Pragmatic, Randomized, Blinded Trial to Shorten Pharmacologic Treatment of Newborns with Neonatal Opioid Withdrawal Syndrome (NOWS)

UAMS IRB (cIRB) Protocol Number 260053

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Summary of Key Changes from Version 01 to Version 02:

Affected Section(s)	Summary of Revisions Made (Version 01 to 02)	Rationale
Cover	Added additional Operational PI, Abhik Das, Ph.D.	There will be an operational PI for UAMS cIRB processes and operational PI for the study processes
Throughout	Expanded study from end time of 4-week post-discharge to child at 24 months of age. Specifically added assessments when child is 6, 12, 18, and 24 months of age. New Assessments added: • Infant weight/length/head circumference • Caregiver questionnaire • Death • Bayley assessment • BITSEA assessment	Study assessments and timing of assessment were revised to align with 2 companion neonatal opioid withdrawal protocols, including ESC-NOW (UAMS IRB # 239729)
Section 1.4, Study Intervention/ Methods	• Added last paragraph, which describes that assessments that will be done.	Study assessments and timing of assessment were revised to align with 2 companion neonatal opioid withdrawal protocols, including ESC-NOW (UAMS IRB # 239729)
Sections 1.6.3.; 3.2.3.; 5.1.2.;	Added secondary outcomes #10, 11, and 12	Internal consistency (to go with new assessments).
Section 1.7, Table 1, secondary objectives section	Added last 3 objectives (listed below), as well as associated endpoints: • To determine whether a rapid- or slow-wean intervention among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS) affects growth over the first 24 months of age • To determine whether a rapid- or slow-wean intervention among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS) affects infant wellness after discharge and until 24 months of age • To determine whether a rapid- or slow-wean intervention among infants receiving an opioid	Study assessments and timing of assessment were revised to align with 2 companion neonatal opioid withdrawal protocols, including ESC-NOW (UAMS IRB # 239729)

Affected Section(s)	Summary of Revisions Made (Version 01 to 02)	Rationale
	(defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS) affects infant development.	
Section 3.3.2 final paragraph in section	Additional background information given.	Provides additional rationale for study/study design.
Section 3.3.3	Added paragraph starting "Site Practice for Weaning Strategies of Pharmacological Treatments of NOWS."	Provides additional rationale for study/study design.
Section 4.2.1 (table 3)	• New assessments added: o Infant weight, length, head circumference o Caregiver questionnaire o Death o Bayley Scales of Infant and Toddler Development, Fourth Edition (Bayley-4): o Brief Infant-Toddler Social and Emotional Assessment (BITSEA) • New time point added o Brief symptom inventory at 24 months (in addition to initial 1-month • New information to be collected Periodically collect participant contact information updates	Study assessments and timing of assessment were revised to align with 2 companion neonatal opioid withdrawal protocols, including ESC-NOW (UAMS IRB # 239729)
Section 4.2.4	Added "If there are any concerns regarding the cognitive status of the mother, the site PI or designee will be consulted. If the infant's mother is cognitively impaired and is unable to provide informed consent to the research study, then an alternative legal guardian may be approached for consent per local guidelines. Sites will follow location-specific requirements for enrollment of wards of the state. If legal guardianship changes, the new legal guardian would be contacted to obtain consent for the study."	Addresses cIRB major contingency #3 (to specify provisions for screening and consenting/assenting mothers with cognitive impairment) and minor contingency #22 (to indicate location-specific requirements will be followed).

Affected Section(s)	Summary of Revisions Made (Version 01 to 02)	Rationale
Section 4.2.17. *Post-hospital procedures.*	Re-wrote 1st paragraph and the majority of the rest of this section.	Clarified wording. Ensured new assessments /assessment time points were consistently described throughout the protocol
Section 4.3.1. *Rapid Wean*	The following statement was added: The rapid wean schedule is used routinely as standard of care at some U.S. hospitals.	Addresses, in part, cIRB major contingency #2 (regarding what is considered standard of care).
Section 4.3.2. Slow Wean	The following statement was added: The slow wean schedule is used routinely as standard of care at some U.S. hospitals.	Addresses, in part, cIRB major contingency #2 (regarding what is considered standard of care).
Section 4.3.4, Maternal opioid use reporting requirements	Added section with the following content: The responsibility for determination of whether neonatal opioid exposure warrants mandatory reporting will rest with the clinical team per local standards. Participation in the clinical study will not affect reporting requirements.	Address, in part, cIRB major contingency #1 (regarding mandatory reporting requirements concerning neonatal opioid exposure)
Section 5.1.4. Analysis of the Primary Hypothesis	Added final paragraph. Specifically: Descriptive statistics (means, medians, SD, percentiles) for number of days of opioid treatment from the first weaning dose to cessation of opioid treatment will be generated and summarized in a table by treatment group.	Simple correction/addition.
Section 5.1.5, Analysis of Secondary Outcomes	Added new bullet points and information (esp. new paragraphs # 4, 7, 8, 9, and 10) after the bullets) about analyses for newly added assessments/assessment time points.	Internal consistency (to go with new assessments/new time points).
Section 5.1.6., Bayesian analysis	Made statistical model/software corrections to paragraphs 5 and 7.	Simple corrections/additions.
Appendix 3. Recruitment plan	Added that initial contact with potential participants will be made by clinical staff rather than research staff (unless research staff are part of the same clinic).	Addresses contingency of UAMS IRB (cIRB).

Summary of Key Changes from Version 02 to Version 03:

Affected Section(s)	Summary of Revisions Made (Version 02 to 03)	Rationale
Section 4.3.4.	Changed that mandatory reporting will rest "with the clinical team per local standards" to reporting will rest "with all mandatory reporters per requirements of those reporters."	Addressing IRB minor contingency bullet 1.
Section 6.0, Data Management (new section)	Added section 6.0, Data Management, to delineate the role of RTI International.	To clarify RTI International's role for ceding purposes.

Summary of Key Changes from Version 03 to Version 04:

Affected Section(s)	Summary of Revisions Made (Version 03 to 04)	Rationale
Section 1.4; Table 1; Table 3; Section 4.2.17; Section 5.1.5; References	Replaced description of Brief Symptom Inventory (BSI) with description of Patient-Reported Outcome Measurement System (PROMIS) Short Forms	Protocol team chose alternate tool for mental health measures for feasibility concerns and to align with other concur
Table 3	Updated windows for follow-up assessment	Clarified and standardized windows for collecting follow up assessments
Section 4.3.3	Revised protocol to indicate triggers for maternal intervention based on PROMIS scores for severe depression	Consistency with revised measures
Section 5.4.1	Clarifying assessment of enrollment targets if there are lags in recruitment	Provide clearer decision tools for DSMC to review enrollment data if there are lags in recruitment
Table 4; Table 5; Appendix 4; Appendix, 5; Appendix 6; Appendix 7; Appendix 8	Dose levels listed changed from numbers to letters	Consistency with Pharmacy Manual
Appendix 8	Updated dosing level language and graphics	Consistency with Pharmacy Manual

Summary of Key Changes from Version 04 to Version 05:

Affected Section(s)	Summary of Revisions Made (Version 04 to 05)	Rationale
4.2.4; Appendix 3	Addition of remote consenting	Changed due to (a) COVID-19 pandemic (b) relative availability of guardian (c) change of guardianship
4.3.3; 4.3.4; table of contents	Updated formatting for section 4.3.3 & 4.3.4	Corrected headers

Summary of Key Changes from Version 05 to Version 06:

Affected Section(s)	Summary of Revisions Made (Version 05 to 06)	Rationale
5.5.1	Updated language for SAE reporting – "Study personnel will promptly report (within 24 hours of knowledge) all SAEs that the study intervention at least possibly relates to or are unexpected to the study sponsor and the DCC. The designated Medical Monitor will review these events and will forward them to the Chair of the DSMC."	Simple Correction. Changed "and" to "or".

Summary of Key Changes from Version 06 to Version 07:

Affected Section(s)	Summary of Revisions Made (Version 06 to 07)	Rationale
1.4	New language for NNNS training and video consent – "Some participating sites may need to train their study staff on the NNNS procedure. The NNNS training requires video recordings of infants sent to the training center at Brown University. Only the trainers at the Brown Center or their trainer designee and site trainees will have access to the video. The video will be deleted from the server once it has been reviewed for training purposes, and training on that video is complete. These infants may or may not be otherwise involved in the protocol. Sites may assess infants	Consent required because we would not be doing this training or exposing these infants to this videotaping at this time if not for the study.

Affected Section(s)	Summary of Revisions Made (Version 06 to 07)	Rationale
	who will not enroll in the study; infants who will enroll, or both for this training. Because this training activity will not yield study data, a separate consent form will be used for this training."	

Summary of Key Changes from Version 07 to Version 08:

Affected Section(s)	Summary of Revisions Made (Version 07 to 08)	Rationale
3.3.4; Rationale & Summary	Correction of typographical/mathematical errors: FROM 8424 TO 9032 (bullet 5) and FROM $7,8484,808 TO $7,848,808 (bullet 6)	Simple corrections for clarification.
4.2.1, Table 3; (Schedule of Activities)	Added: • Screening to "prior to birth" and "at risk" columns • "randomization" to randomization column • Monitoring serious adverse events at "Post Intervention Evaluation" and "Hospital Discharge" • Check/record death for times between "randomization" and "1 Month Post Discharge," inclusive Corrected • "enrollment" to "randomization" in left hand column	Corrections to match protocol to practice.
4.2.3; Screening	Added language to allow for screening of • pregnant mothers who may give birth to babies with NOWS. • medical records of mothers with known opioid exposure/use • infants (medical records of) who may quality	Increase the chances of enrolling mothers when they may be most receptive to the study and to expand the pool of potential participants

Affected Section(s)	Summary of Revisions Made (Version 07 to 08)	Rationale
4.2.4; Consent; Appendix 3;	Re-wrote/expanded most of section. Added new language: • for consenting pregnant mothers. • for consenting post-partum mothers whose babies have not yet met inclusion criteria but whose babies are likely to meet study criteria. • to explain the use of the infant-only and caregiver-only consent forms • to explain custody change processes are site-specific due to variation in state and local laws and requirements Revised • language regarding legal guardians/legally authorized representatives	• Change allowable time frame for consenting process and documentation. This is to facilitate consenting in a potentially calmer environment with less distractions and to decrease the number of remote consents due to parent(s) being away from the site when their infant is placed on pharmacological therapy • To explain the purposes for the various consent forms
4.2.6; Study Intervention	• Added to subsection "Changes in Opioid Dose" o bullet "Escalation of study drug dose is the mechanism to address NOWS… " • Added to subsection "Other Criteria to Exit the Intervention" o unable to take enteral opioid medications • Deleted from subsection "Other Criteria to Exit the Intervention" o "change in feeding strategy (nasal-gastric tube feeds, IV fluids) • Added to subsection "Post Intervention" o Guidance for restarting pharmacological therapy for recurrence of NOWS symptoms	Clarifications/ corrections
4.2.12; Adverse events	Deleted of "use of nasogastric tube for feeding" as an adverse event	Allows for feeding via nasogastric tube
General	• Corrected section numbers that were non-sequential • Added header to pages where it was missing • Reformatted tables in appendices so tables fit pages.	Simple corrections/formatting.

Summary of Key Changes from Version 08 to Version 09:

Affected Section(s)	Summary of Revisions Made (Version 08 to 09)	Rationale
4.2.18; Compensation	Section added. • Increased total amount of 24-month time point reimbursement from $100 to $150. This is to increase reimbursement for the in-person visit from $50 to $100. • Added payments tables related to each consent form.	• Increased amount for in-person visit from $50 to $100 to provide more equitable payment. • Payment information was not previously included in the protocol

Summary of Key Changes from Version 09 to Version 10:

Affected Section(s)	Summary of Revisions Made (Version 09 to 10)	Rationale
4.2.4; Consent	• Requested a waiver of documentation of written consent to allow the disclosure of participant contact information between sites when it is more convenient for a participant to follow-up with a new site.	• Will facilitate participant transfer between sites.

Summary of Key Changes from Version 10 to Version 11:

Affected Section(s)	Summary of Revisions Made (Version 10 to 11)	Rationale
Face page	• Replaced Jessica Snowden with Sherry Courtney in the role of Operational PI for UAMS.	• Jessica Snowden left UAMS at the end of August 2024.
Face page	• Primary Investigator Adam Czynski's affiliation changed from Women & Infants Hospital of Rhode Island to Connecticut Children's Medical Center	• Correction
Face page	• Subcommittee roster updated	• Personnel changes

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SECTION 1. ABSTRACT

1.1. STUDY HYPOTHESIS/QUESTION

Among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS), a rapid-wean intervention will reduce the days of opioid treatment from the first weaning dose to cessation of opioid compared to a slow-wean intervention.

1.2. STUDY DESIGN TYPE

Pragmatic, randomized, blinded, trial

1.3. ELIGIBILITY CRITERIA

1.3.1. Inclusion Criteria

1.3.1.1. Hospital Level

1) Hospital provides pharmacologic treatment to at least an average of 12 opioid exposed infants each year
2) Hospital uses a scoring system to assess for signs of NOWS (original or modified Finnegan Neonatal Abstinence Scoring system, Eat-Sleep or Console)
3) Hospital provides opioid replacement therapy with either morphine or methadone as part of pharmacologic treatment of NOWS

1.3.1.2 Infant Level

Infants need to fulfill all of the following criteria:

1) Gestational age ≥ 36 weeks
2) Receiving scheduled pharmacological therapy with morphine or methadone as the primary drug treatment for NOWS secondary to maternal opioid use
3) Tolerating enteral feeds and medications by mouth

1.3.2. Exclusion Criteria

1.3.2.1. Hospital Level

1) Hospitals discharge > 10% of infants from the hospital on opioid replacement therapy on average per year

1.3.2.2. Infant Level

Any of the following is an infant level exclusion criterion:

1) Major birth defect (e.g. gastroschisis)
2) Any major surgery (minor surgery [e.g., circumcision, digit ligation, frenulectomy] is not an exclusion criterion)
3) Hypoxic-ischemic encephalopathy

4) Seizures from etiologies other than NOWS
5) Treatment with opioids for reasons other than NOWS
6) Respiratory support (nasal cannula or greater) for > 72 hours
7) Planned discharge from the hospital on opioids
8) Use of other opioids (e.g., buprenorphine) as primary drugs for treatment of NOWS
9) Weaning of morphine or methadone as the primary treatment of NOWS has started

1.4. STUDY INTERVENTION/METHODS

This will be a pragmatic, randomized, blinded trial comparing a rapid-wean intervention (15% decrements from the stabilization dose) to a slow-wean intervention (10% decrements from the stabilization dose) to determine whether rapid weaning will reduce the number of treatment days among infants receiving morphine or methadone orally as the primary treatment for NOWS. Participating hospitals must provide pharmacologic treatment to at least an average of 12 opioid exposed infants each year, use a scoring system to assess for signs of NOWS (original or modified Finnegan Neonatal Abstinence Scoring system, Eat-Sleep or Console), and provide opioid replacement therapy with either morphine or methadone as the primary drug for treating NOWS. Hospitals may change use of these two opioids during the trial period. We will stratify randomization by hospital. The study protocol will commence after NOWS signs have been controlled with an opioid (stabilization) and weaning of pharmacologic treatment is to be started. At or before each 24-hour interval, clinical team members will evaluate and score infants, per hospital practice, for signs of NOWS to determine if the infant will tolerate weaning of the study drug.

- If the infant can tolerate weaning and is in the rapid-wean intervention arm, the clinical team will reduce the study drug by 15% of the stabilization dose. The clinical team will terminate the study drug when the infant can tolerate 25% of the stabilization dose without NOWS signs.
- If the infant can tolerate weaning and is in the slow-wean intervention arm, the clinical team will reduce the study drug by 10% of the stabilization dose. The clinical team will terminate the study drug when the infant can tolerate 20% of the stabilization dose without NOWS signs.
- If infants cannot tolerate weaning in either intervention arm, infants will enter a 12-hour period of study protocol guideline that will mandate either weaning or escalating the study drug by the end of the 12-hour interval. If the clinical team escalates the study drug, infants will receive opioid using the prior step of the assigned intervention arm.

To maintain blinding of study drug dose during the interventions, the volume of the syringe will be constant and equal the volume of the opioid at stabilization. As the clinical team decreases the study drug during the interventions, the pharmacist will add normal saline to keep a constant syringe volume. Only the pharmacy will be aware of the opioid dose. The use of placebo (normal saline without opioid) in the rapid-wean intervention arm will ensure comparable duration of both weaning interventions.

As part of a pragmatic trial, clinical teams will follow hospital practice for other care practices related to NOWS treatment (type of scoring system, threshold to initiate treatment, duration of stabilization, use of second-line and third line-drugs, rooming in, breast milk, etc.). After study drug cessation, the clinical team will observe infants in the hospital for at least 48 hours prior to discharge, which is similar to clinical practice. A trained examiner will administer the Neonatal Intensive Care Unit (NICU) Network Neurobehavioral Scale (NNNS) to assess neurobehavioral profiles after infants cease study drug and

prior to discharge. Some participating sites may need to train their study staff on the NNNS procedure. The NNNS training requires video recordings of infants sent to the training center at Brown University. Only the trainers at the Brown Center or their trainer designee and site trainees will have access to the video. The video will be deleted from the server once it has been reviewed for training purposes, and training on that video is complete. These infants may or may not be otherwise involved in the protocol. Sites may assess infants who will not enroll in the study; infants who will enroll, or both for this training. Because this training activity will not yield study data, a separate consent form will be used for this training.

At one month post discharge, primary caregivers will complete the Parent-Reported Outcome Measure Information System (PROMIS) Measures, the Maternal Postnatal Attachment Questionnaire (MPAQ) and a caregiver questionnaire. The site research team will contact the primary caregiver(s) to update contact information and/or complete questionnaires when the infant is 6 months, 12 months, 18 months, and 24 months of age. The questionnaires will assess infant wellness, neurobehavioral functioning and development, postnatal attachment and bonding, and caregiver well-being. At 24 months, the infants will be seen during which a, certified developmental specialists, blinded to the intervention, will administer the Bayley Scales of Infant and Toddler Development, Fourth Edition (Bayley-4) to assess infant neurodevelopment. The PROMIS Measures and the Brief Infant Toddler Social Emotional Assessment (BITSEA) will also be administered during the 24 month visit along with measures of growth.

1.5. PRIMARY OUTCOME

The number of days of opioid treatment (used as primary treatment), including escalation, resumption, and spot treatment, from the first weaning dose to cessation of opioid.

1.6. SECONDARY OUTCOMES

1.6.1. Secondary Efficacy Outcomes

Secondary Outcome 1. The numbers of days of opioid treatment from the first weaning dose to cessation of opioid with a rapid and slow-wean interventions among infants treated with morphine.

Secondary Outcome 2. The numbers of days of opioid treatment from the first weaning dose to cessation of opioid with a rapid and slow-wean interventions among infants treated with methadone.

Secondary Outcome 3. The proportions of infants in the rapid and slow-wean intervention arms who have an escalation or resumption of opioid medication during weaning.

Secondary Outcome 4. The total amounts of opioid from the first weaning dose to cessation of opioid among infants in the rapid and slow-wean intervention arms.

Secondary Outcome 5. The proportion of infants who experience initiation and/or escalation of second-line or third-line drugs to treat NOWS signs from the first weaning dose to cessation of opioid in the rapid-wean and slow-wean intervention arms.

1.6.2. Secondary Safety Outcome

Secondary Outcome 6. The proportion of infants in each intervention arm with safety outcomes of seizures (clinical or EEG), excessive stool output, respiratory disturbances, and feeding tolerance.

1.6.3. Other Secondary Outcomes

Secondary Outcome 7. The proportion of infants in each intervention arm with an atypical NNNS neurobehavioral profile prior to discharge.

Secondary Outcome 8. The lengths of hospital stay for infants in each intervention arm.

Secondary Outcome 9. Assessments of maternal well-being and maternal-infant attachment after discharge in each intervention arm.

Secondary Outcome 10. Assessments of growth in each intervention arm.

Secondary Outcome 11. Assessment of infant wellness after discharge and until 24 months of age in each intervention arm.

Secondary Outcome 12. Assessment of infant development to 24 months of age in each intervention arm.

1.7. STUDY OBJECTIVES AND ENDPOINTS

Table 1 outlines the study objectives and endpoints.

