

**Trial of Late Surfactant to Prevent BPD  
A Study in Ventilated Preterm Infants Receiving  
Inhaled Nitric Oxide**

**“The TOLSURF TRIAL”**

IND # 79,367



**Protocol  
and  
Manual of Operations**

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# I. Manual of Operations

# I. MANUAL OF OPERATIONS-Overview

## 1.0 Screening

- 1.1 After the coordinating center receives all required documentation (FDA, IRB, etc.), four study binders will be distributed (Coordinator, Regulatory, Pharmacy and Respiratory Therapy). The site coordinator will receive patient screening ID list and other study management paperwork along with these binders.

The site research pharmacist will receive guidelines and randomization tables that are stratified by gestational age (< 26 weeks and 26-28 weeks). These randomization tables will accommodate the enrollment of multiple siblings from the same birth mother and ensure that they receive the same treatment assignment. The respiratory therapist will receive guidelines on dosing, completing the Dosing Tolerance Form and handling the Dosing Tolerance Form.

- 1.2. Site coordinator will begin screening of eligible infants (all infants with gestational age  $\leq 28 \frac{0}{7}$  weeks) as soon as IRB has approved study.

Use **TOLSURF Screening Log** to record eligible patients. This site-specific log is sent with screening numbers and secondary IDs pre-filled. Use these numbers on your screening CRF 1A and subsequent enrollment CRFs for patient identification. This log will help us record numbers of eligible patients for the final manuscript.

It is a good idea to place patients on your site screening Log as soon as they are identified. There is a column to put the dates of eligibility for the patient (day 7 thru day 14).

**Example:**

<u>Institution Code</u>	<u>and</u>	<u>First Screening ID</u>
01 (UCSF)		01-001
02 (Children's Oakland)		02-001
03 (Alta Bates)		03-001

- 1.3. Coordinator should complete a CRF Screening Form 1A (2 pages) for each eligible infant added to Screening Log. Infants must be followed for the duration of their eligibility (7-14 days). Coordinator should attempt to obtain early consent (days 2-6) to assure entry into the study as early as possible. Once consent has been obtained, the site coordinator will contact the project manager, Nancy Newton or in her absence, Jeanette Asselin, who will confirm subject's eligibility and assigned study ID. Project manager will then email coordinator a set of patient CRF's pre-filled with patient's study ID, and a set of Patient Tolerance Forms for the dosing RT/RN. When completing screening logs, even though you may follow the child for a week or two, enter the date screened as the date you decide the patient is eligible or not.

Completed screening forms should be faxed to DCC every week. Maintain open screening forms with Screening Log until eligibility has elapsed, infant is enrolled or deemed ineligible. Once Screening Form 1A has been faxed to the DCC, it should be filed for safe-keeping. The screening forms for “Patients not Enrolled” should be saved with other research regulatory data (suggest making folder for patients not enrolled). Screening Forms of infants enrolled should be stored with their other study CRFs.

- 1.4. Records of screened candidates for the study should be reviewed by one of the study investigators and the child’s condition discussed with the attending physician. If infant qualifies, the infant’s parents will be approached by one of the investigators to obtain informed consent preferably within the first 3 days with the expectation that if the infant meets criteria between 7 and 14 d of age, he/she will be randomized and enrolled at that time.
- 1.5. Patient must be clinically stable for enrollment. The study protocol outlines 7 conditions wherein a patient would be considered clinically “unstable” so would not be enrolled, or have dosing continue. Definition of Clinically Unstable includes:
  - Active Pneumothorax with chest tube
  - Active Pulmonary Hemorrhage
  - Uncontrolled hypotension despite more than 20 mcg/kg/min dopamine or 2 pressor agents for > 24 hours (2nd pressor can be Hydrocortisone)
  - Acute NEC –less than 24 hours from diagnosis or surgery
  - Untreated culture positive sepsis (<6h)
  - RSS >14
  - Clinical team feels infant would not tolerate dosing procedure

1.5.1. Once these issues resolve, the infant may be considered for enrollment or continued dosing (if dosing was delayed) in the TOLSURF study.

If you have questions about clinical instability, call CCC:

Nancy Newton MS, RN  
415-517-6257

Jeanette Asselin RRT MS  
510-813-1177

## **2.0 Randomization and Treatment Assignment**

- 2.1. Once parental consent has been obtained, coordinator should notify site staff so they can prepare (respiratory, attending physician, bedside nurse). Coordinator should then contact Project Director, Nancy Newton RN at 415-516-4617, who will review patient's eligibility and assign patient's study randomization ID number.
- 2.2. Similar to the Pilot, Study randomization ID's will be a 6 digit number (00-00-00).
- The first two digits will reflect the site ID
  - The second two digits will reflect the consecutive number from stratification table (infants < 26 weeks will have #'s 49-99, infants 26-28 weeks will have #'s 01-48),
  - The third two digits will be sibling number.
- 2.3. Sibling number: Singletons will always be "01". Twins/triplets will sequentially be assigned "01", "02" and "03" as they become eligible and are enrolled. Only the first infant of a multiple birth will actually be randomized should two or more siblings be eligible. Subsequent eligible siblings, will be assigned to the same treatment group as the randomized infant and treated in a similar blinded fashion. All siblings will have the same first 4 digits of their study randomization ID (1<sup>st</sup> 2 digits=site #, 2<sup>nd</sup> 2 digits =gestation stratification, but last 2 digits=sibling number will differ – eg: 01,02...03). Clinical data will be collected for all siblings who receive therapy.
- If one twin is eligible and the other is not (eg: Twin A is intubated, Twin B on NCPAP), enroll the single twin, if parents consent.
- 2.4. The study or attending physician will write an order for study surfactant to send to pharmacy. Order should include:
- the infants assigned study randomization ID number,
  - infant's gestational age (for stratification verification) and
  - current patient weight (for study drug dosing).

The coordinator will contact the site research pharmacist who will consult his/her treatment assignment list and assign treatment.

- 2.5. The research pharmacist will prepare the syringes (2 equal aliquots (1.5 mL/kg each) of Infasurf or sham) to be sent to the patient care area. These will be labeled with the study randomization ID number assigned, covered and placed in a opaque plastic bag for transport to the patient care area. This sample should not be handled by anyone who should remain blinded. The un-blinded (dosing) respiratory therapist or nurse will retrieve these syringes and administer the surfactant or sham according to the protocol.

Dosing should continue as long as the patient remains intubated, until all 5 doses have been administered or patient reaches 35 days of age. Patients are no longer considered eligible after DOL 35. At this point dosing is considered completed, whether all 5 doses were administered or not.

### **3.0. Inhaled Nitric Oxide Administration**

- 3.1. As of November 2010, Ikaria has agreed to the process of providing “free” gas and INOVents for the TOLSURF study. Contracts are being sent out to study sites and once executed, an initial set of 4-6 tanks of iNO and 2 INOVents will be sent to sites for use on study patients.
- Sites will need to use these INOVents for study patients. If you have issues with availability of these systems because of high enrollment, please call the CCC. Additional INOVents should be available. However, we will address these concerns on an individual site basis.
  - As with most things, free stuff comes with additional paperwork. Sites that were involved in the TOLSURF pilot, will follow similar procedures.
    - Respiratory will need to keep records of study gas inventory received “Receipt Log”, study tanks used “Usage Log” and tanks returned “Return Log”.
    - Copies of Ikaria Logs (Receipt, Usage and Return) are included in the MOP as Appendix H, I, and J.
    - Also keep track of the INOVent machine serial numbers that are sent to your site.
  - Our contact with Ikaria for the study is Tamara Gaymon. Tamara, or one of her colleagues will likely be contacting each of your sites once the contract is executed.
  - Remember, study patients should NOT be billed for iNO gas or maintenance of the INOVent during the time of iNO gas delivery. Some of the RT departments may need to adjust their billing systems accordingly.
- 3.2. After consent has been obtained and the baseline tracheal aspirate has been collected, the subject will be started on iNO if not already receiving it as part of “accepted care” per Clinical BPD Protocol.
- Clinical BPD iNO Dosing:
- 7-14 Days of age – Start iNO at 20 ppm x 96 hours (4 days ± 1 day).
  - Then wean, per site protocol to 10 ppm x 1 week, 5 ppm x 1 week, 2 ppm x 1 week, then OFF.
- 3.3. Methemoglobin samples should be obtained per your individual hospital policy. We will not collect MethHgb for this study.
- 3.4. The iNO for BPD dosing schedule starts between DOL7 and 14 and continues through the end of site NO CLD protocol. If the patient was started on iNO prior to DOL 7, initiate your site’s iNO BPD protocol on DOL 7, or as soon as the patient is eligible to receive iNO per the site BPD protocol. If iNO delivery varies from the NO CLD protocol, complete a protocol deviation form for iNO delivery.
- 3.5. If the patient is extubated during the 25-day iNO treatment period, every attempt should be made to maintain iNO therapy for the duration of the Clinical BPD iNO Protocol. This includes continuing the iNO by nasal CPAP, nasal cannula with oxygen or room air flow.



- 3.6.** If hand ventilation is needed, it is the discretion of the clinical team, whether or not to bag with iNO. Bagging with iNO is not necessary for infants receiving iNO for BPD prophylaxis.

Note: If you bag with iNO, be sure to turn the iNO flowmeter OFF when not in use. Leaving flow on, uses up the gas in the iNO study tanks. It is a good thing to routinely check that bag flow is OFF, when walking by the bedside.

- 3.7.** If the patient is transferred to another hospital for a period of time and then returns to your center, you should restart dosing where you left off and continue to complete the iNO BPD dosing schedule

**Note:** INOvent “monitor failure” alarm occurred when using with a non-invasive device. This situation will happen occasionally when a nasal cannula is used (particularly with higher flows and smaller diameter tubing) and certain CPAP systems (fluidic type) due to back pressure generated in the INOvent monitor sample system. iNO Drug delivery will continue as set, however the INOvent will alarm “monitor failure” and will not display the monitored values for NO/NO<sub>2</sub>/O<sub>2</sub>. A safe and effective remedy to this situation is possible by adding a pressure relief in the monitoring system. This has been done in the past using the monitor calibration "T" (supplied by Ikaria) in line with the sample system (picture below). Some sites have used an IV tubing “wye”.



#### **4.0. Study Procedure Chart**

The Table below represents the timeline for study procedures. Day one of study equals day “0”.

<b>Study Day/Corrected Age</b>	<b>Pre-Study</b>	<b>0</b>	<b>2<sup>b</sup></b>	<b>4<sup>b</sup></b>	<b>6<sup>b</sup></b>	<b>8<sup>b</sup></b>				<b>1wk post iNO</b>	<b>36 wks</b>	<b>40 wks</b>	<b>3, 6 &amp; 9 &amp; 18 mos</b>	<b>12 mos</b>	<b>22 - 26 mos</b>
Informed consent	<b>X</b>														
Randomization		<b>X</b>													
Tracheal Aspirate <sup>a</sup>		<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>									
Study Surfactant or sham procedure <sup>a</sup>		<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>									
iNO		<b>20</b>		<b>10</b>			<b>5</b>	<b>2</b>	<b>0</b>						
Urine sample <sup>c</sup>	<b>X<sup>c</sup></b>	<b>X<sup>c</sup></b>		<b>X<sup>c</sup></b>			<b>X<sup>c</sup></b>	<b>X<sup>c</sup></b>	<b>X<sup>c</sup></b>	<b>X<sup>c</sup></b>					
Oxygen reduction challenge											<b>X</b>	<b>X</b>			
Respiratory status questionnaire												<b>X (DC)</b>	<b>X</b>	<b>X</b>	
Neurodevelopmental evaluation														<b>X</b>	<b>X</b>

<sup>a</sup> If remains intubated and mechanically ventilated. Obtain prior to study dose.

<sup>b</sup> ± 24 h

<sup>c</sup> Urine will be collected prior to iNO (if possible), 24 hours after initiation of iNO, then 24hours after each iNO wean, then 1 week off iNO.

## **5.0. Study Drug Administration:**

- 5.1. Study drug (Infasurf® or sham), will be administered according to the following schedule: First dose on Day 0, then repeated every two days ( $\pm$  24 hours) on Day 2, Day 4, Day 6, and Day 8, if the patient remains intubated.

If infant is extubated and subsequently reintubated, continue to dose per the dosing schedule (e.g. If infant extubated after dose 2 (on day 3) and then gets reintubated on study day 12, administer the next scheduled dose of study drug (dose 3) on day 12.

Dosing should continue as long as the patient remains intubated, until all 5 doses have been administered or patient reaches 35 days of age. Patients are no longer considered eligible for dosing after DOL 35. At this point dosing is considered completed, whether all 5 doses were administered or not.

- 5.2. Pre-dose checklist. Prior to instilling the study surfactant, remember the following:

### **5.2.1. First Instillation**

- 1) Signed informed consent in chart
- 2) Patient already started on iNO at 20 ppm at 7 days of age

### **5.2.2. All Instillations**

- 1) Collect TA sample prior to each dose, on the day of dosing
- 2) Arrange dosing around feeding schedule to insure that an appropriate amount of time has passed since last feed (or feeds have been turned off for enough time).
- 3) Infant's ETT suctioned within 1 hr prior to dosing
- 4) Obtain Unblinded Study Drug Dosing Tolerance Form from study coordinator
- 5) Place screens around bedside. Ask, non-dosing personnel to move away from bedside
- 6) Insure that patient Monitors are on, but alarms silenced
- 7) Check resuscitation bag set-up and test with appropriately sized mask
- 8) Neonatology Attending or Fellow present in unit (in case of reintubation)
- 9) Signed study drug order in chart
- 10) Signed ventilator management order in chart or write "RT to adjust Ventilator as necessary – per study protocol"
- 11) Two person study dosing-team assembled

## **5.3. Ventilator Management Guidelines During Dosing**

### **5.3.1. *Conventional Ventilation***

- 1) If on Assist Control, consider conversion to SIMV if dosing inline on ventilator; specify change with rate in vent study order.

- 2) If on Pressure Control with Pressure Support or Volume Guarantee mode, consider conversion to Pressure Control SIMV if dosing inline on vent. If so, specify rate in vent study order.
- 3) Be careful to watch for surfactant getting in flow sensor as it can make it inaccurate or inoperable and may also unblind caretakers.
- 4) Set termination sensitivity to 'Off' (if using VIP Bird), consider  $T_{insp}$  of 0.4 sec.
- 5) Minimum PEEP during dosing 5 cm H<sub>2</sub>O (may need higher).
- 6) During dosing, adjust PIP as necessary to maintain delivered  $V_T$  of 5-6 mL/kg.
- 7) Adjust FIO<sub>2</sub> if patient desaturates despite adequate tidal volume. Consider further increase in PEEP by 1 cm H<sub>2</sub>O if patient continues to desaturate despite adequate  $V_T$  and FIO<sub>2</sub> > 30 points above baseline.
- 8) May need to hand ventilate briefly if unstable during procedure.

### 5.3.2. High Frequency Oscillatory Ventilation

- 1) Consider an increase of  $P_{aw}$  by 1 cm H<sub>2</sub>O above baseline for procedure.
- 2) During instillation, adjust delta P (Power) as necessary to maintain good chest wiggle.
- 3) Adjust FIO<sub>2</sub> if patient desaturates despite good chest wiggle. Consider further increase in  $P_{aw}$  by 1 cm H<sub>2</sub>O increments if desaturation continues despite change of FIO<sub>2</sub> > 30 points above baseline.
- 4) May need to hand ventilate briefly if unstable during procedure.

NOTE: When using iNO with HFOV, it is important to use the lowest bias flow possible to maintain MAP. This insures that you are not using up and losing a lot of study gas in the bias flow. The majority of small babies can be adequately managed and ventilated with bias flows of 6-8 lpm. If flows above this are being used, please reassess bias flow and reset to lower values.

### 5.3.3. High Frequency Jet Ventilation

- 1) Consider an increase in PEEP by 1 cm H<sub>2</sub>O above baseline before dose.
- 2) During instillation, adjust HFJV PIP as necessary to maintain good chest wiggle.
- 3) Adjust FIO<sub>2</sub> if patient desaturates despite good chest wiggle. Consider further increase in PEEP by 1 cm H<sub>2</sub>O if desaturation continues despite change of FIO<sub>2</sub> > 30 points above baseline.
- 4) Research staff may need to hand ventilate briefly if unstable during procedure.

NOTE: Several sites have noted a problem with the iNOvent at ppm's less than 10 when using the jet (HFJV). This can occur when the SERVO driving pressure is low. The injector needs to see about 2 lpm to appropriately inject the right amount of iNO into the system. If you get a "iNO not being delivered" or "monitor failure" alarm, try the following:

- 1) Switch out the filter with a new, dry filter.
- 2) Check that there are no leaks in the system.
- 3) Call your study area rep for troubleshooting help
- 4) Call the CCC to make them aware of the problem.
- 5) Switch out the iNOvent for a different machine, if possible. Some machines have problems when others do not.
- 6) As a last option, you may need to leave the infant on a higher ppm (usually 10) until you can wean the baby to conventional ventilation. This will require a protocol deviation, but is better than taking the infant off iNO early.  
 Note: If you find that the patient cannot be weaned from HFJV, you can leave the iNO at the higher ppm (ppm that stops the alarm) without weaning. Continue iNO at this level for a maximum of 25 TOTAL iNO days, then turn off. Be sure to inform CCC if this occurs.

#### 5.4. Study Surfactant/Sham Delivery

##### 5.4.1. *Drug instillation*

- 1) Study drug is administered by attaching a syringe containing the pre-measured Infasurf dose (two 1.5 mL/kg aliquots....equals 3.0 mLkg dose) to a catheter that is inserted to a measured depth to reach the distal tip of the endotracheal tube. Site may use Trach Care MAC or other catheter according to individual site protocol. If infant is randomized to receive “sham” simply wait the allotted time behind the screen to blind clinical personnel, no “mock” instillation or manipulation of the ETT should be done.
- 2) Study drug is to be administered in two aliquots. Prior to instillation of surfactant, the respiratory therapist draws back on the study drug syringe to insert an air bubble into the syringe. The syringe is held in the upright position and tapped to move the air bubble behind the fluid. When the syringe is depressed, the air bubble clears all study drug from catheter, ensuring the entire half dose is administered.
- 3) Sites are encouraged to follow their own internal protocol for surfactant administration. In lieu of a protocol, the study suggests that the infant be placed in two positions for instillation, with half of the study drug instilled with the right side of the infant dependent, and half with the left side dependent, as per the Infasurf® package insert. There is a short time period between each dose for re-stabilization of the infant. Time of study drug instillation is 4-6 minutes.
- 4) Sham instillations are exactly that. SHAM! Patients randomized to Sham should not have any manipulation of the airway or ventilator circuit (*the air placebo will not be instilled*). Study staff should remain behind the screen for an appropriate amount of time to mask clinicians to the treatment assignment.

- 5) Immediately after the drug dosing procedure, the unblinded RT/ RN should complete the Dosing Tolerance Form (DTF) for that dose and place it in a pre-labeled envelope. DTF's will have pre-filled bubbles representing doses 1 through 5. These forms will be emailed to the site coordinator when the patient is randomized. Envelopes will be provided by the DCC for this purpose and mailed to the site coordinator. See MOP Data Management, Section III. 2B.1.4
- 6) Complete the appropriate DTF and place in corresponding envelope and seal. The patient's Study Drug Dosing Tolerance Form should be kept confidential (not seen by NICU clinicians/study coordinator).

