SALT Protocol
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Partnering with Parents for Pumping Success: Feasibility of Personalized Lactation Support Utilizing Point-of-Care Human Milk Biomarkers

(short title: Sodium Awareness in Lactation Trial [SALT])

Principal Investigator:
Samantha Anthony SW PhD
PGCRL
Room 6.9710, 666 Bay St., Toronto, M5G 0A4
Samantha.anthony@sickkids.ca
416-813-7654 x 303126

Additional Investigators:
Rebecca Hoban MD MPH
Seattle Children's Hospital, Division of Neonatology
4800 Sand Point Way NE
Seattle, WA 98105, USA
Rebecca.hoban@seattlechildrens.org

Sharon Unger MD
Mount Sinai Hospital, Department of Paediatrics
600 University Ave., Toronto, M5G 1X5
Sharon.unger@sinaihealth.ca
416-586-8593

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Table of Contents

STATEMENT OF COMPLIANCE 1
1 PROTOCOL SUMMARY 2
1.1 Synopsis 2
1.2 Schema 3
1.3 Schedule of Activities (SoA) 3
2 INTRODUCTION 4
2.1 Study Rationale 4
2.2 Background 5
2.3 Risk/Benefit Assessment 6
3 OBJECTIVES AND ENDPOINTS 6
4 STUDY DESIGN 7
4.1 Overall Design 7
4.2 Scientific Rationale for Study Design 8
4.3 End of Study Definition 8
5 STUDY POPULATION 8
5.1 Inclusion Criteria 8
5.2 Exclusion Criteria 8
5.3 Screen Failures 9
5.4 Strategies for Recruitment and Retention 9
6 STUDY INTERVENTION 10
6.1 Study Intervention(s) Administration 10
6.1.1 Study Intervention Description 10
6.2 Study Intervention Compliance 11
7 DISCONTINUATION and WITHDRAWAL 11
7.1 Discontinuation of Study Intervention 11
7.2 Participant Discontinuation/Withdrawal from the Study 11
7.3 Lost to Follow-Up 12
8 STUDY ASSESSMENTS AND PROCEDURES 12
8.1 Assessments 12
8.2 Adverse Events and Serious Adverse Events 13
8.2.1 Definition of Adverse Events (AE) 13
8.2.2 Definition of Serious Adverse Events (SAE) 13
8.2.3 Classification of an Adverse Event 13
8.2.4 Time Period and Frequency for Event Assessment and Follow-Up 14
8.2.5 Adverse Event Reporting 14
8.2.6 Serious Adverse Event Reporting 15
8.2.7 Reporting Events to Participants 15
9 STATISTICAL CONSIDERATIONS 15
9.1 Statistical Hypotheses 15
9.2 Sample Size Determination 15
9.3 Populations for Analyses 15
9.4 Statistical Analyses 16
9.4.1 General Approach 16
9.4.2 Analysis of the Primary Endpoint(s) 16
9.4.3 Analysis of the Secondary Endpoint(s) 16
9.4.4 Baseline Descriptive Statistics 17

9.4.5 Sub Group Analyses 17
9.4.6 Tabulation of Individual Participant Data 17
9.4.7 Exploratory Analyses 17
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 17
10.1 Regulatory, Ethical, and Study Oversight Considerations 17
10.1.1 Study Discontinuation and Closure 18
10.1.2 Future Use of Stored Specimens and Data 18
10.1.3 Key Roles and Study Governance 18
10.1.4 Safety Oversight 18
10.1.5 Data Handling and Record Keeping 19
10.1.6 Protocol Deviations 20
10.1.7 Conflict of Interest Policy 20
10.2 Abbreviations 20
11 REFERENCES 20

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with this protocol, International Council on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Research Ethics Board (REB), except where necessary to eliminate (an) immediate hazard(s) to the trial participants.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented to the study. All changes to the consent form will be REB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Name of Principal Investigator (Print): __Samantha Anthony PhD_____

Signature of Principal Investigator: _____ Date: _____ 2023
<DD Month YYYY>

Site Addresses
The Hospital for Sick Children, Division of Neonatology
555 University Ave., Toronto, M5G 1X8
Canada

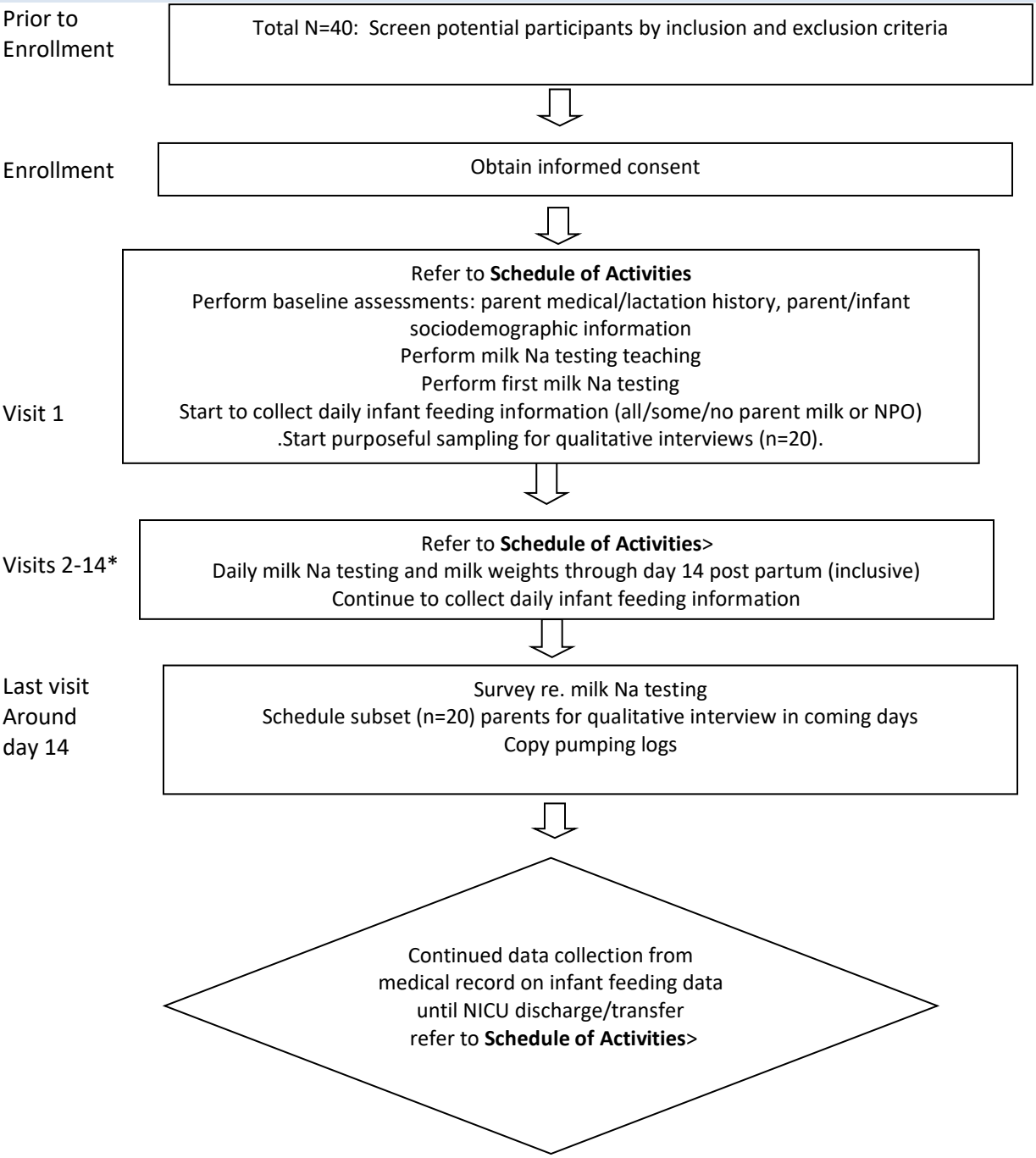
University of Washington Medical Center
1959 NE Pacific St
Seattle, WA 98195
USA

