THE FOLLOWING PAGES HAVE BEEN EXTRACTED FROM SAIL MANUAL OF PROCEDURES FOR USE IN TRAINING:

1. Training and Documentation

1.1. Training on Sustained Inflation (SI) Maneuver

At each site, the Site PI or his/her delegate will be responsible for local training. Specific training will be required for all clinicians who will be performing the Sustained Inflation (SI) maneuver during resuscitation. Training activities include the following:

- review of the SAIL protocol or the protocol slides;
- reviewing SAIL manual of procedures sections on enrollment, delivery room procedures, and the study interventions [**see MOP *Sections 6, 7,and 8***]
- watching the training videos [**see below Section 4.2]**
- practicing the SI maneuver method with the resuscitation team;
- attending local inservice session on infant resuscition.

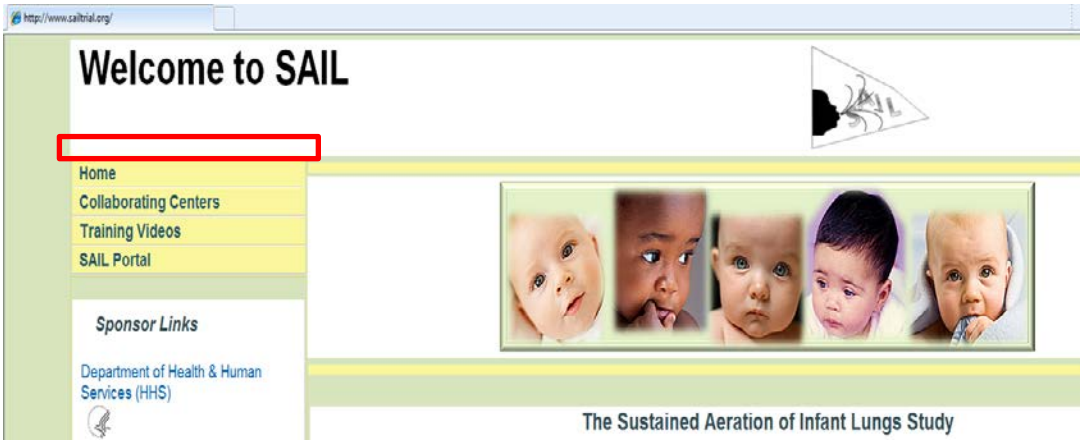
Upon completion of the training activities, the clinician will complete a Training Attestation Checklist *[see Appendix 1]* to document their training. **The Training Attestation form is completed only by the clinicians who will be performing the Sustained Inflation maneuver**.

1.2. Accessing the SAIL Trial Training Videos

To facilitate training, the Penn CCC team has developed 4 brief videos for use in training the delivery room team about the SAIL Study Sustained Inflation (SI) procedure. The videos show the SI procedure and highlight the timing and coordination of events in implementing the SI.

Aside from training the delivery room team during the trial planning and preparation stages, the videos can be viewed by any DR team before a SAIL eligible baby is born to reinforce the procedure and timing. The videos show the team huddle, the SI maneuver and 2 alternate scenarios and are not intended to show all possible scenarios. To view the SAIL trial videos

1. Navigate to the SAIL Trial website at www.sailtrial.org
2. Click on the tab at the top left of the screen labeled 'Training Videos.'



3. When prompted for a username and password, enter '**sailvideo**' in both fields. [See below.]
4. Click on each video to view it.
5. Users who access the training videos from this entry are not able to see any of the protected content on the SAIL Trial website.

1.3. Training on Protocol and Data Management Procedures

The DCC will hold a training webinar with site research team members, befor trial start-up at the site. This webinar will review key elements of the protocol, manual of procedures (MOP) and data collection methods. Specific data management system training will be required for users of the REDCap remote data capture web-based system.

1.4. Research Training in Human Subjects Protection

Training in Human Subjects Protection is a National Institutes of Health (NIH) educational requirement of principal investigators, sub- or co-investigators, study coordinators, and all "key research personnel" involved in the design or conduct of NIH-funded human subjects research. This requirement applies to all NIH studies conducted both nationally and internationally. Training in Human Subjects Protection should be received before research involving human subjects is begun at the clinical site. A current certificate issued from a training program provided at the clinical site institution or a certificate issued from completion of the NIH on-line "Protecting Human Research Participants" training course will fulfill this requirement. The NIH training course takes approximately one to two hours to complete, and is available at: http://phrp.nihtraining.com/users/login.php

1.5. Summary of Training Requirements

Though the composition of the delivery room clinical team and research team varies at each site, some members of the delivery room clinical team may also be members of the site research team. The following table is a summary of study training required for clinical and research team members.