#### 5.4.2. *Post Dose Observation/Documentation*

##### 5.4.2.1. Unblinded personnel:

- a) Once study drug has been delivered, one of the two study dosing team members can leave. The other is to remain behind the screen for a minimum of 20 minutes after study drug dosing regardless of study drug assignment.
- b) Attempt to wean back to baseline settings over ensuing 20-30 min after dosing.
- c) The instillation catheter and study drug syringe should be discarded after use within an opaque disposal bag (or used syringe disposal bin) to avoid unblinding of drug assignment, or disposing in appropriate "Sharps" container.
- d) Check that monitor and ventilator alarms are no longer silenced before removing screens and leaving bedside.
- e) Complete respiratory assessment and documentation per your institution's policy for surfactant delivery. It is good to have documentation in the patient medical record that study drug was delivered. Instruct RT to record vent settings prior to, 1 hour after and 2 hours after the study drug dose is administered.
- f) File the sealed DTF envelope in patient's Respiratory Dosing Binder for safe-keeping.
- g) Once it is decided that dosing has been completed (e.g. when all 5 study drug doses have been administered or when dosing is completed due to death or infant has reached 35 days of age) dosing RT/RN should open the sealed envelopes and review the 5 dosing forms for completeness, then make copies of each of the 5 DTFs. Place the 5 copies in the pre-addressed envelope to the Data Coordinating Center and mail.

Address:

c/o Lisa Palermo  
TOLSURF Data Coordinating Center  
185 Berry Street, Lobby 5, Suite 5700  
San Francisco, CA 94107

- h) The patient's 5 original DTFs should be placed together in the envelope labeled "Completed DTFs, Patient " \_\_\_ - \_\_\_ - \_\_\_" and filed in

Respiratory Dosing Binder or filed away for safekeeping until end of study.

5.4.2.2. Unblinded staff or bedside RT's

a) It is very helpful for documentation purposes (serves as “source document”), if there is an actual vent check done prior to each dose and then at 1 hour and 2 hours after each dose. These data will be recorded on your site coordinator’s data forms 7A and 7B.

5.4.2.3. Study Coordinator:

- a) CRF 7A for initial study drug delivery and 7B for subsequent study drug doses should be completed.
- b) Study Coordinator should observe infant over next 24 hours for evidence of adverse reaction to study drug instillation.
- c) If adverse reaction is seen, also complete AE and SAE form as appropriate.

## **6.0. Tracheal Aspirate Sampling Procedure and Processing**

TA sampling schedule: A TA sample is obtained just prior to each study drug treatment for a maximum of 5 collections.

### **A. Obtaining Sample:**

1. Perform only if infant is stable and will tolerate suctioning. Obtain sample during routine suctioning using 2-person technique.
2. Use a new (sterile) suction catheter and Leuken's trap provided in the collection kit. It is a good idea to do the suctioning at the time when in-line catheters are routinely changed.
3. Draw up 3.0 ml of normal saline into sterile syringe.
4. Instill 0.5 ml of normal saline into the endotracheal tube.
5. Ventilate lungs as per usual protocol prior to suctioning.
6. Suction the effluent into the Leukens trap. Be sure that the catheter tip does not extend beyond the tip of the endotracheal tube.
7. Stabilize the infant and then repeat steps 4, 5, and 6.
8. Rinse the suction catheter with the remaining normal saline. This represents a single sample.
9. Attach ends of Leukens tubing together to keep sample clean. Label trap with "Leukens" sticker (if not dispensing and centrifuging immediately).
10. If more than 5 minutes will elapse before processing, place the trap on ice or in refrigerator until processing. Allow Sharpie ink on label to dry before exposing it to moisture.
11. If preferred, suctioning may be done without instillation of saline. In that case, rinse suction catheter into trap with 2 ml of saline after suctioning.

### **B. Processing Sample:**

1. Empty entire contents of the Leukens trap into a screw top tube provided in the kit. Discard the empty trap.
2. As soon as possible (preferably <5 min), centrifuge sample at ~3000 rpm for 5 min.
3. Separate the supernatant from the cells by decanting supernatant into a new tube, obtaining last drop by touching edges of two tubes.
4. Using a plastic disposable pipette, remove and discard any clumped, mucous material from the supernatant.
5. Enter the requested information (Randomization ID#, date and time, and iNO dose) on the "Supernatant" and "Cells" labels using the Sharpie in the kit and affix labels to appropriate tubes (long-wise---i.e. do not wrap label around tube).
6. Freeze both tubes at  $-70^{\circ}\text{C}$  (preferable),  $-20^{\circ}\text{C}$  (if necessary) in the plastic bag provided. 7. Write infant's Randomization ID# on bag label. Do not mix samples from different patients in the same bag.
7. For subsequent samples, add tubes to the same collection bag.

### **C. Shipping Samples**

1. In complete batches of sample collections (all samples from one infant), pack



- bags with samples in a foam box (ThermoSafe\* Multipurpose Insulated Shippers, Fisher Scientific #03-530-17, if one cannot be obtained from a clinical lab or elsewhere) with dry ice (approximately 1/3 of container volume) and ship by overnight express to address below. Please obtain a PO for FedEx shipments from Karin Knowles (KnowlesK@peds.ucsf.edu or 415-514-8139). Include in the box a listing of samples that are enclosed and your name, institution, phone number and email. Do not send Leukins trap.
2. The day you ship samples, give the lab a “heads-up” that samples are coming via email or phone: Cheryl Chapin (Cheryl.chapin@ucsf.edu) or Philip Ballard (ballardp@peds.ucsf.edu).
  3. Record Samples in the shipment log. Include date and FEDEX Number
  4. Ship only Monday-Wednesday to: Cheryl Chapin, Specialist III/Lab Manager  
Dept. of Pediatrics, UCSF  
Laurel Heights Campus  
3333 California St., Suite 150  
San Francisco, CA. 94118  
415-476-2535
  5. Contact Nancy Newton ([newtonn@peds.ucsf.edu](mailto:newtonn@peds.ucsf.edu) / 415.514.6257 or 415.516.4617), Jeanette Asselin ([JAsselin@mail.cho.org](mailto:JAsselin@mail.cho.org) / 510.813.1177) or Cheryl Chapin with any questions.
  6. If you would like to re-use your shipping box, simply include in the shipment a self-addressed and paid shipping transmittal, and the empty shipping box will be returned to you.
  7. Also, if you would like to save and return your “sharpies”, you can do so. You can also save them for Nancy or Jeanette when they come for a monitoring visit.
  8. To order additional TA or urine kits, please contact Cheryl Chapin or Hart Horneman Horneman(H@peds.ucsf.edu).

## **7.0. Urine Sampling Procedure and Processing**

Urine sample frequency has changed over the course of the study. We now would like one sample prior to starting iNO. The new urine sampling follows the schedule listed below:

- Sample #1 should be collected at study initiation, prior to iNO start and first dosing procedure if possible. Do not delay study drug dosing if unable to collect urine at first attempt.
- Sample #2 should be collected 24 – 48 hours after sample #1 when the infant has received >24 hours on the current iNO dose (20 ppm).
- The remaining samples should be collected approximately once each week, 24-48 hours after each iNO wean. Then one other sample on “0” ppm one week after iNO was discontinued
- Total = 7samples.

		Collect 24-48 hours after iNO change to these doses					
	Pre	20ppm	10ppm	5ppm	2 ppm	0 ppm	1wk post 0 ppm
Urine	x	x	x	x	x	x	x

### **A. Obtaining Urine Sample**

1. Place 2 cotton balls in infant's diaper.
2. Once the infant has voided on the cotton balls, insert them into 10 mL syringe with plunger removed. (Discard cotton balls contaminated with stool.)
3. Insert and depress syringe plunger and squeeze out as much urine as possible into the tube from the collection kit. We need at least a 1 mL sample, but 2 ml is preferable. If you require multiple voids to collect  $\geq 1$ -2 mL of urine, place labeled tube in specimen refrigerator between collections. Make sure that collection tube top is always screwed tightly to minimize evaporative losses.

Complete urine specimen label with the patient Randomization ID # and the date of collection using the Sharpie provided. Place label on tube length-wise (ie, do not wrap around tube. Allow Sharpie ink on label to dry before exposing it to moisture.

4. Freeze labeled specimen (with top screwed tightly to limit evaporation) at -70° C (-20° C is also okay until freezer space is available).

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### **B. Shipping Samples**

1. Send urine samples when you send tracheal aspirate samples to UCSF.
2. Place bags with samples (separate tracheal aspirate and urine samples) in a foam box (Thermo Safe\* Multipurpose Insulated Shippers, Fisher Scientific

3. #03-530-17, if one cannot be obtained from a clinical lab or elsewhere) with dry ice (approximately 1/3 of container volume) and ship by overnight express to address below. Please obtain a PO for FedEx shipments from Karin Knowles ([KnowlesK@peds.ucsf.edu](mailto:KnowlesK@peds.ucsf.edu) or 415-514-8139). Include in the box a listing of samples that are enclosed and your name, institution, phone number and email.
4. The day you ship samples, give the lab a "heads-up" that samples are coming via email or phone: Cheryl Chapin ([Cheryl.chapin@ucsf.edu](mailto:Cheryl.chapin@ucsf.edu)) or Philip Ballard ([ballardp@peds.ucsf.edu](mailto:ballardp@peds.ucsf.edu)).
5. Ship only Monday-Wednesday.

Ship to:

Cheryl Chapin, Specialist III/Lab Manager, Dept. of Pediatrics, UCSF  
 Laurel Heights Campus  
 3333 California St., Suite 150  
 San Francisco, CA. 94118  
 415-476-2535

Record shipment date and Fed Ex number on Samples Shipment Log.

Contact Nancy Newton ([newtonn@peds.ucsf.edu](mailto:newtonn@peds.ucsf.edu) / 415.514.6257 or 415.516.4617), Jeanette Asselin ([JAsselin@mail.cho.org](mailto:JAsselin@mail.cho.org) / 510-813-1177) or Cheryl Chapin with any questions.

## **8.0 Sample Mailing and Supplies**

### 8.1. Instructions for Obtaining PO # TO FED EX Samples

- 8.1.1. Contact Karin Knowles @ [knowlesk@peds.ucsf.edu](mailto:knowlesk@peds.ucsf.edu) for FED EX ACCOUNT NUMBER.
- 8.1.2. Record this number in the area #1 "Sender's Fed Ex Account Number", it will always be the same.
- 8.1.3. Ask for a **PO#** (1 per box) from Karin Knowles ([knowlesk@peds.ucsf.edu](mailto:knowlesk@peds.ucsf.edu)) when the study sites send out samples.
- 8.1.4. Send Karin an email and she will send you the PO number by return email. **The PO number will be different for each mailing.**
- 8.1.5. Put the PO# on the air bill slip under the line of "Your Internal Billing Reference"

**\*\*\*\*\*Very important for our tracking purposes. \*\*\*\*\***

- a) Record the air bill tracking number on your TOLSURF samples tracking log. If possible, email Karin Knowles the tracking number as well [knowlesk@peds.ucsf.edu](mailto:knowlesk@peds.ucsf.edu).
  - b) If you can scan a copy of the air bill and email it to Karin- that would be helpful as well.
- 8.1.6. You will need to purchase your own boxes for shipping. If you wish to re-use your boxes to save money, simply include a self-addressed, paid transmittal in your shipment box and the Laurel Heights lab staff will send the box back to you for re-use.

### 8.2. TOLSURF Pilot Study Spit Kit and Urine Kit Request Form

#### 8.2.1. Ordering Instructions:

- 8.2.1. Please use this email template to request additional TOLSURF Spit Kits and Urine Kits
- 8.2.2. Please send a request when you are down to 10 spit kits and/or 10 urine kits
- 8.2.3. Please send request to Karin Knowles [knowlesk@peds.ucsf.edu](mailto:knowlesk@peds.ucsf.edu) and cc to Nancy Newton at [newtonn@peds.ucsf.edu](mailto:newtonn@peds.ucsf.edu)
- 8.2.4. After sending the request, a confirmation email will be sent out along with the FedEx tracking number which can be used to track your kits at FedEx.com.
- 8.2.5. Email template, please include:
  1. Site (Name and TOLSURF ID number):
  2. Name of requestor:
  3. Phone number of requestor:
  4. Date of request:
  5. Number of *Spit Kits* left:
  6. Number of *Urine Kits* left:
  7. Number of patients currently enrolled as of today:
  8. Number of current potentials as of today:
  9. Notes/Comments:

## **9.0. Procedure for Oxygen/Flow Reduction Challenge Test**

The definition of BPD is the need for supplemental oxygen or positive pressure at 36 weeks postmenstrual age (PMA). One important component of this definition is determining whether an infant who is receiving a small amount of supplemental oxygen or flow support at 36 weeks corrected age requires supplementation. Therefore, infants who are clinically stable but receiving a small amount of supplemental oxygen or supplemental flow via nasal cannula at 36 or 40 weeks PMA will undergo a “room air challenge” to determine whether they can maintain their SpO<sub>2</sub> in the target range of ≥ 88%. This “room air challenge” will be similar to the way we tested the need for supplemental oxygen in the previous NO-CLD trial, and consistent with the current NIH recommendations for assessing BPD. As part of this challenge, infants who are not receiving supplemental oxygen, but only flow (≤ 4 L/min) via nasal cannula will undergo a flow challenge test during which the nasal cannula flow will be reduced.

To complete the Oxygen Challenge Test, use the O<sub>2</sub>/Flow Challenge Worksheet provided (Appendix II.)

### **9.1. Eligibility Criteria:**

#### 9.1.1. Inclusion Criteria

9.1.1.1. Infants ≤ 28 0/7 wk enrolled in the TOLSURF Study now at 36 or 40 (±1 wk) PMA. Infants at 40 wks are eligible to undergo the oxygen/flow reduction challenge test only if they have a diagnosis of BPD at 36 wks.

9.1.1.2. Respiratory support as follows:

- Infants receiving *supplemental oxygen* by nasal cannula at rest<sup>Δ</sup> at flow ≤ 2 lpm, with majority\* of saturations ≥ 90% in prior 24 hours
- Infants receiving *room air* by nasal cannula at ≤ 4 liter per minute (lpm) flow rate at rest<sup>Δ</sup> with majority\* of saturations ≥ 90% in prior 24 hours

#### 9.1.2. Exclusion Criteria

9.1.2.1. Need for mechanical ventilation or continuous positive airway pressure

9.1.2.2. Need for nasal cannula flow at > 2 lpm if on supplemental oxygen

9.1.2.3. Need for nasal cannula flow at > 4 lpm if in room air

9.1.2.4. Oxygen by continuous nasal cannula > 30% EFFECTIVE\*\* oxygen

9.1.2.5. Infants in room air, receiving no respiratory support (ventilation or CPAP, oxygen by hood or nasal cannula or room air nasal cannula)

9.1.2.6. Infants off all respiratory support except intermittent oxygen during feeds

9.1.2.7. Infants with “No BPD” at 36 wk assessment

9.1.2.8 Infants no longer in study hospital, (e.g. transferred back to referring hospital) \*\*\*

<sup>Δ</sup>Supplemental oxygen requirement is determined at rest. Disregard temporary increases in O<sub>2</sub> requirement (desaturation episodes, apnea, bradycardia or procedures where infant returns to baseline in less than 2 hours).

\*majority defined as ≥ 75% of saturation recorded during the previous 24 hour time period

\*\*EFFECTIVE oxygen applies to infants receiving oxygen via nasal cannula only, using tables in Section 2.0.

\*\*\* For infants no longer in study hospital, coordinator MUST contact referral center and/or parents to obtain information about respiratory support at 36 and 40 weeks.

*If infants have been on room air without respiratory support for  $\geq 7$  days at study hospital and are transferred to a referral center off respiratory support, they will be considered “no BPD” regardless of level of respiratory support they are receiving at referral center.*

Note: The flow definitions for nasal cannula hold, regardless of the device that is humidified or non-humidified.

### **9.2.0. Determining Effective $FiO_2$ concentration for Infants on Nasal Cannula**

9.2.1. The Tables below are based on those used in the STOP-ROP trials. The data were derived from equations 3 and 4 in the paper by Benaron and Benitz, “Maximizing the stability of oxygen delivered by nasal cannula”: Arch Pediatr Adolesc Med. 1994; 148: 294-300.

These tables include assumptions made by Benaron and Benitz (constant nasal flow over the inspiratory cycle and that the upper airway does not act as a reservoir) plus the following assumptions made by the STOP-ROP investigators: Inspiration time = 0.3 seconds, Tidal Volume = 5 ml/kg, and that either inspiration is entirely nasal or that cannula flow is sufficiently low that on each inspiration the infant exhales all output from the cannula).

#### **Example:**

*What is the effective  $FiO_2$  in a 2.0 kg infant on 100% cannula at a flow of 0.15 lpm?*

ANSWER: Use 2.0 kg and 0.15 lpm in Table 1 to get a factor of 8. Then use Table 2, and the factor of 8 and 100% oxygen to yield an *effective  $FiO_2$*  of 27%. Thus the effective oxygen concentration is less than 30% and the infant is eligible for the physiologic evaluation.

**Table 1. Factor as a function of flow and weight**

Flow (lpm)	Flow (lpm)	Weight (kg)								
		0.7	1.0	1.25	1.5	2	2.5	3	3.5	4
0.01		1	1	1	1	1	0	0	0	0
0.03	1/32	4	3	2	2	2	1	1	1	1
0.06	1/16	9	6	5	4	3	2	2	2	2
0.125	1/8	18	12	10	8	6	4	4	4	4
0.15		21	15	12	10	8	6	5	4	4
0.25	¼	36	25	20	17	13	10	8	7	6
0.5	½	71	50	40	33	25	20	17	14	13
0.75	¾	100	75	60	50	38	30	25	21	19
1.0	1.0	100	100	80	67	50	40	33	29	25
1.25		100	100	100	83	63	50	42	36	31
1.5		100	100	100	100	75	60	50	43	38
2.0		100	100	100	100	100	80	67	57	50

Factor = 100 \* min (1 lpm/kg)

**NOTES:**

1. If your patient's exact values are not included in the table, round up or down to find the value closest to your patient. If the value is exactly half way in between the two values, then round up.
2. Table 1 can only be used for supplemental oxygen with flows  $\leq 2$  lpm.
3. Explicit in the tables, for most infants, if flow (lpm) exceeds body weight (kg), then effective  $FiO_2 = \text{set nasal cannula } FiO_2$

**Table 2. Effective FiO<sub>2</sub> (x100) as a function of factor and concentration**

Factor	Concentration (%)						
	21	22	25	30	40	50	100
0	21	21	21	21	21	21	21
1	21	21	21	21	21	21	22
2	21	21	21	21	21	22	23
3	21	21	21	21	22	22	23
4	21	21	21	21	22	22	24
5	21	21	21	21	22	22	25
6	21	21	21	22	22	23	26
7	21	21	21	22	22	23	27
8	21	21	21	22	23	23	27
9	21	21	21	22	23	24	28
10	21	21	21	22	23	24	29
11	21	21	21	22	23	24	30
12	21	21	21	22	23	24	30
13	21	21	22	22	23	25	31
14	21	21	22	22	24	25	32
15	21	21	22	22	23	25	33
17	21	21	22	23	24	26	34
18	21	21	22	23	24	26	35
19	21	21	22	23	25	27	36
20	21	21	22	23	25	27	37
21	21	21	22	23	25	27	38
22	21	21	22	23	25	27	36
23	21	21	22	23	25	28	39
25	21	21	22	23	25	28	41
27	21	21	22	23	25	29	42
28	21	21	22	24	26	29	43
29	21	21	22	24	27	29	44
30	21	21	22	24	27	30	45
31	21	21	22	24	27	31	47
33	21	21	22	24	27	31	47
36	21	21	22	24	28	31	49
38	21	21	23	24	28	32	51
40	21	21	23	25	29	33	53
42	21	21	23	25	29	33	54
43	21	21	23	25	29	33	55
44	21	21	23	25	29	34	56
50	21	21	23	25	30	35	60
55	21	22	23	26	31	37	64
57	21	22	23	26	32	38	66
60	21	22	23	26	32	38	68
63	21	22	24	27	33	39	71
67	21	22	24	27	34	40	74
71	21	22	24	27	34	42	77
75	21	22	24	28	35	43	80
80	21	22	24	28	36	44	84
83	21	22	24	28	37	45	87
86	21	22	24	29	37	46	89
100	21	22	25	30	40	50	100



### 9.3.0 Preparation for challenge test

9.3.1. All infants should be studied in the supine position. Feedings and medications should be given 30 minutes prior to the evaluation. Bolus feeds should not be given during the evaluation. Infants on continuous feeding may continue feeds during the evaluation.