Table 1. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of a rapid wean intervention compared with a slow-wean intervention in reducing the number of days of opioid treatment from the first dose of weaning to cessation of opioid among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS)	• The number of days of opioid treatment from the first dose of weaning to cessation of opioid
Secondary	
• To evaluate the efficacy of a rapid-wean intervention compared with a slow wean intervention in reducing the number of days of opioid treatment from the first dose of weaning to cessation of opioid among infants treated with morphine as the primary treatment for neonatal opioid withdrawal syndrome (NOWS)	• The number of days of morphine treatment from the first dose of weaning to cessation of morphine
• To evaluate the efficacy of a rapid-wean intervention compared with a slow wean intervention in reducing the number of days of opioid treatment from the first dose of weaning to cessation of opioid among infants treated with methadone as the primary treatment for neonatal opioid withdrawal syndrome (NOWS)	• The number of days of methadone treatment from the first dose of weaning to cessation of methadone
• To determine whether a rapid- or slow-wean intervention affects escalation or resumption of opioid medication during weaning among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS)	• Escalation or resumption of morphine or methadone medication during weaning
• To determine whether a rapid- or slow-wean intervention affects the total amounts of opioid given from the first dose of weaning to cessation of opioid among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS)	• The total amount of morphine or methadone given from the first dose of weaning to cessation of opioid
• To determine whether a rapid- or slow-wean intervention affects the administration of second or third line drugs to treat NOWS from the first dose of weaning to cessation of opioid among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS)	• Initiation or escalation of second or third line drugs administered to treat NOWS signs from the first dose of weaning to cessation of opioid
• To evaluate the safety and tolerability of a rapid-wean intervention compared with a slow-wean intervention among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS)	• Seizures (clinical or EEG), excessive stool output, respiratory disturbances, and feeding tolerance

Objectives	Endpoints
Secondary (cont'd)	
• To determine whether a rapid- or slow-wean intervention affects neurobehavior among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS)	• Atypical neurobehavioral profile prior to discharge on the NICU Network Neurobehavioral Scale (NNNS) after completion of study drug and prior to hospital discharge
• To determine whether a rapid- or slow-wean intervention affects the total length of hospital stay among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS)	• The total number of days spent in the hospital
• To determine whether a rapid- or slow-wean intervention among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS) affects maternal well-being and maternal infant attachment at four weeks (± 7 days) after discharge	• Parent-Reported Outcome Measure Information System (PROMIS) Measures at 1 month after discharge and at 24 months of age • Maternal Post Attachment Questionnaire (MPAQ) at one month after discharge
• To determine whether a rapid- or slow-wean intervention among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS) affects growth over the first 24 months of age	• Weight (kg), length (cm), head circumference (cm), and weight for length percentile on the World Health Organization (WHO) growth curves. Anthropometric z-scores and BMI-z at 24 months of age
• To determine whether a rapid- or slow-wean intervention among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS) affects infant wellness after discharge and until 24 months of age	• Acute/urgent care and/or ER visits (total number of occurrences) (CQ) • Readmissions (number of occurrences) (CQ) • Death (presence or absence)
• To determine whether a rapid- or slow-wean intervention among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS) affects infant development.	• Bayley Scales of Infant and Toddler Development, Fourth Edition (Bayley 4): Cognitive, Language, Motor, at 24 months of age

1.8. SAMPLE SIZE AND POWER

The projected effect size is a 2.0 day difference in the duration of opioid treatment between infants randomized to a rapid-wean intervention and infants randomized to a slow-wean intervention. We derived this sample size by using results from a recently completed trial comparing morphine-treated

infants and methadone-treated infants in which the standard deviation was 6.9 days for the morphine-treated infants and 8.0 days for methadone-treated infants. We used a standard deviation of 6.9 days to derive the sample size, anticipating that more infants will be treated with morphine. However, the primary analysis compares treatment regardless of drug used, and we based our sample size calculation irrespective of the proportion of infants treated with morphine or methadone. **Table 2** is for illustrative purposes only, and shows the number of patients treated with morphine and methadone if 70% of infants receive morphine as the primary opioid treatment.

Table 2. Sample Size

Intervention Arm	Morphine Treated	Methadone Treated	Total
Rapid-wean	176	75	251
Slow-wean	176	75	251
Total	352	150	502

The study will have two intervention arms (rapid-wean and slow-wean) with 251 morphine/methadone treated infants per intervention arm, for a total of 502 morphine/methadone treated infants. This will achieve 90% power to reject the null hypothesis with a significance level of 0.05 using a two-sided two-sample t-test. The null hypothesis will be morphine or methadone treated infants in both arms will have equal means when the population difference in the duration of opioid treatment is 2.0 days with a standard deviation of 6.9 days. It is difficult to predict the proportion of infants treated with either morphine or methadone in the coming years given potential changes in practice. We will recalculate the sample size by considering the standard deviation from pooled data (without unblinding) after 25% of participant accrual.

1.9. PROJECTED RECRUITMENT TIME

We project that enrollment will require 3.3 years based on a targeted enrollment of 502 infants, with 750 infants available each year and a 20% consent rate. This projection assumes that the research team will not change the sample size estimate during the trial.

SECTION 2. CONFLICT OF INTEREST DISCLOSURES

2.1. FINANCIAL CONFLICTS OF INTEREST OF THE INSTITUTIONS AND INVESTIGATORS

The study investigators have no financial conflicts of interest (FCOI) related to the study outlined in this protocol.

2.1.1. Plan for Managing Identified Financial Conflicts of Interests

We will handle any potential or perceived conflicts of interest, including FCOI, per Title 42, Code of Federal Regulations, Part 50, Subpart F (50.604 Responsibilities of Institutions regarding Investigator financial conflicts of interest). This states that institutional officials (and all subrecipients) are required to notify the grants officer of any FCOI prior to expenditure of any funds and within 60 days of any subsequently identified FCOI. The research team will simultaneously notify NICHD, ECHO office, the NRN Steering Committee and the ISPCTN Steering Committee regarding the COI management plan, following institutional guidelines of each participating hospital.

SECTION 3. STATEMENT OF PROBLEM

3.1. PRIMARY HYPOTHESIS OR QUESTION

Among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for NOWS, a rapid-wean intervention will reduce the days of opioid treatment from the first weaning dose to cessation of opioid, compared to a slow-wean intervention.

3.2. SECONDARY OUTCOMES

3.2.1. Secondary Efficacy Outcomes

Secondary Outcome 1. The numbers of days of opioid treatment from the first weaning dose to cessation of opioid with rapid- and slow-wean interventions among infants treated with morphine.

Secondary Outcome 2. The numbers of days of opioid treatment from the first weaning dose to cessation of opioid with rapid- and slow-wean interventions among infants treated with methadone.

Secondary Outcome 3. The proportions of infants in the rapid- and slow-wean intervention arms who have an escalation or resumption of opioid medication during weaning.

Secondary Outcome 4. The total amounts of opioid from the first weaning dose to cessation of opioid among infants in the rapid- and slow-wean intervention arms.

Secondary Outcome 5. The initiation and escalation of second- or third-line drugs to treat NOWS signs from the first weaning dose to cessation of opioid in the rapid- and slow-wean intervention arms.

3.2.2. Secondary Safety Outcome

Secondary Outcome 6. The proportion of infants in each intervention arm with safety outcomes of seizures (clinical or EEG), excessive stool output, respiratory disturbances, and feeding tolerance.

3.2.3. Other Secondary Outcomes

Secondary Outcome 7.The proportion of infants in each intervention arm with an atypical neurobehavioral profile prior to discharge on the NICU Network Neurobehavioral Scale (NNNS).

Secondary Outcome 8. The lengths of hospital stay for each intervention arm.

Secondary Outcome 9. Assessments of maternal well-being and maternal-infant attachment in each intervention arm.

Secondary Outcome 10. Assessments of growth in each intervention arm.

Secondary Outcome 11. Assessment of infant wellness after discharge and until 24 months of age in each intervention arm.

Secondary Outcome 12. Assessment of infant development to 24 months of age in each intervention arm.

3.3. BACKGROUND AND RATIONALE

3.3.1. Public Health Impact

The incidence of maternal opioid use in the United States has increased substantially since 2000 (1). This includes an increase of opioid use during pregnancy including prescription opioids and illicit drugs, as well as a rise in opioid substitution programs for addiction treatment (2). As a consequence of opioid use during pregnancy, the incidence of neonatal opioid withdrawal syndrome (NOWS) has increased five-fold between 2002 and 2012 (1). NOWS is a clinical syndrome that reflects signs of withdrawal from opioids in a newborn following *in-utero* exposure. Signs typically occur in the first 5-7 days following birth and reflect dysfunction of the brain, gastrointestinal tract and autonomic regulation. Simultaneously during this rise in opioid use, the pattern of use has shifted from an inner city, indigent population to a more socioeconomically diverse population. A systematic literature review indicated rural pregnant women have higher rates of polysubstance abuse, as compared to urban pregnant women (3). The highest incidences of NOWS were reported in the Southeast (i.e., Kentucky, Tennessee, Mississippi, and Alabama) and Northeast (i.e., Maine, New Hampshire, Vermont, Massachusetts and Rhode Island) United States (4). This increase in opioid drugs during pregnancy affects neonatal care across the United States. Multiple cross-sectional analyses show that NICU admission rates for NOWS increased from 7 to 27 cases per 1,000 admissions and that length of stay increased from 13 to 19 days between 2004 through 2013 (5). Mean hospital charges for infants discharged with neonatal abstinence syndrome (NAS) increased from $39,400 to $53,400 between 2000 and 2009, and state Medicaid programs bore 78% of these charges (1). The proportion of neonatal hospital costs due to NAS was estimated to rise from 1.6% to 6.7% between 2004 and 2014 among births covered by Medicaid (6). Pregnancy complicated by opioid use disorder is associated with high rates of polydrug use, mental health disorders, infectious diseases, poor nutrition, chronic illnesses, and limited social support (7). Associated risks for newborns beyond NOWS include preterm birth and fetal growth restriction.

Pregnancy represents an opportunity for entry into the healthcare system and initiation of interventions for the mother-infant dyad. However, there are many knowledge gaps in the care of infants with NOWS. The executive summary of a joint workshop by the National Institute of Child Health and Human Development and multiple other partners identified major domains of research priorities on NOWS, including screening and assessment, treatment of NOWS, and transition out of the hospital and follow up (7).

3.3.2. Background

A recent *Journal of Pediatrics* editorial emphasized the rapid rise of NOWS in the United States and provided a framework to target research initiatives and care delivery innovations for infants with NOWS (8). Specifically, research and quality improvement initiatives should be safe, effective, patient centered, timely, efficient, and equitable. High-quality research is needed to ensure that NOWS care is evidence-based, eliminates non-beneficial practices, and achieves the overarching goals of limiting ongoing opioid exposure for infants, minimizing separation of the mother-infant dyad, and reducing healthcare expenditures. To date, the research community has not rigorously evaluated, through randomized clinical trials, many aspects of NOWS treatment regimens (9).

Signs associated with NOWS reflect dysfunction in several systems: central nervous system (tremors, high-pitched cry, hypertonicity), gastrointestinal (poor feeding, watery, loose stools), and autonomic (hyperthermia). There is widespread acceptance that initial care of infants exposed to opioids *in utero*

should be individualized, supportive, and non-pharmacologic (2). These measures should include minimizing environmental stimuli (e.g., rooming in [10]), encouraging breast-feeding (in the absence of contraindications), and providing sufficient caloric intake. Pharmacological therapy is indicated when signs of NOWS cannot be controlled with non-pharmacological strategies. The objective of pharmacological therapy is to control NOWS signs so that an infant can appropriately bond with her or his mother, tolerate handling and care by healthcare providers, eat effectively with appropriate rest periods to ensure adequate growth, and avoid serious central nervous system dysfunction, such as seizures. Clinical teams traditionally initiate drug treatment when scoring assessments reach a predetermined severity of NOWS signs and include three phases (initiation, stabilization, and weaning). Initiation is the start of drug treatment, and clinical teams progressively increase the dose until the infant achieves stabilization. Stabilization is the interval of time during which the clinical team maintains a drug dose that controls NOWS signs without any indication to further increase the dose. Weaning consists of serial reductions in drug dose and/or lengthening the time interval between doses, and it often begins approximately 48 hours after stabilization. NOWS treatment goals should address four domains: 1) support vital neonatal functions (nutrition, appropriate sleep patterns, etc.), 2) promote family bonding, 3) prevent complications (seizures, excessive weight loss, unmanageable irritability), and 4) provide education for the mother-infant dyad and integration into social services to facilitate a smooth transition out of the hospital (7).

Medical professionals do not universally agree on a standard of care for pharmacologically treated NOWS infants (11). Clinical teams may use different drugs as first-line agents (e.g., morphine, methadone, and buprenorphine) and second-line agents (e.g., phenobarbital, benzodiazepines). At present, morphine is the most commonly used first-line pharmacological treatment for NOWS (12). Cross sectional data from the Pediatrix Clinical Data Warehouse showed that the proportion of infants treated with morphine for NOWS increased from 49% in 2004 to 72% in 2013 (5). Preliminary data from the ACT NOWS Current Experience, a retrospective chart review (Section 3.3.3) conducted among the IDeA States Pediatric Clinical Trials Network (ISPCTN) and Neonatal Research Network (NRN), indicated that morphine was the first-line drug for NOWS treatment in approximately 87% of NOWS infants receiving pharmacological treatment. In contrast, clinical teams used methadone in 13% of pharmacologically treated NOWS infants (**Appendices 1 and 2**).

Quality improvement methods to standardize NOWS treatment have been successful in reducing the length of treatment and hospital stay among NOWS infants (13). In contrast, there are limited randomized clinical trials to guide treatment of NOWS infants who require pharmacological therapy. The trials that do exist compared the duration of treatment with morphine and other pharmacological therapies (14-19); however, these trials were small and collectively included 189 infants treated with morphine and 187 infants treated with phenobarbital, methadone, buprenorphine, or clonidine. There are no clinical trials of different approaches to initiation, stabilization, or the weaning phases of drug therapy. An important rationale for studying weaning of pharmacological treatment for NOWS is that weaning represents the longest time interval of drug treatment. Stopping medications too early may not completely treat NOWS symptoms and may increase the challenges for a family to successfully transition home. Alternatively, excess pharmacological therapy prolongs hospital stay, which increases healthcare utilization and separates the mother-infant dyad.

Kraft et al. summarized the use of morphine and methadone treatment for NOWS (20). Morphine has a relatively short half-life, and medical professionals administer it every three or four hours. Two principal

algorithms for weaning morphine are a percentage reduction (10% of the stabilizing dose every 12-48 hours with cessation at 20% of the stabilizing dose) or a fixed reduction (typically decreases of 0.02 mg morphine/dose each day with cessation at approximately 0.02 mg/dose). Although a standard of care for weaning morphine does not exist, all of the referenced clinical trials weaned morphine by 10% reductions of the stabilizing dose (14-19). However, the research community has not compared weaning by a 10% reduction to a different weaning rate to estimate potential reductions in treatment days without morphine escalation or resumption.

Kraft et al. noted that methadone has a longer half-life than morphine and therefore, may be attractive as a therapy due to less frequent administration (20). However, there is inter-subject pharmacokinetic variability in newborns and children receiving methadone (21-22). A pilot study provided important data on the pharmacokinetics of oral methadone for NOWS treatment (22). Medical professionals have used such a pharmacokinetic-based treatment model to initiate treatment (0.1 mg/kg) with 6-hour dosing intervals. If NOWS signs are controlled, they use 12-hour dosing intervals to wean the dose from 0.075 to 0.01 mg/kg in six weaning steps, until a final 24-hour dose interval. If medical professionals do not readily capture NOWS signs at initiation, they use more frequent dosing intervals (4 to 6 to 8 hours) before decreasing doses in 12-hour intervals. The Ohio Perinatal Quality Collaborative regimen has used this dosing schedule in a pre-post intervention study (23).

In contrast to variations for weaning in clinical practice, randomized trials have used 10% reductions of the stabilizing dose. In a single-site trial that compared methadone to morphine, clinical teams weaned both drugs by 10% reductions of the stabilizing dose with four-hour dosing intervals (15). The most recent, and largest (58 infants in each group), randomized clinical trial of NOWS treatment, performed by Davis et al., was a multi-center trial comparing methadone to morphine (18). In this trial, medical professionals weaned NOWS infants treated with methadone or morphine by 10% of the stabilization dose every 12 to 48 hours with cessation of drug therapy at 20% of the stabilization dose. Administration of methadone alternating with placebo every four hours and morphine every four hours facilitated blinding of nursery personnel to the opioid being used. The trial demonstrated that the length of treatment and hospital stay were shorter with methadone, compared to morphine, and these results may prompt a shift from morphine to methadone as the primary opioid to treat NOWS. There are no randomized trials to inform clinicians of potentially better regimens to wean morphine or methadone.

Common outcomes of clinical trials of NOWS treatment are length of treatment, length of hospital stay, and safety outcomes. Although clinically evident brain injury on a neurological exam is not anticipated among infants with NOWS, there is support for abnormalities of neurobehavior (24). Such information may be important to understand maternal well-being after hospital discharge of a NOWS-treated baby. This is an important domain of NOWS research, and there is a growing recognition that outcomes of NOWS investigations need to broaden to include measures beyond length of treatment and length of hospital stay (7).

The NNNS is a comprehensive evaluation of 12 domains of neurologic and behavioral functioning as well as signs of stress, administered by trained, certified examiners (25). The research community has used the NNNS to study multiple groups of high-risk infants, including those exposed to drugs *in utero* (opioids, cocaine) and prematurity (26). Among 1,248 mother-infant dyads enrolled in the Maternal Lifestyle Study, researchers performed NNNS assessments at one month ***after*** hospital discharge (27). Researchers identified five mutually exclusive neurobehavioral profiles from the 12 neurobehavioral

domains by using latent profile analysis. Profile 5 (black line, **Figure 1**) was the most atypical, and it was characterized by exaggerated scores for arousal, excitability, hypertonicity, quality of movement, and stress abstinence, relative to four other distinct profiles. Researchers have associated Profile 5 with early childhood outcomes, including more externalizing behavior problems, internalizing behavior problems, and total behavior problems at age three, as well as lower IQ scores after adjustment for gestational age and socioeconomic status (27). In this protocol, "atypical neurobehavioral profile" refers to Profile 5 in **Figure 1**.

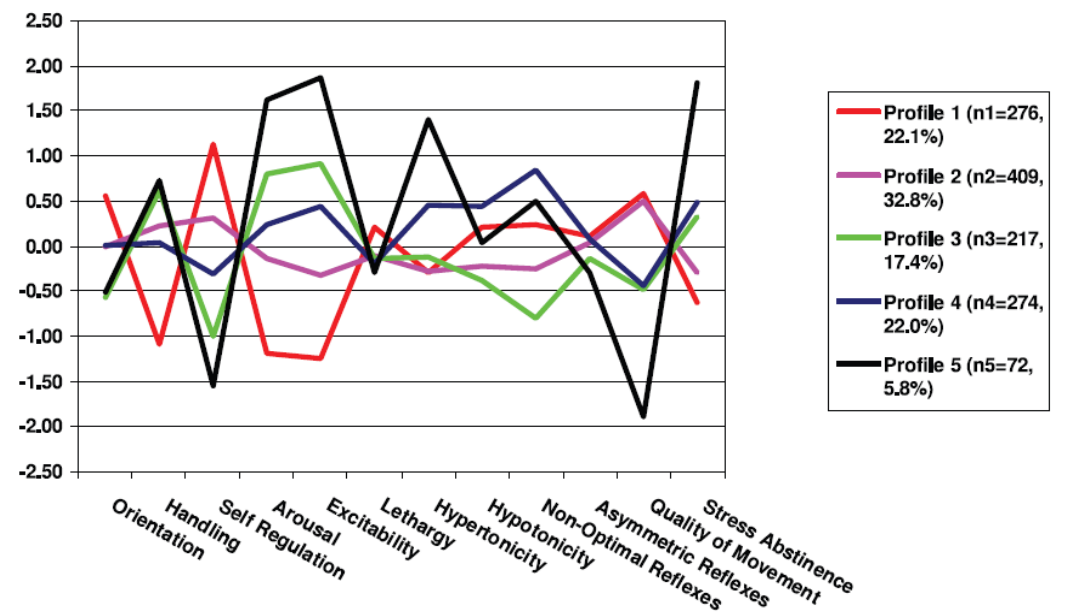

Figure 1. NNNS Examination Results from the Maternal Lifestyle Study. The figure depicts discrete neurobehavioral profiles indentified from 12 NNNS neurobehavioral domains (27). The Y axis represents standard deviation units.

There is a lack of consensus on the effects of prenatal opioid exposure on neurodevelopmental outcomes in early childhood. A recent comprehensive review indicated that there are discrepant findings with respect to the presence or absence of altered neurodevelopment with in-utero exposure (28). This reflects that many studies are small and cannot adjust for potential confounding variables. Potential confounding variables (e.g., prenatal exposures to other substances, nutrition, socio-economic status, medical complications, poor prenatal care) may all impact early childhood development. Few studies have examined neurodevelopment among infants who develop NOWS, and even less among infants who are pharmacologically treated for NOWS. A retrospective chart review of infants born in 2011-2015 and treated for NOWS with morphine, methadone or buprenorphine had lower Bayley Scales of Infant Development III at 23 months compared with normative data for the Bayley Scales (29). Contemporary data on early childhood neurodevelopment of infants with NOWS in the presence or absence of pharmacologic treatment remains a major research gap.