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Partnering with Parents for Pumping Success: Feasibility of Personalized Lactation Support Utilizing Point-of-Care Human Milk Biomarkers Short title: Sodium Awareness in Lactation Trial [SALT])
Study Description:	Data-driven interventions to improve early lactation success are lacking, and parents who deliver preterm are at high risk of lactation challenges. SALT is a multi-centre, non-blinded, non-randomized prospective interventional pilot study. We will be studying feasibility, acceptability, and time cost of teaching lactating parents of hospitalized preterm infants how to test their breastmilk sodium (Na) using point-of-care (POC) meters. As a secondary aim, we will assess the potential to use these POC sodium results to guide personalized lactation care in the form of altered pumping schedules in an attempt to reduce breastmilk Na. A drop in Na is a sign of secretory activation in the breast that is associated with adequate short and long-term breast milk volumes in this vulnerable population.
Objectives:	Primary Objective: Establish feasibility and acceptance of parent-led longitudinal parent milk Na testing in the first 14 days postpartum Secondary Objective: Further investigate relationships between pumping behaviours, lactation risk factors, daily PM Na and lactation outcomes Exploratory Objective: Explore how POC Na data may be used to modify pumping behaviour and milk volumes;
Endpoints:	Primary Endpoints: Ease and time cost of teaching and performing milk Na testing for parents; Parent perceptions of performing and interpreting milk Na measurements: balancing empowerment and stress Secondary Endpoint: Confirmation of previously utilized Na cut-offs with “coming to volume” (pumping at least 500mL/day) in this population; relationships between pumping behaviours and longitudinal Na changes Exploratory Endpoints: Longitudinal changes in Na with changes in pumping and determinations if parents have followed pumping advice
Study Population:	Pump dependent, lactating parents of viable preterm infants born <35 weeks gestation admitted to study NICU with an expected length of stay of at least 2 weeks.
Description of Study Intervention:	Parents will learn to use a commercially available sodium analyzer for the novel use of point-of-care sodium testing. If sodium levels are abnormal, pumping recommendations will be given in an attempt to modify sodium.
Study Duration:	12 months
Participant Duration:	Active participation/intervention: first 14 days post delivery Passive data collection: until infant NICU discharge or transfer from study NICU

1.2 SCHEMA



*actual # will depend on day of enrollment; milk Na testing ends on day 14 post-partum

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening	Enrollment/Baseline Day 1	Day 2-13	Day 14	Day 15 through NICU discharge
Informed consent	X				
Demographics (race/ethnicity, infant gestational age, etc)	X				
Parent medical/lactation history	X				
Parent milk sodium teaching		X	*	*	
Lactation consultation (standard of care)	X	X	*	*	*
Milk collection (1 drop) for Na testing		X	X	X	
Record time required for milk testing/teaching		X	X*	X*	
Weighing of all pumped milk		X	X	X	
Milk pumping log/record (recommended standard of care)		X	X	X	
Survey**				X	
Interview**				***	
Infant milk/feeding data collected		X	X	X	X

*as needed (for time records, depending on variation in initial sampling, may discontinue for remainder of subjects) ; ** around day 14- flexible; *** subset of parents

2 INTRODUCTION

2.1 STUDY RATIONALE

In Canada, 8% of births are preterm, with limits of viability continuing to decrease. Thus, strategies to reduce risks of potentially preventable complications of prematurity are a Canadian priority. Parent's milk (PM) is the only "medicine" that reduces necrotizing enterocolitis, chronic lung disease, sepsis, retinopathy of prematurity, and neonatal intensive care unit (NICU) length of stay, while improving chronic disease rates that are costly to families and society, like obesity and asthma. It does so in a dose-response manner, with even a 10% increase in NICU PM dose showing clinically significant effects and cost effectiveness; 50% of total feeds as PM during the first month of NICU admission has been shown to be a critical threshold to further reduce risks. Further, Dr Johnson, a grant collaborator, found that every mL/kg/day of PM in the first 14 days of life reduced NICU costs by US$534. For a very preterm infant, this translates to cost savings with an increased PM dose of even 1.5-2mL of milk a day! When PM is unavailable, the substitute for preterm infants is pasteurized donor milk, which lacks the

personalized nutritional and bioactive components of PM and carries far fewer benefits. Therefore, there is no substitute for high-dose PM, with an urgent need for lactation strategies to improve PM dose in this vulnerable population. Given that infant feeding requirements are uncoupled from lactation in pump-dependent parents of NICU infants, and the typical supply and demand mechanisms of breastfeeding/chestfeeding are absent, parents must rely on guidance from medical and lactation professionals to initiate lactation with an artificial pump. Lactating parents have a time-limited opportunity to 'program the breasts' for the higher volume PM production that will eventually be required by the growing infant. We know that achieving a threshold PM supply in the first two weeks postpartum, specifically CTV (making 500mL/day PM by day 14), is critical to predicting continued lactation through to NICU discharge.