9.3.2. Confirm that infant is stable for testing with the physician responsible for the infant's care (attending or fellow). An order should be written in the medical record.

9.3.3. A pulse oximeter, if not already in place, should be placed on the infant in good position with a strong signal prior to recording data. Allow 5 minutes after placing the oximeter before starting data collection. Baseline data is collected while the infant is on the current oxygen regime.

### 9.4.0 Baseline Data Collection (**O<sub>2</sub>/Flow Challenge Worksheet- Page 1**)

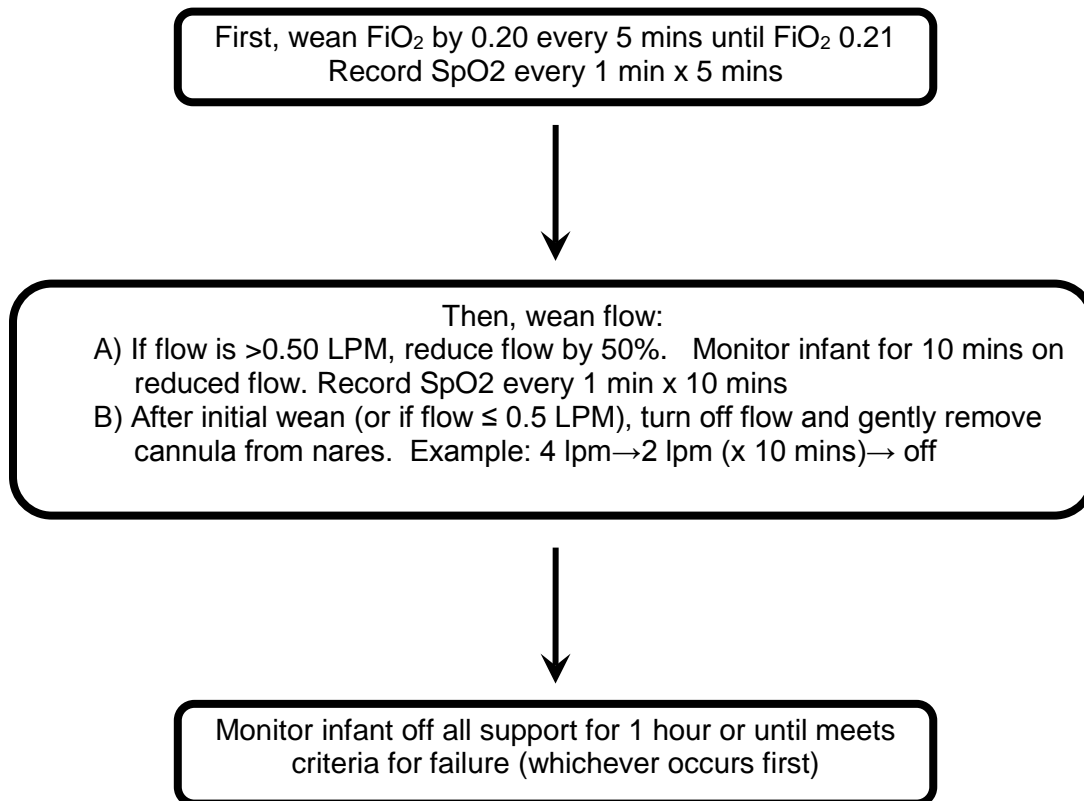
9.4.1. Baseline data is collected with the infant on their current level of oxygen and nasal cannula liter flow/minute support. Data is collected for 5 minutes, recording the time and oxygen saturation every minute on the Oxygen Challenge worksheet, Page 1.

9.4.2. Continue to the oxygen reduction phase if all saturations recorded are  $\geq$  90% after 5 minutes.

### 9.5.0 Oxygen and Liter Flow Reduction Data Collection (**O<sub>2</sub>/Flow Challenge Worksheet Form - Pages 2-3**)

9.5.1. Data is collected on these pages for the duration of the weaning phase of the oxygen and flow reduction challenge exam. Record the FiO<sub>2</sub> and liter flow (for nasal cannula) at the top of each box. The time and oxygen saturation reading are recorded every minute during the challenge.

The weaning instructions are as follows:



9.5.2. Continue weaning until either:

9.5.2.1. The infant is in room air (FiO<sub>2</sub> 0.21,) and off nasal cannula flow with adequate saturations

OR

9.5.2.2. The infant **fails** the oxygen/flow challenge exam with saturations < 90% for 5 continuous minutes OR saturation < 80% for 15 seconds.

9.5.3. Alternative weaning schedule: Supplemental oxygen delivered by nasal cannula without blender/medical air (100% FiO<sub>2</sub> flow meter)

9.5.3.1. Wean flow every by 50% every 10 mins until flow ≤ 0.15 LPM, then gently remove cannula from nares. Note: weans below 1 lpm will require use of a low-flow flow meter.

9.5.3.2. Discontinue wean if:

Infant **fails** oxygen/flow challenge exam with saturations < 90% for 5 continuous mins OR saturation < 80% for 15 seconds.

9.6.0 Room Air Data Collection (**O<sub>2</sub>/Flow Challenge Worksheet Form – See Appendix IV.**)

Once the patient is placed in room air off all support, data collection continues for **one hour** or until the criteria for failure is met. The outcome criteria are:

**Pass:** All saturations  $\geq 90\%$  for 1 hour

**Fail:** Saturation  $< 90\%$  for 5 consecutive minutes  
OR  
Saturation  $< 80\%$  for 15 consecutive seconds

Please indicate the result of the Challenge Test on CRF form 12A and 12B (**Pass** or **Fail**). Complete BPD Outcomes CRF Form12A at 36 weeks PMA and Form12B at 40 weeks PMA. File the Oxygen/Flow Challenge Worksheet with infant's study records.

9.7.0 At the conclusion of the oxygen/flow challenge the infant should be returned to their previous level of supplemental oxygen. The clinical care team should be notified of the results of the challenge test.

## **10.0. Serious Adverse Event/Adverse Event Reporting and Stopping Rules**

The documentation of AE/SAE's depends on their temporal relationship to study drug dosing. The definitions of SAE/AE from the study protocol are listed below:

### **SAEs**

1. Death (Death that occurs within 7 days of dosing is an SAE. This SAE requires expedited reporting)
2. SAE's occurring within 4 h of dosing:
  - a. Severe cardiopulmonary decompensation requiring CPR with cardiac medication/chest compressions
  - b. Increase in RSS >5 sustained for >24 hours
3. SAE's occurring within 24 hrs of dosing:
  - a. Severe pulmonary hemorrhage
  - b. Severe PIE
  - c. Pneumothorax requiring chest tube (from pulmonary disease)
4. Unexpected and related to study drug administration

### **AE's**

*AE's that occur within 4 hours of dosing:*

1. Prolonged (>60 seconds)bradycardia/desaturation
2. Endotracheal tube problems requiring reintubation

*AE's occurring at any time:*

1. Death (Death is only an AE if it occurs >7d after completion of dosing. (also fill out death form)
2. Problems with obtaining tracheal aspirate samples are AE's
4. CPR requiring cardiac meds/compressions (outside of dosing period)
5. Hypotension requiring vasopressor support for > 24 hours (Definition: Dopamine/Dobutamine > 20 mcg/kg/min or two pressor agents for > 24 h)
6. Co-Morbidities occurring after enrollment in study (details are described in CRF and later in MOP)
  - a. Neurologic (IVH, PVL, hydrocephalus)
  - b. GI (NEC, perforation, surgery)
  - c. Pulmonary (PIE, pulmonary hemorrhage, pneumothorax, tracheomalacia, stenosis, vocal chord paralysis)
  - d. Cardiovascular (PDA - with or without surgery, pulmonary hypertension)
  - e. Sepsis (bacterial, fungal, viral)
  - f. ROP
  - g. RSV pneumonia
7. Unexpected adverse events (medication errors, catheter complications etc)

**NOT TO BE CONSIDERED AEs** – Common problems encountered in the clinical care of these infants such as feeding intolerance, or electrolyte imbalance will not be considered AE's. Example: A chest tube inserted after PDA ligation is NOT a pneumothorax requiring chest tube and should not be recorded as such.

**Stopping Rules:** For each individual subject enrolled in the study include respiratory decompensation immediately after study drug delivery procedure in which the RSS increases to > 8 above baseline and is sustained for at least 24 h.

- Notify the site PI and CCC Project Director at 415-516-4617. If this trial's safety analysis indicates a significantly increased risk of death or serious adverse outcome the trial will be stopped.

## **10.1. Documentation of SAE/AE and Comorbidities of Prematurity**

10.1.1. **Serious Adverse Events (SAEs)** will be reported individually as they occur.

- SAE's are only recorded if they occur between the time of enrollment (first study dosing) through 7 days after the 5<sup>th</sup> (or final) study drug dose is given.
- SAE's are recorded only during this time period and depend on event:
  - Event occurs at any time during this dosing time period
    - Death
    - Unexpected AE that is felt to be related to study drug dosing.
  - Event occurs  $\leq$  4 hours after dosing
    - Severe cardiopulmonary decompensation requiring CPR with cardiac medications and chest compressions
    - Increase in respiratory severity score (RSS) > 5 above baseline for > 24 hours
  - Event occurs  $\leq$  24 hours after dosing
    - Severe pulmonary hemorrhage
    - Severe PIE
    - Pneumothorax requiring chest tube

10.1.2. **Adverse Events (AEs or Co-morbidities of prematurity)** will be collected through-out the infant's hospitalization and labeled as adverse events if they occur.

- Co-morbidities are reported differently depending on when they occur:
  - A) BEFORE STUDY ENROLLMENT – These are NOT AE's, rather they are the patient's baseline condition.
    - Includes comorbidities that occur prior to enrollment (first study dosing).
    - Comorbidities occurring prior to enrollment are NOT considered Adverse Events and are recorded only as a part of patient's history.
    - Record on CRF Form 4.
  - B) DURING DOSING
    - Includes comorbidities that occur from enrollment (the time of the first study drug dose) through 7 days after the (or last) study drug dose is given.
    - Comorbidities occurring during this time period are considered adverse events (AEs) and may qualify as SAEs depending on

the temporal relationship between the AE and the study drug/sham dosing procedure

- Record on CRF Forms 11A
- These CRFs should be completed and faxed to DCC within 2 weeks of this date.

C) AFTER DOSING IS COMPLETED

- Includes comorbidities that occur between 8 days after the 5<sup>th</sup> (or last) study drug dose and study hospital discharge.
- Record on CRF Forms 11B
- These CRF's should be completed and faxed to the DCC within 2 weeks after discharge.
- By definition, SAE's will NOT occur during this time period.
- Deaths that occur here, are reported as AE's

- Reportable AE Definitions:

- Deaths that occur > 7 days after 5<sup>th</sup> or last dosing procedure
- Problems with obtaining tracheal aspirate samples
- CPR requiring cardiac meds/compressions
- Hypotension requiring vasopressor support for >24 hours
- Co-Morbidities occurring after enrollment that include:
  - Neurologic (IVH, PVL, hydrocephalus requiring shunt)
  - GI (NEC, perforation, surgery)
  - Pulmonary (PIE, pulmonary hemorrhage, pneumothorax, tracheomalacia, stenosis, vocal chord paralysis)
  - Cardiovascular (PDA that is treated, with or without surgery; pulmonary hypertension)
  - ROP
  - RSV pneumonia
- Unexpected AE and felt to be related to study drug dosing.

10.1.3. Information reflecting the hospital course and treatments (medications, transfusions, TPN, etc.) will be record from admission to discharge from the study hospital.

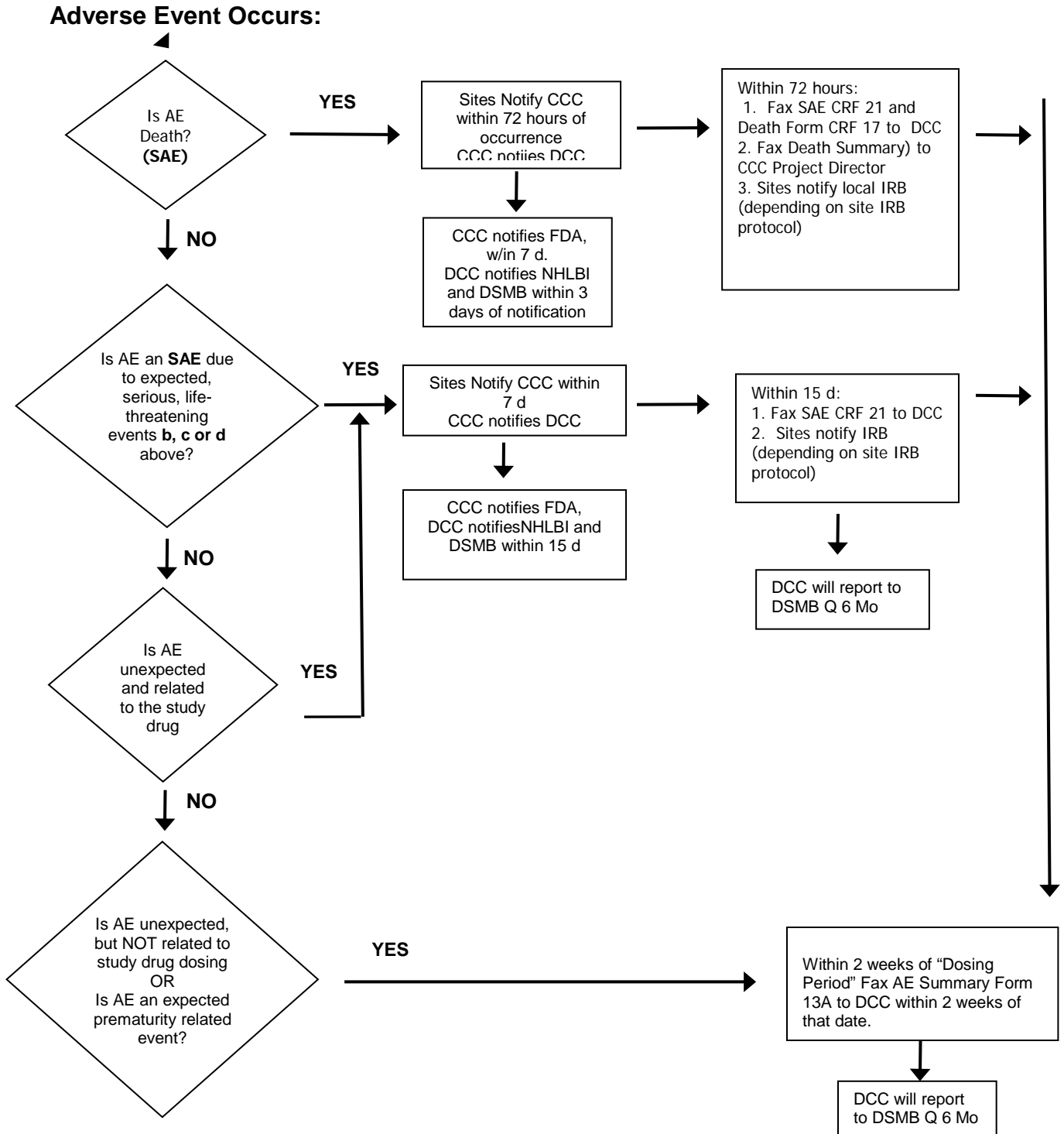
10.1.4. Follow up information will be reported after discharge from the study hospital. (separate Follow Up Phase Manual of Operations)

## 10.2. AE/SAE Reporting Timeline

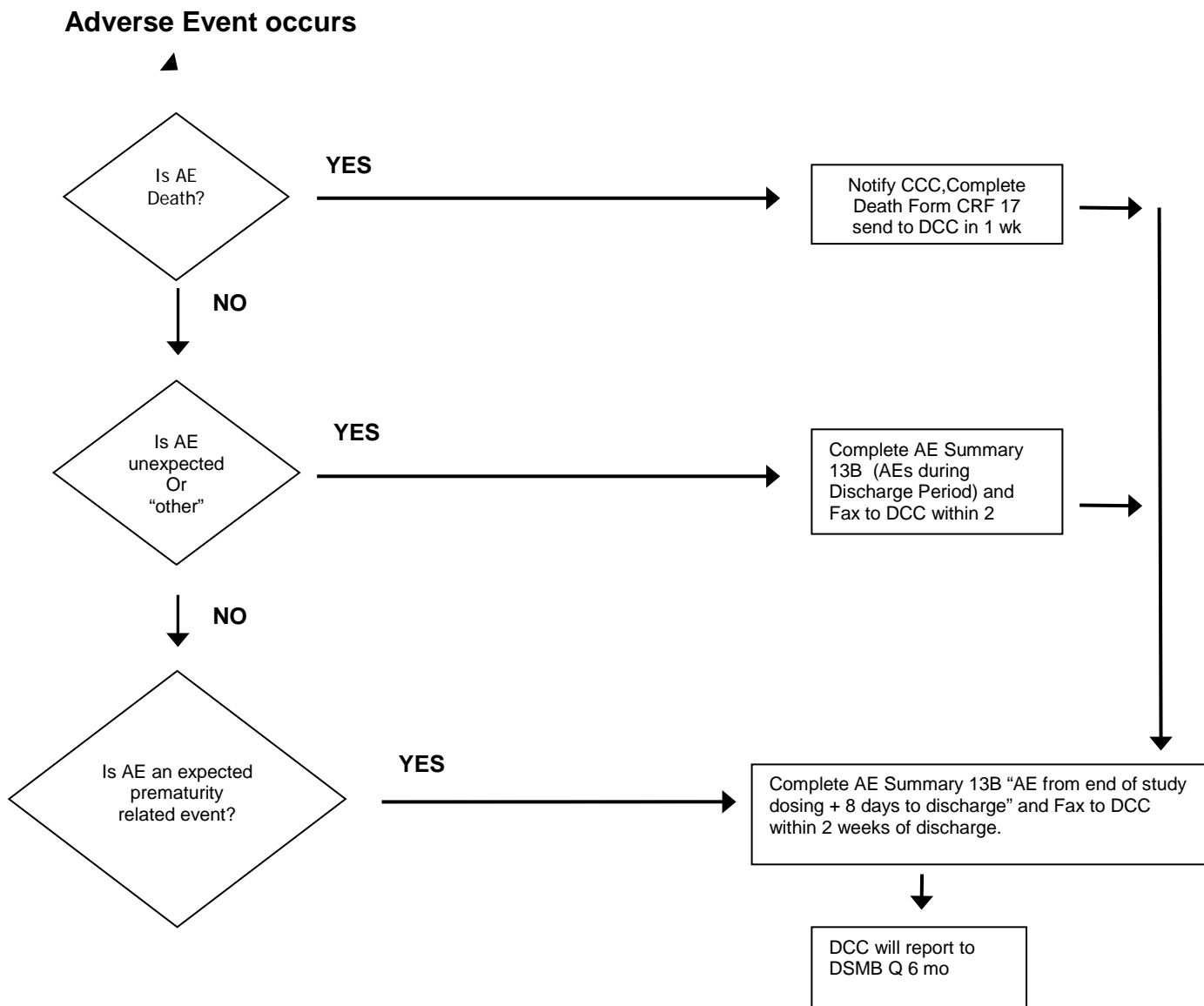
SAE's include the following events:

- death if it occurs between enrollment and 1 week (7 days) after dosing completed:
- severe respiratory decompensation requiring CPR with chest compressions/cardiac meds within 4 hours of dosing
- Increase in RSS >5 from baseline sustained for >24 hours
- severe pulmonary hemorrhage, severe PIE, or pneumothorax within 24 hours of dosing
- unexpected and related to study drug administration

### SCHEMATIC FOR EVENTS THAT OCCUR BETWEEN ENROLLMENT AND 7 DAYS AFTER DOSING COMPLETED:



**EVENT OCCURS > 7 DAYS AFTER DOSING COMPLETED:**



**Fax and contact numbers for SAE reporting:**

- Notify Nancy Newton, CCC Study Project Director
  - Cell phone: 415.516.4617
  - Pager: 415.443.4190
  - Fax: 415.514.6353
  
- Fax SAE Form 21 teleform to the DCC at 1-866-226-4607



### **10.3. Definitions of Selected Co-Morbidities**

Use the definitions below for determining what should be reported as a co-morbidity for the TOLSURF Study on Adverse Event Forms 13A and 13B and Serious Adverse Event for 21. Definition of SAE for some items will depend on the serial relationship of the event to dosing (see section 10.0).