3.3.3. Preliminary Data

Pilot Clinical Data. The ISPCTN and the NRN have undertaken a retrospective chart review to inform the design of clinical trials for infants with NOWS (Advancing clinical trials in neonatal opioid withdrawal syndrome [ACT NOWS] current experience: Infant exposure and treatment). Investigators reviewed medical records for infants ≥ 36 weeks gestational age and born between July 1, 2016 through June 30,

2017, and mothers medical records, when available, when there was opioid use, determined by maternal history, maternal/infant toxicology screen, or NOWS scoring. Data were collected from 1808 infants at 23 of 28 ISPCTN sites and two of five NRN sites. The ACT NOW Current Experience infant characteristics and demographics are presented in **Appendix 1** and infant pharmacological treatment are presented in **Appendix 2**.

The salient findings from the preliminary data of the ACT NOW Current Experience retrospective chart review were:

1) Of infants evaluated for NOWS, medical professionals treated 38.6% with pharmacologic therapy.
2) Of infants treated with pharmacological therapy, the primary medications to control NOWS signs were morphine (86.1%) and methadone (12.9%).

Site Practice for Weaning Strategies of Pharmacological Treatment for NOWS: Multiple clinical guidelines from IDeA States Pediatric Clinical Trials Network and the Neonatal Research Network were reviewed to understand the extent of variation in weaning strategies for morphine and methadone. Among centers that use morphine, weaning strategies included reduction by a fixed dose (n=2), 10% of the stabilization dose (n=6), or 10-20% of the stabilization dose (n=3). Among centers that use methadone, weaning strategies included reduction by a fixed dose with changes in frequency of dosing (n=2), reductions by 10% of that stabilization dose (n=1), and reductions by greater than 10% of the stabilization dose (n=3). This review supports a wide range of clinical practices for pharmacologic treatment of NOWS.

Site Practice after Cessation of Pharmacological Treatment for NOWS. Seventeen ISPCTN and NRN sites submitted guidelines and protocols they use to treat infants with NOWS (morphine use: 12 sites, methadone use: 5 sites). In eight of the 17 guidelines, there were specific directives that clinical teams should monitor NOWS infants receiving pharmacological therapy in the hospital for at least 48 hours after treatment cessation. In the other nine guidelines, there were no comments on the duration of observation after pharmacological treatment cessation.

NOWS Infants Cost of Care. Data was obtained from one ISPCTN site to provide an estimate of the ***costs*** of care for NOWS infants. The cost was $869 per day per infant, which represents the average daily cost among 86 infants born between October 2017 and September 2018. Infants had an average length of hospital stay of 19.4 days, and medical professionals cared for these infants in a family care center that was part of a newborn nursery. The family care center promotes non-pharmacological therapy for newborns exposed to opioids and provides the opportunity for mothers to room in and breast-feed, if there are no contraindications. Costs at hospitals that care for opioid-exposed infants in the NICU may be substantially higher.

3.3.4. Rationale and Summary

Medical professionals pharmacologically treat NOWS infants when non-pharmacological therapy is inadequate to control NOWS signs. The survey data indicate that medical professionals pharmacologically treat a substantial proportion of NOWS infants. There are heterogeneous practices in all aspects of pharmacological treatment (treatment thresholds, initiation, medication type, initial dose, second-line and third-line medications, weaning algorithm, and home therapy). One trial cannot address all the knowledge gaps, and there is limited evidence to guide current clinical management. Clinical trials for this group of patients are challenging for multiple reasons. First, multiple prior randomized trials

closed before meeting the projected sample size due to an inability to enroll subjects (15, 17, and 18). Second, hospitals and medical professionals vary in their NOWS treatment practices. Third, although a larger number of hospitals use morphine to treat NOWS, recent clinical trial data suggests that medical professionals may shift to using methadone as the primary opioid for NOWS treatment (18).

Given the uncertainty of the specific opioid medical professionals will use to treat NOWS in the future, the ideal clinical trial would inform clinical practice for the use of either morphine or methadone. To that end, the proposed study is a pragmatic trial to determine whether a rapid-weaning intervention reduces the number of days of opioid treatment, compared to a slow-weaning intervention, and we powered the proposed study to detect a two-day difference in the length of treatment. Hospitals will be able to use either morphine or methadone with the knowledge that we may find a positive treatment effect for both, one, or neither drugs. We are planning secondary analyses to separately examine the results for each opioid.

The rapidity at which a clinical team can perform weaning with infant tolerance without recurrence of NOWS signs is unknown. In a randomized trial of morphine versus methadone in which clinical teams weaned the drug by 10% of the stabilization dose (18), 48% of morphine-treated and 38% of methadone-treated infants needed dose escalation. With progressive increases in the percent reduction of drug dose, there will, presumably, be an increase in frequency of recurrence of NOWS signs that will mitigate the benefits of more rapid weaning. A 15% reduction of drug dose is large enough to yield important decreases in the length of treatment, which may enable earlier transition out of the hospital and decreasing healthcare costs.

Shortening the weaning phase of NOWS treatment has the potential to impact healthcare costs and minimize the separation of the mother-infant dyad. Opioid use disorder is estimated to occur in 6.5/1000 hospitalizations for infant delivery (30). This allows an estimate of cost savings for infant's ≥ 36 weeks gestations:

- Births per year in the US: ≈ 4,000,000 births
- Percent births ≥ 36 weeks: ≈ 90% x 4 million → 3,600,000
- Opioid exposed: 6.5/1,000 deliveries
- Total opioid exposed: 6.5 x 3600 → 23,400
- Opioid exposed receiving pharmacological treatment: 38.6% x 23,400 → 9032
- Cost of care/day: $869 x 9032 → $7,848,808

A treatment reduction of 2.0 days would reduce healthcare costs by more than $15.7 million per year across the United States. Potential cost savings would be even greater for hospitals that care for infants with NOWS in facilities with higher levels of care (e.g., NICU, special care nurseries).

If successful, this clinical trial would achieve the overarching goals of research initiatives for NOWS (8). Specifically, it would limit ongoing opioid exposure for infants, minimize separation of the mother-infant dyad, and reduce healthcare expenditures.

SECTION 4. METHODS

4.1. ELIGIBILITY CRITERIA

4.1.1. Inclusion Criteria

4.1.1.1. Hospital Level

1) Hospital provides pharmacologic treatment to at least an average of 12 opioid exposed infants each year
2) Hospital uses a scoring system to assess for signs of NOWS (original or modified Finnegan Neonatal Abstinence Scoring system, Eat-Sleep or Console)
3) Hospital provides opioid replacement therapy with either morphine or methadone as part of pharmacologic treatment of NOWS

4.1.1.2. Infant Level

Infants need to fulfill all of the following criteria:

1) Gestational age ≥ 36 weeks
2) Receiving scheduled pharmacological therapy with morphine or methadone as the primary drug treatment for NOWS secondary to maternal opioid use
3) Tolerating enteral feeds and medications by mouth

4.1.2. Exclusion Criteria

4.1.2.1. Hospital Level

1) Hospitals discharge> 10% of infants from the hospital on opioid replacement therapy on average per year

4.1.2.2. Infant Level

Any of the following is an infant level exclusion criterion:

1) Major birth defect (e.g. gastroschisis)
2) Any major surgery (minor surgery [e.g., circumcision, digit ligation, frenulectomy] is not an exclusion)
3) Hypoxic-ischemic encephalopathy
4) Seizures from etiologies other than NOWS
5) Treatment with opioid for reasons other than NOWS
6) Respiratory support (nasal cannula or greater) for > 72 hours
7) Planned discharge from the hospital on opioids
8) Use of other opioids (e.g., buprenorphine) as primary drugs for treatment
9) Weaning of morphine or methadone as the primary treatment of NOWS has started

4.2. DETAILED STUDY PROCEDURES

4.2.1. Overview

Table 3. Schedule of Activities

Activity/Event	Study Time Period													
	Prior to Birth	Prior to Randomization			Randomization	Initiation of Study Intervention/Weaning	Completion of Study Intervention/Weaning	Post Intervention Evaluation	Hospital Discharge	1 Month Post Discharge	6 months of age	12 months of age	18 months of age	24 months of age
		At Risk for NOWS	Initiation of Pharmacological Treatment	Stabilization (opioid dose that controls symptoms)										
Prenatal consultation	X													
In-utero opioid exposure	X	X												
NOWS Scoring		X												
Non-pharmacologic bundle		X												
NOWS symptoms present		X												
Morphine or methadone treatment initiated			X											
Screening	X	X	X											
Start of stabilization dose				X										
Consent	X	X	X											
Randomization					X									
Baseline data collection (includes maternal and infant medial history, infant measurements at birth, etc.)					X									
Eligibility confirmed, stabilization dose tolerated					X									
Wean morphine or methadone						X								
Monitoring of serious adverse events						X	X	X	X					

Activity/Event	Study Time Period													
		Prior to Randomization												
	Prior to Birth	At Risk for NOWS	Initiation of Pharmacological Treatment	Stabilization (opioid dose that controls symptoms)	Randomization	Initiation of Study Intervention/Weaning	Completion of Study Intervention/Weaning	Post Intervention Evaluation	Hospital Discharge	1 Month Post Discharge	6 months of age	12 months of age	18 months of age	24 months of age
Intervention data collection (includes information on primary drug dose, second or third line drugs, etc.)						X	X							
NNNS assessment (24-48 hours following study drug cessation)								X						
Discharge data collection (includes discharge/transfer/death)									X					
PROMIS Measures (PROMIS)										X				X
Maternal Postnatal Attachment Questionnaire (MPAQ)										X				
Infant weight, length, head circumference									X					X
Caregiver Questionnaire (CQ) (enteral feeds, acute/urgent care and/or ER visits and readmissions)										X	X	X	X	X
Death					X	X	X	X	X	X	X	X	X	X
Bayley Scales of Infant and Toddler Development, Fourth Edition (Bayley-4): Cognitive, Language, Motor														X
Brief Infant-Toddler Social and Emotional Assessment (BITSEA)														X
Contact information update									X	X	X	X	X	

*Procedures occurring at 1 month post discharge may occur within ±3 weeks of stated time point. Procedures occurring at 6, 12, and 18 months of age may occur within ±6 weeks of stated time point. Procedures occurring at 24 months may occur between 22 and 28 months of age. If an appointment was made for a 24 month evaluation prior to 28 months, the data will be used provided the evaluation is performed prior to 30 months.

4.2.2. Patient Recruitment Plan

There are 3 major components to a successful recruitment plan as follows:

1. Understand who is providing care for pregnant patients with an Opioid Use Disorder.
2. Disseminate information to clinics, healthcare providers and the medical community regarding research initiatives coupled with hospital care of the mother and newborn.
3. Identify pregnant mothers prior to delivery and use prenatal consultation to establish trust and provide an overview of newborn care and the clinical trial.

The first two of these components are part of a system level recruitment initiative while the third component is patient specific. The single most important element of the recruitment strategy is the prenatal consultation. If prenatal consultation is not feasible, effective antenatal dissemination of information regarding the clinical trial will be exceptionally important when approaching mothers after delivery. A detailed summary of the Recruitment Plan is provided in **Appendix 3**.

4.2.3. Screening

Research personnel will screen medical records of pregnant mothers to identify mothers who use opioids. Moreover, the research team will screen the charts of infants with known opioid exposure *in utero* and infants treated for NOWS in all areas of the hospital in which infants may receive care (e.g., mother-baby unit, NICU, pediatric floor). We will use hospital-specific practices to identify opioid-exposed infants (e.g., history, urine drug screening, etc.). We will encourage research personnel to use information technology systems within hospitals to facilitate identification of potential participants. After an infant is born, research personnel will evaluate potential infant participants against the inclusion and exclusion criteria to determine if the infant is a potential participant. Research personnel will track the infant to ensure study eligibility by verifying the following: NOWS signs occurred, clinical team initiated morphine or methadone treatment, and weaning after stabilization on an opioid dose has not started.

4.2.4. Consent Procedures

Research staff may reach out to, and obtain consent from, pregnant women and post-partum women of eligible or potentially eligible infants at any of the following times: (a) prior to birth, (b) after birth but prior to the determination of the infant's eligibility, (c) after birth and after infant's eligibility has been confirmed. The legal guardian or legally authorized representative may be approached when the mother does not have custody.

Pregnant-women who are using/used opioids while the infant is *in utero*

Research personnel may approach pregnant mothers who are using (used) opioids while the infant is *in utero.* Research personnel may use site-specific practices to introduce the study and start the consent process prior to the mother giving birth. Additionally, the informed consent form may be completed (signed) prior to the mother giving birth. For those mothers that consent before delivery, the research team will meet with the mother after delivery to obtain written confirmation of her continued willingness to allow her infant to be part of study and for her willingness to be a participant herself.

Eligibility of the infant can only be determined after delivery. The mother is not eligible if the infant is not eligible. The research team will tell all mothers whether or not their infant met eligibility requirements.

Post-partum mothers

Research personnel may approach post-partum mothers of potentially eligible infants as well as mothers of infants known to meet the eligibility criteria.

For mothers that sign the consent prior to the infant meeting eligibility requirements, the mothers will be informed of their infants' eligibility status once that status has been determined.

The time period for approaching pregnant women and post-partum mothers, therefore, includes prenatal clinic visits through completion of stabilization of the infant, but prior to the start of opioid weaning of the infant. The mother is not eligible if the infant is not eligible.

General

Research personnel will obtain informed consent from the infant's parent or legal guardian (legally authorized representative or LAR). If there are any concerns regarding the cognitive status of the mother, the site PI or designee will be consulted. If the infant's mother is cognitively impaired and is unable to provide informed consent to the research study, then an alternative legal guardian may be approached for consent per local guidelines. Sites will follow location-specific requirements for enrollment of wards of the state. If legal guardianship changes, the new legal guardian would be contacted to obtain consent for the study.

Infant-only and Caregiver-only consents

The mother may opt to allow her infant to be in the study, but not be a participant herself. If the mother agrees to allow the infant to be a participant, but not be a participant herself, then she will sign the infant-only consent. Similarly, if the legal guardian is not the caregiver or does not want to be a participant him/herself, but the legal guardian is willing to allow the infant to be a participant, the legal guardian will sign the infant-only consent. If a caregiver is not the legal guardian of the infant, but the caregiver is willing to answer questions about him/herself, the caregiver will sign the caregiver-only consent.

Consents for Custody Changes

Laws vary by state. Sites should consult with appropriate entities (e.g., local university/hospital legal counsel, local IRB, central IRB, study team operational principal investigator, et al.) to ensure the correct consents are signed and new consents obtained as needed.

Remote Consent

To facilitate the consenting process, due to (a) the ongoing COVID-19 pandemic, (b) the potential for change in guardianship, and (c) the potential for a non-emancipated minor mother reaching legal age of majority, remote consenting will be allowed. When conducting remote consent, all communications will be done via HIPAA-compliant methods such as telephone, personal delivery of documents, US postal service, REDCap or other compliant electronic platform. The remote consent process will parallel the consent process used for in-person consenting. The only difference will be the method(s) of communication. The study team will ensure that, as with in-person consenting, the participant is given sufficient opportunity to ask questions, is able to understand the nature of this study and what participation entails. The study team will ensure the participant is provided a copy of

the final, completed consent, signed by all parties involved, including the research team member who obtained consent and, when applicable, the site investigator. This final, signed consent will be provided via a HIPAA-compliant method or a method that the participant has agreed to in writing. The study team members working on the consenting process will ensure that any participant who is consenting remotely has the authority to consent.

Participant transfer between enrolling sites

When an enrolled participant(s) needs/want to follow up with a different study site, the original enrolling site will obtain and document verbal consent from the parent/LAR to disclose her/his contact information to the new site. Written consent will not be required for this process. The new site will contact the parent/LAR to obtain site-specific informed consent and HIPAA before completing any study-related activities at the new site. Alternatively, if desired by the parent/LAR, the enrolling site may provide the new site contact information to the parent/LAR and the parent/LAR can contact the new site themselves.

4.2.5. Randomization Procedures

Stratification. We will stratify randomization of infants by hospital. Stratifying by hospital will be critical to minimize the chance of differences between intervention arms in hospital practices, provider practices, and maternal characteristics. Stratification acknowledges that hospitals may have different practices than affiliated hospitals of a given center.

Randomization. We will randomly assign infants to intervention arms of either rapid weaning (15% decrements from the stabilization dose) or slow weaning (10% decrements from the stabilization dose). The Neonatal Research Network Data Coordinating Center (NRN DCC) will centrally randomize participants. They will develop an allocation sequence with randomly varying block sizes, and they will implement this sequence through a central process that will be available 24 hours each day. The NRN DCC will independently randomize multiple births. Pharmacy personnel of each participating hospital will be the only staff with access to group assignment.

4.2.6. Study Intervention and Comparison

This will be a pragmatic, randomized, blinded trial of opioid weaning to determine whether more rapid weaning, compared to slow wean, will reduce the number of days of opioid treatment in infants receiving morphine or methadone as the primary treatment for NOWS. **Figure 2** illustrates when the study interventions will occur during the hospitalization.

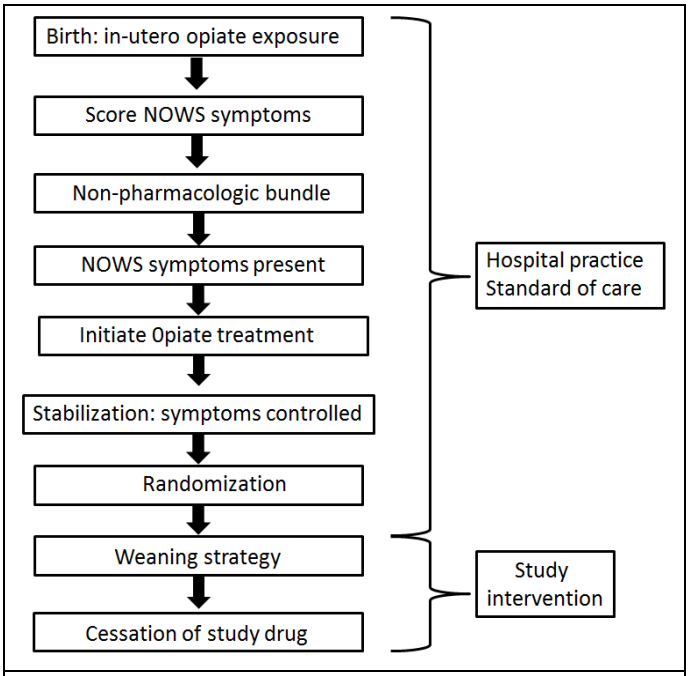

Figure 2. Overview of Study Timing and Intervention

Consistent with the pragmatic design, hospitals will use their specific management practices for opioid treatment among NOWS infants after birth and prior to randomization and the start of opioid weaning. This may include the following management practices:

- Location of care of the infant (mother-baby unit, NICU, Pediatric floor etc.).
- Frequency of monitoring of vital signs and use of cardiopulmonary monitors.
- A non-pharmacological bundle to control NOWS signs. We will recommend a standardized bundle, but hospitals will be able to optimize it for their own use.
- Use of breast milk and breast feeding.
- Scoring assessments of NOWS signs.
- Scoring criteria to initiate opioid therapy.
- Participation in the Eat, Sleep and Console clinical trial[1].
- Choice of opioid (morphine or methadone) as the primary treatment and dosing to initiate pharmacological therapy.
- Initiation and adjustment of dosing of second-line and third-line drugs for NOWS signs (e.g., phenobarbital, clonidine) if NOWS signs are not adequately controlled with an opioid.
- Duration of stabilization whereby the clinical team controls NOWS signs before they initiate opioid weaning.

[1] Eat, Sleep and Console (ESC) is a step wedged, cluster randomized controlled trial to determine if a simplified infant assessment of infants exposed to opioids would reduce the percent of infants treated with pharmacological therapy compared to using a Finnegan score. The trial is being conducted among hospitals of the ISPCTN and NRN.

Study Intervention. We will randomize infants to either a rapid-wean intervention arm or a slow-wean intervention arm (**Figure 3; Table 4**). Infants in the rapid-wean intervention arm will undergo opioid reduction by 15% of the stabilization dose whenever the clinical team weans the opioid. The clinical team will terminate the opioid when the infant can tolerate 25% of the stabilization dose without NOWS signs. Infants in the slow-wean intervention arm will undergo opioid reduction by 10% of the stabilization dose when the clinical team weans the opioid. The clinical team will terminate the opioid when the infant can tolerate 20% of the stabilization dose without NOWS signs.