Unfortunately, individualized protocols to optimize breast programming do not exist, with little evidence to assist pump-dependent parents who struggle with low volumes other than 'pump more. Importantly, recognition of low volumes does not occur in real-time, but retrospectively when PM volumes fail to increase as expected by 1-2 weeks postpartum and parents do not CTV. In addition, for new NICU parents, who may be experiencing stress due to their infant's illness and recovering from delivery themselves, 'pump more', especially when advised after this initial 2-week period, may not initially result in real-time visible PM volume changes, making parental motivation to continue pumping challenging. Instead, parents should be encouraged to 'pump smarter' with personalized, data-driven, real-time lactation care that could predict or diagnose concerns in near real time before they are clinically apparent (ie., before the lactating parent fails to achieve CTV) and still be potentially physiologically modifiable, an actionable opportunity to increase parent motivation. The use of point-of-care (POC) PM Na to help parents 'pump smarter' is an opportunity to optimize lactation care to attempt to increase PM dose. Increased PM dose directly improves short and long-term outcomes to reduce racial disparities in health for preterm infants and their families.

2.2 BACKGROUND

Parents of preterm NICU infants initiate lactation at rates that approach those for healthy populations. However, these rates are not sustained through to NICU discharge and beyond.[1-3]. Insufficient PM volume is cited as the primary reason, preventing parents from following evidence-based recommendations for a minimum of 6 months of lactation [1,3-5] to optimize health outcomes for all infants. Strategies to address insufficient PM must start at birth, but preterm delivery is associated with morbidities including pre-eclampsia, diabetes, obesity, and mammary gland underdevelopment, which are independently linked with lactation difficulties in term populations [1,6]. Pump dependency for lactation initiation further increases risk [1,3]. Due to a higher burden of medical morbidities, combined with socioeconomic challenges and effects of systemic racism like chronic stress and decreased access to quality care, parents of colour are more likely to deliver preterm and less likely to provide PM [2,7,8], further exacerbating disparities in health outcomes. Although breast 'programming' that facilitates long-term lactation occurs in the first days postpartum, insufficient PM supply is often diagnosed weeks later when preterm infant requirements increase as they grow. By this time, problems are no longer physiologically actionable, reducing PM dose [1,3] and placing preterm infants at risk.

PM biomarkers, such as sodium (Na), change longitudinally in the first days postpartum as the breast ideally undergoes secretory activation (SA), a critical phase required for long-term lactation.[1,9-12]. Some, but not all lactating parents, subjectively feel SA as 'milk coming in', but this is not universal and these subjective breast sensations have not been proven to accurately time SA [1,12]. Trends of pumped PM volumes, which require accurate data collection, have been used to estimate SA, but measured PM volume assesses both milk production and removal, and is therefore an indirect measure of SA subject to error [12]. PM biomarkers, in contrast, provide an objective, real-time assessment of SA.

Research has demonstrated potential for point-of-care (POC) measures to identify impaired SA using ion selective electrodes with comparable accuracy to laboratory-based spectrometry[13]. Although POC PM Na has never been done by parents, parent-led testing in the NICU has been championed by the PI's mentor, Dr. Meier, for milk fat (creamatocrit) and breastfeeding intake (test weights). Testing was accurate, valued by parents, and saved staff time[14,15]. As milk Na should dramatically fall in the first days postpartum as SA approaches, we can utilize Na level as an early "upstream marker" of PM volumes. Our previous work has shown that Na cutoffs could predict and dichotomize parents into 'at risk' vs 'not at risk' of not achieving CTV (making at least 500mL/day of PM by postpartum day 14) as early as day 3, well before clinicians would raise concern for low PM volumes[9-12]. We shown that CTV correlates with longer-term PM provision weeks to months later at NICU discharge [9,16]. In addition, these biomarkers change in near real-time with modifications in pumping behaviour, making them a target for personalized, data-driven lactation care that could increase PM supply, care which is lacking in this high-risk, often racialized preterm population[11].

2.3 RISK/BENEFIT ASSESSMENT

We don't expect any risks or harms of the study. As bedside PM Na testing has never been done by parents before, it is possible some parents might find testing their milk or finding out the results stressful. If they find knowing the Na value stressful (aka if Na levels are not going down), they can chose for the research coordinator to assist in testing and for the parent to be blinded to the number itself and/or interpretation of these data. If they find the testing itself stressful, we will offer less frequent testing (aka not daily) or there is always the option to drop out of the testing portion of the study. Since it is a feasibility and acceptability trial, knowledge of challenges that parents face will be critical and we will take them very seriously. Parent representatives are involved in pre-trial discussions/final design and will continue to follow during the trial; enrolled parents will be encouraged to share any concerns with the study team and/or take the survey about study acceptability.

It is possible that the study could have benefits - changing pumping schedules based on PM Na might help milk supply if the parent is having challenges with supply but we are not sure. Although all parents receive lactation support in the NICU, parents in this study will have daily check ins regarding lactation with the research coordinator, so this additional support may also be helpful. Even if parents in the study don't directly benefit, we hope that the information learned from this study can be used in the future to benefit other pumping parents who deliver preterm (and help their infants to get more milk). Given that there are minimal risks and there are potential benefit to the individual as well as society, the value of the information gained outweighs any risks of participation.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Establish feasibility and acceptance of parent-led longitudinal PM Na testing in the first 14 days postpartum in this pilot study	Ease and time cost of teaching and performing milk Na testing for parents Parent perceptions of performing and interpreting milk Na measurements: balancing empowerment and stress (surveys and in a subset, qualitative interviews)	Point of care Na testing has never been done by pumping parents. We have previously successfully recruited for lab-based PM testing in which samples were not analyzed in real time and not shared with participants, but for future powered intervention studies, we would need to show that