#### **10.3.1. Intraventricular Hemorrhage (IVH) Grade definitions**

- Grade 1 or 2: Germinal Matrix Bleed or IVH without dilatation;
- Grade 3 - 4 (IVH with dilatation or parenchymal bleed). Any combination of bilateral IVH Grade 3 and or Grade 4 intracranial hemorrhage

#### **10.3.2. Cystic Periventricular Leukomalacia ( PVL)**

- Only cystic PVL should be recorded. Cystic PVL must be confirmed by HUS or MRI.

#### **10.3.3. Hydrocephalus requiring shunt**

- Record only hydrocephalus that requires shunt placement. Ventricular enlargement not requiring shunt placement should not be recorded.

#### **10.3.4. Necrotizing Enterocolitis (NEC)**

- NEC is defined as pneumatosis, hepato-biliary gas, or pneumoperitoneum AND one or more of the following: bilious gastric aspirate or emesis, abdominal distension, or occult or gross blood in stool not from fissure.
- “RULE OUT” OR “PRESUMED” NEC does not meet the definition of NEC.

#### **10.3.5. Isolated GI Perforation without NEC**

- GI perforation requiring laparotomy or drain placement without laparotomy
- NEC was not diagnosed

#### **10.3.6. Pulmonary Interstitial Emphysema (PIE)**

The goal is to score only “real”, severe PIE. PIE which is equivocal or controversial should not be counted. Severe PIE should only be scored if it is seen on more than one CXR.

PIE is defined as rupture of air from alveoli or small airways into lung perivascular tissues, characterized by irregular air-filled cysts or linear lucencies radiating from the hilum.

PIE is scored as “None”, “Moderate”, or “Severe”.

- None = no PIE, or only perihilar bubbles or “pre-PIE” noted.
- Moderate PIE = lobar, unilateral or bilateral bubbles < 2 mm in size.
- Severe PIE = lobar, unilateral or bilateral bubbles > 2 mm in size.

#### **10.3.7. Severe Pulmonary Hemorrhage**

Pulmonary hemorrhage is defined as frank bleeding and does not include irritation due to suctioning or infection

#### 10.3.8. Pneumothorax requiring a chest tube

Record a pneumothorax only if a chest tube is placed. Expected pneumothorax with chest tube acquired as a result of clinical interventions such as PDA ligation should not be recorded as an AE or SAE. If you have questions, contact CCC.

#### 10.3.9. Tracheomalacia

Record tracheomalacia only if confirmed by bronchoscopy and documented in physician progress notes.

#### 10.3.10. Tracheal stenosis

Record tracheal stenosis only if confirmed by bronchoscopy/xray and documented in physician progress notes.

#### 10.3.11. Vocal cord paralysis

Record vocal cord paralysis only if confirmed by bronchoscopy and documented in physician progress notes.

#### 10.3.12. Patent Ductus Arteriosus (PDA)

Record PDA only if it is treated – either medically or surgically. PDA may be diagnosed clinically or by echo, should be documented in patient progress or cardiology consult notes in medical record and must have resulted in medical or surgical treatment. Do not report PDA that has not resulted in treatment.

#### 10.3.13. Hypotension

Hypotension is defined as requiring one or more of the following treatments to maintain a mean arterial pressure within normal limits for age.

- Dopamine > 20 mcg/kg/min for hypotension for more than 24 hours
- Addition of a second vasopressor agent for more than 24 hours. This 2<sup>nd</sup> agent can be hydrocortisone.

#### 10.3.14. Pulmonary Hypertension

Pulmonary hypertension is defined as elevated pulmonary vascular pressure > systemic pressure resulting in right to left shunting and systemic hypoxemia.

Pulmonary hypertension may be diagnosed clinically or by echo, but should be documented in patient medical progress or cardiology consult notes in medical record.

#### 10.3.15. Sepsis

Culture proven sepsis definition has been expanded since CRF v1.0 was developed. Sepsis has now been modified to allow expanded reporting of infection to include blood, CSF, TA sample or urine sample.

Report the following as sepsis:

- Record all episodes of infection resulting in positive bacterial, fungal or viral cultures from blood, CSF, urine or TA sample that were treated with antibiotics, antifungal or antiviral agents for > 7 days.
- RSV infections are documented with positive culture (or DFA) from tracheal aspirate or nares.

#### 10.3.16. RSV Pneumonia

Record any positive RSV by TA culture or DFA.

#### 10.3.17. ROP

Record any ROP found on ophthalmologic exam.

#### 10.3.18. Other Reportable AE Definition

Prolonged bradycardia or oxygen desaturation, as defined above, occurring  $\leq$  4 hours after dosing is reportable as an AE and is defined as:

- Heart rate < 80 for > 60 seconds
- Oxygen saturation < 75% for > 60 seconds.
- Reintubation required

# III. Data Management

### **III. DATA MANAGEMENT**

#### **1.0 OVERVIEW**

TOLSURF will use Teleform data entry through the UCSF Data Coordinating Center (DCC). With the use of Teleform data entry, Case Report Forms (CRFs) are faxed to the UCSF DCC. This system eliminates the need for manual data entry and minimizes potential data transcription errors. This method requires careful completion of CRF data fields and review of the forms prior to faxing to the DCC. It is important to catch any errors, missing information, or illegible handwriting before faxing the CRFs.

Clinic study staff: 1) receive the forms; 2) print the forms; 3) enter data on the forms; 4) review the forms for accuracy and completeness; 5) contact the Clinical Coordinating Center (CCC) Project Director with any data questions BEFORE faxing the forms; 6) fax the forms to the DCC; and 7) work with the CCC Project Director to address data queries after the forms were faxed to the DCC.

#### **2.0 CASE REPORT FORMS (CRFs)**

This section of the Manual of Operations (MOP) describes the methods and standards for completion of the CRFs so they can be read at the DCC with the Teleform optical reading software.

##### **2A. What is a Teleform?**

Teleforms are paper forms that are designed and read using optical reading software. Computer generated queries will allow the study staff to address data discrepancies and missing data. It is important to follow some simple guidelines to make sure that the forms are readable and that the data entered on the forms is read accurately by the Teleform software. Following the data management guidelines will minimize data queries and corrections, and save precious time.

##### **Rule 1: Do Not Obstruct Cornerstones**

Cornerstones are the four black boxes in the 4 corners of each page (see Table 1). The Teleform software uses the cornerstones to read the form correctly. If the cornerstones are obstructed in any way, such as being written on or damaged, the fields on the form may not match up correctly, making the data on the form unreadable.

##### **Rule 2: Do Not Obstruct Form ID Boxes**

The Form ID Boxes are the 3 - 5 digit numbers and the black/white rectangle located in the upper left and lower right corner of each page (see Table 1). If this part of the form is obstructed in any way, (such as written over, dog-eared, or holes punched in the area), Teleform software cannot read the information on the form. The information on a damaged form not yet faxed to the DCC will need to be transcribed onto a clean form.

Forms are faxed into the data system ONCE. Re-faxing forms will NOT correct the data. But, having said that, the DCC may on a rare occasion ask that you re-fax a specific form, e.g., if the form did not get to the data system because the form was unreadable.

The original paper form is also called the 'source document'. Source documents must be kept on site in the infant's TOLSURF chart (binder or folder) in a secure location.

**Table 1: Anatomy of a Form**

- Anatomy of a Form**
- 1 – Cornerstone
  - 2 – Form ID Box
  - 3 – Screening ID#
  - 4 – Secondary ID
  - 5 – Staff Initials
  - 6 – Randomization #
  - 7 – Bubble Field
  - 8 – Text/Number Field

**FORM 1A: SCREENING FORM**

1 [Cornerstone] 2 [Form ID Box: 7488] 3 [Screening ID#] 4 [Secondary ID] 5 [Staff Initials] 6 [Enter Randomization # or select N/A] 7 [Bubble Field] 8 [Text/Number Field]

**TOLSURF**

1A.1. Gender:  Female  Male 1A.1.a. Date screened: [ ] / [ ] / [ ]

1A.2. Ethnicity: (reported by parent - select one)  
 Hispanic or Latino  NOT Hispanic or Latino  Unavailable/Unknown

1A.3. Race: (reported by parent - select all that apply)  
 White  Black or African American  Asian  
 American Indian/Alaska Native  Native Hawaiian or Other Pacific Islander  Unknown or not reported

1A.4. Infant intubated on DOL 7?  Yes  No

**INCLUSION CRITERIA:** The following questions must be answered "Yes" to be eligible to enroll in this study:

1A.5.a. Gestational Age: Weeks: [ ] Days: [ ] Gestational age ≤ 28 weeks?	<input type="radio"/> Yes <input type="radio"/> No
1A.5.b. Age in days: [ ] (DCB = Day 1) Is infant between 7 - 14 days of life?	<input type="radio"/> Yes <input type="radio"/> No
1A.5.c. Intubated and mechanically ventilated between 7 - 14 days of life?	<input type="radio"/> Yes <input type="radio"/> No
1A.5.d. Plan to treat with Inhaled Nitric Oxide?	<input type="radio"/> Yes <input type="radio"/> No

1A.5.e. Have all 4 Inclusion Criteria listed above been answered "Yes"?  
 Yes  No  **Not eligible. Complete Q1A.9.c.**

**EXCLUSION CRITERIA:** The following questions must be answered "No" to be eligible to enroll in this study:

1A.6.a. Does infant have serious congenital malformations or chromosomal abnormalities? (see MCP)	<input type="radio"/> Yes <input type="radio"/> No
1A.6.b. Is life expectancy < 7 days, starting at DOL 7?	<input type="radio"/> Yes <input type="radio"/> No
1A.6.c. Is infant clinically unstable? (see MCP)	<input type="radio"/> Yes <input type="radio"/> No
1A.6.d. Infant has a bilateral Grade 3 and/or 4 intracranial hemorrhage?	<input type="radio"/> Yes <input type="radio"/> No
1A.6.e. Has it been less than 48 hrs from last dose of early surfactant?	<input type="radio"/> Yes <input type="radio"/> No
1A.6.f. Unlikely to be able to collect primary endpoint data at 36 weeks.	<input type="radio"/> Yes <input type="radio"/> No

1A.6.g. Have all 6 Exclusion Criteria listed above been answered "No"?  
 Yes  **Complete Qs1A.7., 1A.8. and 1A.9.** No  **Not eligible. Complete Q1A.9.c.**

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**2B. Receiving CRFs**

You will receive the TOLSURF CRFs as electronic PDF documents from the CCC Project Director. The study site must have a computer with internet access to receive emails with attachments and Adobe Acrobat Reader software Adobe Reader® or Acrobat® to view PDF documents. If you do not have Adobe Reader already installed on your computer, you can go to <http://get.adobe.com/reader/> to download the free Adobe Reader software. The Clinic Study Coordinator (or designee) must also have access to a printer (preferably laser printer) and a reliable fax machine(s).

CRFs you will receive:

**2B.1. Form22\_FaxMachineRegistrationForm\_v1.0.pdf** (1 page)

Upon CCC approval to start screening patients, the CCC Project Director will email the Fax Machine Registration Form to register the fax machine(s) that will be used to send CRFs to the DCC. One form will be completed for each machine that is registered. The Fax Registration Form is essential since this will be the primary method to submit data to the DCC. The DCC uses a secure fax system to insure privacy of patient information (see section 3A.1 Fax Machine Registration).

**2B.2. Form1A\_ScreeningForm\_v2.0.pdf** document (2 pages)

Form 1A is the Screening Form which will be completed for every patient that is screened for the study. The Clinic Study Coordinator will print the forms, and hand enter the Screening ID # and Secondary ID in the header (top) of the form (see Table 1-Anatomy of a Form). The Screening ID # and Secondary ID will be taken sequentially from the *SitePatientScreeningLog.xls* sent to you by the CCC Project Director.

**2B.3. Forms1B-25\_RandomizedForms\_v2.1.pdf**

Forms 1B through 25 are for infants assigned a Randomization #. For each randomized infant, the CCC Project Director will send you this PDF document with the header information prefilled on each form. The Clinic Study Coordinator (or designee) will print the forms. Before printing the forms packet, please make sure that the prefilled Screening ID# and Secondary ID match the infant IDs on Form 1A (see MOP section IV.Form 1B-25).

**2B.4. DosingToleranceForms\_v1.0.pdf** (5 pages pre-filled with Dose #1 - #5)

**THIS FORM WILL NOT BE FAXED TO THE DCC!**

THESE FORMS WILL BE COMPLETED BY THE UNBLINDED RT/RN AT THE TIME OF DOSING. The CCC Project Director will email the Dosing Tolerance Forms to the Clinic Study Coordinator when the infant is randomized. The handling of this form is unique and described below.

**2C. Dosing Tolerance Form (DTF) Procedures**

After the patient is randomization:

- The Clinic Study Coordinator will receive and print a PDF document that contains five (5) Dosing Tolerance Forms (DTF) for the infant. The Screening ID#/ Secondary ID/ Randomization #/ Dosing # will be pre-filled on the CRFs.
- The Clinic Study Coordinator will give the appropriate DTF to the unblinded RT/RN doing the dosing procedure (study drug versus sham).
- Immediately after the drug dosing procedure, the unblinded RT/RN completes the CRF for that dose, folds it, and places it in the DTF envelope identified with the Randomization # and Dose #1 through Dose #5.
- Each DTF envelope MUST BE IMMEDIATELY SEALED by the unblinded RT/RN and placed in the large envelope that includes the other DTFs and DTF envelopes for that infant.
- All 5 DTFs must be completed even if the infant does not receive all 5 doses of study drug versus sham.
- Once all of the dosing procedures are completed, the Clinic Study Coordinator informs the unblinded RT/RN to open all 5 Dosing Envelopes and make one photocopy of each form.

- **The original DTF's are kept at the study site.** Only photocopies are mailed to DCC.
- The unblinded RT/RN will put all 5 photocopies (NO ORIGINAL FORMS ARE MAILED) in the preaddressed/stamped envelope. This envelope is mailed to the DCC study statistician:
  - TOLSURF Data Coordinating Center
  - ATTN: Lisa Palermo
  - 185 Berry Street
  - Lobby 5, Suite 5700
  - San Francisco, CA 94107
- IT IS IMPORTANT THAT ONLY THE UNBLINDED RT/RN SEES THIS INFORMATION!!!
- The unblinded RT/RN puts the original copies of the 5 Dosing Tolerance Forms ('source documents') in the Dosing Completed Envelope and immediately seals the envelope. The Clinic Study Coordinator stores the sealed envelope in a secure onsite location.

The DCC will provide the clinical sites with seven (7) Dosing Tolerance Form envelopes for each randomized infant:

- Envelopes #1 - #5: DOSE TOLERANCE FORM ENVELOPES (one envelope for each dose)
- Envelope #6: DOSE MAILING ENVELOPE (preaddressed/stamped envelope)
- Envelope #7: DOSING COMPLETE ENVELOPE (secure onsite storage of source document CRFs)

## 2D. Printing CRFs

Each site is responsible for printing the forms at the study site (preferably on a laser printer). Make sure that:

- Toner supply is not low when printing.
- Forms are printed on 1 side only.
- Forms are printed on white paper.
- Printer setting is not set for "shrink to fit."
- NEVER photocopy CRFs; all forms must be printed on a printer.

## 2E. Completing CRFs

### 2E.1. The basics

- Use a black pen (not any other color ink pen).
- Do not use a felt tip pen that bleeds.
- Do not use a pencil.



## 2E.2. Fill in the bubbles completely

- Stay within the lines.
- Fill the bubble in completely; do not use an “X” or a “√.”

The best way to mark a choice in a bubble field is illustrated below in Table 2.

**Table 2: Appropriate Way to Mark Bubble Fields**

●	✍	●	✕
Excellent	Acceptable	Less advised	Not Advised

## 2E.3. Letters and numbers

- Print in capital letters.
- Print only one letter or number per box.
- Keep the letter or number completely inside the box. The letter or number should not touch or cross any of the box lines.
- Do NOT cross your zeros (0), sevens (7), or the letter Z.
- Avoid “curly-cues” on letters and numbers.
- Make your letters and numbers as similar as possible to the example in Table 3.

**Table 3: Letters and Numbers**

0	1	2	3	4	5	6	7	8	9																
A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z

Take extra care in printing the following groups of letters, since they are often difficult for the Teleform software to distinguish the difference.

A, R	D, O	I, L	U, V
------	------	------	------

## 2E.4. Screening ID #, Secondary ID and Randomization #

The Screening ID # and Secondary ID will be hand-written on Form 1A (2 pages) by the Clinic Study Coordinator. These IDs are provided to each site by the CCC Project Director in the Screening ID and Secondary ID List. Once Form 1A has been faxed to the DCC, the 'gold standard' Screening ID # and Secondary ID will be established for all subsequent CRFs for that infant.