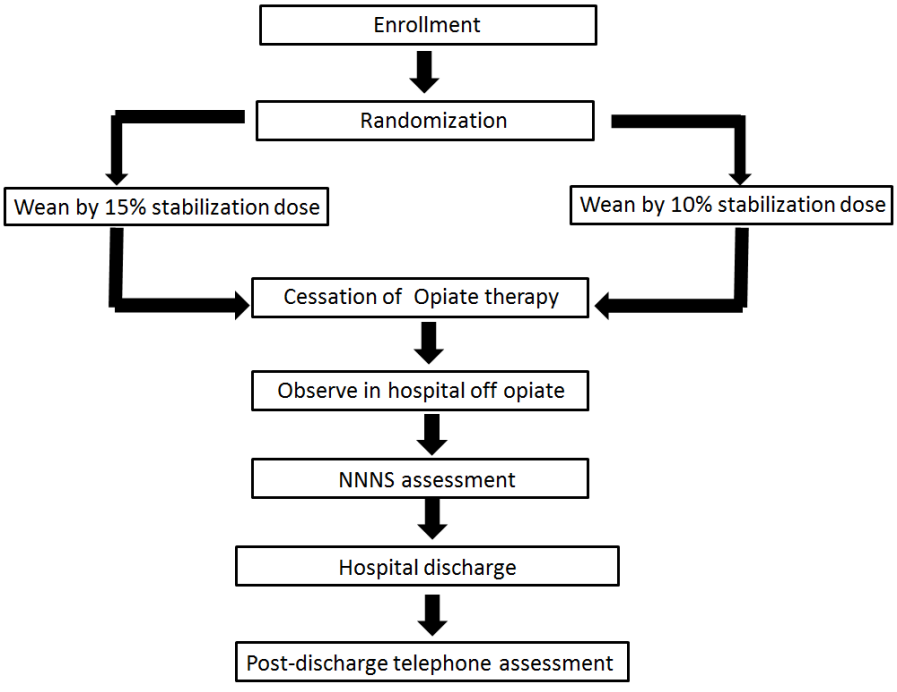

Figure 3. Overview of the Study Interventions

Table 4. Dose Levels of the Rapid-Wean and Slow-Wean Interventions

Dose	Rapid wean: % of stabilization dose	Slow wean: % of stabilization dose
Stabilization Dose	100	100
Dose level A	85	90
Dose level B	70	80
Dose level C	55	70
Dose level D	40	60
Dose level E	25	50
Dose level F	Placebo	40
Dose level G	Placebo	30
Dose level H	Placebo	20

The research team will distinguish dose levels from study steps for the clinical team and the pharmacy during training in-services. There are eight dose levels for the rapid- and slow-wean intervention arms, each representing the amount of opioid the clinical team will administer. Study steps represent the number of time intervals between different dose levels. If opioid escalation does not occur, the infant will receive eight dose levels in eight study steps. However, if there are escalations, the clinical team will need to repeat dose levels and there will be more study steps than dose levels. The distinction between dose level and study steps is depicted in **Table 5**.

Table 5: Differences Between Dose Level and Study Steps for Study Drug Escalation

Steps	Rapid-Wean Intervention		Slow-Wean Intervention	
	Dose Level	% of Stabilization Dose	Dose Level	% of Stabilization Dose
Step 0	Stabilization	100%	Stabilization	100%
Step 1	Dose level A	85%	Dose level A	90%
Step 2	Dose level B	70%	Dose level B	80%
Step 3	Dose level C	55%	Dose level C	70%
Step 4	***Dose level B***	***70%****	***Dose level B***	***80%****
Step 5	Dose level C	55%	Dose level C	70%
Step 6	Dose level D	40%	Dose level D	60%
Step 7	Dose level E	25%	Dose level E	50%
Step 8	Placebo	Placebo	Dose level F	40%
Step 9	***Placebo***	***Placebo****	***Dose level G***	***30%****
Step 10	Dose level E	25%	Dose level F	40%
Step 11	Placebo	Placebo	Dose level G	30%
Step 12	Placebo	Placebo	Dose level H	20%

The asterisks indicate that the dose level at a given study step was not successfully completed and resulted in an escalation. The pharmacy will track dose levels to know where an infant is within a rapid- or slow-wean intervention arm. The clinical team will be blinded to the dose level and will only be aware of the study steps. Both the rapid- and slow-wean intervention arms are depicted to indicate that if each intervention arm has the same number of escalations, the study steps will be identical. This is critical to maintaining the clinical team blinding.

Choice of Opioid and Dose Frequency.

- The choice of opioid will be per individual hospital practice.
- The dose interval for morphine will be either every 3 or 4 hours, per hospital practice.
- The dose interval for methadone will be every 8 or 12 hours, per hospital practice.
- **Appendices 4-7** illustrate **EXAMPLES** of the magnitude of difference in doses between the rapid- and slow-wean intervention arms. The appendices list the absolute dose of morphine (**Appendices 4 and 5**) or methadone (**Appendices 6 and 7)** that infants will receive based on dose frequency. We will determine the dose on the day of randomization for enrolled infants by hospital practice, and will likely differ from the values listed in **Appendices 4-7**.

Changes in Opioid Dose. The following are general considerations for **both** rapid- and slow-wean intervention arms from the first weaning dose to cessation of study drug:

- The clinical team will use hospital specific tools to determine the severity of NOWS signs (Finnegan; modified Finnegan; Eat, Sleep, Console; etc.).

- The clinical team will assess infants for NOWS signs every three or four hours prior to care times (clinical assessment, vital signs, and feeding).
- The clinical team will use hospital thresholds of NOWS signs (e.g., wean if all Finnegan scores are < 8, escalate for an average of three scores ≥ 8 or two scores ≥ 12) to trigger changes in study drug dose.
    - We will have one exception to hospital thresholds for changes in opioid dose based on a prior randomized trial (31). Clinical teams will give an infant whose NOWS score is above the threshold for an increase in dose the current dose, feed the infant, and rescore the infant within one hour of the start of the feed. We will use the lower of the two scores to examine serial scores.
- We will provide each hospital's pharmacy a dosing calculator (**Appendix 8**). After randomization, the pharmacy will input the weaning intervention (wean by 10% or 15% of the stabilization dose), the stabilization dose (mg/kg/day), the infant's weight, and the dosing interval (every 3, 4, 8, or 12 hours) to identify the steps of the intervention arm. The dosing calculator will provide the absolute dose (mg) at each step of the intervention arm.
- Frequency of dose changes for **weaning**:
    - We will encourage clinical teams to wean study drug at least every 24 hours.
    - Clinical teams may wean infants at ≤ 24 hours of a given dose (< 8 doses when given every 3 hours, < 6 doses when given every 4 hours, < 3 doses when given every 8 hours and < 2 doses when given every 12 hours), per hospital guideline.
    - Infants not weaned by 24 hours of a given dose will enter a 12-hour period of study protocol guidelines (**Figure 4**). During this 12-hour period, the clinical team **must** wean infants who do not meet hospital specific criteria for escalation. Hospitals do not need to use the total 12-hour period to either wean or escalate if the infant meets the criteria prior to 12 hours. The research team will use dedicated in-services for all clinical teams of participating hospitals prior to study start on the specifics of the trial intervention including the 12-hour study protocol guideline.
    - The clinical team will order, "wean opioid per protocol" to trigger weaning.

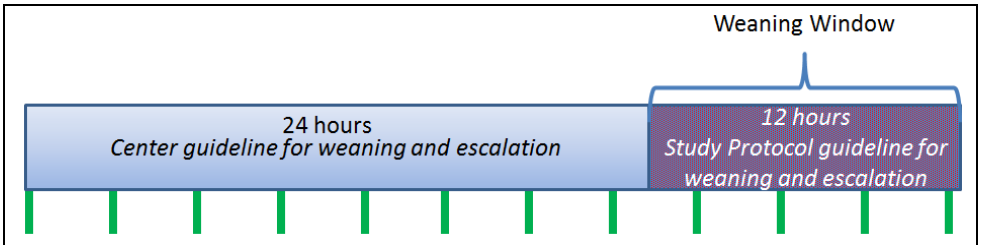

Figure 4. Overview of the Time Periods Used by Clinical Team to Either Wean or Escalate Study Drug. A 24-hour period for weaning or escalation, per hospital guidelines (light blue bar). Multiple vertical green lines represent dosing intervals; in this example the infant is receiving an opioid every 3 hours. If the opioid dose does not change after 24 hours of dosing, the infant enters a 12-hour period of study protocol guideline (purple bar) to ensure that hospitals either wean or escalate and do not remain on the same dose. This approach will be applied to both weaning interventions.

- Frequency of dose changes for **escalation**:
    - Clinical teams may escalate the opioid at any time during the study intervention based on hospital guidelines; clinical teams do not need to wait for 24 hours of dosing.
    - The clinical team will order, "Escalate opioid per protocol" to initiate escalation.
    - When the clinical team orders opioid escalation, the pharmacy will resume the preceding step of the intervention arm. For example, an infant receiving placebo in the rapid-wean intervention arm will escalate to the last opioid dose (25% of the stabilization dose). The clinical team will maintain the escalated dose for 24 hours, and then follow hospital guidelines to evaluate subsequent changes in drug dose.
    - There are no limits on the number of escalations or resumptions of opioid for either intervention arm.
    - Escalation of the study drug dose is the mechanism to address NOWS signs that require additional pharmacotherapy per each hospital's specific assessment tool. Spot doses or rescue doses are not part of this trial intervention
- We provide examples of decisions to wean or escalate opioid within a 24-hour period using a hospital guideline and a 12-hour period of protocol guideline (see **Appendix 9**).
- The pharmacy will inform the clinical team when an infant has two dose levels remaining, which will allow the clinical team to be timely with discharge preparation.

Exiting the Study Intervention. Infants will exit the study intervention without unblinding (but remain in the trial) if they have not weaned off study drug by 35 days (inclusive of the 35th day) from the first weaning dose. This represents more than twice the median and mean length of treatment for the morphine arm in the Davis et al. trial (18). This will avoid prolongation of treatment and length of hospital stay due to inability to tolerate the intervention guideline.

Other Criteria to Exit the Intervention.

- Participant who cannot ingest anything by mouth and needs intravenous opioid due to an increase in acuity or need of an operative procedure.
- Unable to take enteral opioid medication
- Participant who has a serious adverse event, including seizures, increased respiratory support, or intravenous fluid for increased stool output.
- Parents or legal guardians wish to withdraw their infant from the intervention.
- The clinical team feels it is in the best interest of the infant to be withdrawn from the intervention.

Post Intervention. Similar to clinical practice, the clinical team should monitor participants who have weaned off study drug for 48-72 hours prior to discharge to ensure that recurrence of NOWS signs do not occur. If there is a recurrence of NOWS signs during the 48-72 hour post-intervention period, and if that recurrence merits pharmacologic therapy per the institution's guideline, study drug will be restarted at the prior dose of the rapid wean (25% of stabilization dose) or the slow wean (20% of the stabilization dose) interventions. Tolerance for weaning will then be re-evaluated after 24 hours of study drug administration. When the infant has been off the opioid and prior to discharge, a trained examiner will administer the NNNS. The assessment takes approximately 20-25 minutes to complete.

We will not administer the NNNS at the same time relative to the last opioid exposure due to the unpredictable number and timing of opioid escalations in each weaning intervention and to avoid potential unblinding of the intervention.

Data Collection. We will collect data about maternal drug use and medication assisted treatment programs, obstetric history, delivery events, out-born status, infant demographics, NOWS signs, initiation and stabilization of opioid treatment, use of second- and third-line drugs, start and end of the study intervention, adverse events, study outcomes, NNNS examination results, length of hospital stay, and post-discharge maternal assessment.

4.2.7. Blinding/Masking

We will blind all clinical providers (e.g., nurses, physicians, nurse practitioners, and physician assistants), parents, and research personnel to group assignment and opioid dose during the intervention. Pharmacy personnel will be the only unblinded individuals.

To maintain treatment blind, the volume of opioid will remain constant throughout the intervention for the rapid-wean and slow-wean intervention arms. At the time of opioid dosing, infants will receive one syringe with study drug at a volume equivalent to the volume of the stabilization dose, or a volume greater than the stabilization to facilitate maintaining a set volume (e.g. a stabilization dose of 0.28 ml may be set at 0.5 ml for ease of drawing up medication with saline during weaning). As infants progress through the dose levels, the research pharmacist will reduce the opioid volume and the pharmacist will make up the difference by normal saline so that the volume of the syringe is constant throughout all dose levels. To ensure that infants in the rapid-wean intervention arm have an equal number of study steps as infants in the slow-wean intervention arm, the pharmacy will use a placebo (normal saline without opioid) for three dose levels. **Appendix 10** provides examples of the use of placebo when escalation or resumption of opioid occurs in the rapid-wean intervention arm. Depending on the timing of escalations, the three placebo dose levels do not need to occur consecutively. We will label the study drugs as either morphine/study drug and the respective volume or methadone/study drug and the respective volume.

4.2.8. Control or Monitoring of Co-interventions

The clinical team may initiate treatment of NOWS signs with second- and third-line drugs after randomization, per hospital indications. The clinical team may escalate or wean the dose of these drugs during the study intervention per hospital guidelines.

4.2.9. Primary Outcome

The primary outcome will be the number of days of opioid treatment (used as primary treatment), including escalation, resumption, and spot treatment, from the first weaning dose to opioid cessation. We will assess the primary outcome by analyzing data from all infants undergoing rapid-wean, compared to slow-wean, with morphine or methadone. Predefined secondary analyses will examine the results for each opioid separately. We will define days on a 24-hour basis, e.g., 18 hours will represent 0.75 days. We will express days and dosages to the nearest hundredth, and we will round up at five. Days of opioid treatment is a single outcome that will be a function of a) the weaning algorithm and b) the extent of recurrence of NOWS signs. The use of hospital guidelines combined with study protocol

guidelines will ensure that NOWS signs deemed clinically important result in appropriate treatment of the infant.

4.2.10. Secondary Outcomes

Secondary outcomes are listed in **Section 3.2.**

4.2.11. Safety Outcomes

Rapid weaning, compared to slow weaning, of opioid treatment for NOWS could precipitate an increase in withdrawal signs. As described in the study intervention section, clinical teams will provide infants with opioid treatment if the assessment used by the hospital justifies escalation or resumption of an opioid in either weaning intervention arm. The latter approach is identical to clinical practice.

4.2.12. Adverse Events

All study personnel will assess for adverse events from the start of study drug to hospital discharge (i.e., "study period" in corresponding CRF) while being blinded to the weaning intervention. Adverse events will include the following:

Seizures. The clinical team will evaluate abnormal movements for potential seizure activity. A seizure is defined clinically as a paroxysmal change in neurological function including motor, behavioral and/or autonomic function. If there is a high index of suspicion for seizures that results in a change of clinical management (e.g., escalation of care, initiation of anti-epileptic drugs, re-initiation or escalation of morphine/methadone for presumed seizure activity), infants should exit the weaning intervention and clinical management of NOWS should be assumed by the clinical team. We do not know the frequency of seizures during the weaning phase with current maternal and infant treatment. Researchers reported clinical seizures in 2% to 11% during the acute phase of abstinence from infants born in the 1960s to 1970s when treatment approaches differed (32-34). EEGs were performed in a small group of infants in these reports (< 10%, [33, 34]) and firm conclusions cannot be drawn. More recently, small cohorts of infants at risk or treated for NOWS have been investigated with EEG. Amplitude integrated EEG recordings in 9 infants did not indicate seizures but did have abnormalities of background and sleep cycles (36). Among 40 infants with NOWS referred for clinical seizures, EEG and video EEG indicated an abnormal background in 27.5% and electrographic seizures in 7.5% (36). The latter does not represent the frequency of seizures among infants with NOWS since this report only reported on infants with presumed clinical seizures.

Stool output. An increase in stool output that the clinical team treats with intravenous therapy.

Respiratory Disturbances. Tachypnea (respiratory rates > 80 bpm consistently recorded over 4-6 hours with decreases in oxygen saturation < 85%), shallow breathing (respiratory rates < 30 bpm consistently recorded over 4-6 hours with decreases in oxygen saturation < 85%), or increased respiratory support (nasal cannula or greater for infants previously on room air).

Feeding Strategy. A change in feeding strategy (e.g., IV fluids) due to poor feeding or emesis.

Other Adverse Events. This will include any change in clinical status during the weaning interventions that is clinically significant by the Site Principal Investigator.

4.2.13. Serious Adverse Events

All study personnel will consider adverse events serious if they include any of the following:

1) Death

2) Life threatening adverse event
3) Inpatient hospitalization or prolongation of existing hospitalization
4) Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) Important medical events that may not result in death, be life-threatening, or require hospitalization, but based on medical judgment may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above in this definition.

Participants with serious adverse events will exit the intervention without unblinding the treatment intervention assignment, unless the clinical team considers unblinding essential to the provision of clinical care. The clinical team will assume the care of a participant who exits the intervention, and we will provide the current dose of opioid to the clinical team.

4.2.14. Compliance Monitoring

Strategies to improve or monitor adherence to the study protocol will include the following:

- Monthly recruitment reports of infants screened and enrolled (accrual figures)
- Monthly reports detailing data received at the NRN DCC, data consistency, missing data, performance measures, and adherence to the study protocol (with appropriate measures taken to preserve the blinding of study personnel and investigators)
- Supplementary blinded reports requested by the study investigators or subcommittee that do not disclose allocation group specific outcomes (primary, secondary, or any safety outcomes).

The DCC will generate the aforementioned reports.

4.2.15. Data Quality Monitoring and Assurance

To assure the quality of the data collected, the trial investigators will conduct training sessions on protocol implementation, data acquisition and data transfer. Sites will be required to attend a mandatory training session that engages multiple research team members, including at least one site investigator, one study coordinator, and one data entry staff. This training will consist of a walkthrough of the protocol, randomization procedures, study intervention, data collection procedures, the Manual of Operations (MOP), and demonstration of the electronic data capture system. The training will provide guidance specific to accuracy of data acquisition for the research coordinators at each site. The data collection forms will be piloted by a subset of sites to minimize the potential for errors. Additionally, in-depth pharmacy training will be held with site pharmacists that will consist of a walkthrough of the protocol, randomization procedures, study drug dispensing, blinding, and demonstration of the EDC. Sites will be required to attend both the protocol and pharmacy training prior to study launch. Sites will also be required to attend annual protocol refresher sessions until enrollment is complete.

The NRN DCC will employ a mixed method data quality monitoring approach that will involve a combination of the following methods: centralized monitoring, chart re-abstraction, and on-site monitoring.

4.2.15.1 Central Monitoring

Central/remote monitoring will incorporate a variety of methods to detect and resolve potential data quality issues. Within the EDC, preprogrammed data edit checks (e.g., out-of-range values, required fields, skip patterns etc.) will trigger queries to hospitals in real time (e.g., upon data entry). The NRN DCC will also manually review the data monthly, which may result in the data manager manually entering queries in the EDC that site study staff must complete. Email communications with the site will be used to resolve more complex questions about the data.

The NRN DCC will generate study-level and hospital-level status reports that will be updated and reviewed on a monthly basis (see **Section 4.12.14**). These reports will identify issues such as missing forms, major protocol violations, or safety events that require follow up. The trial subcommittee will then discuss these study-level and hospital-level status reports on monthly subcommittee calls to identify overall study and hospital trends that suggest deviations from the specified protocol procedures, data quality concerns, or occurrence of safety events of concern. Sites identified with concerning trends will meet with selected members of the trial subcommittee to discuss the errors and potential solutions. Following the conference call, if the site is identified again with concerning trends, the sponsor will meet with the site and remediation plan will be requested.

4.2.15.2 Chart Re-abstraction

The site research team will re-abstract a subsample of their hospitals charts and assess the error rate. Re-abstraction will focus on critical data elements related to the primary and secondary objectives of the protocol. The number of charts to be re-abstracted for each 6-month interval will be based on the number of patients who enroll in the study during the 6-month period at each site as shown below:

No. of patients enrolled in a 6-month period	No. of charts to be re-abstracted
0	0
1-14	1
15-24	2
25-34	3
35-44	4
45-54	5
55-64	6

The DCC will provide sites with the randomly selected subject IDs for re-abstraction. The site research team will identify an independent site Quality Control (QC) abstractor who will re-abstract and enter data into the EDC only for the QC process and will not abstract study data while QC activities are taking place. The DCC will generate a discrepancy report comparing study data abstracted by the site with the source information abstracted by the independent QC abstractor. The site manager will hold a QC Review Meeting with the independent site QC abstractor, study coordinator, and site abstractor(s) to review the discrepancies and identify errors. Together they will discuss and document the corrective action for each error identified. The DCC will create manual queries in the EDC to make any necessary corrections to the data that were identified during the QC Review Meeting. The research team will provide hospitals that have an error rate above the predefined threshold (five errors per review) with additional training, a hospital-specific assessment of the data collection process, and suggestions for

process improvement. The research team will track hospitals by their error rates. The research team will share practices of those hospitals with exceptionally low error rates with hospitals working to improve their own process. The trial subcommittee will review error rates and re-abstraction data during monthly team calls. If errors exceed five errors per review, on two consecutive reviews, a remediation plan will be requested and shared with the study sponsor.

