMR databased by linking study IDs (Aim 3). Data on PDC patients for Aim 4

will be extracted from the EMR and/or additional patient records and data from household interviews will be collected using KoboCollect and securely stored with an SSC connection and password protection. Data on PDC patients will be appended to de-identified comparison datasets for study aims 4a and 4b for analysis.

Expanding-PDC Phase Three:

Data will be extracted from the EMR system and exported into Stata for statistical analysis. All participants will be assigned a study ID. Any additional data that is not in the EMR will be entered from paper-based patient files or gathered through interviews into KoboCollect, or other comparable software, database for data management and cleaning. Additional paper-based data extracted from patient charts and entered into KoboCollect will be merged into the EMR databased by linking study IDs. Cost-data will also be entered into a KoboCollect, or other comparable software, database for data management and cleaning. Qualitative data will be collected using audiorecorders. Kinyarwanda transcripts of recorded interviews and focus groups will be translated into English for analysis.

3.6.4. Analysis Plan

Pre-PDC Phase One:

Aim 1: Describe the baseline outcomes of a selected sample of infants discharged from a rural hospital neonatal unit.

Analysis Plan:

The primary analysis will be a univariate analysis describing the proportion of children discharged from the neonatal unit with developmental delay at two years of age. This is the primary outcome of the study and will provide vital data regarding neonatal outcomes at two years after discharge from neonatal unit. Proportions will be calculated for categorical variables and means with standard deviations will be calculated for continuous variables.

Categorical variables include: sex, sector, alive/dead, malnutrition (yes/no), malnutrition category (low, moderate, severe), medical comorbidities (anemia, respiratory disease,

possible hydrocephalus, and feeding difficulty), ubudehe category (measure of economic status), and education level of the caregiver.

Continuous variables are birth weight, gestational age, age at the time of data collection, and household size.

Aim 2: Identify specific patient-level predictors of developmental delay

Analysis Plan:

We hypothesize that birth weight (< 1kg, 1-1.5kg, 1.5-<2kg, ≥ 2 kg), gestational age (<32 weeks, 32-36weeks, ≥ 37weeks), and malnutrition (yes/no) will be significantly associated with developmental delay in bivariate and multivariable analyses.

Chi square test will be performed to test for associations between these categorical variables and the primary outcome (developmental delay). A multivariable logistic regression model will be created to identify predictors of developmental delay controlling for potential covariates using the same list of descriptive variables. However, this analysis will only be performed if there are a sufficient number of children with the primary outcome to have sufficient power to detect predictors.

Post-PDC Phase Two:

Aim 3: Describe the PDC and patients enrolled in the PDC

Analysis Plan:

Demographic characteristics, services provided to patients, and clinical, nutritional and developmental outcomes will be described using descriptive statistics. For continuous variables, mean and standard deviations will be reported unless the distribution is not normal and then medians and inter-quartile range will be reported. Frequencies and percentages will be reported for categorical variables.

Aim 4a: Compare developmental, medical, and nutritional outcomes of children who were enrolled in the PDC to medically vulnerable children who did not receive PDC support (from Baseline Phase One)

Analysis Plan:

We will use bivariate analyses to compare the outcomes of infants who received PDC services with those who did not receive these services (the baseline data from Phase One). Developmental delay will be scored as a binary outcome looking at the proportion of children who failed one or more ASQ-3 domain at baseline to the proportion of children enrolled in PDC who failed one or more ASQ-3 domain. We will use a chi square test or fishers exact test look for significant differences in the number of children with developmental delay between children who received PDC services and those who did not. Chi squared or fishers exact tests will also be used to assess for differences in nutritional outcomes (normal, moderate, and severe malnutrition indicators) and medical outcomes among the two groups.

If we have sufficient power, we will conduct logistic regression analyses to look at predictors of developmental delay in the sample. Using backwards selection, all variables associated with developmental delay at $p < 0.10$ in bivariate will be included in the full model. We will report Odds Ratio, p-value, and 95% confidence intervals for multivariate analyses.

Aim 4b: Compare developmental, medical, and nutritional outcomes of children who were enrolled in the PDC to a sample of Rwandan children from ten rural sectors across the country.