Role	Performs Resuscitation Sustained Inflation Maneuver?	Receives Training in Sustained Inflation Maneuver and Completes Attestation	Is a Member of the Research Team?	Receives Training in Human Subjects Protection
Neonatologist in charge of Delivery Room Team (team leader)	YES	YES	YES	YES
			NO	NO
Principal Investigator and/or Co-Investigators in charge of Research Team	YES	YES	YES	YES
Neonatal Attending Physician; Neonatal Fellow	YES	YES	YES	YES
			NO	NO
Other Delivery Room Clinicians such as: Respiratory Therapist; Nurse Practitioner; Nurse; Pediatric Resident; Physician Assistant	YES	YES	YES	YES
	NO	NO	NO	NO
Neonatal Nurse assisting with delivery room care/or recording resuscitation information	NO	NO	NO	NO
Research Coordinator	NO	NO	YES	YES
	YES	YES		

1.6. Approvals and Documents

Prior to the SAIL Study initiation at each individual clinical site, the following documents must be submitted to the DCC:

- Each clinical site must have IRB/Ethics Committee review of the study protocol and receive approval to conduct the study. A copy of the IRB/Ethics Committee approval letter and and a copy of the approved informed consent/patient information document(s) must be on file with the DCC before a site can begin study start.
- A copy of the Investigators delegation of responsibilities log, identifying the roles and responsibilities of key research personnel involved in conducting the study.
- A copy of the Investigator Agreement page (located in forward section of protocol) signed by the Principal Investigator
- A copy of current certificate of training in Human Subjects Protection for all site research personnel involved in the design or conduct of the study.

2. Enrollment

Any mother/parents who consents to the trial is considered enrolled in the study. If at the time of birth, the infant is not eligible for the study because he/she is breathing well on CPAP and

does not need resuscitation or for some other reason, this baby will not be randomized. However, this child is considered enrolled and should be followed for the duration of the time hospitalized. This information will be recorded on the Screening and Enrollment [SCREEN] form and the full set of data will be collected on this baby according to the SAIL trial schedule.

2.1. Participant Eligibility

Only infants who are born in participating NICUs (which do not use prophylactic surfactant) and who are deemed at birth to be eligible will be randomized into the study ***(please also refer to MOP Section 7.7 Assessing Eligibility and Defining Respiratory Effort)***

2.2. Inclusion Criteria

In order to qualify for participation in the study, the infant must meet the following inclusion criteria at birth:

a. Gestational age (GA) at least 23 weeks but less than 27 completed weeks by best obstetrical estimate

b. Requiring resuscitation/respiratory intervention at birth – "apneic, labored breathing, gasping"

2.3. Exclusion Criteria

Infants who have any of the following at birth will be excluded:

a. Considered non-viable by the attending neonatologist
b. Known major anomalies, pumonary hypoplasia
c. Refusal of antenatal informed consent
d. Mothers who are unable to consent for their medical care and who do not have a surrogate guardian will not be approached for consent.

It is anticipated that there will be a small number of infants who, because of acute clinical deterioration are treated according to the preference of their medical team rather than as assigned by randomization in study protocol. In this case, record this information on the Screening and Enrollment form [SCREEN]

2.4. Trial Withdrawals

Parents are free to withdraw from the trial at any time. Withdrawal of consent could be made after signing consent and before the birth of the infant, or at anytime after the birth of the infant. It is important to note that parents' withdrawal from the trial does not indicate refusal to data collection unless the parents specifically inform the research team that they withdraw consent for the collection of their child's medical data. When the research staff becomes aware of a study withdrawal, the RC should complete a STUDY STATUS form and enter it in the REDCap data management system. [See Study Status Data Instructions –Section 16.1].

2.5. Concurrent Research Enrollment

The SAIL Study has been cleared for concurrent enrollment with the NICHD Neonatal Research Network (NRN) trials with the exception of the *Inositol to Reduce Retinopathy of Prematurity (INS 3)* trial. This approval will enhance recruitment efforts at those SAIL clinical sites that are part of the NICHD Neonatal Research Network (NRN).