Once eligibility has been confirmed, the CCC Project Director will assign the Randomization # and send the Clinic Study Coordinator two “customized” sets of CRFs for each infant with the Screening ID #, Secondary ID, and Randomization # pre-filled in the header of each page. Please double check to make sure that the pre-filled Screening ID # and Secondary ID match the Screening Form 1A for each randomized infant BEFORE printing the forms packet **Forms 1B-23\_RandomizedForms.pdf** and the **DosingToleranceForms.pdf** documents.

## **2E.5. Staff Initials**

The initials of the staff person responsible for the information on the form should be hand-entered in the header (see Table 1). Staff initials will be the first letter of first and last name.

## **2E.6. Filling out Descriptions and “Please specify” boxes**

Some of the forms contain a large box to write in comments or notations. These fields should be completed with the following rules in mind:

- Use only black pen.
- Print neatly using uppercase letters, no cursive handwriting. Avoid the use of “curly-cues” or additional lines or marks (such as slashes through the number seven) that could be misinterpreted.
- Minimize use of medical abbreviations and symbols.
- Try to be as concise as possible.

## **2E.7. Form Logic**

Be careful to follow the form logic and complete all required questions. Do not leave a question blank unless the directions state to skip that question. If a question asks for a Yes or No response, answer it, even if the response is No. A blank will not be interpreted as a No response - it will be assessed as missing data. Use “Unknown” or “Unavailable” if the medical record is incomplete.

Each item should be answered and the response(s) marked individually rather than by using vertical lines or “ditto” marks.

## **2E.8. CRF Review**

The Clinic Study Coordinator is responsible for making sure that information is complete, legible and accurate BEFORE faxing the CRFs. If there are any questions, discuss them with the CCC Project Director before faxing the CRFs to the DCC.

## **2E.9. CRF Handling**

- Do not mark or write in or around the Cornerstones or Form ID Box (upper right and lower left corners).
- Do not make any unnecessary stray marks on the forms.
- Do not fold (*except Dosing Tolerance Form*), staple, or mutilate the CRFs in any way

## **2E.10. Source Documents**

The Clinic Study Coordinator is responsible for keeping the original CRFs (“source documents”) in an organized fashion and secure location. Source documents will be reviewed during site monitoring visits and audits.

## **2F. Correcting Mistakes on CRFs**

This section of the MOP describes the conventions for correcting mistakes on the CRFs including: General Rules; Bubble Field Corrections; Text or Number Field Corrections; and Making a Response Null. Corrections can be made on the forms before they are faxed to the DCC, or after they are when you work with the CCC Project Director to make data query corrections.

### **2F.1 General Rules**

### **DOs:**

- Draw a line through the wrong answer.
- Fill in the correct answer in the appropriate bubble.
- Circle the correct answer.
- Initial and date the correct answer.
- Number and letter corrections should be made outside the data field box.

### **DON'Ts**

- Erase.
- Use correction tape/white out (i.e. Liquid Paper).
- Overwrite mistakes.

### **2F.2. Bubble Field Corrections** (see Table 4)

If you make an error on a bubble field, do the following:

- Strike-through the incorrect bubble field
- Fill-in the correct bubble field using the conventional method of filling in a bubble field (see Table 2)
- Circle the correct answer
- Initial and date the correction

### **2F.3. Text or Number Field Corrections** (see Table 5)

If you make an error in a text or number field, do the following:

- Strike through the incorrect text field
- In the white space near the text boxes (but not in the boxes), write the correct answer.
- Circle the correct answer.
- Initial and date the correction.

**Table 4: Making Corrections to a Bubble, Text or Number Field**

**Example 1: Changing a response to a YES/NO or multiple choice question.**  
 In this example, the participant marked incorrect marital status category. She is actually divorced but marked married by mistake.

① **What is your current marital status?**

Married or living in a married-like relationship  
 Divorced  
 Widowed  
 Single, never married  
 Separated

PM, 11/13/2001

**Example 2: Changing a response to a YES/NO, multiple choice or fill in the blank question to null.**  
 In this example, the participant marked answers to parts a and b when she was not supposed to. The answers to these questions should be blank, or null.

③ **In the last 12 months, have you fallen and landed on the floor or ground or fallen and hit an object like a table or chair?**

Yes     No     Don't know

a. How many times have you fallen in the last 12 months?

falls    NULL    PM, 11/13/2001

b. When you fell during the last 12 months, did you fracture any bones?

Yes     No    NULL    PM, 11/13/2001

Which bones?

*Make sure the line goes through the circles of all the other options!*

**Example 3: Changing a response to a fill in the blank question.**  
 In this example, the participant wrote in 22 years when she meant to write in 24 years.

④ **How long have you been in this current living arrangement?**

years    24    PM, 11/13/2001

Do NOT correct mistakes as the following:

years    4    WRONG!  
  years    24    WRONG!

**2F.4. Making a Response Null (see Table 6)**

If a question or response should have been left blank (because the question was to be skipped) you can change the response to Null.

- Write the word “NULL” next to the correction.
- Circle the word “NULL”.
- Initial and date the correction.

**Table 5: Making a Response Null**

**Example 2:** Changing a response to a YES/NO, multiple choice or fill in the blank question to null.

In this example, the participant marked answers to parts a and b when she was not supposed to. The answers to these questions should be blank, or null.

③ **In the last 12 months, have you fallen and landed on the floor or ground or fallen and hit an object like a table or chair?**

Yes     No     Don't know

a. **How many times have you fallen in the last 12 months?**

\_\_\_\_\_ falls    NULL PM, 11/13/2001

b. **When you fell during the last 12 months, did you fracture any bones?**

Yes     No    NULL PM, 11/13/2001

Which bones? \_\_\_\_\_

*Make sure the line goes through the circles of all the other options!*

**3.0 DATA COORDINATING CENTER (DCC) DATA SYSTEM**

**3A. Sending CRFs Via Fax**

TOLSURF CRFs will be faxed to the UCSF DCC. This section of the MOP provides important information to make the faxing of forms go smoothly.

**ALWAYS keep the original CRFs in your site research file.**

**3A.1. Fax Machine Registration - IMPORTANT**

CRFs must be faxed to the DCC from a registered fax machine(s). Prior to faxing any CRFs, the Clinic Study Coordinator must complete the Fax Machine Registration Form and fax the form to the DCC (Fax # **1-866-226-4607**).

The fax machine(s) must be programmed to print the clinic's fax number at the top of the sent faxes. It is crucial that the fax # signal be programmed to go with each fax sent. If your fax machine has speed-dial capabilities, it is convenient to program the DCC Teleform fax number **1-866-226-4607** as a programmed speed dial. You should contact your clinic's IT department with any questions about programming the fax machine(s). Please contact the TOLSURF Help Desk ([TOLSURFHelpDesk@psg.ucsf.edu](mailto:TOLSURFHelpDesk@psg.ucsf.edu); 415-514-8157) for assistance with any fax machine set-up or registration questions.

### 3B. Faxing Instructions

- Always feed the form into the fax machine TOP FIRST.
- Generally fax machines require that the paper is fed FACE DOWN into the machine.
- Do NOT include a cover sheet.
- NEVER fax lab reports or any progress notes to the DCC (ONLY CRFs ARE FAXED TO THE DCC).

Fax CRFs to the DCC via secure fax server (**no cover sheet!**)

**1-866-226-4607**

*(Please note that this fax number is different from the TOLSURF Pilot Study.)*

Please follow the TOLSURF CRF Faxing Log.

### 3C. Tracking Faxed Forms

The Clinic Study Coordinator (or designate) will track CRF faxing using the TOLSURF Forms Faxing Schedule and initial/date the fax date for each form. It is recommended that the fax confirmation print-out be kept with the CRF packet to track confirmation that the forms have been successfully faxed. Data transfer questions should be emailed to the TOLSURF Help Desk ([TOLSURFHelpDesk@psg.ucsf.edu](mailto:TOLSURFHelpDesk@psg.ucsf.edu)). Data corrections after the CRFs are faxed should be directed to the CCC Project Director.

You can track the status of your faxed forms on the TOLSURF website (<http://keeptrack.ucsf.edu>) under the “Faxed forms” link 24 hours after faxing the forms. The site coordinator will maintain a log of all successfully faxed CRF packets. Keep this log up to date so data transfer queries can be easily resolved.

### 3D. Correcting Mistakes on CRFs AFTER Faxing

CRFs are ONLY FAXED ONCE. **Re-faxing forms will NOT correct the data.** You must contact the CCC Project Director if there are data corrections or revisions after the CRFs are faxed. On very rare occasions, the DCC may ask that you re-fax a specific form, e.g., if the form did not get to the data system for some unusual reason.

Data queries will be reviewed by the CCC Project Director or Coordinator who will then resolve them and make corrections o the data system. All data corrections made after the CRFs are faxed MUST to be corrected on the source document at the clinic using the established conventions for making CRF corrections (see Tables 4, 5, 6). Source document corrections will be reviewed during site monitoring visits.

### **3E. Addressing DTF Missing Forms, and Data Edits**

DTF procedures are unique and described in 2C. There are also unique procedures for addressing the potentially unblinding information contained on the CRF.

Once a month, the clinical sites will receive a DTF Data Cleaning Report listing any missing, inconsistent and out of range data for each randomized infant. The TOLSURF Project Assistant will ship this report in a labeled sealed envelope to the Clinic Coordinators, along with the DTF return packet materials. The Clinic Coordinators will give this report to the responsible RN to reconcile the queries for these forms.

Once the RT resolves these queries, s/he will photocopy and put the following material in an envelope addressed to the DCC:

- 1) DTF Data Cleaning Report, with addressed queries initialed.
- 2) Corrected photocopies of DTFs with all changes and additions initialed and dated
- 3) Missing DTF Forms, as listed on the Missing DTF Report.

This material will then be mailed to the DCC at the following address:

TOLSURF DATA COORDINATING CENTER  
UCSF Coordinating Center  
C/O LISA PALERMO  
185 Berry Street, Suite 5700  
San Francisco, CA 94107

### **3F. EXPECTED FORMS FOR RANDOMIZED PATIENTS**

1. All CRFs are expected in the DCC for infants randomized into the study (1A thru 24) with a few caveats:
  - a. Patients who die while in the hospital:
    - i. Expected CRFs are 1A thru 21
  - b. Patients who die after discharge from the hospital:
    - i. Expected CRFs are 1A thru 21 and FU forms 23-24 up to the time of death.
  - c. Patients who are withdrawn from study dosing-continuing data collection:
    - i. Expected CRFs are 1A thru 21 up to the time of discharge/death
  - d. Patients who re withdrawn entirely from study participation (consent withdrawn):
    - i. Expected CRFs 1A up to the time of withdrawal and F12A/B, F20, and F21. This includes partial completion of all forms up to the date of withdrawal of consent
    - ii. All other blank CRFs should NOT be faxed to the DCC. Talk with the CCC to confirm which CRFs need to be submitted on any individual infant.
  - e. Patients randomized, but never dosed:
    - i. Expected CRFs are 1A thru 24 (including FU)
    - ii. For evaluation of Co-morbidities, the "Dosing Period" for these infants who were never dosed will be the date of randomization plus 7 days.





# III. Case Report Form (CRF) Completion Guidelines

## **IV. CRF Completion Guidelines**

### **1.0 Table of FORMS**

Form 1A:	Screening Form
Form 1B:	Documentation of Eligibility and Randomization
Form 2:	Perinatal Data
Form 3:	Infant Delivery Data
Form 4:	Pre Enrollment Co-Morbidities of Prematurity
Form 5:	PRE- ENROLLMENT Respiratory Parameters
Form 6:	Inhaled Nitric Oxide Delivery
Form 7A:	Initial Study Drug Delivery
Form 7B:	Subsequent Study Drug Delivery
Form 8:	Study Day 0 - 31 Respiratory Parameters
Form 9A:	Study Day 32- 120 Respiratory Parameters
Form 9B:	Study Day 121- Discharge Respiratory
Form 10A:	Extubation Data
Form 10B:	Additional Extubation Data
Form 11A:	Co-Morbidities of Prematurity Post- Enrollment to Date of Last Study Dosing Procedure + 7 days
Form 11B:	Co-Morbidities of Prematurity from Date of Last Study Dosing Procedure + 8 Days to Discharge from Study Hospital
Form 12A:	BPD Outcomes – 36 weeks PMA
Form 12B:	BPD Outcomes – 40 weeks PMA
AE/SAE Overview	
Form 13A:	Adverse Events Post- Enrollment to Date of Last Study Dosing Procedure + 7 Days
Form 13B:	Adverse Events from Date of Last Study Dosing Procedure + 8 Days to Discharge from Study Hospital
Forms 14A/B:	Hospital Course while at Study Hospital
Form 15:	Medications While at Study Hospital
Form 16A:	Discharge Report
Form 16B:	Hospital Discharge Breathing Outcome Questionnaire
Form 17:	Death Report
Form 18:	Protocol Deviations
Form 19:	Protocol Violations
Form 20:	Early Termination/Permanent Discontinuation of Study Medication
Form 21:	Serious Adverse Events
Form 22:	Fax registration form
Form 23:	Breathing Outcome Questionnaire (3,6,9,12 and 18 Mo) (see FU MOP)
Form 24:	Neurodevelopmental FU (see FU MOP)
Form 25:	Comments Form

## **2.0 Case Record Form (CRF) Completion Guidelines**

### **Overview**

- The CRFs are organized in sections generally reflecting the phases of study participation.
  - Screening
  - Randomization and pre-enrollment (pre-dosing)
  - Dosing Period: Enrollment to date of last study drug dosing procedure + 7 days
  - Discharge Period: Date of last study drug dosing procedure +8 days to hospital discharge
  - Overall hospital course
  - Follow Up phase: post discharge to 2 years corrected age
  
- Co-morbidities of prematurity will be reported as AEs
  
- There are two reporting points for co-morbidities of prematurity (AEs)
  1. Within 1 week after the date of last study drug procedure + 7 days
  2. Within 1 week of the date of discharge from the study hospital
  
- Serious Adverse Events (SAEs) will be reported individually as they occur
  
- Adverse events (AEs) may qualify as SAEs depending on the temporal relationship between the AE and the study drug/sham dosing procedure
  
- Information reflecting the hospital course and treatments (medications, transfusions, TPN, etc.) will be record from admission to discharge from the study hospital
  
- Follow up information will be reported after discharge from the study hospital. (separate Follow Up Phase Manual of Operations)
  
- It is a good idea to maintain a “Notes” page for each study patient. Here you should record additional details of patient course with regard to patient status, deviations, violations, AE’s, SAE’s. This will prove helpful if we have to revisit the study course of your patient 6 mos or 12 mos after discharge.
  
- If an infant is re-admitted after discharge home for  $\geq 6$  weeks, please otify the CCC.

Record of faxing CRFs to DCC: See MOP Appendix G. CRF Faxing Log timeline for faxing forms to the Data Coordinating Center (DCC).

### **3.0 CRF Completion Guidelines**

#### **Form 1A: Screening Form (2 pages)**

This form is used to screen and track all patients admitted to the NICU who were  $\leq 28$  weeks, 0 days gestational age at birth. Patients should be tracked for eligibility criteria until parents consent or decline to participate, exclusion criteria are met, or the baby reaches day of life (DOL) 14. Date of birth is counted as DOL 1.

Screen patients as soon after admission as possible.

#### **Banner data:**

- Record Screening ID# and Secondary ID letters (these are not the patient initials). These can be found on the Study Site Screening/Tracking Log. These ID's are determined by the Data Coordinating Center and are assigned sequentially as patients are admitted.
- For enrolled subjects, include the assigned randomization study ID (obtained from Nancy or Jeanette) where indicated. This unique patient ID sequence will be pre-populated in the banner at the top of every subsequent CRF page.
- Enter staff initials of the person who collects and/or verifies the data on Form 1A.
- If the patient is never randomized, fill in the N/A bubble in the upper right corner of the banner.

**1A.1.** Enter patient gender and date that definitive outcome of screening is known (that is, patient is enrolled or not – 1A.9a, 1A.9b or 1A.9c question is answered)

#### *1A.1.a. Date Screened:*

Enter the date that the definitive outcome of patient eligibility was determined. That is, enter the date information was ascertained allowing completion of line 1A.9a, 1A.9b, or 1A.9c. Example: you start screening a patient on 10/1/10, but Date Screened is 10/14/10, because that is the date the patient got intubated, and consent was obtained to enroll patient.

**1A.2.** Enter ethnicity as reported by the parent(s). Select only one option.

**1A.3.** Enter all race categories that are reported by the parent(s).

**1A.4.** Indicate if patient is intubated on DOL 7. Select one: Yes or No

#### **INCLUSION CRITERIA**

All inclusion criteria must be marked "Yes". If one or more are marked "No", the patient does not meet study inclusion criteria and is not eligible for enrollment.

Complete the Inclusion/Exclusion tables on the day you determine eligibility for randomization. You may start screening on DOL 7, but do not make the determination that an infant was not eligible until DOL 14 when you record that the infant was never intubated.

**1A.5.a. Gestational Age:**

Enter completed weeks and days. Use the following hierarchy of estimates of gestational age:

1. Ultrasound performed at less than 20 weeks.
2. Good Dates
3. Physical Exam

If ultrasound or dates were not available then physical exam can be used. If a range is estimated for gestational age, use the lower end of the range. For example, 27-28 weeks should be rounded off to 27 weeks. The subsequent date for recording the 36 week and 40 week Post-Menstrual Age (PMA) data (Forms 12A and 12B) will be determined from the gestational age recorded on Forms 1A and 1B.

Gestational age at birth must be  $\leq 28\ 0/7$  weeks to be eligible for study participation.

\* This number should coincide with the “Gestational Age” recorded on form 1B.

**1A.5.b. Age in days.**

Day of life one is the day the infant is born. Example: Infant born on 3.2.10 at 23:48 is DOL 2 on 3.3.10 at 00:01 AM. Enter the DOL that you made the determination of eligibility (or not).

\* This number should coincide with the “Age in days” recorded on form iB.

**1A.5.c. Intubated and mechanically ventilated:**

Intubated: Infant has endotracheal tube in place and is currently on mechanical ventilator

**1A.5.d. Plan to treat with Inhaled Nitric Oxide**

The clinical attending physician must be willing to treat with inhaled nitric oxide if the patient qualifies for the study, as it is part of the study protocol. In most cases, choose “Yes”, if you intend to consent this infant for enrollment.

**EXCLUSION CRITERIA**

All exclusion criteria must be marked “**No**” to be eligible for study enrollment.

**1A.6.a. Serious congenital malformations or chromosomal anomalies**

Serious congenital malformations are defined as those *which are*

- *life threatening*
- *have the potential to effect pulmonary development*

- *have inherent adverse pulmonary consequences,*
- *effect, or have the potential to effect, neurodevelopment*

**1A.6.b.** Life expectancy

If life expectancy is clearly < 7 days from day of enrollment starting on DOL #7, mark “yes”. If life expectancy is unknown, continue to follow the patient throughout the eligibility period or until parents consent or decline study participation or other exclusion criteria are present.