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		parents are willing and able to participate in POC NA testing.
Secondary		
Investigate relationships between pumping behaviours, lactation risk factors, daily PM Na and lactation outcomes	Confirmation of previously utilized Na cut-offs with "coming to volume" (pumping at least 500mL/day) in this unique Canadian population; relationships between pumping behaviours and longitudinal Na changes. This is first study of this kind in Canada; previous PM Na/biomarker studies have primarily focused on African American and Caucasian American populations.	Worldwide, only a few hundred pumping parents of preterm infants have any PM Na or biomarker data in addition to detailed lactational risk factors and pumping records. We are currently working with other research groups to collate these few cohorts, and with data transfer agreements would add this study to this database. To add to these very limited data will help design and power future studies.
Exploratory		
Explore how POC Na data may be used to modify pumping behaviour and milk volumes.	Explore in parents with high PM Na the Longitudinal changes in Na with changes in pumping and determinations if parents have followed pumping advice	PM Na has never been used in real time to attempt to drive lactation care. We will explore this outcome to plan for future RCTs.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This prospective, non-randomized feasibility study will collect longitudinal PM data for the first 14 days postpartum from 40 parents of preterm infants born <35 weeks gestation from a diverse cohort. In this 1-year study**,** using mixed methods we will utilize parent-driven approaches to develop tools to educate and support parents to collect, measure, and interpret daily POC PM Na – our primary outcome is to explore feasibility and acceptability of this approach. This feasibility study will not have a control arm, and all parents will have access to standard of care lactation support. Barriers and facilitators of parent POC testing will be detailed by surveys with a subset (n=20) undergoing structured qualitative interviews; time costs for parents and staff will be collected. As secondary outcomes, daily Na levels will be compared to published levels.

As an exploratory intervention, we will utilize these Na levels suggest modifications in pumping behaviours, and follow subsequent Na levels and PM volumes. We will also measure pumped PM volumes, record pumping information (which is recommended as standard of care), and collect lactation risk factors to assess how PM Na is associated with these parameters, as well as add to existing data sets in pump-dependent parents of preterm infants to study larger populations. Our hypothesis is that postpartum parents of preterm infants are capable of using POC Na devices and will find this use, interpretation of results, and use of these results to suggest pumping modifications acceptable.

To avoid bias, we will utilize a prospective trial design, with quantitative and qualitative components both occurring at the time of active study involvement. We will attempt to control for known confounders of lactation (which we will collect) during statistical analysis, although we will have a small, unpowered "n" for this exploratory study, so our ability to do so will be limited.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a non-randomized pilot study without a control group. Point of care Na testing has never been done before in real time nor by a patient, so we need to first gather feasibility and acceptability data prior to larger powered trials.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in **Section 1.3, Schedule of Activities (SoA)**. The active duration of participation for each individual participant who completes all study visits will be 2 weeks. Data collection on infant feeding will continue via utilization of the electronic medical clinical records (without any need for additional parent/subject involvement) until infant NICU discharge or transfer.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally. It is estimated that it will take 9 months from when the study opens to enrollment until the end of the study.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Consent provided
2. Have delivered a preterm singleton or twin infant at <35 weeks gestation admitted to a study NICU at birth or transferred into a study NICU from another NICU within the first 72 hours postpartum
3. Day 5 or less postpartum (Day 1 = day of delivery) upon enrollment (ideally day 3 or less)
4. Plans to lactate at least 2 weeks and initiate lactation with a breast pump
5. Expected infant NICU stay of 7+ (ideally 14+) days in enrollment NICU(s)

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Potential study participant's infant is critically ill and not expected to survive or has lethal diagnosis with plans by medical team/family to redirect care
2. Has delivered triplets or higher order multiples (potential confounder for lactation challenges; of note, triplets or higher are rare, on the order of a few parents annually at all sites)
3. Lactation contraindication(s) (i.e., active chemotherapy) or declines lactation initiation
4. History of breast surgery that may affect ability to lactate (i.e., breast reduction; breast augmentation that utilized nipple incisions)
5. Using or planning to use hormonal birth control in the first 14 days post-partum as may affect secretory activation/lactation

6. Unable/unwilling to be present in study NICU during any of first 5 days postpartum
7. Presumption by the medical team that infant will be in study NICU for <5 days

5.3 SCREEN FAILURES

Screen failures are defined as participants who would be eligible to participate in the clinical trial but are not subsequently approached for consent in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography, screen failure details and eligibility criteria.

Individuals who do not initially meet the criteria for participation in this trial because of an unclear infant prognosis (ie considering redirection of care) or an unclear plan for lactation (ie still deciding on whether to initiate lactation) may be rescreened after 2 days to a maximum of 1 time. Rescreened participants should be assigned the same participant number as for the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Prior to study launch, all study materials and planned recruitment strategies will be discussed with parent advisors to ensure acceptability with a vulnerable post-partum populations. Participants will be recruited from parents of inpatient infants of the main perinatal center in urban Seattle, Washington, USA, as the original PI of the study, Dr Rebecca Hoban, has transferred her appointment to this institution, and is key for performing the daily study activities involving milk Na testing. NICU admissions will be screened daily for eligible infant-parent dyads. If a site has multiple active prospective studies in the same target population, a plan will be set in place a priori regarding allotment of study patients to prevent parents from being approached for multiple studies, although unlike this study, the majority of NICU studies would primarily involve the infants, not the parents. Potential participants will first be approached by someone in their circle of care to give them an informational letter and ask permission for the study team to approach them to learn more about the study.

All participants will be biologic women as they will be postpartum and lactating; we will use gender inclusive language such as parent milk that would apply to all regardless of gender identity. Ideally, we would have a study population representative of Seattle's diverse population and specifically include racialized populations as well as low socioeconomic status patients – to assist in this pursuit we will perform purposeful sampling for race/ethnicity, socioeconomic status (utilizing Medicaid status as a proxy for mean household income), and factors that we a priori determine are important for acceptability such as primiparity/multiparity. Our goal is to have racialized and/or lower resourced families as at least 30% of our enrollees.

We hope to recruit approximately 6 parents/month for a total of 40; additional participants may be recruited if we have subjects drop out prior to providing at least 2 PM Na sample and/or there are participants who do not have at least 2 days of usable data for other reasons (repeat maternal hospitalization, etc).