The policy on Concurrent Research is as follows:

i. All randomized trials that likely involve patients who are also eligible for the SAIL trial, must be discussed with the SAIL executive committee, and the protocols shared.

ii. All such studies may or may not be compatible with the SAIL trial, and full discussion will be undertaken to resolve potential for co-enrollment.

iii. Enrollment of SAIL participants in concurrent studies that involve consent for the child and family should be documented on the SAIL Screening For Consent and Enrollment [SCREEN] case report form.

3. Delivery Room Procedures

Upon the birth of the infant in the delivery room, determination of the infant's eligibility for the trial will be made. If deemed eligible, the infant will be randomly assigned to receive either resuscitation based on NRP Guidelines, or Sustained Inflation (SI) intervention followed by standard of care.

3.1. Delivery Room Resuscitation Team

A Neonatologist or designee will lead the resuscitation team, which is comprised of the clinical providers who will perform the delivery room (DR) intervention and all delivery room procedures. Some members of the clinical team may also be members of the research team. It is the members of the SAIL research team who will collect study data, communicate with the DR and NICU staff, and document trial events. The exact composition of the delivery room team may vary among sites.

In the following table, the composition and role designation for members of the team at U Penn are described. This might serve as a potential model especially for US and Canadian sites, but the SAIL team recognizes that each site may have differing solutions. However, while team composition is likely to vary considerably across sites, the site PI in general and the team leader at an individual resuscitation should consider which members of the available clinical team are responsible for performing these duties.

3.2. Table showing Team Composition used at U Penn

Role	***Performed by***	***Responsibilities***
Team Leader	Neonatal Attending or Fellow	• Leads pre-resuscitation huddle • Makes final determination of study eligibility and directs RT to open the randomization envelope • Ultimately responsible for ensuring adherence to study algorithm • Generally not involved with hands-on care
SAIL Study Coach	Neonatal nurse practitioner, fellow, or nurse	• Assists leader in ensuring adherence to intervention algorithm for infants assigned to SI arm. • Uses stopwatch to ensure appropriate time intervals are used, counts down these intervals aloud for the team. • Anticipates and announces next step of algorithm in advance.
Airway provider	Neonatal fellow or nurse practitioner	• Clears airway and manages the facemask • Assesses for visible spontaneous breathing pattern
Additional medical provider	Pediatric resident or neonatal nurse practitioner	• Stimulates infant and wraps in plastic • Performs clinical HR assessment and assessment of breathing pattern • Occludes Neopuff to deliver the SIs, so that airway provider can use 2 handed hold on mask
Respiratory therapist	Respiratory therapist	• Opens randomization envelope and announces allocation • Sets and adjusts appropriate settings on the Neopuff, titrates FiO2
Bedside nurse	Neonatal nurse	• Stimulates infant, wraps in plastic • Applies pulse oximeter probe • Assists with clinical assessment of HR, breathing pattern
Recorder	Neonatal nurse	• Not involved in hands-on care • Real time recording of HR, respiratory effort every 30 seconds for the first 2 minutes: may need to prompt team for these assessments • Records all study interventions and infant's response to interventions • Thereafter records resuscitation per unit protocol

3.3. The Team Huddle

If time allows, it is suggested that the team leader should lead a brief huddle of the team prior to the delivery of the infant ('Just-in-time training). This should review the tasks and assignments of each participating team member involved in the delivery room and study procedures.

1. Ensure all required roles (see table above) are taken by a specific individual
2. Review initial steps and timing for assessment, determination of eligibility, process for randomization.
3. Ensure randomization envelope for correct gestational age stratum is available.
4. Perform checklist to ensure all equipment is present and functional
5. Review resuscitation algorithms for the control arm and sustained inflation arm
6. If time permits, briefly review SI intervention training video**
7. Address all questions and concerns

A SAIL training video demonstrating the team huddle, the sustained inflation (SI) maneuver, and the SI algorithm following alternate clinical scenarios is available at: http://www.sailtrial.org

Click on the tab at the top left of the screen labeled 'Training Videos.' The User Name and Password are the same: Log in: User Name: **sailvideo** Password: **sailvideo**

3.4. Steps in Determining Eligibility and Resuscitation

3.5. Time Zero

After birth and cord clamping as per each unit's normal practice, potentially eligible infants ($23^{0/7}$ -$26^{6/7}$weeks GA) will be taken to a resuscitation trolley, placed in a plastic wrap, stimulated, and have a pulse oximeter probe placed on the right hand. The time the infant is received by the resuscitation team is when the SAIL resuscitation time clock starts and is taken to be time 'zero.'