**1A.6.c.** Clinically unstable is defined as presence of one or more of the following (at the time of enrollment):

- Active Pneumothorax with chest tube (*Does not include CT after PDA ligation*). For baby to be considered eligible, any CT should be removed without re-accumulation for  $\geq 24$  hours.
- Active Pulmonary Hemorrhage (frank bleeding not related to irritation from suctioning or infection)
- Uncontrolled hypotension requiring more than 20 mc/kg/min dopamine or 2 pressor agents for > 24 hours
- Acute NEC ( $\leq 24$  hours from diagnosis or surgery)
- Untreated culture positive sepsis (<6h)
- Respiratory severity score (RSS) >14. RSS = FiO<sub>2</sub> x MAP
- Clinical team feels infant would not tolerate dosing procedure

NOTE: Once clinical instability issues stabilize or resolve, the patient may be considered for enrollment in TOLSURF with initial dosing to occur between DOL 7 through DOL 14. Continue to evaluate patient for study eligibility by tracking clinical instability through DOL #14.

NOTE: If a patient has diffuse “severe PIE” (>2mm bubbles), this patient probably should not be enrolled. In this case, the “clinical team” would state that dosing is not appropriate in the face of severe PIE. If you have any question about eligibility, call CCC.

NOTE: If a patient has severe PIE or has a pneumatocele prior to enrollment, discuss with CCC prior to approaching parents.

**1A.6.d.** Severe intracranial hemorrhage defined as:

- Bilateral Grade 4: Bilateral IVH with parenchymal extension

**1A.6.e.** Patients should not receive the first dose of study drug sooner than 48 hours after the last dose of clinically indicated early surfactant. Patient becomes eligible for enrollment and dosing after 48 hours have passed since the last clinical dose of early surfactant.

**1A.6.f.** If it is unlikely you will be able to collect primary BPD outcome endpoint at 36 weeks PMA, the baby should be excluded from study participation. Consider potential barriers such as return transport to other hospital from which information cannot be obtained, adoption, foster care, death, etc.

**1A.6.g.** If all exclusion criteria have been answered “No”, fill in the “Yes” bubble. Proceed to questions 1A.7 through 1A.9.

If one or more exclusion criteria are answered “Yes” at the end of the eligibility period at DOL 14, the patient is not eligible. Proceed to Question 1A.9.c.

**1A.7. Are there other reasons infant will not be randomized?**

Select one: Yes or No. If Yes is selected, complete section 1A.7.a.

**1A.7.a.** If Yes to 1A.7a, indicate all reasons not randomized. Mark all that apply. Then, proceed to line 1A.9.b. Mark the N/A bubble in the upper right corner of the banner.

If No is selected on line 1A.7. above, the patient is eligible and will be randomized. Proceed to section 1A.8.a. and mark the bubble. Contact the Project Director to obtain the randomization number. Enter the randomization number on Form 1A in the upper right corner of the banner on pages 1 and 2.

**1A.8. Has consent been obtained?**

If patient is eligible, mark “Yes”.

If patient is eligible, but consent is NOT obtained, mark “No”.

**1A.9. Enrollment status after Screening:**

Mark the appropriate bubble:

1A.9.a: Patient is eligible and will be randomized. Enter randomization study ID # to banner at the top of pages 1 and 2 of Form 1A.

1A.9.b: Patient is eligible, but will NOT be randomized. Mark the N/A bubble in the upper right corner of the banner on pages 1 and 2 of Form 1A..

1A.9.c: Patient is not eligible. Mark the N/A bubble in the upper right corner of the banner on pages 1 and 2 of Form 1A..

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After Form 1A is completed, fax the form to the DCC.

- All original forms should remain at the study site. If the patient is enrolled, file Form 1A and form 1B with the subject’s CRF.
- If the patient is not enrolled, retain Form 1A in the study files. Form 1B is not required for patients who are not enrolled in the study, regardless of their eligibility status.
- For Enrolled patients, be sure to fax Form 1A to the DCC first, before any other CRFs. Form 1A serves as a “placeholder” for this patient. If other CRFs are faxed first, they will be rejected by the DCC.

## **Form 1B: Documentation of Eligibility and Randomization (2 pages)**

When the patient meets all eligibility criteria between DOL 7 and DOL 14 and consent to participate has been obtained, the patient may be randomized. Call the Project Director (or Project Coordinator if PD is unavailable) to review and confirm that all eligibility criteria have been met. A randomization number will then be assigned by the PD. The patient Screening ID, Secondary ID and Randomization Number will be pre-populated in the banner of the subject's CRFs prior to emailing them to the site coordinator.

Enter Randomization Date and time in space provided. Enter date and time the randomization number was assigned.

**1B.1. Enter your center name.** Be sure to enter it the same way for all patients.

**1B.2. Enter assigned randomization number.** Although this seems a bit redundant, enter the randomization number for this patient (should match the number pre-filled on banner).

**1B.3. Enter date and time of birth:** For date, use mm/dd/yy format and time of birth use 24 hour clock

**1B.4. As a sibling(s) been enrolled int this study?**

**1B.4.a.** List the Randomization ID number(s) of other sibling(s)enrolled. If randomization of subsequent sibling(s) is a possibility, do not Fax Form 1B until the enrollment status of subsequent sibling(s) has been determined and their randomization number(s) can be documented on the prior sibling(s) Form1 B.4.a.

If you have questions about multiples, contact the Project Director.

**1B.5. Inclusion Criteria**

All inclusion criteria must be marked "Yes" for study enrollment.

**1B.5.a.** Gestational Age: Enter completed weeks and days. This number should coincide with 1A.5.a.

1B.5.a.i. How was GA determined? When determining gestational age, use the following hierarchy of estimates of gestational age:

1. Ultrasound performed at less than 20 weeks.
2. Good Dates
3. Physical Exam

If ultrasound or dates were not available then physical exam can be used. If a range is estimated for gestational age, use the lower end of the range. For example, 27-28 weeks should be rounded off to 27 weeks. The subsequent date for recording the 36 week and 40 week Post-Menstrual Age (PMA) data on FORMs12A and 12B should coincide with the gestational age recorded on Form 1B.5a.



1B.5.a.ii. Gestational age at birth must be  $\leq 28 \frac{0}{7}$  weeks to be eligible for study participation.

**1B.5.b.** Enter age in days – Day of life (DOL) one is the day the infant was born. Example: Infant born on 3.2.10 at 23:48 is at DOL #2 on 3.3.10 at 00:15 Infant's age from birth must be DOL 7-14 to be randomized. This number should coincide with 1A.5.b.

**1B.5.c.** Ventilated: Infant must be currently intubated and mechanically ventilated between DOL 7-14 to be eligible for the study. The goal is to enroll infants as close to DOL 7 as possible, before they have too much lung injury. Patients may be enrolled up to DOL 14.

**1B.5.d.** Plan to treat with Inhaled Nitric Oxide (iNO)  
Patients enrolled in the study will receive iNO per NO/CLD protocol. If the infant meets eligibility and is consented, check "yes", there is a plan to treat with iNO for the study, per the NO CLD protocol.

**1B.5.e.** All 4 inclusion criteria must be marked "Yes" for the patient to enter the study. If any inclusion criteria are marked "No" the patient is not eligible and cannot be randomized. If the patient was consented and randomized, and any inclusion criteria are marked "No", a protocol violation occurred. Complete Form 19, Q19.2.a. Notify Project Director within 3 working days of the protocol violation, and fax Form 19 to the DCC.

## **1B.6 Exclusion Criteria Review:**

All exclusion criteria must be checked "**No**" for study randomization.

### **1.B.6.a. Serious congenital malformations or chromosomal anomalies:**

*Infants with known chromosomal abnormalities or serious congenital malformations will be excluded from study participation..*

*Serious congenital malformations which should result exclusion include those which are:*

- *life threatening*
- *have the potential to effect pulmonary development*
- *have inherent adverse pulmonary consequences,*
- *effect or have the potential to effect neurodevelopment*

### **1B.6.b.** Life expectancy less than seven days

If the NICU attending physician and/or study investigators strongly suspect the patient is unlikely to survive to DOL # 14, it may not be appropriate to enroll the patient. If life expectancy is uncertain, the patient should be monitored through DOL 14 for a change in status. If life expectancy prognosis improves during the enrollment window, the patient may be enrolled anytime during the DOL 7 through DOL14 period.

### **1B.6.c. Clinically Unstable**

Clinically unstable is defined as the presence of one or more of the following:

- Active Pneumothorax with chest tube (Does not include CT after PDA ligation). For baby to be considered eligible, any CT should be removed without re-accumulation for  $\geq 24$  hours.
- Active Pulmonary Hemorrhage (frank bleeding not related to irritation from suctioning or infection)
- Uncontrolled hypotension requiring more than 20 mc/kg/min dopamine or 2 vasopressor agents for  $> 24$  hours
- Acute NEC –less than 24 hours from diagnosis or surgery
- Untreated culture positive sepsis ( $<6$ h)
- Respiratory Severity Score (RSS)  $>14$ . RSS = FIO<sub>2</sub> x MAP
- Clinical team feels infant would not tolerate dosing procedure

NOTE: If these issues stabilize or resolve by DOL 14, the infant may be considered for randomization in TOLSURF.

### **1B.6.d. Bilateral Grade 4 intracranial hemorrhage**

- Grade 4: IVH with parenchymal extension

**1B.6.e.** Patient should not receive the first dose of study drug sooner than 48 hours after the last dose of clinically indicated early surfactant. Patient becomes eligible for enrollment and dosing after 48 hours have passed since the last clinical dose of early surfactant.

**1B.6.f.** If unlikely to be able to collect primary BPD outcome endpoint at 36 weeks PMA, the baby should be excluded from study participation. Consider potential barriers such as return transport to other hospital/institution from which information cannot be obtained, adoption, foster care, death, etc.

**1B.6.g.** All 6 exclusion criteria must be marked “No” for the patient to enter the study. If any exclusion criteria are marked “Yes”, the patient is not eligible and should not be enrolled. If the patient was consented and randomized, and any exclusion criteria are marked “Yes”, a protocol violation occurred. Complete Form 19, Q19.2.b. Notify Project Director within 3 working days of the protocol violation, and fax Form 19 to the DCC.

## **1B.7. Consent and HIPAA Forms Review**

**1B.7a** Have main study consent and HIPAA consent forms been signed and dated? Select one: Yes or No.

Both consent and HIPAA forms must be signed and dated before “Yes” can be marked. (Note: Some IRBs request inclusion of HIPAA language main study consent, so that a single document is required).

**1B.7.b.** If Yes, record the date parental signatures were obtained. If consent was obtained by telephone, record the date consent was documented on the consent form.

If consent cannot be obtained in person, **DO NOT COMMENCE STUDY ACTIVITIES**. Consent forms must be signed prior to study entry. If telephone consent was obtained, document verbal consent by telephone in medical record and on consent form with date/time obtained, name(s) of parent(s) giving consent, person obtaining consent, and translator and witness (when appropriate). Then mark the Yes bubble. If possible, obtain signed consent by Fax. As soon as parents visit the hospital, ask them to record original signatures on the consent form documenting the consent by telephone.

If you notice that study activities were begun prior to consent, **CEASE ALL STUDY ACTIVITIES** until consent is obtained and documented. Notify the PI and complete Protocol Violation Form 19, Q19.2.c. Notify Project Director within 3 working days of the protocol violation, and fax Form 19 to the DCC.

Also complete the following:

**1B.7.c.** Indicate whether parents gave permission to bank tracheal aspirate and urine samples for future research related to airway inflammation and development of BPD. Select one: Yes or No

**1B.7.d.** Indicate whether parents gave permission for banking DNA from tracheal aspirate sample. DNA will be used to develop a repository for genetic studies of gene variants. Select one: Yes or No.

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Fax From 1B to the DCC at 1-866-226-4607 within 2 working days.

## **Form 2: Perinatal Data (1 page)**

### **2.1 Mother's Age: Indicate mother's age in years**

### **2.2 Ethnic Origin of Mother:**

Ethnicity should be self-identified. Select only one option.

Use the following NIH categories:

- Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
- Not Hispanic or Latino
- Unavailable/Unknown

### **2.3 Racial Origin of Mother:**

Race should be self-identified. Select all options identified by mother.

Use the following NIH categories:

- White: A person having origins in any of the original peoples of Europe, the Middle East or North Africa.
- Black or African American: A person having origins in any of the black racial groups of Africa.
- Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent; including Cambodia, China, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.
- American Indian or Alaskan native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment:
- Native Hawaiian or Other Pacific Islander:
- Unavailable/Unknown

**2.4 Maternal Education:** Please indicate the highest level of education completed by the infant's mother. Select one option only. If Maternal Education is determined later in the infant's hospital course, return to this Form 2 and edit Maternal Education. Send revised Form 2 to your contact at CCC.

- Some education, high school not complete
- High school graduate
- Some College
- College graduate
- Graduate Study
- Unavailable/Unknown

### **2.5 Maternal Medical History**

Select all that apply to current medical history. Indicate conditions listed, applicable for this pregnancy, which are identified in the labor and delivery record or the Neonatologist's admission notes. Talk with your attending, if not mentioned in notes, Likely means "No". For those moms who deliver with no PNC, indicate "Unknown".

**2.6 Pregnancy History:** The data should include this pregnancy

**2.6.a.** Gravida: Enter the total number of pregnancies for the mother (number should include this infant)

**2.6.b.** Para: Enter the total number of live births (number should include this infant)

**2.6.c.** Multiple Gestation: Indicate the total number of infants delivered from this pregnancy.

2.6.c.i. If multiples, indicate if this infant is monozygous (Identical)

2.6.c.ii. Indicate if uterine demise during this pregnancy

**2.6.d.** Indicate if mother obtained prenatal care (any) prior to hospitalization for delivery.

- Select Yes, if mother received any prenatal care, regardless of the number of visits.
- Select No, if mother did not receive any prenatal care prior to hospital admission resulting in delivery.
- Select Unknown, if the information is not available.

**2.7 Maternal Corticosteroid Administration:**

**2.7.a.** Indicate if the mother received any antenatal corticosteroids during this pregnancy. Select one: Yes, No or Unknown

2.7.a.i If Yes, indicate if mother received full course\* of antenatal steroids.

\*Full course of antenatal steroids is defined as two doses of 12 mg of betamethasone given intramuscularly 24 hours apart or four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart, as recommended by the NIH Consensus Development Panel in 1994<sup>2</sup>.

## **Form 3: Infant Delivery Data (1 page)**

**3.1. Gender:** Indicate assigned gender. If infant has ambiguous gender assignment at admission, wait to record until gender has been assigned.

**3.2. Birth weight:** Enter birth weight in grams

**3.3. Physical Measurements at Birth:** Head Circumference (HC): Record the infant's head circumference in centimeters. If the HC is recorded at birth use it. If not recorded at birth, use the earliest recorded measurement. Round off to the nearest 0.5 cm. Use zeros as necessary to complete all 3 fields. If HC has not been recorded, ask the clinical team to measure and record HC in the medical record as soon as possible after birth.

**3.4. Delivery Routes:** Indicate vaginal, caesarian or unknown if information not known. Select one. Indicate the final route of delivery.

**3.5. Apgar Scores:** Fill in one, five and ten minute Apgar scores when available. Use a leading zero (eg:08). If not available indicate as Not Recorded.

### **3.6. Delivery Resuscitation Required**

Select one: Yes or No

Indicate Yes, if any resuscitation measures listed occurred at delivery or in the resuscitation area. Mark as Unknown if the records of the delivery are not available.

**3.6.a** If Yes, mark all that types of resuscitation administered.

- Oxygen: Indicate if the infant received any supplemental oxygen by any route
- Bag and Mask Ventilation: Indicate if the infant received bag and face mask ventilation
- Intubation/Ventilation: Indicate if the infant received ventilation through an endotracheal tube
- NCPAP: Indicate if the infant received nasal CPAP in the resuscitation area
- Chest compressions: Indicate if chest compressions were given in the delivery room or resuscitation area
- Epinephrine: Indicate if IV, intra-cardiac, or intra-tracheal epinephrine was given in the delivery room or resuscitation area.

### **3.7 Surfactant Therapy Prior to Enrollment**

Indicate if patient received any surfactant at any time including doses administered in the delivery room. Select one: Yes, No or Unknown

**3.7.a.** List the date and time for all surfactant doses given prior to enrollment. Fill-in bubbles for the type(s) of surfactant given.

## **Form 4: Pre Enrollment Co-Morbidities of Prematurity (3 pages)**

Co-morbidities of prematurity which occur before study enrollment are not adverse events (Do not record on the Adverse Event Forms). They are recorded here to determine a “baseline” status of the infant. Record conditions diagnosed up to the date and time of study enrollment.

### **4.1 Neurologic**

These items are designed to capture information about intraventricular hemorrhage (IVH) and cystic periventricular leukomalacia (PVL) related to prematurity.

#### **4.1.a.** IVH by head ultrasound, MRI or CT scan

Select one: Indicate Yes, No or Unknown.

Enter No if no IVH has been diagnosed.

4.1.a.i. If Yes IVH, enter the worst grade seen prior to enrollment, e.g. if the grading is defined as Grade 2-3, use the worst grade and indicate Grade 3.

##### o Grade definitions

- Grade 1 or 2: Germinal Matrix Bleed or IVH without dilatation;
- Grade 3 - 4 (IVH with dilatation or parenchymal bleed). Includes unilateral Grade 3 or 4 or a bilateral Grade 3 IVH, or Grade 3 on one side and Grade 4 IVH on the other. **Bilateral Grade 4 is a study exclusion.** It should not be present pre-enrollment.

4.1.a.ii. Indicate how IVH was determined: MRI, HUS, CT scan, or Unknown. Select all that apply.

#### **4.1.b.** Cystic PVL: PVL must be confirmed by: MRI, HUS, CT scan.

Select one: Indicate Yes, No or Unknown.

Enter No if no cystic PVL has been diagnosed.

4.1.b.i. If “Yes”, Indicate how PVL determined: MRI, HUS, CT scan. Select all that apply.

NOTE: If patient has diagnosis of porencephalic cysts or encephalomalacia prior to enrollment, record on 13A/B as an “Other AE” with the original pre-enrollment diagnosis date.

### **4.2. Gastrointestinal**

#### **4.2.a.** Necrotizing Enterocolitis (NEC)

NEC is defined as pneumatosis, hepato-biliary gas, or pneumoperitoneum AND one or more of the following: bilious gastric aspirate or emesis, abdominal distension, or occult or gross blood in stool not from fissure. Indicate if infant developed NEC prior to study enrollment.

Select Yes, No or Unknown.

- Indicate “No NEC”, if NEC was not diagnosed prior to study enrollment. Diagnoses of “RULE OUT” OR “PRESUMED” NEC do not qualify. They should be recorded as “No NEC”.
- Indicate “Yes NEC”, if NEC that met the above diagnoses was diagnosed prior to study enrollment
- Indicate Unknown NEC, if you cannot determine if infant had NEC that met our definitions (eg: had NEC at a referral center)

4.2.a.i. If Yes NEC, enter date of definitive NEC diagnosis.

4.2.a.ii. NEC Treatment Outcome

Indicate whether or not there was surgical intervention.

- Record “NEC with Surgery” if patient received surgery for NEC, including placement of peritoneal drain, indicate by selecting bubble and enter date of first surgical intervention.
- Date of surgery can be in the dosing or discharge period (if delayed).
- If both a drain and laparotomy were performed for treatment , mark the date of the laparotomy as it is the most invasive therapy.
- Record “NEC without surgery”, if NEC was diagnosed, but only treated medically.

**4.2.b.** Isolated GI Perforation without NEC:

Indicate if infant developed a focal GI perforation requiring laparotomy or no laparotomy but drain placement.