If patients are set to be transferred to a community hospital prior to day 14, we will discuss potential for continued study participation using home PM Na testing, with the parent bringing the analyzer home and keeping records at home (ideally using REDCap links), with study coordinator phone follow-up. We would utilize a courier to return the analyzer (and provide the end of study gift cards) after day 14.

To encourage compliance with daily Na testing and daily NICU visitation through day 14 postpartum, we will provide transport/travel reimbursement/incentives of US$12/day for 10 days (total $120/subject with $60 given after 7 days and the final $60 at study completion in the form of gift cards). It is presumed that most parents would visit nearly daily in the first days/weeks of infant's life regardless of study participation and the parents will be inpatient typically for 2-3 days postpartum and would visit the NICU while still inpatient, hence the 10 days of travel support.

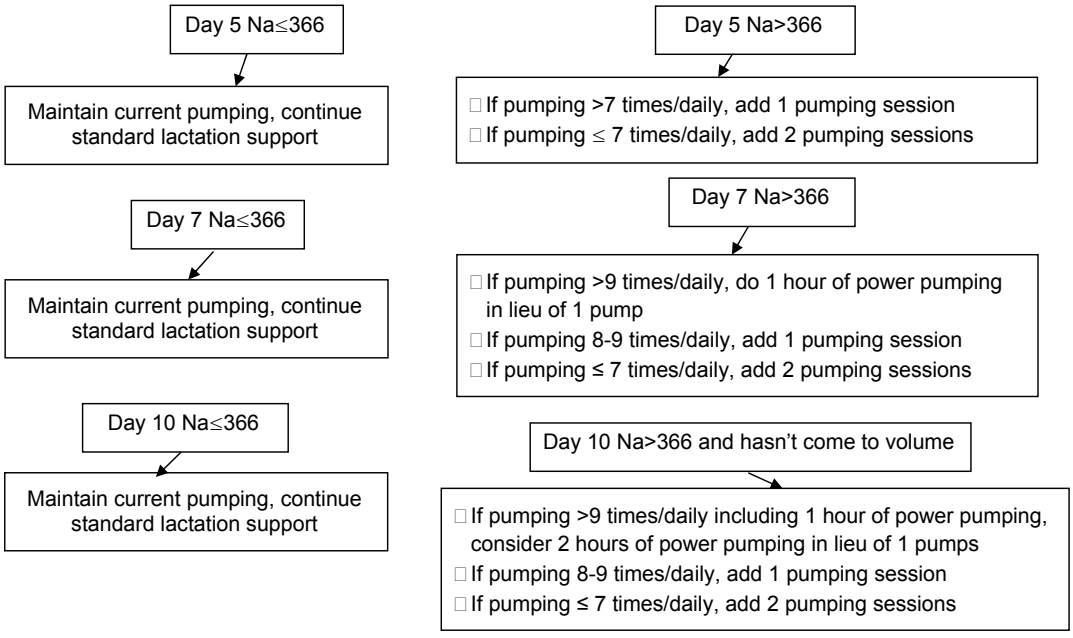
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Once daily for the first 14 days postpartum, when visiting the NICU, parents will pump as usual with a double electric pump (preferably the hospital pump). After pumping, using a sterile enteral syringe, a drop of PM will be removed from the pumping container prior to sending the milk for infant feeds. After parent teaching by study staff, this drop of milk will be placed on a sodium sensor at the bedside and the output recorded. The Na sensor, the Horiba Compact Sodium Ion Meter (Horiba, Japan), is a commercially available product that can be used for any fluid and has been validated with breastmilk. Of note, this is a general sodium analyzer (can be used to analyze any fluid, from foods to liquids in the environment to biologic/human samples), not specifically a healthcare product, so does not have a Health Canada number. This drop of milk will then be discarded. The sensor will be calibrated and cleaned per the company's product recommendations. PM Na norms, taken from term literature, will be used to dichotomize parents by postpartum day 5 into low and high-risk categories for later not CTV by day 14.

In this initial pilot study, parents whose PM Na level is 'high risk' on postpartum day 5 (>366ppm, converted from the >16mM used in the literature), typically prior to clinically relevant low POM volumes are noted, will have their pumping assessed by lactation consultants to ensure no concerns with suction, flange fit, or pump operation. If parents are open to modifying pumping based on PM Na 'risk', this will be noted, and we will start an optimization protocol based on recommendations for pumping at least 8x/daily, as well as utilizing a 'power pumping' strategy, in which parents pump for 1 hour with breaks (pump 20 minutes, rest 10, pump 10, rest 10, pump 10).



We will follow and graph daily POC Na until postpartum day 14 to determine if Na starts to fall/normalize based on changes in pumping, and continue to modify pumping as above. In addition, we will record if parents have followed pumping advice (monitoring pumping logs that are standard of care and correlating with PM volumes brought to NICU). All milk brought to the NICU will also be weighed on scientific scales to determine exact volumes (with 1g =1mL PM). Milk weights will be performed by the

parents, study coordinator, bedside nurses, or the milk room, depending on the site and preference. Paper bedside study records will be utilized, although parents will have the option of using a secure REDCap link via email if they prefer an electronic option for pumping or other self-completed records. We will ask parents to note how long it takes to sample the milk. If the first 10-15 parents have very similar results, which we anticipate given the presumed ease of use of the meter, we may not continue this portion of the data collection for the entire sample to limit participant record burden.

Of note, it is possible that some parents might find receiving the PM Na results stressful (such as if the Na levels aren't decreasing). At study entrance, we can discuss parents' preferences about receiving results. Options include (a) parents perform the daily Na testing data and receive interpretation/trend information, (b) parents perform the daily testing but do not receive interpretation/trend information, (c) test in a "blinded" manner with the research coordinator doing the testing and not sharing interpretation. If parents find the testing or finding out results stressful, they can modify their decision re. receiving results and/or decide to stop testing at any time.

6.2 STUDY INTERVENTION COMPLIANCE

Participant milk pumping logs (recommended as standard of care) will be assessed during and at the end of the study to determine if those parents who were recommended to modify their pumping behaviour have recorded increased pumping sessions. As self report isn't always reliable, and parents may forget to record, we will also assess the more objective measure of daily PM output, weighed on a scientific scale.