After ensuring airway patency, the infant will be placed on facemask, nasopharyngeal tube, or nasal prong CPAP at 5-7 cm H2O and FiO2 0.30, via a T-piece resuscitator.

3.6. Cord Clamping

This trial does not specify the duration of cord clamping, recognizing that this remains an area of controversy and uncertain uptake into clinical practice for this group of infants. But the time of cord clamping will be recorded.

3.7. Assessing Eligibility and Defining Respiratory Effort

Within 30 seconds of receiving the infant upon the resuscitation trolley (SAIL Time Zero), the resuscitation team will assess respiratory effort and heart rate. Throughout the resuscitation, inadequate respiratory effort is defined as apnea or gasping respirations, and bradycardia is defined as heart rate (HR) <100 beats per minute (bpm).

Infants with adequate respiratory effort and HR>100 bpm will not meet inclusion criteria and will not be enrolled in the trial. Those infants subsequently will be treated according to local resuscitation protocols. Infants with inadequate respiratory effort (defined as apnea or gasping respirations) or HR <100 bpm will be eligible for trial enrollment. At the moment an infant is deemed eligible for enrollment, the resuscitation team leader should instruct the responsible member of the resuscitation team to randomize the infant (See below). **In the case of multiple births, each infant will be assessed for study eligibility individually.** The same treatment allocation will be used for all eligible infants within the set of multiples.

In most cases, the process of determining trial eligibility should occur within 30 seconds of receiving the infant on the resuscitation table, and this process should always be complete

within 60 seconds of receiving the infant. If the infant is deemed eligible before 30 seconds have elapsed, the team should randomize the infant immediately at that point (i.e., the team need not wait 30 seconds to make this assessment).

There are situations in which judging "adequacy" of respiratory effort is difficult due to the inherent subjectivity of this assessment. In general, infants who are deemed ineligible for trial enrollment should have unequivocal and sustained strong respiratory effort. **If providers are in doubt regarding the adequacy of respiratory effort because the assessment is not unequivocal as described, the infant should be randomized.**

3.8. Randomization Process

An infant is randomized into the SAIL Trial when he/she has been assessed as eligible regarding respiratory effort and heart rate to either the Control Arm (NRP-PPV) or the Intervention Arm (Sustained Inflation). The resuscitation team leader/neonatologist should instruct the RT/ responsible member of the resuscitation team to open the randomization envelope. The team member should loudly and clearly announce the randomization arm.

3.9. Randomization Envelopes

Randomization envelopes are color-coded to reflect the different stratification scheme based on the 2 GA groups: 1) 23 & 24 weeks (Green) and 2) 25 & 26 weeks (Orange).

The DCC will send to each clinical site a total of 24 envelopes which will be delivered in batches of 12 envelopes for each strata. The envelopes in each strata will be sequentially assigned to infants in that strata.

Envelope is Color Coded by Age Group*

GREEN – is for Infants born at 23 & 24 weeks

ORANGE – is for Infants born at 25 & 26 weeks

Envelopes should be stored in a secure but accessible location in the delivery room (DR).