4.2.15.3 Site Monitoring Visits

Concerning trends identified through centralized monitoring and/or re-abstraction may prompt site monitoring visits. Staff from the Coordinating Center and NIH/NICHD personnel will visit the site(s) with concerning trends in order to ensure data quality and regulatory compliance and to evaluate the performance of site investigators and staff. Site monitoring visits will be structured and planned in advance. They will involve onsite review and inspection of study participant charts, essential documents, and research staff qualifications and responsibilities. It may also include direct observation of study procedures and protocol implementation, as well as inspection of facilities and pharmacies and interviews with key stakeholders and senior leadership at the sites. If pandemic related travel restrictions remain in place, such site monitoring visits may also be conducted virtually.

4.2.16. Study Specimens

Not applicable; we will not collect biological specimens during the conduct of this study.

4.2.17. Post-Hospital Procedures

Primary caregiver(s) for infants for whom the protocol study team have obtained informed consent will receive questionnaires via electronic application or via phone interview, if caregiver(s) have limited access to cellular/internet service or prefer this modality of communication. Assessments may also take place in person, if there is a scheduled visit. Caregiver(s) will complete these questionnaires at 1 month after discharge, 6 months, 12 months, 18 months, and 24 months of age. These questionnaires will gather information on infant wellness, and primary caregiver(s) contact information, maternal well-being, infant attachment, and infant behavior. In addition, there will be an in-person follow-up visit with neurodevelopmental assessment at 24 months of age. Study staff will maintain contact in between study assessments at regular intervals. Respondents to these assessments will receive a reimbursement to compensate them for their time.

We will assess maternal well-being with Patient Reported Outcomes Measurement Information System (PROMIS) short forms (37). Standardized short forms examining mental health, specifically the areas of anxiety (PROMIS Short Form v1.0 - Anxiety - 8a 31May2019), depression (PROMIS_SF_v1.0_-_ED-Depression_8a_5-31-2019), anger (PROMIS Short Form v1.1 - Anger - 5a 27Apr2016), life meaning and purpose (PROMIS Short Form v1.0 - Meaning and Purpose - 8a 18Jul2017), and social support (PROMIS v2.0 - Emotional Support Short Form 4a 23June2016) will be completed by the primary caregiver and will be sent to a central location for review by the protocol study team. The standardized short form for each of the PROMIS Measures consists of between four to eight 5-point Likert scale questions. The PROMIS Depression Short form has been validated in the postpartum period and has been found to be strongly correlated with the Edinburgh Postnatal Depression Scale, the most extensively studied measure of depression in the postpartum period (38,39). In addition, the PROMIS anxiety measure has been correlated with the Mood and Anxiety Questionnaire (MASQ) and has been shown to be a valid measurement tool for anxiety in the post-partum period in a sample of parents whose infants were

hospitalized in the NICU (39). Administration takes approximately 10 minutes and includes a total of 33 questions.
The PROMIS Measures will be administered at 1-month after discharge and again at 24 months of age.

We will briefly assess mother-infant attachment with the Maternal Postnatal Attachment Questionnaire (MPAQ; [40]), a 19-item questionnaire that assesses quality of bonding, absence of hostility, and pleasure in interaction. Higher MPAQ scores reflect higher levels of mother-infant bonding. The MPAQ requires approximately 5 minutes to complete, and researchers have validated the MPAQ among postpartum women with substance abuse problems (41). The MPAQ will be administered at 1-month after discharge.

Caregiver(s) will complete the caregiver questionnaire (CQ) to assess enteral feeding, number of ER visits and/or acute/urgent care visits, and hospital readmissions.

We will assess infant neurobehavioral functioning at 24 months of age using the Brief Infant-Toddler Social and Emotional Assessment (BITSEA). The BITSEA is 42-item parent report screener used to indicate social-emotional/behavioral problems in children 12-36 months (42). It will be administered at the 24-month in-person visit. We chose this measure because it is brief, easy to administer, and has good reliability and validity (43,44).

We will assess infant development with the Bayley Scales of Infant and Toddler Development, Fourth Edition (Bayley-IV): Cognitive, Language, Motor at 24 months of age. The Bayley-IV is recognized internationally as one of the most comprehensive tools to assess developmental outcomes in children. With the Bayley-IV, it is possible to obtain detailed information even from non-verbal children as to their functioning. Children are assessed in the 3 key developmental domains of cognition, language, and motor. Reliability and validity of the previous version of the instrument have been well established (45).

4.2.18. Compensation

Participants will be reimbursed for their time according to the tables below. These payments will be provided at the contact time or shortly thereafter. The mechanism of payment (gift card, check, etc.) will be site specific and will be according to each site's mechanism for making such payments.

For those parents/guardians signing the primary consent (parent/guardian+infant):

Contact Time	Participated in	Reimbursement/ Compensation Amount
1-month post discharge (of baby from hospital)	Answering Questionnaires	$50.
Baby 6 months of age	Answering Questionnaires	$50.
Baby 12 months of age	Answering Questionnaires	$50.
Baby 18 months of age	Answering Questionnaires	$50.
Baby 24 months of age	Bringing baby in for in-person Bayley's exam and answering questionnaires	$150.*

* If the parent/guardian participant answers the 24-month questionnaires, but does not bring their child in for the 24-month in-person visit, the parent/guardian will receive only $50.00 for the 24-month time-point.

For those parents/guardians signing the infant-only consent:

Contact Time	Participated in	Reimbursement/ Compensation Amount
1-month post discharge (of baby from hospital)	Answering Infant/child-specific Questionnaires	$25.
Baby 6 months of age	Answering Infant/child-specific Questionnaires	$50.
Baby 12 months of age	Answering Infant/child-specific Questionnaires	$50.
Baby 18 months of age	Answering Infant/child-specific Questionnaires	$50.
Baby 24 months of age	Bringing baby in for in-person Bayley's exam and answering Infant/child questionnaires	$130.*

* If the parent/guardian participant answers the 24-month infant/child-only questionnaires, but does not bring their child in for the 24-month in-person visit, the parent/guardian will receive only $30 for the 24-month time-point.

For those parents/guardians/caregiver signing the caregiver-only consent:

Contact Time	Participated in	Reimbursement/ Compensation Amount
1-month post discharge (of baby from hospital)	Answering caregiver-specific Questionnaires	$25.
Baby 6 months of age	n/a	n/a
Baby 12 months of age	n/a	n/a
Baby 18 months of age	n/a	n/a
Baby 24 months of age	Answering caregiver-specific Questionnaires	$20.

4.3. POTENTIAL RISKS AND BENEFITS TO PARTICIPANTS

4.3.1. Rapid Wean

The rapid wean schedule is used routinely as standard of care at some U.S. hospitals. Among infants in the rapid-wean intervention arm, potential risks of the study intervention include a recurrence of NOWS signs and need to escalate and/or resume opioid treatment. If this trial is successful, potential benefits of the rapid-wean intervention include a shorter duration of opioid treatment, and possibly a shorter length of hospital stay.

4.3.2. Slow Wean

The slow wean schedule is used routinely as standard of care at some U.S. hospitals. Among infants in the slow-wean intervention arm, potential risks include a longer duration of opioid treatment. Benefits of the slow-wean intervention include potentially fewer recurrences of NOWS signs.

4.3.3. Primary Caregiver Well-Being

The research team will assess primary caregiver well-being (e.g., parenting stress, attachment, and bonding, depression, anxiety, etc.) during the follow-up portion of the study. Primary caregiver well-being will be assessed via the five PROMIS Measures and MPAQ questionnaires. It is possible that these questionnaires may reveal that the primary caregiver is experiencing psychological distress potentially requiring support. Mothers who have exposure to opioids during pregnancy may be vulnerable to suicidal ideation.

The study team has determined that a standardized scoring threshold for the PROMIS Depression Measure will be used to identify these individuals. As thresholds specific to postpartum women with opioid dependency have yet to be established and given that severe depression (a t-score >70, or 2 standard deviations above the mean for the normative population is the threshold for severe depressive symptoms) (46,47) is most likely to impact family well-being, a score of >70 was chosen for this threshold.

If a primary caregiver has a t-score >70 on the PROMIS Depression measure, the primary caregiver will be provided with national hotline support numbers within the electronic questionnaire platform. In addition, after the questionnaire is completed in REDCap an email will be automatically generated and sent to the study coordinator and PI. Each site will develop a plan to provide support for the primary caregivers at risk and connect them with local mental health resources in response to those emails. The protocol study team will collect a copy of this plan from each site.

We will train all personnel who administer the PROMIS Measures and MPAQ for appropriate responses if the caregiver expresses suicidal thoughts. This training will include additional questions to gauge the severity of the situation. We will require each hospital to develop a safety plan to provide the research team member immediate access to the Principal Investigator, designee, or other qualified individuals for further evaluation and direction. If there is an immediate concern by the research team member, knowledge of how to access local emergency responses will be available.

4.3.4. Maternal opioid use reporting requirements

The responsibility for determination of whether neonatal opioid exposure warrants mandatory reporting will rest with all mandatory reporters per requirements of those reporters. Participation in the clinical study will not affect reporting requirements.

SECTION 5. ANALYTICAL PLAN

5.1. STATISTICAL ANALYSIS PLAN

5.1.1. Primary Hypothesis

Among infants receiving an opioid (defined as morphine or methadone) as the primary treatment for neonatal opioid withdrawal syndrome (NOWS), a rapid-wean intervention will reduce the days of opioid treatment from the first weaning dose to cessation of opioid compared to a slow-wean intervention.

5.1.2. Secondary Outcomes

Secondary Efficacy Outcomes.

Secondary Outcome 1: Compare the numbers of days of opioid treatment from the first weaning dose to cessation of opioid with a rapid- and slow-wean intervention among infants treated with morphine.

Secondary Outcome 2: Compare the numbers of days of opioid treatment from the first weaning dose to cessation of opioid with a rapid- and slow-wean intervention among infants treated with methadone.

Secondary Outcome 3: Compare the proportions of infants in the rapid- and slow-wean intervention arms who have an escalation or resumption of opioid during weaning.

Secondary Outcome 4: Compare the total amounts of opioid from the first weaning dose to cessation of opioid among infants in the rapid- and slow-wean intervention arms.

Secondary Outcome 5: Compare the proportion of infants who experience initiation and/or escalation of second- or-third line drugs to treat NOWS signs from the first weaning dose to cessation of opioid in the rapid- and slow-wean intervention arms.

Secondary Safety Outcome.

Secondary Outcome 6: Compare the proportion of infants in each intervention arm with safety outcomes of seizures (clinical or EEG), excessive stool output, respiratory disturbances, and feeding tolerance.

Other Secondary Outcomes.

Secondary *Outcome 7*: Compare the proportion of infants in each treatment intervention arm with an atypical neurobehavioral profile prior to discharge on the NICU Network Neurobehavioral Scale (NNNS).

Secondary Outcome 8: Compare the lengths of hospital stay for each treatment intervention arm.

Secondary Outcome 9: Determine assessments of maternal well-being and maternal-infant attachment in each intervention arm.

Secondary Outcome 10: Assessments of growth in each intervention arm.

Secondary Outcome 11: Assessment of infant wellness after discharge and until 24 months of age in each intervention arm.

Secondary Outcome 12: Assessment of infant development to 24 months of age in each intervention arm.

5.1.3. Other Collected Data

Initial descriptive analyses will include weaning intervention group characteristics. We will collect data to characterize the following.

- Stratification data
- Hospital variables: participation in ESC
- Maternal variables (e.g., socioeconomic status, obstetric complications, opioid medication, medication assisted treatment program, non-opioid drugs, cigarettes, alcohol, selective serotonin reuptake inhibitors, and psychiatric diagnoses)
- Infant demographics at birth (e.g., gestational age, birth weight, sex, multiples, growth parameters, out-born, and location of care)
- Characteristics of NOWS treatment (e.g., stabilization dose, age at stabilization, use of adjunctive drugs to the primary NOWS drug treatment)
- Infant characteristics at the start of the intervention (e.g., weight, postnatal age) and when medically ready for discharge per the hospital standard.

We will include the stratification variable (hospital) in regression modeling as a random effect, and we will include stabilization dose and maternal treatment as covariates. With respect to maternal treatment, it will be a categorical variable with four categories:

1) Methadone use
2) Buprenorphine ± naloxone
3) Prescribed opioids other than methadone and buprenorphine ± naloxone
4) Non-prescribed opioids

There will be some mixing among these four groups; therefore, we will use the following rules to classify infants:

- If methadone is used with other opioids, classify as methadone.
- If buprenorphine is used with other opioids, classify as buprenorphine ± naloxone.
- If methadone is used with buprenorphine, classify based on which drug has been in use for a longer time interval.

Depending on the descriptive comparisons across weaning intervention groups, we may add other variables to the regression models such as medication assisted treatment programs. If the difference of a variable across the weaning intervention is statistically significant at a two-sided alpha of 0.05, then we may include the variable as a covariate in the regression models. Beyond the significant difference, we will consider other factors, such as the type of analysis, correlation with other variables in the model, and trial subcommittee discussion about the nature of the potential covariate.

5.1.4. Analysis of the Primary Hypothesis and Outcome

We will determine the outcome of the primary hypothesis on an intention to treat basis. We will assign infants who exit the intervention at 35 days of methadone/morphine treatment either as 35 days of opioid treatment or we will treat them as a censored value at 35 days. We will determine intervention differences of two means by analyzing the average number of days of opioid treatment from the first

weaning dose to cessation of opioid treatment. We will analyze the data using regression models that will include the intervention as a fixed effect and will include maternal treatment and stabilization dose as covariates. We will include site (hospital) in the model as a random effect. The primary test of interest will be the F-test of the intervention effect, and we will report the intervention difference along with 95% confidence interval (CI).

Because of possible censoring and removal of participants due to intervention failure, we will conduct sensitivity analysis of the primary outcome using several methods. The first sensitivity analysis will replicate the analysis, described above, and include other covariates in the model that were significantly different across the two weaning intervention groups. Sensitivity analyses will also be conducted to evaluate the effects of infants who were and were not part of the Eat Sleep Console trial as a covariate or effect modifier (see **Section 5.2.2**). Another possible sensitivity analysis will include non-parametric and/or survival regression (e.g., negative binomial, median regression, or survival analyses), as there is potential for skewness and censoring in the primary outcome.

Finally, sensitivity analysis will include fitting a competing risks model to the data where the possible competing risk states are weaned, parental withdrawal, physician withdrawal, and treatment failure (unable to wean by 35 days of methadone/morphine treatment). We will fit Cox proportional hazards models to the data to estimate the intervention effect and other covariate effects on "cause-specific hazards." The analysis of the "cause-specific hazards" will allow for additional inquiry into the intervention effect on the primary outcome while accounting for competing safety and withdrawal risks.

Descriptive statistics (means, medians, SD, percentiles) for number of days of opioid treatment from the first weaning dose to cessation of opioid treatment will be generated and summarized in a table by treatment group.

5.1.5. Analyses of Secondary Outcomes

We will use the same approach described in the primary outcome analysis to compare the number of days of opioid treatment with only infants receiving morphine as the primary pharmacological treatment for NOWS (Secondary Outcome 1). We will use this same approach to compare the number of days of opioid treatment using only infants receiving methadone as the primary pharmacological treatment for NOWS (Secondary Outcome 2).

We will use adjusted logistic regression models to provide an odds ratio (OR) and 95% Confidence Intervals (CI) for binary secondary outcomes measured only once. These outcomes will include:

- the proportion of infants by intervention arms that escalate or resume opioid medication during weaning,
- for the proportion of infants by intervention arms with an atypical neurobehavioral profile (**Profile 5, Figure 1**),
- the proportion of infants who receive an escalation of a second-line or third-line drug to treat NOWS signs from the first weaning dose to cessation of opioid.

We will adjust these models for the stratification variable (hospital), covariates of maternal treatment and stabilization dose, and baseline variables that may differ between groups by chance. We define the covariates that we may adjust for earlier in this section in the paragraph on other collected data.

We will analyze the secondary outcome of the total opioid exposure from the first weaning dose to cessation of opioid in a similar manner as the primary outcome. We will use a regression model that will include: a fixed treatment effect (intervention arms) and adjustment for the stratifying variable, covariates of maternal treatment and stabilization dose, and baseline variables that may differ between groups by chance as fixed effects. We will include hospital (site) as a random effect. The primary test of interest will be the F-test of the intervention arm effect, and we will report the treatment difference along with 95% CI.

We will measure the secondary outcome of maternal well-being and maternal- infant attachment by using PROMIS Measures and MPAQ total scores. We will analyze these in a similar manner as the primary outcome. We will use a regression model to analyze PROMIS Measures and MPAQ total scores. This model will include a fixed treatment effect (intervention arms), an adjustment for the stratifying variable, and fixed effects for the covariates of maternal treatment and stabilization dose. The PROMIS Measures outcomes are measured at 1-month after discharge and 24-months of age. The models for PROMIS Measures outcomes will include the 1-month after discharge PROMIS Measures outcome as a covariate. The F-test of the intervention arm effect will be the primary test of interest. We will report the intervention arm difference along with 95% CI. We will conduct analyses among the entire group and among those where the biologic mother is the primary caretaker.

We will measure the secondary outcome of infant neurobehavioral functioning using BITSEA scores. The BITSEA consists of two multi-item scales, a Problem scale (31 items) and a Competence scale (11 items). A high score on the Problem scale or a low score on the Competence scale is less favorable. We will analyze these in a similar manner as the primary outcome. We will use regression models to analyze the BITSEA total and subscale scores. This model will include a fixed treatment effect (intervention arms), an adjustment for the stratifying variable, and fixed effects for the covariates of maternal treatment and stabilization dose. The F-test of the intervention arm effect will be the primary test of interest. We will report the intervention arm difference along with 95% CI. We will conduct analyses among the entire group and among those where the biologic mother is the primary caretaker.

We will calculate binomial proportion and their corresponding 95% CI by intervention arm for each of the following safety adverse events: seizures (clinical or EEG), excessive stool output, respiratory disturbances, and feeding tolerance. We will use chi-square tests to compare the proportion of seizures (clinical or EEG), excessive stool output, respiratory disturbances, and feeding tolerances between intervention arms. In addition to unadjusted analyses, we will compare AEs across the weaning interventions by using adjusted logistic regression models that adjust for the stratification variable (hospital), covariates of maternal treatment and stabilization dose, and possibly any baseline variables that were significantly different between weaning interventions. We define covariates that we may adjust for earlier in this section within the paragraph on other collected data.

We will analyze the length of hospital stay in a similar manner as the primary outcome. We will use a simple, unadjusted regression model to analyze the total length of stay and will include a fixed treatment effect (intervention arms). A second regression model will include a fixed treatment effect and will include adjustment for the stratifying variable and covariates of maternal treatment and

stabilization dose. The F-test of the treatment effect will be the primary test of interest. We will report the treatment difference along with 95% CI. Sensitivity analysis will involve time-to-event analyses using survival models to account for skewness and possible censoring of each outcome.

We will analyze the caregiver questionnaire outcomes and the death outcome using a longitudinal GLMM or GEE model appropriate for the outcome type since the data will be collected at multiple time points after discharge. Count data that tend to have more than 0 or 1 events counted will be analyzed using a Poisson model while binary or count data that rarely goes beyond 1 occurrence will be analyzed using a Logistic model. In case of count data that rarely goes beyond 1 occurrence, this data will be transformed to binary data (occurrence/no occurrence). We will present mean outcome ratios for count data (from Poisson models) and odds ratios for binary data (from logistic models) with respect to the intervention effect as well as 95% CI of the intervention effect. All analyses will be adjusted for repeated measures over time, so that patterns of change for these outcomes over time can be assessed by treatment group.

In addition to time of discharge and 24 months of age, anthropometric outcomes will be measured at birth. We will calculate anthropometric z-scores at each of the three assessment periods for the purpose of analysis based on age and gender specific WHO norms. The approach to analyzing weight is given next.

We will provide the mean and SD of infants' weights (z-scores) separately for each treatment group. We will use a mixed linear model to evaluate the effect of treatment arm on weight (z-scores). The model will examine how the treatment means differ (i.e., main treatment effect), how treatment means change over time (i.e., main time effect), and how differences between treatment means change over time (i.e., treatment-by-time effect). We will carry out assessment across 3 time points: birth, hospital discharge, and 24 months of age. The mixed model longitudinal analytical approach allows us to analyze correlated data obtained repeatedly from the same participant and account for the ICC among participants nested within with same clinical site. To account for potential imbalance in key demographic and site-level characteristics, unadjusted and adjusted GLMMs will be fit to the data. Initially, the unadjusted mixed model will include the fixed categorical effects of intervention, time, and intervention-by-time interaction and the random-site effect. We will calculate the point estimates and their respective CIs for the changes in infants' weights for each intervention group and for the difference in the estimated change between intervention groups. Additionally, the team will present the p-value of the difference in point estimates between intervention groups.