7 DISCONTINUATION AND WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If parents find knowing the Na value stressful (aka if Na levels are not going down), they can chose for the research coordinator to assist in testing and for the parent to be blinded to the number itself and/or interpretation of these data. If they find the Na testing itself stressful, we will offer less frequent testing (aka not daily) or there is always the option to drop out of the testing portion of the study. Since it is a feasibility and acceptability trial, knowledge of challenges that parents face will be critical and we will take them very seriously. Parent representatives are involved in pre-trial discussions/final design and will continue to follow during the trial; enrolled parents will be encouraged to share any concerns with the study team and/or take the survey about study acceptability.

Discontinuation from PM Na testing does not mean discontinuation from the study, and remaining study procedures (survey, daily milk weighing though postpartum day 14, and infant feeding data through NICU discharge) should be completed if the participant is agreeable as indicated by the study protocol.

We do not anticipate any related serious adverse events (AEs) to PM testing, but if parents report significant stress and request to stop testing, that would be recorded as an AE and appropriate follow-up provided. With the exploratory aim of pumping interventions, it is recommended as standard of care to pump at a minimum of 8 times daily, with parents pumping up to 12 times a day to mimic a newborn's natural feeding schedule. Pumping and breastfeeding in the first days postpartum often results in nipple discomfort and potential breakdown/abrasions/bleeding that would be expected at baseline regardless of study participation, and would not be considered an AE.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Withdrawal of informed consent (participant withdrawal for any reason)
- If any clinical Adverse Event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Significant study intervention non-compliance or lack of visitation to the NICU in the first 5 days postpartum
- Initiation of prohibited concomitant medication(s) (aka hormonal birth control) that requires discontinuation of the study intervention
- Participant chooses to discontinue lactation/pumping
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to perform at least 2 PM Na tests (2 days of testing)

The reason for participant discontinuation or withdrawal from the study will be recorded in the study file. Participants who sign the informed consent form but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, may be replaced if we have subjects withdraw prior to providing at least 2 PM Na sample and/or there are participants who do not have at least 2 days of usable data for other reasons (repeat hospitalization, etc). The data collected up to the time a participant is withdrawn or discontinued from the study will be used in the analysis unless the participant requests otherwise.

7.3 LOST TO FOLLOW-UP

Loss to follow-up is anticipated to be minimal as the participants' infants are anticipated to be inpatients in the NICU for the duration of the study, hence parents typically would visit their infants. A participant will be considered lost to follow-up if (s)he fails to return for a second Na PM testing session after the initial training and is unable to be contacted by the study site staff by postpartum day 15.

The following actions must be taken if a participant fails to return to the NICU for a study visit:

- The site will attempt to contact the participant and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Principal Investigator or designee will make every effort to regain contact with the participant (3 telephone calls and/or emails if participant email address is on file with the NICU and we have permission to use it as well as discussion with the inpatient NICU medical team re. visitation). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ASSESSMENTS

As part of the study, at study entry, study staff will obtain initial medical and lactation history. They will then teach participants how to perform POC NA testing; study staff will record how long POC Na teaching/learning takes. On subsequent days, daily PM Na testing will be performed and recorded by the parents if they feel comfortable. The study staff will be available to ensure data are recorded properly, record the time testing takes, weigh all pumped milk brought to the NICU, and check pumping

records. Of note, keeping/checking pumping records and monitoring milk volumes is routine for lactation support in the NICU regardless of study participation. As previously noted, paper records will be the standard unless parents prefer a secure REDCap link emailed by the study coordinator. No PM samples will be kept/collected. If Na levels are not decreasing appropriately, parents will be counseled as to the exploratory aims of modifying pumping schedules, and adherence to this advice will be assessed when pumping records are looked at by the study team.

At the end of the active portion of the study, all participants will be asked to fill out a survey about their experience testing PM Na. A subset will also be asked (with compensation for their time) to participate in a qualitative interview done by the SickKids PI over a secure online platform.

Infant feeding outcomes (feeding parent's own milk none/any/all) will be collected during the active study (first 14 days) as well as at NICU discharge. If the infant is transferred out of the study NICU, we will ask parent permission to contact them around the time of expected discharge to follow up on infant's feeding status at time of discharge to home.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

We do not anticipate any related serious adverse events (AEs) to PM testing, but if parents report significant stress and request to stop testing, that would be recorded as an AE. With the exploratory aim of pumping interventions, it is recommended as standard of care to pump at a minimum of 8 times daily, with parents pumping up to 12 times a day to mimic a newborn's natural feeding schedule. Pumping and breastfeeding in the first days postpartum often results in nipple discomfort and potential breakdown/abrasions/bleeding that would be expected at baseline regardless of study participation, and would not be considered an AE or causal AE.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Given the trial content, we do not anticipate the possibility of any related serious adverse events. As stated above, in theory the PM testing could potentially be stressful in a vulnerable population. Postpartum depression/stress requiring medical/psychological assessment would be considered a SAE, although given the postpartum population, would be difficult to determine causality.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

The severity of an AE is assessed by a qualified physician who is part of the study team, who should use the following definitions when assessing the intensity of an AE:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All Adverse Events (AEs) must have their relationship to the study intervention assessed by a qualified physician who is part of the study team based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease. The response to discontinuation of the study intervention should be clinically plausible.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after the study intervention, is unlikely to be attributed to concurrent disease, and follows a clinically reasonable response on discontinuation.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- **Unlikely to be related** – A clinical event whose temporal relationship to study intervention makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after the study intervention) and in which underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Unrelated** – The AE is completely independent of study intervention, and/or evidence exists that the event is definitely related to another etiology.

8.2.3.3 EXPECTEDNESS

A qualified physician who is part of the study team will be responsible for determining whether an Adverse Event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All Adverse Events (AEs) or Serious Adverse Events (SAEs) with start dates occurring any time after the study intervention until 2 days (for non-serious AEs) or 7 days (for SAEs) after the last day of study intervention will be documented. The occurrence of an AE or SAE may be detected during spontaneously reported by the participant to the research team or elicited by appropriate questioning during clinical evaluations and/or the end of the study survey. At each study visit, the participant will be asked about any change in their health since the last visit and for any changes to AE and SAEs that were ongoing at the last visit.