Analysis Plan:

We will use bivariate analyses to compare the outcomes of infants who received PDC services with a random sample of children from rural communities in Rwanda (a pre-existing dataset). Developmental delay will be scored as a binary outcome looking at the proportion of children who failed one or more ASQ-3 domain in the random sample of Rwandan children from rural areas to the proportion of children enrolled in PDC who failed one or more ASQ-3 domain. We will use a chi square test or fishers exact test look for significant differences in the number of children with developmental delay between children who received PDC services and those who did not. We will use chi squared or fishers exact test to assess for differences in nutritional (normal, moderate, and severe malnutrition indicators) among the two groups. Medical outcomes will not be assessed because the comparison database only collected data on demographics and current

developmental and nutritional status.

Expanding-PDC Phase Three:

Aim 5: Analyses of PDC expansion will be focused on descriptive analyses of process, output and selected outcome measures including, patient outcomes, quality of care, and quality improvement interventions according to defined standards, training and mentorship activities, referral rate, retention, barriers and facilitators to care, patient and provider experiences, and patient health, nutritional, and developmental outcomes. These data will be used to monitor impact of PDC on patient outcomes as well as continuous quality improvement of the model, such as the introduction of the new mHealth application to improve quality of growth monitoring. As appropriate, bivariate and multivariate analyses will be used. Qualitative analysis will use thematic coding.

Aim 5. 1. Descriptive analyses to evaluate the implementation of interventions to promote breastfeeding from as early as day one of life among newborns in the referring hospital neonatal units will focus on analysis of exclusive breastfeeding rates and proportion of newborns requiring formula pre-post quality improvement interventions.

4. Study Limitations

Pre-PDC Phase One:

1. Data is based on caregiver report and therefore subject to recall bias of the caretakers.
2. The high-risk infants who were hospitalized in the neonatal unit were not from one specific sector. The Rwinkwavu Neonatal unit serves as a referral center for the Southern Kayonza district. Each of the sectors within the district may not be environmentally identical. Specifically the availability of food, amount of rain and distance to health centers are factors that could influence the outcomes of the high-risk neonates and therefore could result in residual confounding.
3. The gestational age and birth weight are subject to misclassification.
4. This is cross sectional data, and therefore any associations found are unable to assess causality.
5. Exclusion criteria undiagnosed by register are subject to misclassification.

Post-PDC Phase Two:

1. This study will be a cross-sectional study, and therefore associations may be found, but we will be unable to assess causality.
2. For the Aim 4b comparing PDC participants and UNICEF sample, only similar age groups will be compared; therefore, the number of children may be reduced which might affect the power of the study and its external validity.
3. As this is a secondary dataset analysis, missing values are expected.
4. The gestational age and adjusted age are subject to misclassification due to recall bias.

Expanding-PDC Phase Three:

1. As this is primarily a secondary dataset analysis of routinely collected data, missing values are expected.

5. Ethical Considerations

5.1. Risks and discomforts

Breach of confidentiality is a potential risk. Section 6.3 illustrates how we will address this.

5.2. Potential benefits

Pre-PDC Phase One:

This study offers potential direct benefits to the patients participating in the study, as patients identified with medical or nutritional abnormalities will be referred to appropriate services (in addition to future enrollment in the Pediatric Development Clinic if applicable). Participation offers the indirect benefit of providing key insights into creation of a patient-centered Pediatric Development Clinic.

Post-PDC Phase Two:

There are no direct benefits to the patients included in the study. However, there are indirect benefits as the study will allow us to better understand the services provided, medical, nutritional, developmental, and social needs of the patients enrolled in PDC, the quality of care delivered in the clinic, and therefore be used to improve services to the overall PDC patient

population. In addition, the study sample consists primarily of PDC patients who are benefiting from the PDC intervention, including the provision of essential social supports such as food packages for eligible patients.

Expanding-PDC Phase Three:

There are no direct benefits to the patients included in the study. However, there are indirect benefits as the study will allow us to better understand the services provided, medical, nutritional, developmental, and social needs of the patients enrolled in PDC, the quality of care delivered in the clinic, and therefore be used to improve services to the overall PDC patient population. In addition, the study sample consists primarily of PDC patients who are benefiting from the PDC intervention, including the provision of essential social supports such as food packages for eligible patients.

5.3. Confidentiality

Data will be stored securely and entered into a de-identified, password protected database with access limited to the investigative group. EMR data is only accessible to MOH care providers, approved PIH/IMB staff members working with the EMR, as well as study staff. Paper records (consent forms and any paper-based data collection) will be stored in a locked cabinet and destroyed after two years. Patient identifiers, such as names, will be removed from final research databases.