Select one: Indicate Yes, No or Unknown

4.2.b.i. If Yes, Record date that GI Perforation occurred.

### 4.3. Pulmonary

**4.3.a.** Severe Pulmonary Interstitial Emphysema (PIE):

The goal is to record only “real” PIE. PIE which is equivocal or controversial should not be counted. PIE should only be scored if it is seen on more than one CXR.

PIE is defined as rupture of air from alveoli or small airways into lung perivascular tissues, characterized by irregular air-filled cysts or linear lucencies radiating from the hilum.<sup>3</sup>

Note: Do not record pneumatoceles as PIE.

Note: Severe PIE must be resolved prior to enrollment.



PIE is scored as “None”, “Moderate”, or “Severe”.

- None = no PIE, or only perihilar bubbles or “pre-PIE” noted.
- Moderate PIE = lobar, unilateral or bilateral bubbles < 2 mm in size.
- Severe PIE = lobar, unilateral or bilateral bubbles > 2 mm in size.

PIE: Select One: Indicate Yes, No or Unknown

Select Yes, if patient had severe PIE as defined above AND radiological diagnosis of PIE consistent with the severe definition on 2 or more chest x-rays before enrollment.

4.3.a.i. If “Yes”: indicate date of 1<sup>st</sup> chest x-ray with diagnosis of PIE.

Select “No”, if no PIE as defined above.

Select Unknown, if no chest x-rays were taken

#### **4.3.b. Severe Pulmonary Hemorrhage**

Pulmonary hemorrhage is defined as frank bleeding and does not include irritation due to suctioning or infection. Indicate if patient had a pulmonary hemorrhage before enrollment.

Select “Yes”, if infant has Pulmonary Hemorrhage as defined above

4.3.b.i. If Yes, indicate date of diagnosis.

Select “No”, if no Pulmonary Hemorrhage was diagnosed as defined above

Select “Unknown”, if unable to determine

#### **4.3.c. Pneumothorax requiring a chest tube**

Indicate if patient had a pneumothorax requiring chest tube before enrollment. *Those expected pneumothoraces requiring a chest tube acquired as a result of clinical interventions such as PDA ligation should not be recorded as a co-morbidity, AE or SAE.* Chest tubes placed for pneumothorax prior to enrollment must be discontinued for 24 hours without re-accumulation of air, prior to eligibility for enrollment. If you have questions, contact CCC.

Select one: Yes, No or Unknown

4.3.c.i If Yes, indicate date of diagnosis.

### **4.4. Cardiovascular**

**4.4.a.** Indicate whether the infant was treated with prophylactic indomethacin or ibuprofen for prevention of PDA/IVH.

Select one: Indicate Yes, No or Unknown

**4.4b.** Did infant have a PDA that resulted in either medical or surgical treatment prior to study enrollment.

Select one: Indicate Yes, No or Unknown.

Report PDA ONLY if it is treated – either medically or surgically. Do not record subclinical patent ductus that has not required treatment.

4.4.b.i. If “Yes” PDA, was PDA treated medically with indomethacin or ibuprofen?

Select one: Indicate Yes, No or Unknown.

4.4.b.ii. If “Yes” PDA, record if PDA was treated surgically (ligation).

Select one: Indicate Yes, No or Unknown.

4.4.b.iii. If “Yes” Ligated, record the date of surgery.

Note: If PDA is recorded on form 4 AND is ongoing during the dosing or discharge period (s), it will NOT be recorded on 11A/B unless new treatment for PDA is given during those time periods.

#### **4.4.c.** Hypotension

For this study, hypotension is defined as hypotension requiring vasopressor support for > 24 hours with one of the following treatment regimens to maintain mean blood pressure within normal limits.

- Dopamine > 20 mcg/kg/min > 24 hours
- Addition of a second vasopressor agent and treated > 24 hours (e.g. treatment with dopamine 10 mcg/kg/min plus dobutamine or hydrocortisone added)

Hypotension, Select one: Indicate Yes, No or Unknown.

Record Yes, If patient had hypotension, as defined above, before study enrollment, and identify qualifying treatment regimen:

4.4.c.i. Was infant treated with Dopamine > 20 mcg/kg/min for >24 hours? Select one: indicate Yes, No or Unknown. Mark unknown if information is not available from referring hospital.

4.4.c.ii. Was infant treated with 2 or more pressor agents for > 24 hours? Select one: indicate Yes, No or Unknown. Mark unknown if information is not available from referring hospital.

Note: If a patient met definition of hypotension prior to enrollment, must be improved or resolved before infant can be entered into study.

#### **4.4.d. Pulmonary Hypertension**

Pulmonary hypertension is defined as elevated pulmonary vascular pressure > systemic pressure resulting in right to left shunting and systemic hypoxemia. Pulmonary hypertension may be diagnosed clinically or by echo, but should be documented in patient medical progress or cardiology consult notes in medical record.

Select one: indicate Yes, No or Unknown. Mark unknown if information is not available from referring hospital.

4.4.d.i. If Yes, Indicate how diagnosis of pulmonary hypertension diagnosis was determined (clinical, echocardiogram, unknown). Select all that apply.

4.4.d.ii. Enter date pulmonary hypertension diagnosis first recorded in medical record by attending physician or cardiologist.

Note: If pulmonary hypertension (PH) is recorded on form 4 AND is ongoing during the dosing or discharge period (s), it will also be recorded on 11A/B with the same pre-enrollment diagnosis date. HOWEVER, these PH episodes that were diagnosed pre-enrollment will not be reported on 13A/B, even if the outcome is death.

#### **4.5. Culture Proven Sepsis**

Report the following as sepsis:

Record all "episodes of infection" resulting in positive bacterial, fungal or viral culture from blood, CSF, urine or tracheal aspirate that were treated with antibiotics, antifungal or antiviral agents for  $\geq 7$  days. Our intent is to report each, discreet episode of sepsis, not each time a repeat culture from the same episode, remains positive with the same organism. If a new organism is identified and treated for  $\geq 7$  days, add as new episode.

**4.5.a.** Did infant have sepsis? Select one: Yes, No, or Unknown

Mark unknown if unsure of culture results at previous hospital (if patient was transferred)

4.5.a.i. Record all specimens that meet the above criteria.

- Indicate date specimen drawn that resulted in positive culture.
- Indicate specimen type.
- Indicate type of organism(s) isolated.

**4.5.b.** Did infant have RSV prior to enrollment? RSV infections are defined as a positive culture (or DFA) from tracheal aspirate or nares.

Indicate Yes, No or Unknown.

4.5.b.i. Record date of first positive TA culture or DFA collected

## **Form 5: PRE- ENROLLMENT Respiratory Parameters (5 pages)**

(Collect from birth up to first study dosing procedure)

These forms are used to document the respiratory parameters for the dates and times listed before the first study drug/sham dosing procedure. Date of birth is DOL1.

Parameters are recorded every 8 hours (24 hour clock), ideally at 0800, 1600 and 2400.

If parameters are not documented at these times, record those closest to these time points. Try to record parameters at the same time points every day.

Each calendar day is indicated by "D01, D02, D03.....etc, and is divided into 8 hour segments. All entries for a given study day should reflect the same calendar date. (eg: study day dates should not cross from one calendar day to another...cross from D01 to D02).

Place first recorded settings in the appropriate time row for that day e.g. infant born at 2 pm should have first settings in the 16 hour row because time infant born was between 0800 and 1600). Choose settings close to the indicated time.

The values written should correspond to documentation in the infant's medical record (ventilator flow sheet or nursing flow sheet/notes) at the time of entry. Complete these forms up to the date and time of enrollment, e.g. if a patient is enrolled on 03.03 at 17:10, record respiratory parameters up to the time of enrollment on Form 5. After the patient is enrolled complete continue subsequent entry of respiratory parameters on Form 8.

At top of page – Record Birth date (this should correspond with date on Form 1B).

The Hour (HR) and DOL (D) will be pre-populated in the patients individualized CRF.

Leading and trailing zeros are not necessary in the respiratory parameter fields.

- Enter date of respiratory parameter selected as recorded in the medical record.
- Enter time of respiratory parameter selected as recorded in the medical record. Note: Time must be recorded in both hours and minutes
- PEEP/CPAP: Record the positive end expiratory pressure (PEEP) or continuous positive airway pressure (NCPAP).
- MAP: Record mean airway pressure for ventilator or NCPAP. Record only whole numbers. Round up if number fraction is  $\geq 0.5$ . (e.g. if 8.5, record 9)
- FiO<sub>2</sub>: Record the fraction of inspired oxygen e.g. .21
- NC Flow LPM: Record nasal cannula flow in liters per minute (x.xx)
- Record iNO delivery in parts per million (PPM)
  - Always make an entry to indicate the parameters on the date the iNO is discontinued. i.e. when iNO PPM = 0
  - After the zero PPM is entered to indicate the end of weaning, it is not necessary to continue recording the iNO level as 0

- If iNO is restarted, resume recording the iNO PPM level and continue recording until it is discontinued and “0” PPM is recorded again

### Respiratory Status:

Respiratory Status must be recorded until the patient is discharged from the study hospital. Using the key provided at the bottom of Form 5, record the corresponding number to indicate mode of respiratory support.

- 1=CMV: Conventional mechanical ventilation (either pressure or volume pre-set)
- 2=HFV: High Frequency Flow Interrupter (Infrasonics) or High Frequency Jet Ventilation (Bunnell), High Frequency Oscillatory Ventilation (Sensormedics)
- 3=NIMV: Nasal Intermittent Mandatory Ventilation (airway not intubated through vocal cords although patient is receiving mechanical breaths from the ventilator), SiPAP, BiPAP.
- 4=CPAP: Continuous Positive Airway Pressure ONLY
- 5=HFNC or NC > 2 lpm: Nasal cannulae with flow > 2 lpm
- 6=O<sub>2</sub> via NC or Oxyhood: Oxygen delivered by nasal cannulae at flows ≤ 2 lpm or high flow Oxyhood.
- 7=Ext in RA: Extubated and in room air

When the infant is in room air without any respiratory support, enter Respiratory Code 7. Continue to enter Code 7 until the infant is discharged from the study hospital or respiratory support is resumed.

It is not necessary to enter FiO<sub>2</sub> of 0.21 when Respiratory Code 7 is entered.

Note: if you have an entry where you know you do not have the data, please write a small note in the page margin indicating this. That way, the CCC will not have to call you for query on that item.

## **Form 6: Inhaled Nitric Oxide Delivery (1 page)**

Use this form to record nitric oxide received for CLD while in the study hospital. Record initiation of iNO and all iNO dose changes on this form. Infants must receive iNO to be eligible to participate in the TOLSURF Study. Infants who remain intubated and mechanically ventilated at 7 days of age are at risk of BPD and, when enrolled in the TOLSURF study, will receive iNO therapy per the NO/CLD protocol.

**If the patient received iNO prior to 7 days for pulmonary hypertension, DO NOT record on this sheet. Any iNO administered prior to 7 days will be recorded on Form 5 Respiratory Parameters Sheet and does not need to be recorded elsewhere.**

NO CLD Protocol:

- iNO is initiated on DOL 7 (or when eligibility criteria are met) at 20 parts per million (PPM)
- Wean to 10 PPM at 4 days  $\pm$  24 hours after iNO started
- Wean to 5 PPM at 11 days  $\pm$  24 hours after iNO started
- Wean to 2 PPM at 18 days  $\pm$  24 hours after iNO started
- Discontinue iNO at 25 days  $\pm$  24 hours after iNO started

If the patient is extubated during the iNO course, continue to deliver iNO per the NO CLD protocol via nasal CPAP or nasal cannula.

**6.1. Report Date and time that iNO treatment began (for CLD-per the NOCLD treatment schedule) and concentration at iNO start.** Indicate exact date started and record the concentration used at iNO start (for CLD). If the infant was started on the iNO for CLD protocol on DOL 7, but not entered until DOL 10, that is OK, iNO recording should begin with the start of iNO treatment for CLD.

**6.1.a.** On lines 2-5, record date, time and amount of iNO for each subsequent wean of iNO. Be sure to record when iNO turned off "00".

**6.1.b.** Did any iNO dose listed in 6.1a above deviate from the NO-CLD protocol at the top of the page? Indicate Yes or No.

If Yes, document on form 18 as Protocol deviation. (Q18.2.b.)

**6.2. Did patient receive additional iNO after completing the NO CLD iNO course.** Select one: Yes, No or Unknown

**6.2.a.** If patient received iNO after completion of iNO courses per the NO/CLD protocol, record all dose changes as they occur (either increased or decreased doses) on lines 6-9. Be sure to record when iNO turned off "00".

**6.2.b.** Did any iNO dose listed in 6.2a above deviate from the NO-CLD protocol at the top of the page? Indicate Yes or No.

If Yes, document on form 18 as Protocol deviation. (Q18.2.c.)

Note: If you do not have enough space to record all dose changes, be sure to record the duration of the highest dose used for these additional courses (eg:

record start date of 20 ppm and the wean to 10 ppm). Be sure to record when iNO discontinued (0 ppm).

**6.3. Record final date iNO discontinued** (last date iNO received). This date should coincide when iNO turned off date from 6.1a or 6.2a.

## **Form 7A: Initial Study Drug Delivery (1 page)**

This form is used to record the first study drug/sham dose given as part of the TOLSURF Study. The bubble indicating Dose #1 will be pre-filled.

**7A.1a.** Indicate if study drug/sham dose #1 was administered by selecting Yes or No.

If infant has been randomized but dosing is delayed due to clinical instability, you may dose once infant is stable, up to DOL 14. If infant remains too unstable for dosing by DOL 14, contact the CCC for further instruction. In some instances, sites may be cleared by the CCC to administer Dose #1 after DOL 14. If this occurs, report this as a protocol deviation on Form 18. "Other". Briefly describe in the text box the reasons dose #1 was given after DOL 14.

If No is selected because the patient never received a study drug dose/sham procedure, a protocol violation has occurred. Discuss with CCC before completing form. Record the violation as a study drug administration error on Form 19. If the patient is surviving and has not been withdrawn from the study, but withdrawn only from receiving study drug/sham dosing, continue to collect study data on the patient. When patient is withdrawn from dosing, study iNO must be discontinued and CCC notified. If patient requires iNO, they should be placed on clinical gas.

If the patient is withdrawn from part, or all, of the study procedures, report discontinued participation on Form 20.

**7A.1.b.** Age in days: verify once again that the patient is eligible to receive the first study drug dose. Record the patient's age in days when the first dose/sham is given. Day of birth counts as day 1.

**7A.1.c.** Tracheal Aspirate:

Indicate if patient had a tracheal aspirate sample obtained prior to the initiation of study drug dose/sham #1.

If yes, indicate date and time tracheal aspirate was obtained.

If No, complete "no" bubble. A missed or late TA sample is not reportable as a protocol deviation.

**7A.1.d.** Indicate whether there was a problem obtaining the TA sample.  
Select one: Yes or No

If Yes, record patient related problems as adverse events on Form Q13A..20  
Examples of problems include significant bradycardia (HR < 80 for > 60 sec) and/or desaturation (<75% for > 60 sec) during TA sampling procedure, accidental disconnection of endotracheal tube (ETT) adaptor, accidental extubation, etc.

**7A.1.e.** Is the patient is receiving iNO at the time that study drug/sham #1 was administered.  
Select Yes if the patient was receiving iNO at any PPM dose.



7A.1.e.i. Record the iNO PPM dose the patient was receiving at the time of the study drug/sham dosing procedure #1

Select No, if the patient was not receiving iNO, record a protocol violation on Form 19, Q19.2.g.

## **7A.2. Study Drug/Sham-Date & Time of Dosing Procedure #1**

Record the date and time of Dosing/Sham procedure #1 (in hours and minutes)

Record the respiratory support parameters at 3 time points associated with the study drug/sham dosing procedures. Record parameters at; 0 minutes (pre) just prior to dosing procedure, then at one hour, and again at two hours after the dosing procedure. At each time point, record the following:

- Time: Record hours and minutes
- Ventilator Mode: select the appropriate bubble for conventional mechanical ventilation (CMV) or high frequency ventilation (HFV)
- PIP /  $\Delta$  P: Record either the Positive Inspiratory Pressure for CMV or the Delta Pressure (aka “amplitude”) for High Frequency Ventilation
- PEEP: Record Positive End Expiratory Pressure only if the infant is on CMV
- MAP: Record the mean airway pressure. Round up if number fraction is  $\geq$  0.5. (e.g. if 8.5, record 9)
- FiO<sub>2</sub>: Record the fraction of inspired oxygen (x.xx)
- Oxygen saturation: Record percentage

Note: Respiratory parameter recordings should coincide with data entry items found in the infant’s medical record.

If possible, try to avoid suctioning the endotracheal tube for at least 4 hours after the dosing/sham procedure.

## **Study Drug/Sham Dosing Tolerance within 4 Hours and 24 Hours After Dosing Procedure**

Definitions of adverse events after completion of the dosing/sham procedure are defined by the temporal relationship of the event to the dosing/sham procedure.

**7A.2.a.** Study drug dose/sham tolerance within 4 hours after dosing procedure #1 has been completed

Answer questions in this section Yes or No as appropriate. Indicate if the infant developed any of the following within 4 hours of the study drug/sham dosing procedure:

7A.2.a.i Severe Respiratory Decompensation

- Record as “Yes”, if infant had an increase in Respiratory Severity Score (RSS)  $> 5$  above pre-dosing baseline and sustained for  $>24$  hours. (RSS = FiO<sub>2</sub> x MAP).

- If Yes, this event will be reported as an **SAE**. Answer Questions 13A.3. through 13A.4.a.i on Form 13A. Then complete SAE Form 21.

7A.2.a.ii. Severe Cardiopulmonary Decompensation

- Defined as requiring cardiopulmonary resuscitation (CPR) with chest compressions AND cardiac medication(s)\*.
- If Yes, record an Adverse Event (AE) on AE Form 13A and on SAE Form 21.

\*Note: Resolution of bradycardia with resumption of normal heart rate after chest compressions, without administration of cardiac medications, should not be recorded as severe cardiopulmonary decomposition. Do not record as an AE or SAE.

7A.2.a.iii. Required reintubation

- Defined as requiring replacement of the endotracheal tube either during dosing or within the 4 hours after dosing.
- If Yes, record an Adverse Event (AE) on AE Form 13A

**7A.2.b.** Study drug dose/sham intolerance within 24 hours after dosing procedure #1 has been completed.

Answer questions in this section Yes or No as appropriate. Indicate if the patient developed any of the following within 24 hours of the study drug/sham dosing procedure

7A.2.b.i. Severe Pulmonary Interstitial Emphysema

- PIE is defined as rupture of air from alveoli or small airways into lung perivascular tissues, characterized by lobar, unilateral or bilateral bubbles > 2 mm in size.
- The goal is to score only “real” PIE. PIE which is equivocal or controversial should not be counted. PIE should only be scored if it is seen on more than one CXR. Pneumatocoles should not be counted as PIE.
- Select Yes, if patient had severe PIE as defined above AND radiological diagnosis of PIE consistent with the severe definition on 2 or more chest x-rays before enrollment.
- If Yes is selected, record an Adverse Event on AE Form 13A AND record a SAE on SAE Form 21.
- Select No, if PIE does not meet the definition above.

7A.2.b.ii. Severe Pulmonary Hemorrhage

- Severe Pulmonary hemorrhage is defined as frank bleeding. It does not include irritation due to suctioning or infection.