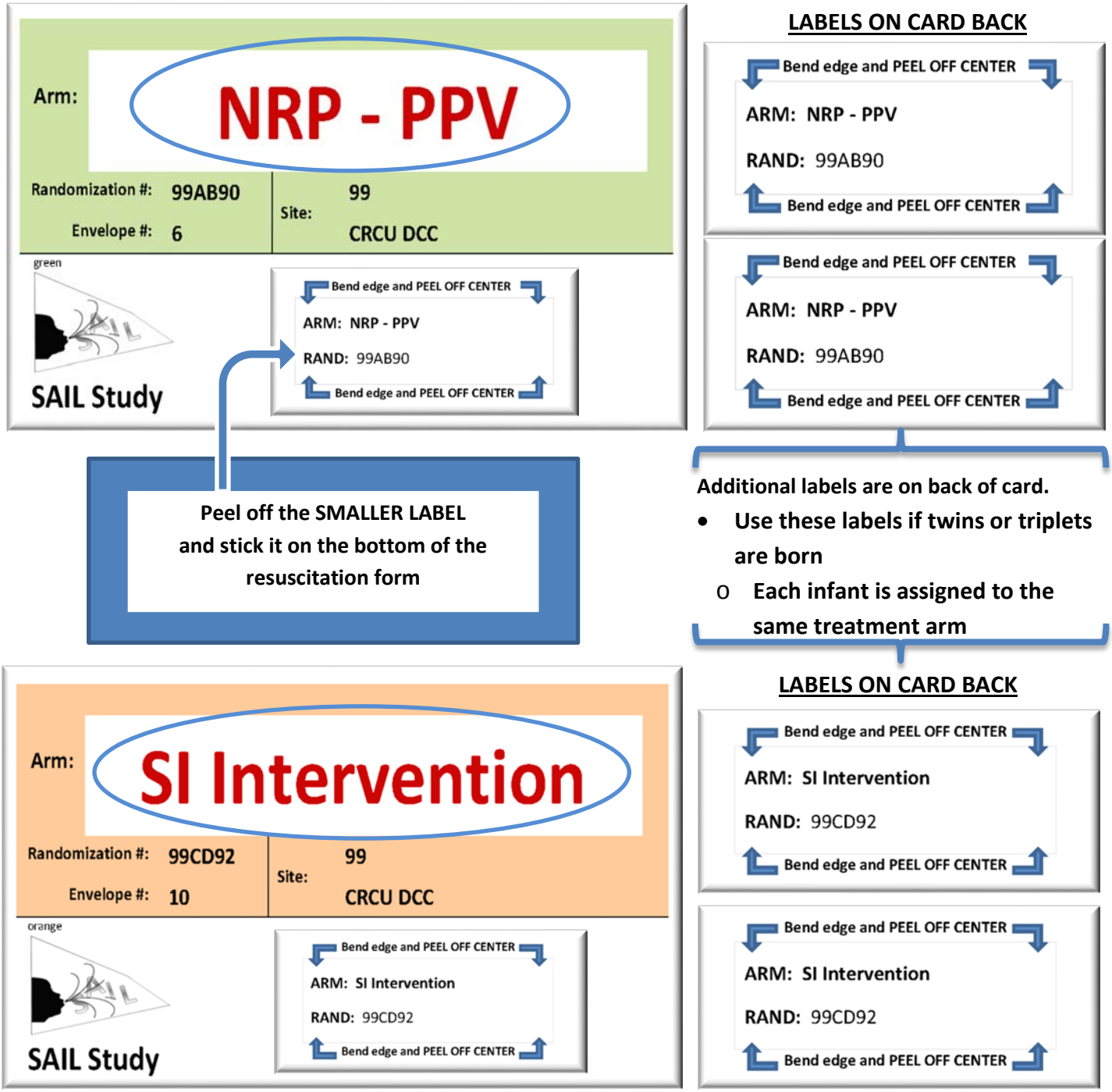
Before the infant's imminent delivery in the DR/resuscitation unit, the person responsible for opening the randomization envelope should select the next envelope in the sequence based on the infant's estimated GA. The envelope should be nearby and ready to open for allocation once the lead clinician has verified eligibility.

Inside the Envelope is the Randomization Card

This Card tells you the treatment arm assignment the infant is to receive

The treatment arm assignment is either NRP-PPV or SI Intervention

Here is where you find the treatment arm assignment…



As indicated above, a card containing 3 labels is *inside* of the randomization envelope. Remove the label from the front of the card and place it in the space indicated at the bottom of the RESUSCITATION form. This label has the following information: Arm assignment (*NRP-PPV* **OR** *SI Intervention* AND Randomization Number

For quality assurance, it is important that the torn opened envelope is saved and returned to the DCC. A scan or copy of the opened randomization envelope will be sent to the DCC project manager via e-mail (sail-pjm@lists.upenn.edu or fax: 215-573-6262) in a timely manner, after the infant leaves the delivery room. Once all envelopes for both strata have been used at your site, please mail the used envelops to the DCC using the UPS return label provided with the batch. It is important to note that after six randomizations have occurred in each strata, you must send an e-mail notification to the DCC project manager so that the next batch of randomization envelopes can be mailed to your site.