We will examine the impact of the treatment arm on length, HC, and infant weight for length (z-scores) using the same analytical methods described for weight (z-scores) above. Additionally, we will provide the mean and SD of infant BMI-z at 24-months for each treatment group. The team will use a GLMM with an identity link to compare average BMI-z between the groups, and the team will report point estimates for the group mean difference along with a 95% CI.

To compare Bayley-IV scores between intervention arms, we will perform a linear mixed-effects model with a fixed effect for the intervention group and a random effect for study site. We will report point estimates for the group mean difference along with a 95% CI, and the team will repeat this analytical approach for each of the Bayley-IV domains.

Descriptive statistics (means, medians, SD, percentiles) for continuous secondary outcomes and frequency based statistics (N and percentages) for binary secondary outcomes will be generated and summarized in a tabular form by treatment group.

5.1.6. Bayesian Analyses

Other randomized trials of NOWS have ended prior to meeting the projected enrollment, indicating the challenges in studying this population (15, 17, and 18). In case of insufficient enrollment, we will pre-specify Bayesian analyses of the final data in addition to the frequentist analyses, defined above. Below, we first define the Bayesian analyses that will mirror the above defined frequentist analyses of the primary outcome.

We will analyze the primary outcome with a linear regression that will include treatment group (intervention arms), stabilization dose and maternal treatment as covariates, and we will include hospital as a random effect. We will use a neutral prior for treatment effect that is centered at a mean difference of 0 and a standard deviation of three, normal (μ=0, σ=3) distribution. For the intercept term, we will use a normal (μ=0, σ=10) prior. For all other baseline covariates in the model, we will use weakly informative neutral normal (μ=0, σ=2) priors. We will use a weakly informative half-normal (μ=0, σ=1) prior for the standard deviation of the random hospital effect. For all models, we will report posterior medians and 95% credible intervals (CrI) for the group mean differences and the probability that a rapid-wean intervention will reduce the days of opioid treatment, compared to a slow-wean intervention. For sensitivity analyses, we will analyze the primary outcome with skeptical and enthusiastic priors. We will center the skeptical prior at a mean difference of two, indicating the view of a skeptic with belief that the study intervention will increase the number of days of opioid treatment by two days. We will center the enthusiastic prior at a mean difference of -2, meaning a priori that an enthusiast expects the study intervention to reduce the number of days of opioid treatment by two days. In both the enthusiastic and skeptic priors, the standard deviation will be three. As with the primary frequentist analysis, sensitivity analyses may be done using Bayesian analyses, where normal (μ=0, σ=2) priors will be placed on all covariates.

Subgroup analysis for secondary outcomes 1 and 2: To estimate possible treatment effect heterogeneity for the primary outcome, we will use a Bayesian hierarchical model with main effects and interaction term between intervention group and type of narcotic (morphine or methadone). This approach allows us to specify a priori how likely (or unlikely) it is for subgroup differences to be present and to shrink the subgroup estimates to the overall mean treatment effect. We will specify a model that allows different standard deviations of the outcome for the two subgroups (as observed in Davis et al). Prior distributions for main effects will be the same as for the primary outcome. Neutral and skeptical priors will be used for the interaction terms. Point estimates of treatment effect and 95% credible intervals will be reported for each subgroup along with probability of subgroup treatment differences.

We will analyze secondary binary outcomes with Bayesian logistic regression models, including treatment group, maternal treatment, and stratification dose as covariates, and we will include hospital as a random effect. We will use a neutral prior centered at 1.0 with 95% CrI of 0.33-3.0 (to allow for large range of ORs) for the treatment effect. In the log OR scale, this prior will be normal (0, SD=0.57), and all other priors will be the same as above.

We will analyze secondary outcomes of the total opioid exposure and assessments of maternal well-being, maternal-infant attachment, infant neurobehavioral functioning, infant development, and growth with a similar linear regression model used for the primary outcome.

We will analyze secondary outcome of length of stay with a linear regression model similar to the one used to analyze the primary outcome; however, we will also fit survival analysis models to study the effects of skewness.

We will implement all Bayesian models via Markov chain Monte Carlo methods (MCMC) by using R or SAS software. For SAS, the procedure will be PROC MCMC. For R, possible software is 'RJAGS' which is an interface to JAGS MCMC software, 'rstan,' 'rstanarm' and 'brms, ' which are packages that interface with the Stan language. For each analysis, we will run three MCMC chains with randomly drawn starting values. We will use a burn-in of 3,000 iterations, with sampling from a further 30,000 iterations for each chain. Thinning will be used as necessary to reduce autocorrelation among the samples to improve posterior sampling. To monitor convergence, we will use trace plots and the Gelman-Rubin convergence diagnostic (Rhat < 1.1 indicating convergence) for all parameters.

5.2. DESIGN CONSIDERATIONS, SAMPLE SIZE, AND POWER ESTIMATES

5.2.1. Overall Trial Design

During our initial sample size analyses, we considered trial designs that would power two hypothesis tests: one test for the weaning effect of morphine and one test for the weaning effect of methadone. These designs accounted for multiple comparison adjustment (adjusted for two comparisons) and unadjusted comparisons. When we adjusted the two comparisons for multiple comparisons using a Bonferroni adjustment, we rejected a test if the p-value is ≤ 0.025, and we would require at least 1,032 randomized infants for 90% power. If we did not use an adjustment, then the required sample size was still at least 826 randomized infants. In both cases, the assumed standard deviation was 6.9 days. If the standard deviation is larger, then in both cases the required sample sizes would be even larger. Given the low probability of enrolling around 1,000 infants, we chose a design that would compare weaning interventions regardless of drug used (morphine/methadone). Given that the chosen design would primarily focus on estimating the weaning intervention effect regardless of drugs, we added two secondary analyses examining the intervention effect within each drug (Secondary Outcomes 1 and 2). In addition to frequentist analyses of Secondary Outcomes 1 and 2, Bayesian analyses are planned to derive evidence that may be clinically meaningful from the limited data available for each drug.

5.2.2. Compatibility with the ESC Trial

We expect that a substantial number of sites in the IDeA States Pediatric Clinical Trials Network and NRN may participate in both this trial and the concurrent Eat, Sleep, and Console (ESC) trial, a stepped-wedge cluster randomized controlled trial that will compare the ESC care approach to usual institutional care with the Finnegan Neonatal Abstinence Scoring Tool (FNAST) or modification thereof. Thus, babies enrolled into the Weaning trial may also be co-enrolled into ESC. This situation presents both statistical benefits and challenges.

The benefits of co-enrollment with the ESC trial mainly derive from better control over variability in site practice differences (that are apparent from the results of the ACT NOW Current Experience Study—a medical record abstraction of 1808 opioid-exposed neonates across 30 clinical centers) that would not otherwise be possible outside of the ESC trial. Specifically, clinical sites have a wide range of practice differences, and there are indications that practice may be drifting increasingly towards ESC because of

the currently well documented limitations of the FNAST approach. This is an especially pertinent issue for the Weaning trial because of its relatively long expected enrollment period of 3.3 years. Without co enrollment into the ESC trial, we may have difficulty knowing when and how site practices imperceptibly shift from FNAST to ESC and the different variations thereof, and imbalance in such site practices could make it difficult to achieve overall balance on this criterion across the Weaning treatment arms. This will likely increase center differences, potentially in an imbalanced manner, increasing the overall variability in the data, which makes it more difficult to detect a treatment signal.

In contrast, co-enrollment into the ESC trial will allow us to precisely know when groups of sites switch over to ESC from FNAST, with all sites having transitioned to the ESC care tool at the end of that trial, which will have a shorter duration than the Weaning trial. Together with randomization within site for Weaning, this ensures that we have precise and detailed information on site practices at all times through the duration of the ESC trial, increased opportunity to achieve overall balance for this aspect of clinical practice across the Weaning treatment arms, and more uniformity in site practices at the end of the trial. This will reduce center differences and provide more detailed information on center practices over time which will reduce the overall variability in the data.

The challenges of co-enrollment mainly involve potential confounding issues between the different interventions being tested across the different trials and any biases that may thus result. However, confounding is less of a concern here because of the following reasons:

a) The two interventions in the two trials are applied at different levels – Weaning tests an individualized intervention whereby each baby within a center is randomized. ESC tests a practice change at the center level using a stepped wedge design, whereby entire groups of sites switch to ESC according to a randomized schedule.
b) Bias will be further minimized by ensuring that the Weaning trial randomizes individual babies within each site (regardless of when it is scheduled to switch over to ESC), using a block randomization approach to assure a relatively equal distribution of babies in each arm within each center within a unit of time. In contrast, ESC uses block randomization (using time as a blocking factor) to randomize entire groups of sites to switch over to ESC.

In order to further address concerns regarding confounding and bias, we will conduct sensitivity analyses by adding a variable that represents whether a baby in the Weaning trial was 1) in the FNAST stage of the ESC trial, 2) in the ESC stage of the ESC trial, or 3) was at a site that was not participating in the ESC trial as a covariate and potential effect modifier for babies in the Weaning trial.

5.2.3. Sample Size and Power Estimates

Eligible infants are those in the ISPCTN and NRN sites that clinical teams are pharmacologically treating for NOWS with an opioid as the primary drug treatment and have a gestational age ≥ 36 weeks (see **Section 4.1**). We used the most recent randomized trial comparing morphine to methadone to determine sample size and power estimates (18). In that trial, researchers enrolled 116 pharmacologically treated NOWS infants from February 2014 until March 2017. The research team randomly allocated 58 infants to morphine treatment and 58 infants to methadone treatment. The standard deviation for the morphine arm was 6.9 days, while the standard deviation for the methadone arm was 8.0 days. We used these statistics to derive sample size estimates (**Table 6**). The total sample size estimates given in Table 6 assume that the clinical team will treat 70% of enrolled infants with

morphine. This trial will enroll a total of 502 infants (251 infants to each of the rapid and slow wean interventions) irrespective of the proportion of infants treated with morphine or methadone.

Table 6. Sample Size Estimates

Power	N per Arm	Total N	Morphine* N	Methadone* N	LOT-difference	SD	alpha
0.9	**251**	**502**	**352**	**150**	**2**	**6.9**	**0.05**
0.9	296	592	414	178	2	7.5	0.05
0.9	337	674	472	202	2	8.0	0.05
0.85	214	428	300	128	2	6.9	0.05
0.85	253	506	354	152	2	7.5	0.05
0.85	288	576	403	173	2	8.0	0.05
0.80	187	374	262	112	2	6.9	0.05
0.80	221	442	309	133	2	7.5	0.05
0.80	252	504	353	151	2	8.0	0.05

*includes infants randomized to either rapid-wean or slow-wean interventions
‡LOT: length of treatment days

A difference of 2.0 days in the length of treatment represents the minimum clinically important treatment effect for clinical care. If we can demonstrate a 2.0-day difference, there will likely be a reduction in hospital resources (bed, nursing, pharmacy, and physician) and cost. In addition, this effect size should facilitate a faster transition out of the hospital and keep the maternal-infant dyad together in a better environment than a hospital. The proposed intervention difference is similar to a recent trial comparing morphine to methadone (18). Group sample sizes of 251 infants per treatment arm (total enrollment, 502 infants) will achieve 90% power to reject the null hypothesis of equal means when the population difference is 2.0 days with a standard deviation of 6.9 days and with a significance level of 0.05 using a two-sided two sample t-test. If the standard deviation is as high as 8.0 days, a similar sample size will achieve 80% power to reject the null hypothesis using a two-sample t-test and a two-sided significance level of 0.05.

With respect to analysis of the Bayley IV at 24 month follow-up, if the FU is at least 60%, then with a two=sided alpha of 0.05 we will be able to detect a difference in any composite score of 5.7 or greater with at least 80% power and will be able to detect a difference in any scaled score of 1.06 with at least 80% power.

5.2.4. Interval Sample Size Reassessment

We defined length of treatment for the proposed trial as the average number of days of opioid treatment from the first weaning dose to cessation of opioid treatment. Due to a lack of available studies with published parameter estimates, we based the standard deviation used in the power calculations (6.9 to 8.0 days) on the number of days of opioid treatment for the *entire* interval of drug treatment, from initiation to cessation of morphine or methadone treatment (18). We anticipate that a

smaller standard deviation may be present in the proposed trial since we are only studying weaning. To address the concerns that the standard deviation may be lower than 6.9 days for our primary outcome, we will perform an interval sample size reassessment.

The interval sample size reassessment will occur after 25% of the enrolled infants are medically ready for discharge, which will be 126 infants, assuming full enrollment of 502 infants. This coincides with the first Data Monitoring and Safety Committee (DSMC) safety review (see **Section 5.5.2**). The NRN DCC will re-estimate the sample size and provide the DSMC with this report. To re-estimate the sample size, we will use the pooled variance estimate calculated across both intervention groups from blinded data observed in 126 study participants. This blinded look at the interim data used for sample size refinement will not require any alpha adjustment in the final primary outcome analysis.

5.3. AVAILABLE POPULATION

In the fall of 2017, a ISPCTN and NRN site survey found that during a one-year period, there were approximately 2,700 infants exposed to opioids, of which, medical professionals pharmacologically treated approximately 43%. Among those treated pharmacologically, medical professionals treated 76% with morphine, 24% with methadone, and 4% with buprenorphine. These observations provide a starting to point to estimate the number of participants available for this trial. However, there is some uncertainty regarding how many NOWS infants would meet the inclusion criteria without meeting any exclusion criteria (Exclusion Criteria, Section 1). In addition, there may be changes in hospital practices within the ISPCTN and NRN given ongoing NOWS initiatives. Multiple clinical trials have not achieved enrollment of the projected sample size (15, 17, and 18), and we expect low consent rates in this population. Use of the Recruitment Plan (**Appendix 3**) was associated with a 35% consent rate at Women and Infants Hospital for the methadone vs morphine trial conducted by Davis et al (18) in contrast to 26% among all participating centers. **Table 7** provides an estimate of the number of infants enrolled per year based on estimates of available infants ranging from 1,250 to 750 and consent rates ranging from 20% to 30%. Twenty hospitals in the NRN and ISPCTN have expressed interest in participation in this clinical trial.

Table 7. Estimated Enrollment per Year

Consent Rate	Enrollment by Consent Rate and Infant Numbers		
	1,250 available infants	1,000 available infants	750 available infants
20%	250	200	150
25%	313	250	188
30%	375	300	225

5.4. PROJECTED RECRUITMENT TIME

Based on the estimates of the available population and a target enrollment of 502 infants, a conservative estimate to complete the trial would be 3.3 years (750 infants available for the trial each year and a consent rate of 20%). This translates to an average monthly enrollment requirement of 12-13 infants. If enrollment is slower than projected, we may consider other hospitals through the National Center for Advancing Translational Science and the National Institutes of Drug Abuse Clinical and Translational Science Awards.

5.4.1. Assessment of Enrollment Target

The study subcommittee will review subject accrual at two years after 100% of participating hospitals have been IRB approved and are screening infants for enrollment. This review will permit a more precise determination of attainable sample size with continued enrollment into the trial. The projected sample size and recruitment duration requires an enrollment of 12-13 infants each month. Variables that we could evaluate, other than meeting the projected enrollment rate, include an increasing enrollment rate between year one and two, and/or enrollment of >75% of the target. In addition, if the monthly recruitment into the trial at this point, based on a three-month moving average, falls below 5, the DSMC will be asked to conduct a review of study feasibility. This review may include ad hoc safety, efficacy and futility analyses that will allow the DSMC to make a recommendation regarding trial termination or continuation to the leadership of the participating Networks and NIH.

Meeting Recruitment Targets. Infants with NOWS are a challenging patient group to study given parental concerns about social or legal ramifications of enrolling their infants in trials, as seen in randomized trials that have been unable to enroll the projected sample size (15, 17, and 18). The approach to the care and management of opioid addiction during pregnancy and the newborn has shown a growing appreciation that care should be multidisciplinary, collaborative, non-judgmental, and centered on the mother-infant pair (2). To minimize the number of hospitals with slow recruitment, we will provide participating hospitals the following framework.

- Prior to the initiation of screening, each hospital will provide a hospital specific recruitment plan, the expected number of available patients and a proposed schema to identify patients (before and after birth), including a plan for tracking to ensure eligibility and establishing points of contact(s) with the mother.
- Once screening has been ongoing for six months, the Data Coordinating Centers (DCCs) of both networks will review screening logs, the number of eligible infants, consent rates, and reasons for eligible but not consented infants.
- We will conduct conference calls with hospitals that are not meeting recruitment metrics. The calls will involve the DCCs, trial Principal Investigators and NIH personnel. The purpose of these calls is to ensure that hospitals have examined their process and identified changes in their approach to improve recruitment. The DCCs will offer successful recruitment practices from other hospitals.

5.5. STUDY MONITORING PLAN

5.5.1. Reporting Adverse Events

Study personnel will report all AEs (**Section 4.2.12**) and SAEs (**Section 4.2.13**) on the appropriate form and enter the data into the electronic data capture system (EDC). Refer to **Section 4.2.12** for a listing of the adverse events.

Study personnel will promptly report (within 24 hours of knowledge) all SAEs that the study intervention at least possibly relates to or are unexpected to the study sponsor and the DCC. The designated Medical Monitor will review these events and will forward them to the Chair of the DSMC. Study personnel must complete an initial SAE form, including details of the current SAE, and provide an Investigator

assessment of the causal relationship between the event and study procedures. Study personnel must document information not available at the time of the initial report on a follow-up SAE form.

5.5.2. Data Monitoring Plan and Stopping Rules

There is wide variability in weaning opioid drug treatment across IDeA States and NRN hospitals. Well-characterized AEs and a DSMC will be critical to monitor the trial and to assure that the interventions are safe. The DSMC will assess safety after 25%, 50%, and 75% of the enrolled infants are medically ready for discharge, and it will assess efficacy and futility after 50% of the enrolled infants are medically ready for discharge. All interim analyses will utilize Bayesian modeling and predictive posterior inference based on neutral, enthusiastic, and skeptical priors. We will use Bayesian modeling for the interim analyses because the predictive posterior inference makes a clear statement about what to expect when we complete frequentist analysis on final data, given the interim results. The DSMC will receive an independent presentation of interim results, prepared by the study statistician. In preparation for the DSMC meeting, we will prepare a summary report of recruitment (by hospital), known outcome events, and any AEs (including medication side effects).

Interim Futility and Efficacy Analysis. For interim efficacy, we will use Bayesian posterior predictive probabilities to predict the final outcome of the trial based on interim results. For this predictive probability calculation, we will use a frequentist criterion: reject null hypothesis if final analysis p-value is less than or equal to 0.05. Given this criterion and the neutral, enthusiastic, and skeptical priors defined above, we will calculate three predictive probabilities of success (PPoS) when 50% of the total sample is collected by using the three reference priors: neutral, skeptical, and enthusiastic. To calculate a PPoS, we will take the following steps:

4. Choose the neutral, enthusiastic, or skeptical prior for the treatment effect.
5. Fit a Bayesian linear regression model to the primary outcome using the interim data. Include maternal treatment and stabilization dose as covariates.
6. Calculate the posterior distributions for all regression terms.
7. Use the interim data to calculate the observed distribution of maternal treatment.
8. Use the interim data to calculate the observed distribution of the stabilization dose. May approximate with a normal distribution if suitable.
9. Determine how many infants we still need to randomize in each arm.
10. For each arm, generate data for the required number of hypothetical participants by doing the following for each required hypothetical participants:
    - Sample a single value from each posterior distribution.
    - Make a random draw from the observed distribution for maternal treatment.
    - Make a random draw from the observed or approximated distribution for stabilization dose.
    - Use the appropriate sampled values from steps 7a – 7c to generate a hypothetical outcome.
11. Use the data observed plus the hypothetical data generated in Step 7, above, to create a hypothetical complete trial and calculate the p-value under the null hypothesis of $\theta = 0$. Use a linear regression model that includes treatment, maternal treatment, and stabilization dose.

12. Repeat Steps 7 and 8 many times. The PPoS is the proportion of hypothetical completed trials that achieve a p-value for the treatment effect that is 0.05 or less.[2]

The PPoS will be a helpful measure for the DSMC to use as it makes decisions about stopping the trial early for efficacy or futility or continuing to enroll. Below are two suggested guidelines for using the PPoS, but as stated in the DSMC charter, all protocol suggested stopping guidelines are advisory and the DSMC can choose to ignore them. If the PPoS is 0.99 or greater under the skeptical prior, then the DSMC may consider stopping the trial for efficacy. If the frequentist PPoS is 0.1 or less under the enthusiastic prior, then the DSMC may consider stopping the trial for futility. The PPoS under the neutral prior will also be available to aid interpretation of the PPoS estimates calculated under the skeptical and enthusiastic priors.