All AEs and SAEs occurring while on study must be documented regardless of relationship. Information to be collected includes event description, date and time (if possible) of onset, date and time (if possible) of resolution/stabilization of the event, outcome, and the assessment of seriousness, expectedness, relationship to study intervention and severity by a delegated qualified physician. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

Events will be followed for outcome information until resolution or in the opinion of the PI or qualified physician delegate, the participant is stable and does not require further follow-up, or the participant is deemed lost to follow-up.

8.2.5 ADVERSE EVENT REPORTING

AE will be reported to the Clinical Trials Ontario Research Ethics Board according to The Hospital for Sick Children's Adverse Event Reporting requirements and as per local institutional and regulatory requirements at each site.

As stated above, breast/nipple discomfort with pumping/breastfeeding is common/expected in the study population and will not be reported per the standard process for reporting.

8.2.6 SERIOUS ADVERSE EVENT REPORTING

Adverse Events will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children's Adverse Event Reporting Requirements, as well as any applicable local institutional or regulatory regulations.

8.2.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be informed in a timely manner of any new information that is relevant to that participant's willingness to continue participation. The communication of this information will be documented through a revised REB approved Informed Consent Form, where possible, based on the timeliness of the information.

In the event that the study procedure detects a new clinically important secondary finding/incidental finding, which in this study could be asymptomatic mastitis (which in studies has been shown to be associated with an acute elevation in milk Na when it has previously been normal/low), the qualified physician will notify the participant's/NICU's lactation consultant to assess the participant. If there are any clinical concerns of mastitis, the patient would then, as per routine with mastitis, a common problem in the postpartum population, be encouraged to follow up with their primary doctor.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This is an unpowered pilot project with no comparison group.

- Primary Endpoint(s): Parent-performed PM Na testing will be feasible and acceptable in this pilot project that will not have a comparison group. Time costs will be collected and reported for planning for future studies but again will not have a comparison group. We will collect data from the first 10-15 parents on time data. If times are all very similar in this initial sampling, we may not continue for the entire sample to reduce participant burden.
- Secondary Endpoint(s): Parent milk Na cutoffs used in a Chicago/midwest populations will hold true in a Seattle/west coast population with a different racial/ethnic makeup and will be associated with CTV (coming to volume) in our population. Pumping behaviours will be associated with longitudinal Na changes and CTV.
- Exploratory Endpoint(s): Parents will not always follow pumping advice, but when they do we hypothesize that PM Na will drop/start to normalize.

9.2 SAMPLE SIZE DETERMINATION

This is an unpowered pilot project that will for the first time explore POC Na testing in the hands of parents. The sample size of 40 is a convenience sample determined by amount of funding, with the subset of 20 for qualitative interviews based on expert opinion by Dr Anthony, a co-I, of the number required to reach saturation.

9.3 POPULATIONS FOR ANALYSES

In this pilot study, the following study populations are defined and will be analyzed as specified below.

- Feasibility/acceptability population: all enrolled patients who completed at least one PM Na test and had adequate assessment of competence of doing so. A subpopulation will be studied with more detailed qualitative interviews. All enrolled patients who completed at least one PM Na test will also be included for descriptive analyses and associations between PM Na, milk volumes, and parental risk factors.
- Efficacy population: in this exploratory aim, all enrolled patients who received modified pumping instructions based on high PM Na will be included to study associations with declining Na

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

- For descriptive statistics, we will describe categorical data (such as primiparity vs multiparity) as n (percentage). For continuous data (such as gestational age), we will test for normality. Given the small n, data will likely be non-normal. We will then report means/standard deviations if normal or medians/interquartile ranges if non-normal.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

- Time cost of teaching and performing milk Na testing for parents
    - Means or medians of time required will be reported for initial as well as subsequent teaching (by study staff) as well as performing (by parents). Our health economist will then convert these time requirements to time costs using standard methods such as minimum wage equivalents.
- Parent perceptions of performing and interpreting milk Na measurements: balancing empowerment and stress
    - Survey results will be reported as n (percent) who agreed with each question, and a qualitative summary written about acceptability and feasibility
    - Qualitative interviews will be coded by qualitative specialists and described

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For each secondary endpoint:

- Confirmation of previously utilized Na cut-offs with “coming to volume” (CTV; pumping at least 500mL/day) in this new geographic population, given the paucity of data overall in the preterm population
    - We will dichotomize parents into “CTV” vs “didn’t CTV,” and compare between-group differences with Fisher exact test and t tests for normally distributed data or the Mann–Whitney U test for non-normally distributed data, assessing previously utilized Na cut-offs as well as comparing mean/median Na on various postpartum days. We will also make receiver operator characteristic curves for PM Na levels on specific days (such as day 3 and 5) and CTV to determine if in our unique population, if the areas under the curve are different than previously published cut-offs (aka Na <366ppm or <16mM as normal).
- Relationships between pumping behaviours, maternal risk factors, and longitudinal Na changes
    - We have studied both of these endpoints in different prospective cohorts in the past, and will use similar statistical analyses. To assess prediction of CTV, we will use

multivariable logistic regression with CTV achievement as the outcome variable, and add in maternal risk factors such as high BMI as well as day 5 Na. We will use pumping frequency as both a continuous variable as well as categorize it (such as, pumped on average at least 5x/daily in the first 5 days) based on previous literature, and assess how these pumping behaviours are associated with both rate of change of Na as well as achievement of Na cut-offs.

- As missing data are common for parent reported pumping data, we will also measure all pumped PM, which has the date/time of pumping recorded. Using these PM volume records with the associated pumping date/time, we can have an additional "source of truth" for pumping records and fill in missing pumping sessions.

9.4.4 BASELINE DESCRIPTIVE STATISTICS

Summary statistics will be used to describe baseline characteristics and other outcomes of interest such as CTV and provision of PM at NICU discharge. Categorical endpoints (such as survery results) will be summarized using proportions and frequencies. Continuous endpoints (such as time cost) will be summarized using the mean, median, range or standard deviations.

9.4.5 SUB GROUP ANALYSES

Given the small "n" in a group of soley biologic females who are immediately postpartum, this pilot project will not perform sub group analyses based on age or sex. Regression analyses will attempt in this small study to assess parental risk factors, but separate subgroup analyses will not be performed. We will attempt, however, in survey results and qualitative interviews, if we have enough parents of differing racial/ethnic groups and socioeconomic status, to break down responses by group, as we hypothesize that parent's response to this POC testing may differ by group. Given the small n, we do not anticipate this portion to be powered, but we will attempt to describe any differences that we could then delve into more in larger powered trials.