3.10. Important Randomization Guidelines

1. The envelope with the lowest available sequential number for a given stratum should be used.

2. The randomization envelope should not be opened in advance in anticipation of the baby's birth.

3. If a randomization envelope is opened that is not used, that randomization label should not be used for another qualified infant, and it should be reported to the DCC as soon as possible as this will alter the randomization scheme. Such envelopes should also be saved and returned to the DCC.

4. In the event that twin or additional infants are born, they will all be given the same randomization number and treatment arm assignment as the first born infant. Two additional labels are on the back of the enclosed card.

5. If a randomization envelope is opened in error, the protocol violation form should be completed and sent to the DCC project manager to explain the situation.

3.11. When is the Randomization Envelope Not Opened?

The randomization envelope is not opened when:

- It is determined at birth that baby is not eligible for the trial

- Parents refuse to gives consent or give consent to only allow collection of data

4. The Study Interventions

4.1. NRP -PPV

Infants randomized to this arm will be treated with intermittent positive pressure ventilation (IPPV) with PEEP via T-piece resuscitator and either facemask, nasopharyngeal tube (NPT) or nasal prongs, following NRP compliant practice.

Peak pressures will be set initially at 20 cm H_2O. Ongoing assessment of adequacy of IPPV will be made using heart rate and respiratory effort. Ventilation corrective steps are applied as needed (See MR SOPA below) as recommended by NRP guidelines, including increasing peak pressure to 25 H_2O cm, or as local clinical practices allow.

4.2. Sustained Inflation (SI)

Infants randomized to this arm should receive respiratory support via the T-piece resuscitator and either facemask, nasopharyngeal tube (NPT) or nasal prongs – according to local preference. A summary timeline of interventions for the SI group is given below.

Infants will be given the first SI for 15 seconds using pressure of 20 cm H_2O. An assessment for respiratory effort and heart rate will be made. Infants with adequate respiratory effort and heart rate above 100 bpm after the first SI will continue on CPAP, as study intervention has ended for these infants and they revert to standard NRP procedures.

After the first SI, if the infant has persistent inadequate respiratory effort (apnea or gasping) or bradycardia (HR<100 bpm), a second SI using a pressure of 25 cm H_2O for 15 seconds will be given. Between the first SI and the second SI, the team will follow standard NRP procedures as described in the next paragraph (MR SOPA). Decisions about need for a second SI will be based on repeat assessment of HR and respiratory effort.

During this period between SIs, as per NRP recommendations, ventilation corrective steps can be made to ensure no residual lack of seal or obstruction is impeding the infant using the MR SOPA mneumonic as described in the U.S. NRP manual:

M: Mask adjustment

R: Reposition

S: Suction Airway

O: Open Mouth

P: Pressure

A: Airway

If the infant is eligible for a second SI due to inadequate respiratory effort (apnea or gasping) or HR<100, the clinician will ensure airway patency and deliver the second SI with a pressure 5 cm higher than the initial pressure. This step is in accordance with the P (Pressure) step of MR. SOPA.

The final ‘A’ in MR. SOPA stands for Airway. There will be rare situations where the clinician must respond with intubation immediately – such infants will be also randomized into an SI or standard arm. While these infants data will be pooled, it will also be treated separately in a sub-group analysis.

At any point in the algorithm, if the HR is < 60 and not increasing, PPV may be given with rate in accordance with NRP and peak inspiratory pressure equal to the SI that would otherwise be performed. Observation after a 15 second period will assess whether there is an improving heart rate. If the heart rate improves to >60, the algorithm will be resumed from the point of departure.

Throughout the entire period, cardiac compressions will start if HR remains < 60 despite effective respiratory support for > 30 seconds.