5.4. Informed consent

Pre-PDC Phase One:

A written consent form will be administered to all caregivers by the data collection officer. Participants will be informed that their decision to participate or to not participate will have no effect on the medical care that they receive from their community cell supervisor or health centers. The participant may stop the data collection at any point. The data collectors selected to collect the data will be compensated for their time irrespective of the forms completed in order to prevent any coercion to participate.

Post-PDC Phase Two:

Aim 3 will be using routinely collected data and analysis of existing datasets consent will be obtained. The existing datasets for comparison groups identified in Study Aim 4a and 4b were both conducted, as household surveys where caregivers provided written informed consent. In addition, patients contacted in Aim 4 for household data collection will complete informed consent for themselves and their child.

Expanding-PDC Phase Three:

All children enrolled in the PDC, and their caregivers, are eligible and the study will primarily use routinely collected data. When routinely collected data is being used, we will not conduct additional informed consent. Any PDC provider who participates in the study will provide written informed consent. Any caregiver who participates in non-routine data collection (qualitative evaluation components or household interviews), will provide written informed consent for themselves and their child.

5. Ethical approval

Ethical approval will be obtained from the Rwanda National Ethics Committee and Boston Children's Hospital (BCH) Institutional Review Board. Technical approval will be sought from Inshuti Mu Buzima Research Committee and Rwanda National Health Research Committee.

6. Logistics

6.1. Distribution of responsibilities

Mutaganzwa Christine, MD: Overall study supervision, input on study design, data collection oversight, ASQ scoring, data analysis and interpretation, manuscript writing and review. Partners In Health, 10%.

Catherine Kirk, MPH: Overall study supervision, input on study design, data collection supervision, data analysis, data interpretation, manuscript writing and review and mentorship of junior researchers on the PDC team. Partners In Health, 5% time.

Hema Magge MD, MS: Input on study design, data collection oversight, review of data analysis and interpretation, manuscript writing and review. Boston Children's Hospital, 2.5% time.

Merab Nyishime: Input on study design, oversight of eligibility determination and sampling strategy, data interpretation, manuscript writing and review. Partners In Health, 2.5% time.

Fulgence Nkikabahizi, MD: MOH study supervisor, data collection supervision, data interpretation, Manuscript preparation and review. Rwanda Ministry of Health 2.5%

Eric Ngabireyimana, MD: Input on study design, data interpretation and manuscript review. Manuscript preparation and review. Rwanda Ministry of Health 2.5%

Olivier Bigirumwami: Input on study design, data interpretation and manuscript review. Manuscript preparation and review. Rwanda Ministry of Health 2.5%

Kim Wilson, MD: Input on study design, data interpretation, and manuscript preparation. Boston Children's Hospital, 2.5% time

Ann Miller, PhD, MPH: Input on study design, data analysis and interpretation, manuscript writing and review, and mentorship of junior researchers on the PDC team. Harvard Medical School, 2.5% time.

Francois Biziyaremye: Input on study design, data analysis and interpretation, manuscript writing and review. Partners In Health, 2.5% time.

Scheilla Bayitondere, MD: Input on study design, data analysis and interpretation, manuscript writing and review. Ministry of Health, 2.5% time.

Jessica Bradford, MD: Input on study design, data analysis and interpretation, manuscript writing and review. Partners In Health, 2.5% time.

Kathryn Beck, RD, MPH: Input on study design, data analysis and interpretation, manuscript writing and review. Partners In Health, 2.5% time.

Emery Kwizera, MD: Input on study design, data analysis and interpretation, manuscript writing and review. Ministry of Health, 2.5% time.

Silas Havugarurema: Input on study design, data analysis and interpretation, manuscript writing and review. Ministry of Health, 2.5% time.

Patient Ngamije, MD: Input on study design, data interpretation, and manuscript review. Ministry of Health, 2.5% time.

Alphonse Nshimyiryo: Input on study design, leading all data analysis and interpretation, manuscript writing and review. Partners In Health, 25% time.

Chiquita Palha De Souza, MD: Input on study design, data analysis and interpretation, manuscript writing and review. Partners In Health and Austin Children's Hospital, 2.5% time.

Ryan McBain, ScD: Input on study design, advisor for data analysis, manuscript writing and review. Partners In Health and Austin Children's Hospital, 2.5% time.