9.4.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be published, only summary data. The exception to this may be deidentified graphs showing individual parent's PM Na trend over time versus their pumping behaviours and milk volumes.

9.4.7 EXPLORATORY ANALYSES

We plan to explore in parents with high PM Na the longitudinal changes in Na (if any) with changes in pumping as well as determine, by looking at pumping records, if parents have followed pumping advice. We will perform descriptive statistics regarding the number of parents with high Na who eventually normalized their Na, and report percent who did this with increased pumping based on our protocol. We will explore with chi square whether a various thresholds (such as 8x/day) of pumping were associated with normalization of Na and CTV in those parents who initially had high Na.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

In this pilot study that doesn't involve active interventions other than pumping recommendations (aka no drugs/biologics, devices, labs, etc) we do not anticipate any circumstances in which we would have to discontinue/close the study. That being said, this study may be prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the REB and the funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted and be informed of changes to study visit schedules. The study may resume once concerns are addressed, and satisfy the REB.

Participant confidentiality and privacy is strictly held in trust by the participating Investigators and their staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. All research activities will be conducted in as private a setting as possible.

Any research information obtained about the patient in this study will be kept confidential. A patient will not be identified by name, only by unique study ID number and all outcome/study information will be in this deidentified database. The patient's name or any identifying information will not appear in any reports published as a result of this study. All identifying information will be kept behind at least 2 security measures (password protected document on a password protected computer in a locked office) or as per equivalent institutional policy, under the supervision of the study/site PI. Data transfer agreements will be utilized for all sites. The study data entry and study management systems used by clinical sites will be secured and password protected. Deidentified study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at SickKids, and an existing data transfer agreement will be utilized for statistical analysis.

Representatives of the Research Ethics Board (REB) or regulatory agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records for the participants in this study. The clinical study site will permit access to such records.

10.1.2 FUTURE USE OF STORED SPECIMENS AND DATA

De-identified data collected for this study will be analyzed and stored at SickKids. After the study is completed, the de-identified, archived data from this pilot project may be added to larger datasets with which the PI is involved with REB approval, given the rarity of PM Na data in the preterm population. Permission to use deidentified data for future related studies or datasets will be included in the informed consent. No biologic samples will be collected/stored.

10.1.3 KEY ROLES AND STUDY GOVERNANCE

Samantha Anthony SW PhD
PGCRL
Room 6.9710, 666 Bay St., Toronto, M5G 0A4
Samantha.anthony@sickkids.ca
416-813-7654 x 303126

10.1.4 SAFETY OVERSIGHT

Given that this is a feasibility study, the short duration of this study, and the lack of clinical intervention, adverse events will be reviewed by the study team every 3 months. They will evaluate individual and cumulative participant data to decide whether the study should continue as is or whether any changes

need to be made to the protocol. Parents will also be provided the contact information of the study team and the REB should they wish to express any issues.

10.1.5 DATA HANDLING AND RECORD KEEPING

10.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data and uploaded to REDCap in a timely manner for each participant. As potential participants will be approached due to their infants' admission to the NICU, we won't necessarily have access to the parents' primary medical chart, depending on the site (aka at SickKids, which is not a delivery hospital). Therefore, as we would not necessarily be able to note study participation in the parent's chart, it will be noted instead in the infants' chart. We do not plan to access parent charts unless the parent gives us permission to do so if they do not, for example, know their relevant medical history to answer the questions in the 'Health and Lactation History" form (ie did they have pre-eclampsia, chorioanmionitis, etc). This access with permission would only be done if the parent delivered at the hospital in which the infant is admitted, facilitating easy record access.

Where the source data is not collected as part of the participant's medical record, hardcopies of the worksheets (such as for recording POC PM Na at bedside, recording milk weights, recording parental medical/lactation history or participant surveys) will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Copies will be made of participant's paper pumping logs that they will fill out at home when pumping. If parents prefer, electronic records (particularly for pumping) can be utilized using REDCap as a primary source. For qualitative interviews, interviews will be audio recorded but all identifiers will be removed for analysis – this will be reiterated to participants at the beginning of the interview.

Study data from all sites will be entered into REDCap (Research Electronic Data Capture), a secure, web-based application designed exclusively to support data capture for research studies. REDCap is developed and maintained by a team at Vanderbilt University and licensed free of charge by the Research Institute at The Hospital for Sick Children. The application and data are housed on servers provided by The Hospital for Sick Children. These servers are located within SickKids secure data center. Local support for REDCap is provided by SickKids Research IT. The data will be transferred (with appropriate data transfer agreements) to UHN, which was previously associated with SickKids and is contracted with the SickKids Division of Neonatology for statistical analysis. SickKids and UHN have a hospital to hospital executed master agreement in place for the provision of statistical support by the Ted Rogers Computational Program to various Divisions within SickKids. This agreement includes provisions for the transfer of data to UHN, and funds to pay for any analyses. All work is billed to the appropriate SickKids Division. This agreement is not study specific and includes Neonatology. UHN is a service provider with respect to this study and will be involved only for statistical analysis of de-identified data. Only de-identified data is transferred to UHN for analysis using a secure file transfer portal.

10.1.5.2 STUDY RECORDS RETENTION

To enable evaluations and/or audits, the Principal Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition in a secure location for a minimum of 7 years in accordance with SickKids policy.

If the Principal Investigator relocates, retires, or for any reason withdraws from the study, then the study records must be transferred to an acceptable designee, such as another Investigator.

10.1.6 PROTOCOL DEVIATIONS

In this feasibility and acceptability pilot study, protocol deviations may be possible, as we are unsure if parents will find PM Na testing acceptable (primary aim), or altered pumping schedules acceptable for the exploratory aim, for example. All protocol deviations will be documented for future trial planning. The Principal Investigator is responsible for knowing and adhering to the reviewing REB requirements.

10.1.7 CONFLICT OF INTEREST POLICY

The independence of studies from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Hospital for Sick Children has established policies and procedures to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
MRP	Most Responsible Physician
Na	Sodium
PM	Parent Milk
PI	Principal Investigator
POC	Point of Care
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SOP	Standard Operating Procedure

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