Interim Safety Analysis. In addition to monitoring AEs and SAEs, as described in section 5.5.1 above, the DSMC will use Bayesian analyses to monitor seizure occurrence. The DSMC will assess seizure occurrence at three interim reviews, 25%, 50%, and 75% of enrollment. Within the slow-wean intervention, we expect the seizure proportion to be 0.03, and within the rapid-wean intervention, we expect this proportion to be higher. Based on clinical experience, the study team offers the following guideline for stopping the trial early for safety. Yet as with Efficacy and Futility, per the DSMC charter, all protocol suggested stopping guidelines are advisory and the DSMC can choose to ignore them. If the seizure proportion is 0.03 in the slow-wean intervention, and the seizure proportion is greater than 0.10 in the rapid-wean intervention, then the DSMC may consider stopping the trial for safety. As such, the interim analyses of safety will focus on reporting information about the seizure proportion in the slow-wean intervention and the difference between seizure proportions in both interventions. At each interim analysis of safety, we will calculate the posterior distribution of seizure proportion within each intervention by using a simple Bayesian logistic regression model, intercept and treatment effect parameters with neutral priors on the intercept and the intervention effect parameter. We will place a normal (μ=0, σ=10) on the intercept, and we will place a normal (μ=0, σ=3) on the intervention effect term. Let θ_1 = proportion of infants with seizures in the rapid-wean intervention and θ_2 = proportion of infants with seizures in the rapid-wean intervention minus the proportion of infants with seizures in the slow-wean intervention. We will calculate the posterior distribution of θ_1 and θ_2 by using transformations of the MCMC values that make up the estimated posterior distributions for the intercept and the intervention effect parameter. If $Pr(\theta_1 > 0.1 \mid Data) \geq 0.95$, and $Pr(\theta_2 > 0.07 \mid Data) \geq 0.95$, then the DSMC may want to consider stopping the trial for safety.

Under this guideline, the DSMC may consider stopping the trial for safety, if there is convincing evidence that the seizure proportion among rapid-wean infants is greater than 0.1 and there is convincing evidence that the seizure proportion among rapid-wean infants is more than seven percentage points greater than the seizure proportion among slow-wean infants. Finally, as with efficacy and futility, the DSMC charter states trial stoppage guidelines can be ignored if the DSMC determines it is necessary.

[2] Based on presentation by Ben Saville at Berry Consultants. Presentation located at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=2ahUKEwjJyaaQmePeAhVPm-AKHcr_DCYQFjACegQIBxAC&url=https%3A%2F%2Fwww.diaglobal.org%2Fen%2F~%2Fmedia%2Fdiaglobal%2Ffiles%2Fresources%2Ftopics-of-interest%2Fedm%2Fthe-utility-of-bayesian-predictive-probabilities.pdf&usg=AOvVaw1XpV0DJ1qy_h0h-iUS-QdZ

SECTION 6. DATA MANAGEMENT

RTI International will provide the following:

- Collaborates in the development, implementation, and monitoring of Weaning protocol.
- Provides biostatistical leadership in statistical design aspects of Weaning protocol.
- Provides data management, including development of CRFs and appropriate data collection systems.
- Supervising data entry activities, including instructing and certifying data entry personnel in software and hardware usage, quality assurance of data entry, etc.
- Designs and maintains central randomization system.
- Manages the Data Safety and Monitoring Committee for the trial. Including scheduling meetings, the DSMC charter and preparing interim monitoring reports for the DSMC.
- Oversees the receipt and reconciliation of safety data.
- Supervises NRN site quality assurance efforts, including conducting site visits and remote monitoring of data.
- Prepares and distributes monthly reports, detailing data received, data consistency, miss data and adherence to protocol.
- Disburses capitation payments to clinical centers on the basis of enrolled patients and other study-specific milestone triggers specified in the study protocols.
- Provides the logistical support necessary to run an efficient and productive network.
- Provides biostatistical leadership for collaborative analysis of study data and publication of results.
- Prepares public-use data files.

SECTION 7. PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. The study will also comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule.

As such, this study will:

- Register with ClinicalTrials.gov and submit results. We will submit primary outcome results from this trial to ClinicalTrials.gov.
- Publish results. We will make every attempt to publish results in peer-reviewed journals. We will submit all final peer-reviewed journal manuscripts from this study to the digital archive PubMed Central upon acceptance for publication.
- Deposit data for data sharing with other researchers. Within the bounds of relevant Institutional Review Board (IRB) approvals and guidelines for protection of personally identifiable data, we will deposit de-identified data from this study in an appropriate, NIH-approved data repository.

SECTION 8. REFERENCES

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SECTION 9. DATA FORMS

9.1. SCREENING LOG

9.2. RANDOMIZATION FORM

9.3. MATERNAL MEDICAL HISTORY FORM

9.4. INFANT MEDICAL HISTORY FORM

9.5. WEANING INTERVENTION FORM

9.6. PHARMACY DRUG ADMINISTRATION FORM

9.7. STATUS FORM

9.8. POST DISCHARGE FORM

9.9. ADVERSE AND SERIOUS ADVERSE EVENTS FORM

9.10. PROTOCOL VIOLATION FORM

9.11. STUDY WITHDRAWAL FORM

SECTION 10. APPENDICES

APPENDIX 1. INFANT CHARACTERISTICS AND DEMOGRAPHICS (ACT NOW CURRENT EXPERIENCE)

Data listed in Appendices 1 and 2 represent a summary of selected infant characteristics and variables related to NOWS from a retrospective chart review for infants exposed to opioids during pregnancy (Advancing clinical trials in neonatal opioid withdrawal syndrome [ACT NOW] current experience: Infant exposure and treatment). These researchers reviewed the medical records for infants ≥ 36 weeks of gestational age and born between July 1, 2016 through June 30, 2017, and mothers medical records, when available, when there was opioid use (maternal history, maternal/infant toxicology screen, or NOWS scoring). In Appendices 1 and 2, we provide the results for full data from 1,808 infants collated from submitted records.

Variable	N	Value
Birth weight, kg (mean ± sd)	1,805	3.1 ± 0.5
Gestational age wks (mean ± sd)	1,800	38.7 ± 1.3
Apgar 1 min, median IQR	1,776	8 (8-9)
Apgar 5 min, median IQR	1,775	9 (9-9)
male %	934	51.7
female %	873	48.3
Race - % white/black/other	1,338/217/253	74.0/12.0/14.0
urban %	1,713	94.7
in-born %	1,518	84.0
Location of care %[1]		
newborn nursery	1,351	74.7
special care nursery	309	17.1
NICU	446	24.7
regional NICU	346	19.1
pediatric unit	77	4.3

[1] Infants may be cared for in more than on location.

APPENDIX 2. PHARMACOLOGIC TREATMENT (ACT NOW CURRENT EXPERIENCE)

Variable	N	Value
Drug treatment %	698 out of 1,808	38.6
Scoring assessment	698	
Finnegan (original) %	285	40.8
Finnegan (modified) %	383	54.9
Primary medication	698	
morphine %	601	86.1
methadone %	90	12.9
buprenorphine %	2	0.3
phenobarbital %	2	0.3
clonidine %	3	0.4
Secondary medication	223	
clonidine %	123	55.2
phenobarbital %	81	36.3

APPENDIX 3. RECRUITMENT PLAN

As documented in the protocol, enrollment of infants in clinical trials to improve the treatment of NOWS has been challenging. There are three major components for a successful recruitment plan:

1. Understand who is providing care for pregnant patients with an Opioid Use Disorder.
2. Disseminate information regarding research initiatives coupled with hospital care of the mother and newborn.
3. Identify pregnant mothers prior to delivery and use prenatal consultation to establish trust and provide an overview of newborn care, an overview of the clinical trial and obtain consent as appropriate.

The first two of these components are part of a system level recruitment initiative while the third component is patient specific. The summary below provides important lessons learned from Women & Infants Hospital of Rhode Island on the approach to mothers with an Opioid Use Disorder concerning clinical care and research initiatives.

NOTE: Initial contact with potential participants will be made by clinical staff rather than research staff (unless research staff are part of the same clinic).

1) Who is providing care for pregnant patients with Opioid Use Disorder (System Level):

Mothers with Opioid Use Disorder during pregnancy will acquire opioids through 4 major pathways:

a) Methadone treatment programs
b) Buprenorphine treatment programs
c) Pain management or primary care providers
d) Illicitly

Methadone and buprenorphine treatment programs will be the easiest to identify; while identifying specific providers in the community may be more challenging.

The Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Substance Abuse Treatment, Division of Pharmacologic Therapies) provides a user friendly link to locate all methadone and buprenorphine providers by state. Use the links below to find providers:

- **Methadone providers:** https://dpt2.samhsa.gov/treatment/directory.aspx
- **Buprenorphine providers:** https://www.samhsa.gov/medication-assisted-treatment/practitioner-program-data/treatment-practitioner-locator

2) Disseminate information to clinics, healthcare providers and the medical community regarding research initiatives coupled with hospital care of the mother and newborn (System Level):

Disseminating information regarding the trial should occur in two phases. The first phase should be a face to face contact with methadone clinics, buprenorphine providers, support groups, peer recovery

coach networks, and other community support programs for women with opioid use disorders. The goal of the first phase is to establish a working dynamic with community partners. The research team should communicate to the community that they are a critical member of the team. The second phase will be to maintain contact with the community partners and support their efforts to identify patients. To improve the success of either of these phases the research team should have prepared marketing material to share with the community. This recruitment plan will benefit by the creation of marketing material before engaging the community.

Methadone Clinics / Community Support Programs / Peer Recovery Coach Networks:

Before the team makes contact with any community support programs they should identify programs that have a trusted reputation among mothers who utilize the services. Use available information (electronic records, hospital data bases, social workers, discussions with mothers with Opioid Use Disorder) to understand which of the many community programs are used most frequently by pregnant patients delivering or being transferred to the hospital participating in the trial. Since there will be many programs in the community, prioritize those programs where mothers with Opioid Use Disorder feel best supported and who they trust. The research team should build a list of high value programs to focus the team's efforts. In some states the local health department lists programs that are considered to be excellent performers for their mission. Trusted centers are more likely to have a network that is able to identify eligible patients.

- Establish contact with a community program/methadone treatment program is an essential first step. Initial contacts should be done face to face with members of the research leadership team and the community program/methadone clinic leadership team. The first meeting should discuss national gaps in NOWS care, the local model of NOWS care, how the trial is addressing gaps in NOWS care, and how the community program/methadone treatment program can help support the clinical trial. Identification of a liaison at the treatment program is ideal for continued contact. The research team should prepare to leave informational material with the center. Follow-up contact can occur by phone calls, mailings, and/or e-mail.
- The research team should identify a liaison at each center as points of contact. The point of contact should be a member of the treatment program who would champion the clinical trial. The team would depend on this person to alert the research team when a patient becomes pregnant or if a new patient is pregnant.
- Contacts with community program/methadone treatment programs typically need to be repetitive to maintain an awareness of the clinical trial. The research team should verify the accuracy of contact information, intake of new patients and the status of previously identified patients as they progress to birth. In addition, women who attend methadone treatment centers are likely to receive substance use counseling in other group settings and often share new information with others. Word of mouth within the community can be powerful.
- There could be discussion of the research team attending a group meeting to enable study personnel to have a better understanding of the challenges that women with Opioid Use Disorder are confronted with.
- In addition to addressing knowledge gaps, the research team should provide a clear line of communication for referral of a pregnant mother for a prenatal consultation.
- The research team should maintain a log of the number of referrals from specific methadone treatment programs and monitor patient progression to delivery. Logs should be reviewed and updated at frequent intervals. Depending on local practice, the research team may need to

communicate with clinical providers at the birthing hospitals to ensure awareness of pregnant mothers during pregnancy.

Buprenorphine Providers / Pain Management Specialists / Obstetricians

Buprenorphine providers, pain management specialists and selected obstetricians represent another group of medical providers caring for pregnant mothers with an Opioid Use Disorder. Women with an opioid use disorder that do not attend methadone clinics and are not obtaining illicit opioids will have a buprenorphine provider. Medication-assisted treatment with buprenorphine is an accepted form of treatment. Buprenorphine can be prescribed by any medical provider who obtains a waiver from the FDA. The study team can work with local health departments, professional organizations and Opioid Use Disorder support groups to identify a group of buprenorphine providers in the community. The SAMHSA link above can also help locate buprenorphine providers in your local community.

- Establishing contact with these specialists will be more challenging than community programs or methadone clinics. The team should prepare a brief communication or script in advance that addresses the key elements of the trial and provides clear directions or how to request a prenatal consultation for NOWS. Providers with office based practices will often not be able to provide substantial time to review the details of the trial. The goal when speaking with these practices is for the research team to communicate the opportunity for prenatal NOWS consultation.
- In addition to the providers above, the research team should raise awareness of the proposed clinical trial in the medical community. This can involve mailing and/or email a description of the trial with study marketing materials to hospital affiliates such as Maternal Fetal Medicine, Family Medicine programs, Obstetric practices, Prenatal Clinics and Primary Care clinics. Marketing and/or Human Resource Departments may facilitate obtaining a list of providers. Organizing Grand Rounds or other lecture/symposium formats within the hospital, community, Health Department outreach, or support groups may be effective ways to disseminate information regarding NOWS and the clinical trial.
- In addition to addressing knowledge gaps, the research team should provide a clear line of communication for referral of a pregnant mother for a prenatal consultation.
- The research team should maintain a log of the number of referrals from specific providers and monitor patient progression to delivery. Logs should be reviewed and updated at frequent intervals. Depending on local practice, the research team may need to communicate with clinical providers at the birthing hospitals to ensure awareness of pregnant mothers during pregnancy.

Marketing Material:

- The primary study team will create attractive marketing materials that will be approved by the central IRB. Marketing materials may include study brochures, posters with tear off contact information, business cards, badge buddies, and social media posts. Materials will have places to insert local contact information.
- Marketing material should be considered for specific research initiatives in addition to any specific information regarding care practices at the birthing facility which mothers should be aware of.
- Educational material about NOWS including current approaches to NOWS treatment, current gaps in NOWS care, local barriers to improving care, the purpose of the proposed clinical trial

and identifying ways in which the research team can help support medication assisted treatment programs.

The research team should consider offering educational forums (community based, hospital based) which can be used to disseminate information regarding NOWS, maternal and newborn care in the birthing facility and the proposed clinical trial.

3) Identify pregnant mothers prior to delivery and use prenatal consultation to establish trust and provide an overview of newborn care and the clinical trial. (Patient Specific):

The single most important element of the recruitment strategy is the prenatal consultation. The prenatal consultation is most likely the first time that the family will meet the research study PI or designee. The mother may be aware of the clinical trial if the system wide elements of the recruitment strategy are in place. The consultation is the opportunity for the provider to gain and strengthen the trust with the family and reaffirm a partnership with the family. The consultation will include establishing a foundation of knowledge about NOWS, outlining gaps in current national care, a detailed description of the local approach to NOWS, and the research opportunities at the local hospital to improve care. The prenatal consultation should also be an opportunity for the medical team to remove any guilt or anxiety the family might have about having a baby at risk for NOWS.

Specific areas of focus during a consultation include:

- Address any fears the family may have of NOWS or the hospital course. Providers should be prepared to hear questions about child protective services, breastfeeding, length of hospitalization and long term risk to their infant. An awareness of the local state's laws will help guide families to the best resource with regards to child protective services.
- Establish a common, core understanding of NOWS. Families should be informed about how NOWS develops and manifests. Providers should be objective and reinforce that the mother did not cause NOWS and her medication treatment did not harm her baby. Reinforcing objective knowledge should help remove potential maternal guilt.
- Identify gaps in the current understanding of NOWS to show the family that the medical community is aware of limitations in the approach to care, and a willingness to improve.
- Review local practices to reduce anxiety about delivering a baby at risk for NOWS. Provide as much concrete information about the clinical team's approach to NOWS care with the goal of reducing the number of "unknowns" for the family. Examples are the location of care, the number of different nurses who will care for the baby, visitation hours and what happens after the mother is discharged. Families that have fewer unknowns feel more empowered and are willing to engage in conversation about research.
- Discuss the research protocol with families. This should include gaps in care and the potential impact of a clinical trial on the overall care of NOWS. The family should be free to discuss the possibility and given time to review privately. The study team should collect contact information for the family and plan to contact them at a later date or if necessary in the hospital.
- If prenatal consultation is not feasible, effective ante-natal dissemination of information regarding the clinical trial will be exceptionally important to approach mothers after delivery. Since randomization needs to occur prior to the start of weaning, there should be time for research personnel to meet the mother, establish a relationship and introduce or remind mothers about the research initiative to improve the care of infants exposed to opioids. Follow-

up visits to the mother can be coordinated with other maternal and infant providers to be able to present the clinical trial during a quiet time with as little interruptions as possible. When in-person contact is not available or advisable, due to COVID-19 pandemic, remote contact can be made via a HIPAA-compliant method such as telephone, personal delivery of documents, US postal service, REDCap or other compliant electronic platform. The remote contact process will parallel the contact process used for in-person contact. The only difference will be the method(s) of communication.

APPENDIX 4. MORPHINE: EXAMPLE OF WEANING WITH DOSING EVERY THREE HOURS

For this and subsequent scenarios (**Appendices 5-7**), the difference in opioid dose between rapid and slow wean interventions is illustrated. Since there are no escalations, the intervention steps correspond to the dose levels listed in Table 4 (**Section 4.2.6**).

Scenario. 3.2 kg infant treated with morphine, stabilized on 0.06 mg/kg/dose, and undergoing either a rapid-wean or slow-wean intervention with medication administered at **three-hour intervals**.

Protocol. At the start of weaning, the morphine dose is decreased by 15% of the stabilization dose (rapid wean) or 10% of the stabilization dose (slow wean). The dose represents the actual mg administered.

Intervention Dose Level	Rapid Wean
Day of **Randomization** 100% of stabilization	0.19 mg q 3 h
Dose level A 85% of stabilization	0.16 mg q 3 h
Dose level B 70% of stabilization	0.13 mg q 3 h
Dose level C 55% of stabilization	0.11 mg q 3 h
Dose level D 40% of stabilization	0.08 mg q 3 h
Dose level E 25% of stabilization	0.05 mg q 3 h
Dose level F 0% of stabilization	Placebo
Dose level G 0% of stabilization	Placebo
Dose level H 0% of stabilization	Placebo
	Observe off study drug
	Observe off study drug

Intervention Dose Level	Slow Wean
Day of **Randomization** 100% of stabilization	0.19 mg q 3 h
Dose level A 90% of stabilization	0.17 mg q 3 h
Dose level B 80% of stabilization	0.15 mg q 3 h
Dose level C 70% of stabilization	0.13 mg q 3 h
Dose level D 60% of stabilization	0.11 mg q 3 h
Dose level E 50% of stabilization	0.10 mg q 3 h
Dose level F 40% of stabilization	0.08 mg 3 h
Dose level G 30% of stabilization	0.06 mg q 3 h
Dose level H 20% of stabilization	0.04 mg q 3 h
	Observe off study drug
	Observe off study drug

APPENDIX 5. MORPHINE: EXAMPLE OF WEANING WITH DOSING EVERY FOUR HOURS

Scenario. 3.2 kg infant treated with morphine, stabilized on 0.08 mg/kg/dose, and undergoing either a rapid or slow wean with medication administered at **four-hour intervals**.

Protocol. At the start of weaning, the morphine dose is decreased by 15% of the stabilization dose (rapid wean) or 10% of the stabilization dose (slow wean). The dose represents the actual mg administered.

Intervention Dose Level	Rapid Wean
Day of **Randomization** 100% of stabilization	0.26 mg q 4 h
Dose level A 85% of stabilization	0.22 mg q 4 h
Dose level B 70% of stabilization	0.18 mg q 4 h
Dose level C 55% of stabilization	0.14 mg q 4 h
Dose level D 40% of stabilization	0.10 mg q 4 h
Dose level E 25% of stabilization	0.07 mg q 4 h
Dose level F 0% of stabilization	Placebo
Dose level G 0% of stabilization	Placebo
Dose level H 0% of stabilization	Placebo
	Observe off study drug
	Observe off study drug

Intervention Dose Level	Slow Wean
Day of **Randomization** 100% of stabilization	0.26 mg q 4 h
Dose level A 90% of stabilization	0.23 mg q 4 h
Dose level B 80% of stabilization	0.21 mg q 4 h
Dose level C 70% of stabilization	0.18 mg q 4 h
Dose level D 60% of stabilization	0.16 mg q 4 h
Dose level E 50% of stabilization	0.13 mg q 4 h
Dose level F 40% of stabilization	0.10 mg q 4 h
Dose level G 30% of stabilization	0.08 mg q 4 h
Dose level H 20% of stabilization	0.05 mg q 4 h
	Observe off study drug
	Observe off study drug

APPENDIX 6. METHADONE: EXAMPLE OF WEANING WITH DOSING EVERY EIGHT HOURS

Scenario. 3.2 kg infant treated with methadone, stabilized on 0.1 mg/kg/dose, and undergoing either a rapid or slow wean with medication administered at **eight-hour intervals**.