6.2. Timeline

Pre-PDC Phase One

Period (months) Activities	Oct - Nov 2013	Dec '13- Jul '15	Nov - Dec 2015	Jan - Feb 2015	Mar - May 2015
IMBRC/NHRC/MOH/Hospital approvals					
Data collection and entry					
Data analysis and interpretation of results					
Preparation of manuscript					
Paper submission for publication					

Post-PDC Phase Two

Period (months) Activities	Jun - Jul 2015	Aug - Oct 2015	Nov- Dec 2015	Jan - Feb 2016	Mar - May 2016
Protocol amendment					
Data extraction for the aim 3					
Data extraction for the aim 4					
Data analysis and interpretation of results					
Preparation of manuscript					
Paper submission for publication					

Expanding-PDC Phase Three:

Period (months) Activities	October 2016	Nov- Dec 2016	Jan-Jun 2017	Jul-Dec 2017	2018 and on
Protocol amendment					
First expansion of PDC to Kirehe Health Centers					
Routine data extraction for aim 5					
Household data collection for aim 5					
Data analysis and interpretation of results					
Preparation of manuscript(s)					

6.3. Budget

Pre-PDC Phase One

Activity	Unit Cost (RWF)	Total number	Total cost (RWF)
RNEC Application	850,000	1	850,000
NHRC Application	195,000	1	195,000
Data Collectors meals (breakfast, dinner)/15 days		1	500,000
Community Health Workers airtime		1	150,000
Incentives for Study participants	150	120	180,000
Equipments for anthropometric measures	-	-	45,000
Miscellaneous (printing/photocopying,..)	-	-	140,000
Data entry and analysis In kind	-	-	0
Total Budget for Phase One			2,060,000

Post PDC Phase Two

Activity	Unit Cost (RWF)	Unit Number	Total cost (RWF)
RNEC Application	425,000	1	425,000
Data entry In kind	-	-	0
Data analysis In kind	-	-	0
Paper submission fee	72,000	1	72,000
Total Budget for Phase Two			497,000
Total Budget for PDC Study (Phases One and Two)			**2,557,000**

Expanding-PDC Phase Three

Activity	Unit Cost (RWF)	Unit Number	Total cost (RWF)
RNEC Application	425,000	1	425,000
Data entry/collection	340,972	24	8,183,320
Data analysis	112,575	24	2,701,809
Total Budget for Phase Three			11,310,129
Total Budget for PDC Study (Phases One, Two, and Three)			**15,927,120**

Acronyms

1. ASQ: Ages and Stages Questionnaire
2. BCH: Boston Children's Hospital
3. BWH: Brigham and Women's Hospital
4. FSI: Family Strengthening Intervention
5. IMB: Inshuti Mu Buzima
6. IMBRC: Inshuti Mu Buzima Research Commitee
7. IRB: Institutional Review Board
8. MD: Medical Doctor
9. MOH: Ministry of Health
10. MS: Masters of Science
11. NCD: Non Communicable Diseases
12. NHRC: National Health Research Committee
13. PIH: Partners In Health
14. RNEC: Rwanda National Ethics Committee
15. U.S: United States

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Approved by Rwanda National Ethics Committee, 9 September 2017

Appendix A: Household Data Collection Tools

Previously Approved tools include:

- Informed Consent form for study Aim 4
- Early Childhood Development Survey for study Aim 4

New tools include:

- Informed consent form for study Aim 5
- Developmental screening tools for study Aim 5

Appendix B: New Tools Phase 3

New tools include:

- New/revised medical record forms for the PDC
- Neonatal Unit Register
- Breastfeeding quality improvement project data tracker
- Guide for Monitoring Child Development
- Qualitative interview guides and consents

Appendix C: CVs of New Investigators

- Alphonse Nshimyiryo, Partners In Heatlh
- Chiquita Palha de Sousa, MD, Boston Children's Hospital Global Pediatrics Fellow
- Ryan McBain, ScD, Partners In Health

Approved by Rwanda National Ethics Committee, 9 September 2017

Appendix D: Prior RNEC Approvals

Appendix E: Payment Receipt for August RNEC Review

Appendix F: Previously Approved Study Tools

Previously approved study tools that are still in use in the PDC program are included here. These include routine Pediatric Development Clinic Medical Record forms, a mentorship checklist, and the Ages and Stages Questionnaires administered starting at age 6 months in the clinic.