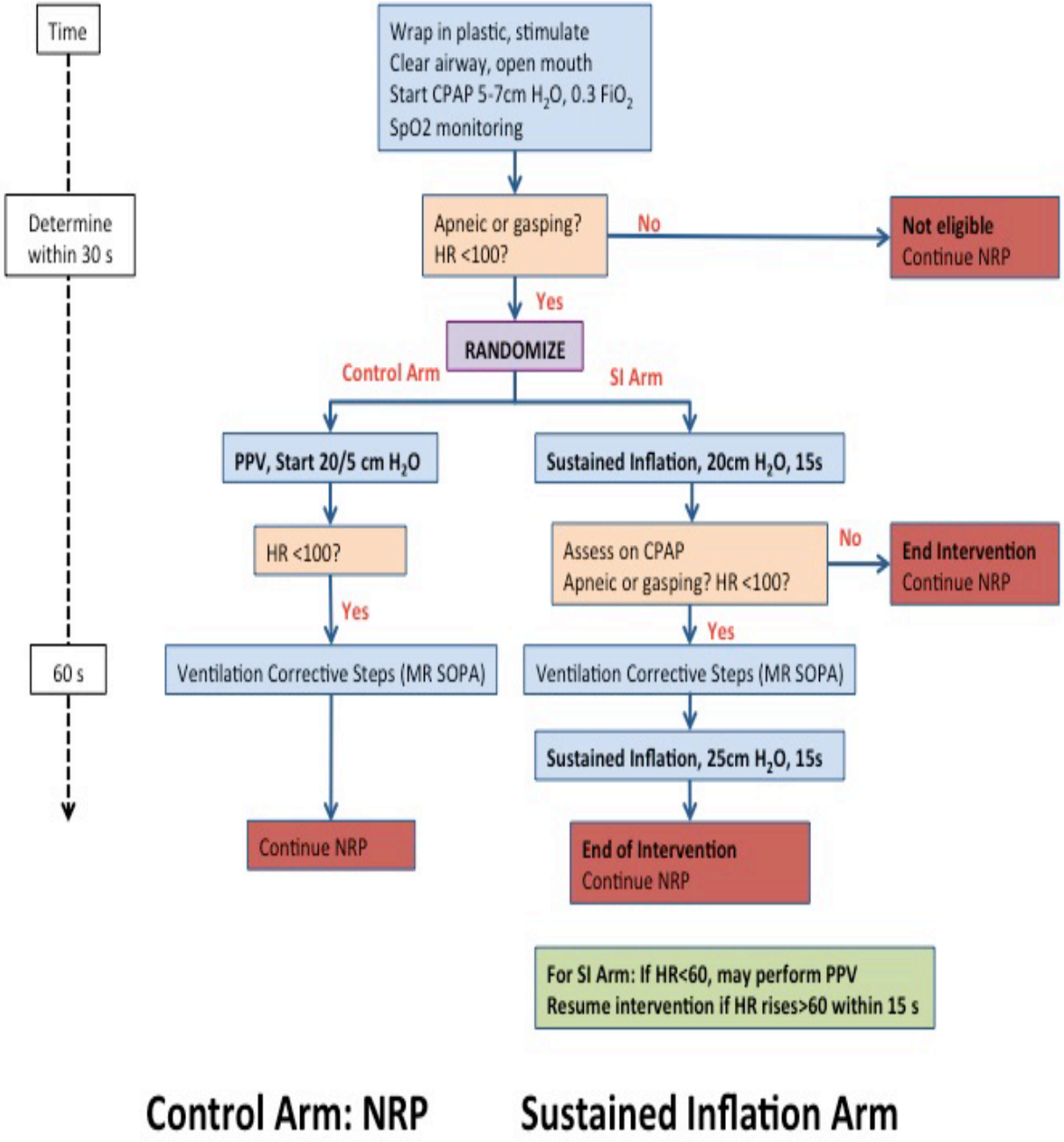


Figure: Algorithm depicting flow of assessments and interventions for infants in both arms of the trial.

4.3. Sustained Inflation Intervention - Resuscitation Timeline

The following describes the timing and flow of assessment and intervention steps for infants assigned to the Sustained Inflation (SI) Intervention arm. ***The time intervals listed are relative to Time Zero, the time the infant is placed on the resuscitation trolley.*** In the case that clinical assessments and interventions result in deviations from performing interventions within the intervals described, teams should still conform to the proscribed duration of time required for key interventions (i.e., a SI should still last 15 seconds, even if it starts at 40 seconds into the resuscitation, rather than at 30 seconds).

Time of birth: Time of birth (defined as when the body is delivered) should be recorded, but this is **not** considered time 0 for the resuscitation.

Time zero: Time zero for the resuscitation is defined as the moment the infant is placed on the resuscitation trolley.