Protocol. At the start of weaning, the methadone dose is decreased by 15% of the stabilization dose (rapid wean) or 10% of the stabilization dose (slow wean). The dose represents the actual mg administered.

Intervention Dose Level	Rapid Wean
Day of **Randomization** 100% of stabilization	0.32 mg q 8 h
Dose level A 85% of stabilization	0.27 mg q 8 h
Dose level B 70% of stabilization	0.22 mg q 8 h
Dose level C 55% of stabilization	0.18 mg q 8 h
Dose level D 40% of stabilization	0.13 mg q 8 h
Dose level E 25% of stabilization	0.08 mg q 8 h
Dose level F 0% of stabilization	Placebo
Dose level G 0% of stabilization	Placebo
Dose level H 0% of stabilization	Placebo
	Observe off study drug
	Observe off study drug

Intervention Dose Level	Slow Wean
Day of **Randomization** 100% of stabilization	0.32 mg q 8 h
Dose level A 90% of stabilization	0.29 mg q 8 h
Dose level B 80% of stabilization	0.26 mg q 8 h
Dose level C 70% of stabilization	0.22 mg q 8 h
Dose level D 60% of stabilization	0.19mg q 8 h
Dose level E 50% of stabilization	0.16 mg q 8 h
Dose level F 40% of stabilization	0.13 mg q 8 h
Dose level G 30% of stabilization	0.10 mg q 8 h
Dose level H 20% of stabilization	0.06 mg q 8 h
	Observe off study drug
	Observe off study drug

APPENDIX 7. METHADONE: EXAMPLE OF WEANING WITH DOSING EVERY 12 HOURS

Scenario: 3.2 kg infant treated with methadone, stabilized on 0.15 mg/kg/dose, and undergoing either a rapid or slow wean with medication administered at **12-hour intervals**.

Protocol: At the start of weaning, the methadone dose is decreased by 15% of the stabilization dose (rapid wean) or 10% of the stabilization dose (slow wean). The dose represents the actual mg administered.

Intervention Dose Level	**Rapid Wean**
Day of **Randomization** 100% of stabilization	0.48 mg q 12 h
Dose level A 85% of stabilization	0.41 mg q 12 h
Dose level B 70% of stabilization	0.34 mg q 12 h
Dose level C 55% of stabilization	0.26 mg q 12 h
Dose level D 40% of stabilization	0.19 mg q 12 h
Dose level E 25% of stabilization	0.12 mg q 12 h
Dose level F 0% of stabilization	Placebo
Dose level G 0% of stabilization	Placebo
Dose level H 0% of stabilization	Placebo
	Observe off study drug
	Observe off study drug

Intervention Dose Level	**Slow Wean**
Day of **Randomization** 100% of stabilization	0.48 mg q 12 h
Dose level A 90% of stabilization	0.43 mg q 12 h
Dose level B 80% of stabilization	0.38 mg q 12 h
Dose level C 70% of stabilization	0.34 mg q 12 h
Dose level D 60% of stabilization	0.29 mg q 12 h
Dose level E 50% of stabilization	0.24 mg q 12 h
Dose level F 40% of stabilization	0.19 mg q 12 h
Dose level G 30% of stabilization	0.14 mg q 12 h
Dose level H 20% of stabilization	0.10 mg q 12 h
	Observe off study drug
	Observe off study drug

APPENDIX 8. PHARMACY DOSING CALCULATOR

We will provide hospital pharmacies with access to a web based dosing calculator. (see below). Once the research team consents and randomizes an infant, the pharmacist can enter the infant's dosing weight, drug (medication), dose interval, and stabilization dose (mg/kg/dose) in the appropriate boxes. The pharmacist will only have the option to select morphine or methadone from the program for the drug (medication). Once the drug is selected the pharmacy team will only have the option of selecting the dosing interval matched to each drug. For infants receiving morphine the dosing interval will be either every 3 hours or 4 hours. For infants receiving methadone the dosing interval will be either every 8 hours or 12 hours. Once the pharmacist chooses these variables, the spreadsheet will generate the randomization dose (mg/dose) and the sequential dose reductions for each dose level of the rapid-wean (Image A) and slow-wean (image B) interventions. The calculator also provides the final (cessation) dose of study drug.

ACTNOW-Weaning | RTI_DEV | W002-00766 | Dosing Schedule

Subject: **W002-00766**
Page: **Dosing Schedule**

Calculation Parameters	
Dosing Weight	2.000 kg
Drug	Morphine
Dosing Interval	3 hrs
Stabilization Dose	0.07 mg/dose
	0.28 mg/kg/day
Treatment Arm	Rapid Wean
Final Dose	0.018 mg/dose

#	Weaning Schedule Dosing Level	Dose
1	Stabilization	0.07
2	A	0.06
3	B	0.05
4	C	0.04
5	D	0.03
6	E	0.02
7	Placebo	0.00
8	Placebo	0.00
9	Placebo	0.00

Image A: Rapid Wean

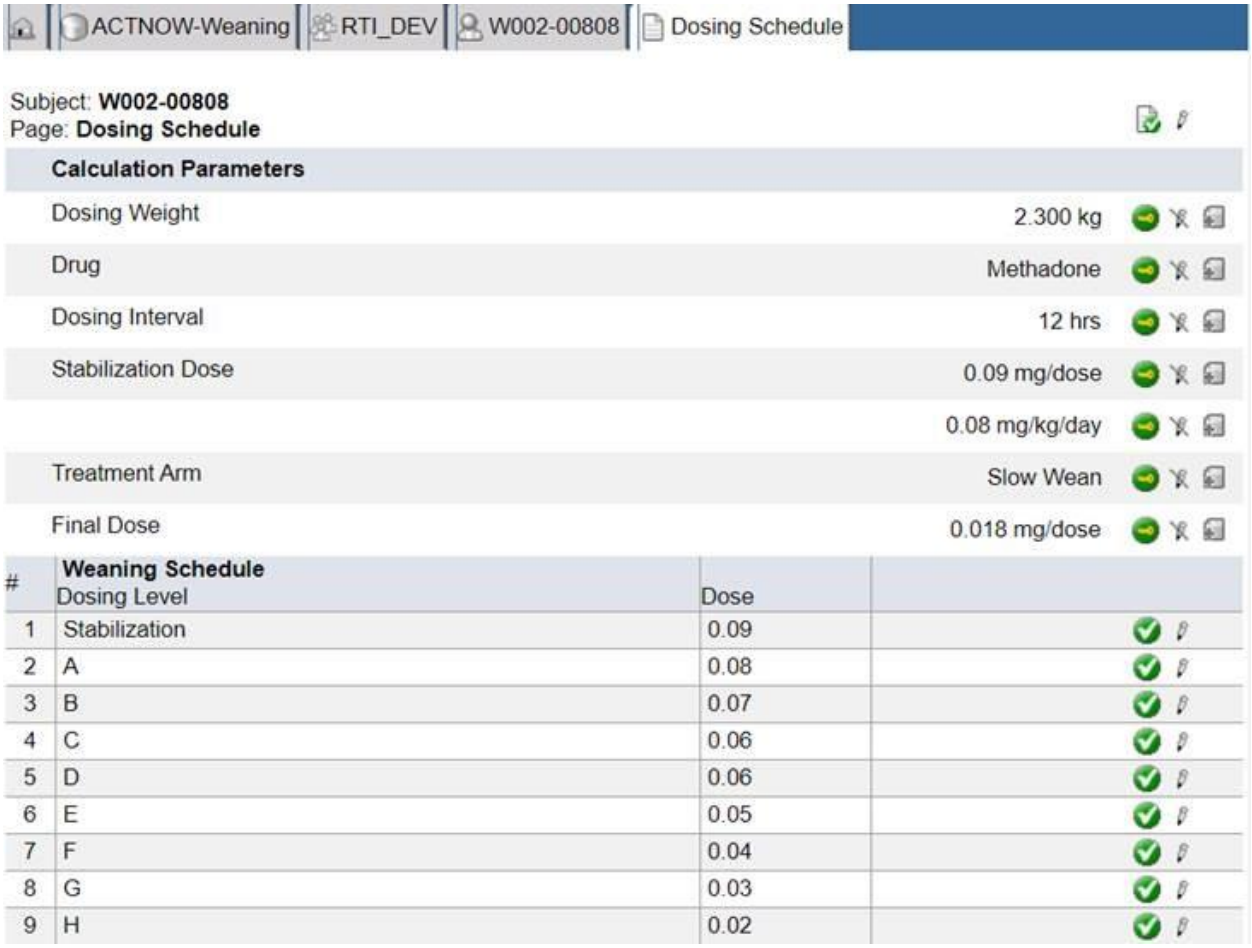
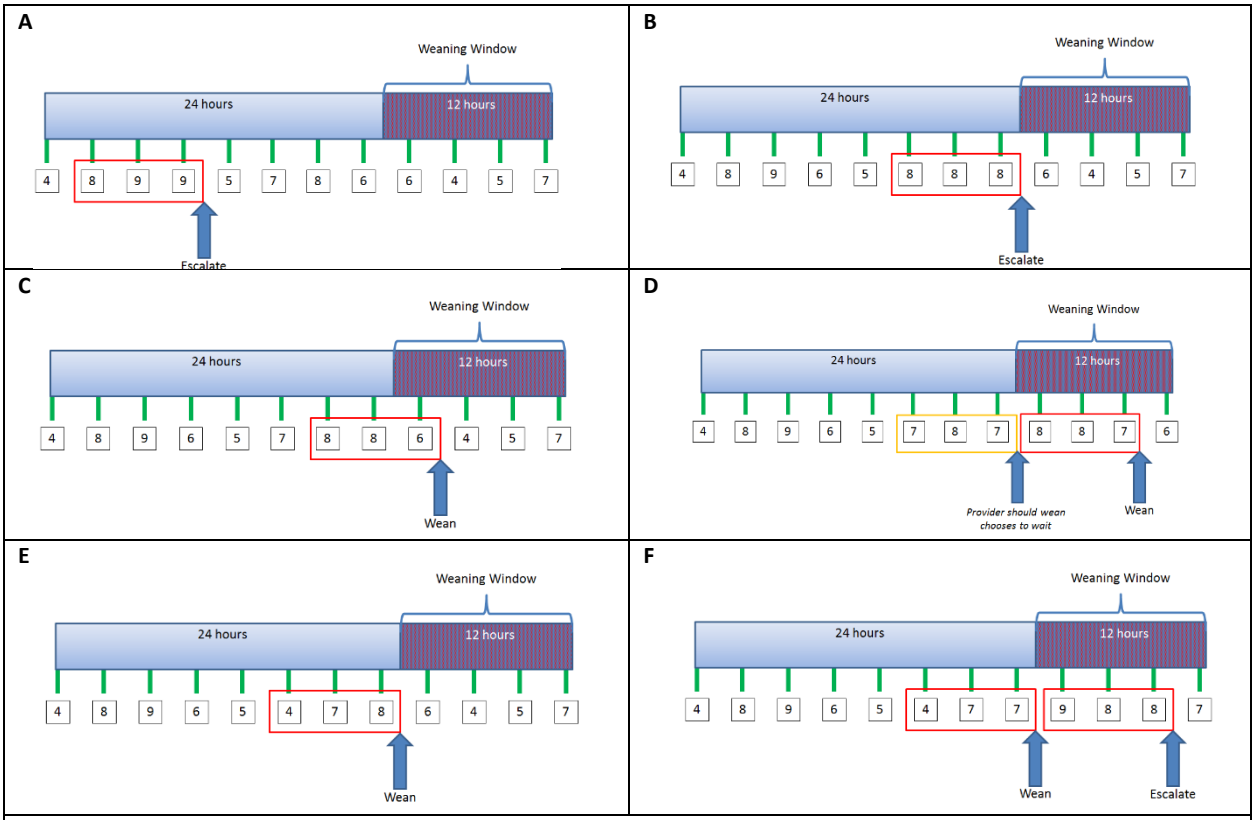


Image B: Slow Wean

APPENDIX 9. CHANGES MORPHINE/METHADONE DOSE USING HOSPITAL GUIDELINES AND PROTOCOL GUIDELINES

The examples below illustrate decreases or increases opioid dose based on hospital specific guidelines and study protocol guidelines. In each example, there is a 24-hour interval after a previous change in opioid dose for hospitals to use their guidelines to change the opioid (light blue horizontal bar, labeled 24 hours). If the clinical team does not change the opioid dose by 24 hours, infants enter a 12-hour period of study protocol guidelines (horizontal purple bar, labeled weaning window). During this 12-hour period, clinical teams must wean infants who do not meet hospital specific criteria for escalation. The clinical team does not need to use the total 12-hour period to either wean or escalate, if the infant meets criteria prior to 12 hours.

In the examples below, the green lines indicate the time of opioid administration and the boxes contain the assessment score. These examples depict a hospital that uses Finnegan or modified Finnegan scores and the hospital guideline is to wean opioid if the average of three consecutive Finnegan scores is < 8. Hospitals would use a parallel process that follows assessment criteria of ACT NOWS Eat, Sleep, Console.



A. Elevated scores occur prior to 24 hours and the clinical team should escalate the opioid dose. **B.** Elevated Finnegan scores occur at the end of the 24-hour interval, and the clinical team should escalate the opioid. **C.** Finnegan scores during the 24-hour interval of hospital guidelines do not meet escalation criteria. Once in the 12-hour study protocol guideline, the Finnegan scores meet the hospital guidelines and the clinical team should wean the opioid, preferably as early in the 12-hour interval, as possible. **D.** Finnegan scores during the 24-hour window of using hospital guidelines should have prompted weaning the opioid. Once in the 12-hour study protocol guidelines, the Finnegan scores do not meet the hospital's escalation requirements, and the clinical team should wean the opioid. **E.** Finnegan scores at the end of the 24-hour window do not meet the hospital escalation criteria, and the clinical team weans the opioid. **F.** Finnegan scores at the end of the 24-hour interval meet criteria for weaning the opioid. Subsequently, Finnegan scores increase and meet hospital criteria for opioid escalation, and the clinical team escalates the dose.

APPENDIX 10. PLACEBO DOSE UTILIZATION TO MAINTAIN THE BLIND IN THE RAPID-WEAN INTERVENTION

All infants that are randomized to the rapid-wean intervention will need to complete three placebo dose levels to maintain the blind (Appendices 4-7). Placebo administration only occurs after the infant has weaned from the 25% of stabilization dose level. We will consider a placebo dose level complete if the infant meets the following two criteria:

1) The infant tolerates the placebo without NOWS signs prompting a resumption of opioid.
2) The clinical team starts the next dose level in the intervention (i.e., the clinical team orders "wean opioid."). If during a placebo dose the clinical team orders "escalate opioid", then we will not consider the placebo dose complete. The clinical team needs to repeat a placebo dose that is not complete.

For infants who experience the same number of escalations or resumptions, placebo use in the rapid-wean intervention will result in study drug discontinuation after the same number of study steps as infants in the slow-wean intervention. Examples below demonstrate how placebo use in the rapid-wean intervention will maintain the blind (infant A). These examples include an infant without escalations (example A), an infant who has two escalations prior to reaching placebo (example B), an infant with one escalation that occurs during a placebo dose level (example C), an infant with two escalations: one that occurs during an opioid dose level and one that occurs during a placebo dose level (example D), and an infant with two escalations that both occur during the placebo levels (example E). For each example, we show an infant randomized to the slow-wean intervention with an identical number of escalations or resumptions of opioid (infant B).

We present the examples in terms of steps (not dose levels) to illustrate that there will be more study steps than dose levels when there are escalations of the opioid. In the examples, every infant randomized to the rapid-wean intervention needs to complete three placebo dose levels. We will consider placebo dose levels incomplete if opioid resumption interrupts them. The three placebo dose levels do not need to occur consecutively. For the research team to consider a placebo level complete, it needs to lead to a successful wean to another placebo level or off study drug.

A

	Infant A	Infant B
	Rapid wean: 15 % of stabilization dose	Slow wean: 10 % of stabilization dose
Stabilization Dose	100	100
Step 1	85	90
Step 2	70	80
Step 3	55	70
Step 4	40	60
Step 5	25	50
Step 6	Placebo*	40
Step 7	Placebo*	30
Step 8	Placebo*	20

Key:
Placebo Step
Dose Medication is discontinued

B

	Infant A	Infant B
	Rapid wean: 15 % of stabilization dose	Slow wean: 10 % of stabilization dose
Stabilization Dose	100	100
Step 1	85	90
Step 2	70	80
Step 3	85	90
Step 4	70	80
Step 5	85	90
Step 6	70	80
Step 7	55	70
Step 8	40	60
Step 9	25	50
Step 10	Placebo*	40
Step 11	Placebo*	30
Step12	Placebo*	20

Key:
Placebo Step
Dose Medication is discontinued
Escalation

A. No Escalations. Infant A stops opioid at step 5. Infant B continues opioid until step 8. To maintain the blind, infant A receives placebo for steps 6-8. Both infants stop receiving "opioid/study drug" at step 8. **B. Two Escalations during Opioid Steps.** Both infants escalate at steps 3 and 5. Infant A discontinues opioid at step 9. Infant B discontinues opioid at step 12. Infant A receives 3 steps of placebo (10-12) to preserve blind. Both infants discontinue "study drug" at step 12.

C

	Infant A	Infant B
	Rapid wean: 15 % of stabilization dose	Slow wean: 10 % of stabilization dose
Stabilization Dose	100	100
Step 1	85	90
Step 2	70	80
Step 3	55	70
Step 4	40	60
Step 5	25	50
Step 6	Placebo*	40
Step 7	Placebo*	30
Step 8	25	40
Step 9	Placebo*	30
Step 10	Placebo*	20
Key:		
Placebo Step		
Dose Medication is discontinued		
Escalation		
Incompleted Placebo Step		
Escalation from Previous Dose and Discontinue		

D

	Infant A	Infant B
	Rapid wean: 15 % of stabilization dose	Slow wean: 10 % of stabilization dose
Stabilization Dose	100	100
Step 1	85	90
Step 2	70	80
Step 3	55	70
Step 4	40	60
Step 5	25	50
Step 6	40	60
Step 7	25	50
Step 8	Placebo*	40
Step 9	25	50
Step 10	Placebo*	40
Step 11	Placebo*	30
Step12	Placebo*	20
Key:		
Placebo Step		
Dose Medication is discontinued		
Escalation		
Incompleted Placebo Step		
Escalation from Previous Dose and Discontinue		

C. One Escalation after Start of Placebo. Both infants have one escalation at step 8. Infant A step 8 occurs after placebo initiation. Infant A completes first placebo step (step 6) because the clinical team weans the study drug and starts placebo (step 7). Placebo dose at step 7 is not complete because it prompted the clinical team to escalate study drug and an opioid is resumed (25% of stabilization dose). Placebo step 7 will need to be repeated when the clinical team weans study drug. The latter will represent step 9. Three complete steps of placebo ensure that both infants end "study drug" at step 10.

D. Two Escalations: One during Opioid and One during Placebo. Both infants have two escalations at steps 6 and 9. The escalation at step 6 follows the same approach as example B. The escalation at step 9 occurs after the patient was started on placebo and study drug increases to 25% of the stabilization dose. The step 8 placebo for infant A is not complete and the clinical team needs to repeat it (step 10). Three complete steps of placebo (10-12) ensure that both infants end "study drug" at step 12.

E.

	Infant A	Infant B
	Rapid wean: 15 % of stabilization dose	Slow wean: 10 % of stabilization dose
Stabilization Dose	100	100
Step 1	85	90
Step 2	70	80
Step 3	55	70
Step 4	40	60
Step 5	25	50
Step 6	Placebo*	40
Step 7	Placebo*	30
Step 8	25	40
Step 9	Placebo*	30
Step 10	25	40
Step 11	Placebo*	30
Step 12	Placebo*	20

Key:
Placebo Step
Dose Medication is discontinued
Escalation
Incompleted Placebo Step
Escalation from Previous Dose and Discontinue

E. Two Escalations during Placebo Steps. Both infants have two escalations at steps 8 and 10 after infant A starts placebo. NOWS signs reoccur during step 7 causing opioid resumption at 25% of the stabilization dose. Infant A does not tolerate weaning opioid at step 9, and the clinical team resumes 25% of the opioid stabilization dose. Steps 7 and 9 of placebo for infant A did not end in a successful wean to another placebo step and neither is complete. Three complete placebo steps (6, 11, and 12) ensure that both infants end "study drug" at step 12