Time 0-30 seconds: Start resuscitation and determine eligibility for trial

1. Baby is received on resuscitation trolley by resuscitation team
2. Placed immediately under radiant warmer on gel mattress, wet towels removed, placed in plastic covering (neowrap or plastic bag), hat placed on head, stimulated by team (bedside nurse, medical provider, airway provider, RT).
3. Airway cleared and mask CPAP initiated via T piece with initial settings of 5-7cm H_2O, 0.3 FiO_2, breathing pattern assessed and announced by airway provider.
4. Pulse oximeter placed on right hand by bedside nurse.
5. Clinical assessment of HR determined and announced by medical provider
6. HR, respiratory effort, intervention, and determination of eligibility recorded at 30 seconds by recording nurse
7. *<u>Before or at 30 seconds: Determine eligibility for SAIL study</u>. If infant has inadequate respiration effort (defined as apnea or gasping) <u>OR</u> has HR<100, s/he is eligible for the SAIL trial. Team leader will announce eligibility and instruct the provider responsible for randomization to open stratified randomization envelope and announce the treatment allocation.*

Time 30-45 seconds: Perform first SI, if so randomized

1. Airway provider holds mask in place with 2-handed technique
2. Assisting medical provider occludes T-piece
3. SI delivered with PIP 20cm H_2O for 15 seconds
4. Coach monitors stopwatch, counts down final 5 seconds to team

Time 45-60 seconds: Evaluate response to first SI

1. Infant maintained on CPAP, response to first SI (HR and breathing pattern) assessed, announced, and recorded.
2. *If infant has inadequate respiratory effort (apnea or gasping) <u>OR</u> has HR<100, s/he is eligible for a **second SI**. It is expected that most infants will require a second SI.*

a. Infants who have a strong respiratory effort AND HR>100 after the first SI will be maintained on CPAP, with further resuscitative efforts dictated by local protocols. The intervention is complete for this subset of infants.

3. Corrective ventilation steps performed if necessary: airway cleared, mouth opened, and mask repositioned.
4. It is expected that most infants who require a second SI will need corrective ventilation steps performed, to ensure airway patency and a good mask seal prior to performing the second SI.
5. The process of determining response to the first SI and performing corrective steps should take no more than 15 seconds

Time 60-75 seconds: Perform second SI

1. Airway provider holds mask in place with 2-handed technique
2. Assisting medical provider occludes T-piece
3. Respiratory therapist increases PIP on T-piece to 25cm H_2O
4. SI delivered with PIP 25cm H_2O for 15 seconds
5. Coach monitors stopwatch, counts down final 5 seconds to team

Time 75-90 seconds: Evaluate response to second SI

1. Infant maintained on CPAP, response to second SI assessed, announced, and recorded (HR and breathing pattern)
2. Intervention is complete at this point
3. Further resuscitative efforts to be determined by local protocols

4.4. Additional Clinical Guidelines

The SAIL Study CCC team has developed the clinical guidelines below for incorporation into the clinical research site practice, as applicable.

4.5. Intubation and Extubation

Guidelines for **Intubation** include meeting any of the following criteria:

1. FiO2 ≥0.5 to maintain SpO2 ≥88%
2. pH ≤7.22 or PCO2 ≥70 mm Hg
3. >1 apneic event requiring IPPV within 6 hours
4. ≥6 apneic events requiring stimulation within 6 hours
5. Hemodynamic instability
6. Need for surgery

Extubation should be attempted within 24 hours after meeting all following criteria:

1. PCO2 ≤ 55 mm Hg
2. pH ≥7.25
3. FiO2 of ≤ 0.4 with an SpO2 of ≥ 88%
4. Mean airway pressure of ≤ 8 cm of water

5. Hemodynamic stability

4.6. Caffeine Use

The use of caffeine and the timing of caffeine administration will vary among the clinical site delivery room standard practices. The SAIL Study CCC advocates that if at the end of the resuscitation maneuver, the baby is NOT intubated and the intention is to leave the Delivery Room on CPAP, then a loading dose of caffeine should be administered within the first 4 hours of life. This information is recorded on the Growth and Medication Assessment [GMA] case report form. Document the time of the initial caffeine load the first time caffeine is given after birth. Future caffeine bolus doses given once a baby is on maintenance caffeine therapy do not need to be documented.