- If Pulmonary Hemorrhage Yes, record an Adverse Event on AE Form 13A AND record a SAE on SAE Form 21.

7A.2.b.iii. Pneumothorax requiring chest tube

- Indicate if the patient developed a spontaneous pneumothorax\* requiring chest tube within twenty-four hours of receiving the study drug.
- If Pneumothorax Yes, record an Adverse Event on AE Form 13A AND record a SAE on SAE Form 21.

**\*Note: Expected pneumothorax with chest tube acquired as a result of clinical interventions such as PDA ligation should be not be recorded as an AE or SAE.**

**\*Note: Severe respiratory decompensation or cardiopulmonary decompensation within 4 hours after study drug/sham dosing; severe pulmonary hemorrhage; pneumothorax requiring a chest tube; and, severe PIE occurring within 24 hours after study drug/sham dosing are considered serious adverse events which require expedited reporting.**

**NOTIFY THE SITE PI AND THE TOLSURF PROJECT DIRECTOR OF ALL SERIOUS ADVERSE EVENTS WITHIN 3 WORKING DAYS. NOTIFY YOUR LOCAL IRB ACCORDING TO INDIVIDUAL IRB REPORTING REQUIREMENTS.**

**NOTE: Unblinded Dosing Tolerance During Study Drug/Sham Dosing Procedure Form**

- This form will be emailed to the site study coordinator when the patient is randomized. The site coordinator should give this form to the unblinded dosing personnel prior to the dosing procedures.
- The form will be completed by the unblinded dosing personnel during the dosing procedure.
- If a patient has significant dosing intolerance\* during the dosing procedure, the unblinded dosing persons who are performing the dosing procedure behind the screen will record the patient's response on the Unblinded Dosing Tolerance Form. Instructions for completion can be found in Respiratory MOP
- The completed form should not be seen by blinded clinical or study personnel. It will be handled separately from the other CRF forms. See MOP Data Management, Section III.2B.1 for detailed instructions.

\*Significant intolerance is defined as:

- Oxygen desaturation <75% for > 60 seconds;
- Bradycardia < 80 for > 60 seconds;
- Re-intubation required.

Contact the Project Director if you have questions about the handling of this form.

## **Form 7B: Subsequent Study Drug Delivery (4 pages, 1 for each dose)**

These forms are used to record subsequent study drug/sham procedures #2 through #5 and concurrent nitric oxide doses. **Complete one 7B page for each of the four subsequent study drug/sham dosing procedures, regardless of whether dose is given or not.**

### Delayed Dosing

If a patient who has been randomized between DOL 7 and 14 becomes clinically unstable prior to the dosing procedure #2, dosing may be delayed. The window for dosing closes when the study iNO is discontinued (usually around DOL35).

### **DEFINITION OF CLINICALLY UNSTABLE INFANT**

1. Active Pneumothorax with chest tube
2. Active Pulmonary Hemorrhage
3. Uncontrolled hypotension requiring more than 20 mc/kg/min dopamine or 2 pressor agents for > 24 hours
4. Acute NEC –less than 24 hours from diagnosis or surgery
5. Untreated culture positive sepsis (<6h)
6. RSS >14
7. Clinical team feels infant would not tolerate dosing procedure

If the patient is deemed clinically unstable at the time any of the doses are due to be given, but later stabilizes during the study treatment period (while receiving iNO per NO-CLD protocol) , the patient should continue to receive study drug/sham dosing per the q 1-3 day dosing schedule. The patient is eligible for a total of 5 study doses while receiving study iNO per NO-CLD protocol.

### **7.B.1. The bubble will be pre-filled to indicate dose number.**

**7.B.1.a.** Indicate if dosing procedure was performed per protocol within 1-3 days after the previous dosing procedure.

- If “Yes”, proceed to 7B.1.b, and complete rest of form,
- If No, proceed to 7.B.1.a.i. and indicate the reason dosing procedure was not performed according to the protocol. If Yes is marked, proceed to 7.B.1.b

7.B.1.a.i. Indicate reason dosing procedure was not performed.

- If study drug dosing procedure was permanently discontinued, or patient was withdrawn from partial or full study participation, complete Form 20 Study Drug Discontinuation
- If dosing procedure was not performed because the patient expired, complete Form 17 Death Report and Form 21 SAEs. Notify Project Director within 3 working days. Fax Form 21 to the DCC.

- If the dosing procedure was delayed due to extubation, clinical instability or weekend/holiday, continue to monitor the patient. If dosing is resumed, proceed to 7B.1.b.
- If dosing procedure delay was due to error, complete Form 19 Protocol Violations. Resume dosing procedures as ordered by the PI and proceed to section 7.B.1.b.
- If subsequent doses are never administered, for whatever reason, complete sections 7B.1.a. through 7B.1.a.i. for each of the 4 subsequent dosing procedures (all 4 pages o 7B)
- Complete Form 20 and continue data collection on Forms 8-21.
- If the patient was eligible, but the dose was not given (eg: dose missed in error, not due to one of the choices above) record this as a drug dosing error and record on Form 19: Protocol Violations, Q19.2.e.

7.B.1.a.ii. Indicate if this study dose was subsequently administered.

- If the study dose was subsequently administered, complete sections 7B.1.b. through 7B.2.b.iii.

**7B.1.b.** Tracheal Aspirate: Indicate if patient had a tracheal aspirate sample obtained on the day of dosing, prior to study drug doses/shams procedures #2, #3, #4 or #5.

- If TA obtained, mark “Yes” and indicate date and time tracheal aspirate was obtained.
- If TA sample not obtained, mark “No”. A missed or late TA sample is not reportable as a protocol deviation.

**7B.1.c.** Indicate whether there was a problem obtaining the TA sample.  
Select one: Yes or No

- Examples of problems include significant bradycardia (HR< 80 for > 60 sec) and/or desaturation (<75% for > 60 sec) during TA sampling procedure, accidental disconnection of endotracheal tube adaptor, accidental extubation, etc.
- If “Yes” is selected, record patient related problems as adverse events on Form 13A.
- Record “No”, if no problems occurred.

**7B.1.d.** Indicate if the patient is receiving iNO when study subsequent study drug/sham procedures #2 - #5 were administered.  
Select one: Yes or No

- Mark “Yes”, if the patient was receiving iNO at any PPM dose.

7.B.1.d.i. Record the iNO PPM dose the patient was receiving at the time of the study drug/sham dosing procedure #1.

- Mark No if the patient was not receiving iNO. Record a protocol violation on Form 19. Notify the Project Director within 3 working days. Fax Form 19 to the DCC.

## **7B.2. Study Drug/Sham Date & Time of Dosing Procedures #2 - #5**

Record the dates and time in hours and minutes of Dosing/Sham procedure #2 - #5.

If possible, try to avoid suctioning the endotracheal tube for at least 4 hours after the dosing/sham procedure.

Record the respiratory support parameters at 3 time points associated with the study drug/sham dosing procedures. Record parameters at; 0 minutes (pre) just prior to dosing procedure, then at one hour, and again at two hours after the dosing procedure. At each time point, record the following:

- Time: Record hours and minutes
- Ventilator Mode: select the appropriate bubble for conventional mechanical ventilation (CMV) or high frequency ventilation (HFV)
- PIP /  $\Delta$  P: Record either the Positive Inspiratory Pressure for CMV or the Delta Pressure for High Frequency Ventilation
- PEEP: Record Positive End Expiratory Pressure only if the infant is on CMV
- MAP: Record the mean airway pressure. Round up if number fraction is  $\geq$  0.5. (e.g. if 8.5, record 9)
- FiO<sub>2</sub>: Record the fraction of inspired oxygen (x.xx)
- Oxygen saturation: Record percentage

### **Study Drug/Sham Dosing Tolerance within 4 Hours and 24 Hours After Dosing Procedure**

Definitions of adverse events after completion of the dosing/sham procedure are defined by the temporal relationship of the event to the dosing/sham procedure.

**7B.2.a.** Study drug dose/sham intolerance within 4 hours after dosing procedure has been completed

Answer questions in this section Yes or No as appropriate. Indicate if the patient developed any of the following within 4 hours of the study drug/sham dosing procedure:

#### **7B.2.a.i Severe Respiratory Decompensation**

- Defined as an increase in Respiratory Severity Score (RSS)  $>$  5 above pre-dosing baseline and sustained for  $>$ 24 hours. (RSS = FiO<sub>2</sub> x MAP). If Yes, this event will be reported as an SAE. Answer

Questions 13A.3. through 13A.4.a.i on Form 13A. Then complete SAE Form 21.

**7B.2.a.ii. Severe Cardiopulmonary Decompensation**

- Defined as requiring cardiopulmonary resuscitation (CPR) with chest compressions AND cardiac medication(s)\*. If Yes, record an Adverse Event (AE) on AE Form 13A and on SAE Form 21.

[\*Note: Resolution of bradycardia with resumption of normal heart rate after chest compressions, without administration of cardiac medications, should not be recorded as severe cardiopulmonary decomposition. Do not record as an AE or SAE.]

**7A.2.a.iii. Required reintubation**

- Defined as requiring replacement of the endotracheal tube either during dosing or within the 4 hours after dosing.
- If Yes, record an Adverse Event (AE) on AE Form 13A

**7B.2.b.** Study drug dose/sham intolerance within 24 hours after dosing procedure #1 has been completed.

Answer questions in this section Yes or No as appropriate. Indicate if the patient developed any of the following within 24 hours of the study drug/sham dosing procedure

**7B.2.b.i. Severe Pulmonary Interstitial Emphysema**

- PIE is defined as rupture of air from alveoli or small airways into lung perivascular tissues, characterized by lobar, unilateral or bilateral bubbles > 2 mm in size.
- The goal is to score only “real” PIE. PIE which is equivocal or controversial should not be counted. PIE should only be scored if it is seen on more than one CXR. Pneumatoceles should not be counted as PIE.
- Select Yes, if patient had severe PIE as defined above AND radiological diagnosis of PIE consistent with the severe definition on 2 or more chest x-rays before enrollment.
- If Yes is selected, record an Adverse Event on AE Form 13A AND record a SAE on SAE Form 21.
- Select No, if PIE does not meet the definition above.

**7B.2.b.ii. Severe Pulmonary Hemorrhage**

- Severe Pulmonary hemorrhage is defined as frank bleeding. It does not include irritation due to suctioning or infection.

- If Pulmonary Hemorrhage Yes, record an Adverse Event on AE Form 13A AND record a SAE on SAE Form 21.

7B.2.b.iii. Pneumothorax requiring chest tube

- Indicate if the patient developed a spontaneous pneumothorax\* requiring chest tube within twenty-four hours of receiving the study drug.
- If Pneumothorax Yes, record an Adverse Event on AE Form 13A AND record a SAE on SAE Form 21.

**\*Note: Expected pneumothorax with chest tube acquired as a result of clinical interventions such as PDA ligation should be not be recorded as an AE or SAE.**

**\*Note: Severe respiratory decompensation or cardiopulmonary decompensation within 4 hours after study drug/sham dosing; severe pulmonary hemorrhage; pneumothorax requiring a chest tube; and, severe PIE occurring within 24 hours after study drug/sham dosing are considered serious adverse events which require expedited reporting.**

**NOTIFY THE SITE PI AND THE TOLSURF PROJECT DIRECTOR OF ALL SERIOUS ADVERSE EVENTS WITHIN 3 WORKING DAYS. NOTIFY YOUR LOCAL IRB ACCORDING TO INDIVIDUAL IRB REPORTING REQUIREMENTS.**

**NOTE: Unblinded Dosing Tolerance During Study Drug/Sham Dosing Procedure Form**

- This form will be emailed to the site study coordinator when the patient is randomized. The site coordinator should give this form to the unblinded dosing personnel prior to the dosing procedures.
- The form will be completed by the unblinded dosing personnel during the dosing procedure.
- If a patient has significant dosing intolerance\* during the dosing procedure, the unblinded dosing persons who are performing the dosing procedure behind the screen will record the patient's response on the Unblinded Dosing Tolerance Form. Instructions for completion can be found in Respiratory MOP
- The completed form should not be seen by blinded clinical or study personnel. It will be handled separately from the other CRF forms. See MOP Data Management, Section III.2B.1.for detailed instructions.

\*Significant intolerance is defined as:

- Oxygen desaturation <75% for > 60 seconds;
- Bradycardia < 80 for > 60 seconds;
- Re-intubation required.

Contact the Project Director if you have questions about the handling of this form.



## **Forms 8, 9A and 9B: Respiratory Parameters:**

These forms are used to record respiratory support from first study instillation procedure until discharge from the study hospital. Use the following guidelines when entering respiratory data on Forms 8, 9A and 9B.

Each calendar day is indicated by "D01, D02, D03.....etc, and is divided into 8 hour segments. All entries for a given study day should reflect the same calendar date. (eg: study day dates should not cross from one calendar day to another...cross from D01 to D02).

Leading and trailing zeros are not necessary in the respiratory parameter fields.

- Enter date of respiratory parameter selected as recorded in the medical record.
- Enter time of respiratory parameter selected as recorded in the medical record. Note: Time must be recorded in both hours and minutes
- PEEP/CPAP: Record the positive end expiratory pressure (PEEP) or continuous positive airway pressure (NCPAP).
- MAP: Record mean airway pressure for ventilator or NCPAP. Record only whole numbers. Round up if number fraction is  $\geq 0.5$ . (e.g. if 8.5, record 9)
- FiO<sub>2</sub>: Record the fraction of inspired oxygen e.g. .21
- NC Flow LPM: Record nasal cannula flow in liters per minute (x.xx)
- Record iNO delivery in parts per million (PPM)
  - Always make an entry to indicate the parameters on the date the iNO is discontinued. i.e. when iNO PPM = 0
  - After the zero PPM is entered to indicate the end of weaning, it is not necessary to continue recording the iNO level as 0
  - If iNO is restarted, resume recording the iNO PPM level and continue recording until it is discontinued and PPM is recorded again

### Respiratory Status:

Respiratory Status must be recorded until the patient is discharged from the study hospital. Using the key provided at the bottom of Form 5, record the corresponding number to indicate mode of respiratory support.

- 1= CMV: Conventional mechanical ventilation (either pressure or volume pre-set)
- 2= HFV: High Frequency Flow Interrupter (Infrasonics) or High Frequency Jet Ventilation (Bunnell), High Frequency Oscillatory Ventilation (SensorMedics)
- 3= NIMV: Nasal Intermittent Mandatory Ventilation (airway not intubated through vocal cords although patient is receiving mechanical breaths from the ventilator), SiPAP, BiPAP.
- 4= CPAP: Continuous Positive Airway Pressure ONLY
- 5= HFNC or NC > 2 lpm: Nasal cannula with flow > 2 lpm
- 6= O<sub>2</sub> via NC or Oxyhood: Oxygen delivered by nasal cannula at flows  $\leq 2$  lpm or high flow Oxyhood.
- 7= Ext in RA: Extubated and in room air

- When the infant is in room air without any respiratory support, enter Respiratory Code 7. Continue to enter Code 7 until the infant is discharged from the study hospital or respiratory support is resumed.
- It is not necessary to enter FiO<sub>2</sub> of 0.21 when Respiratory Code 7 is entered.
- If a value is missing, you can make a note in the margins about this. Doing this in advance will minimize query calls from the CCC (something you all want to do, I'm sure!).
- For patients who are trached on a trach collar, use code 6 while they are receiving oxygen. Once they have weaned to 21% and have the collar for humidification only, use code 7 (room air).
- For patients who are "sprinting", code the mode they receive for > 50% of the day (> 12 hours)...that is, record what they are on the majority of the day.

## **Form 8: Study Day 0 - 31 Respiratory Parameters (11 pages)**

These forms are used to document the respiratory parameters from study drug dose/sham #1 through Study Day 31. The day the patient receives study drug dose/sham #1 is recorded as Study Day "00". Parameters are recorded every 8 hours (24 hour clock), ideally at 0800, 1600 and 2400. If parameters are not documented at these times, record those closest to these time points. Try to record parameters at the same time points every day. Place first recorded settings in the appropriate time row for that day e.g. infant dosed at 2 pm should have first settings in the 16 hour row because time infant dosed was between 0800 and 1600. Choose settings close to the indicated time. The values written should correspond to documentation in the infant's medical record (ventilator flow sheet or nursing flow sheet/notes). Complete these forms through SD 31.

At top of page – Record date of study entry (should correspond with randomization date on Form 1B). Record all dates as mm/dd/yy.

Hour (HR) and Study Day (SD) will be pre-populated.

## **Form 9A: Study Day 32- 120 Respiratory Parameters (10 pages)**

These pages are used to document the respiratory parameters from Study Day 32 through Study Day 120. Parameters are now recorded only once per day. Try to record parameters at the same time every day, preferably in the morning when the baby is in a quiet, stable state. The values recorded should correspond to documentation in the infant's medical record (ventilator flow sheet or nursing flow sheet/notes. Continue to record daily respiratory data through Study Day 120, or day of discharge..

Record date of study entry at top of page (should correspond with randomization date on Form 1B).

Study Day (SD) will be pre-populated. Record all dates as mm/dd/yy.

It is not necessary to enter FiO<sub>2</sub> of 0.21 when Respiratory Code 7 is entered.

### **9A.1. Indicate if infant is still in study hospital on study day 121.**

- **Do NOT complete this information until page 10.**
- If infant is still in study hospital on day 121, mark "Yes" and proceed to Form 9B to record respiratory parameters from Study Day 121 until discharge from study hospital.
  - **9A.1.a.** At the time of discharge from the study hospital return to Form 9A to indicate the total number of pages of Form 9B completed for this infant.
- If infant is not in hospital on Study Day 121, mark "No" for 9.A.1. Do not enter anything for the 9B number of pages used (leave Null).
  - If "No" is checked, there is no need to send in form 9B.

## **Form 9B: Study Day 121- Discharge Respiratory Parameters (multiple pages)**

This form is used to document the respiratory parameters beyond Study Day 120. Record parameters once a day until patient is discharged from study hospital. Try to record parameters at the same time every day, preferably in the morning when the baby is in a quiet, stable state. The values recorded should correspond to documentation in the infant's medical record (ventilator flow sheet or nursing flow sheet/notes).

Record date of study entry at top of page (should correspond with randomization date on Form 1B). Enter 01 in the Additional Form 9B# fields in the upper right corner of the banner if Form 9B is submitted. Continue numbering sequential form 9B's with "02, 03, 04.....etc"

When all rows on the first page (Form 9B #01) have been completed, indicate at the bottom of Form 9B, whether another page(s) of Form 9B will be needed because patient is not yet discharged.

If patient still hospitalized, select "Yes", and initiate a second Form 9B. Enter "02" in the additional Form 9B Banner fields (upper right corner of the form). Continue sequential numbering for each additional 9B used. Continue this process until the patient is discharged from the study hospital.

**NOTE:** If discharge from the study hospital is after SD 120, return to Form 9A. and enter the total number of Form 9B pages used in **9A.1.a.**

## **Form 10 A: Extubation Data (1 page)**

This form is used to record extubations and reintubations during entire hospitalization in the study hospital. Include extubations and reintubations which occur both before and after study enrollment. **Do not include elective reintubations within 6 hours after self-extubation or elective endotracheal tube changes.**

Extubations resulting from the withdrawal of life support should not be recorded as extubations....patient died intubated.....leave extubation date blank.

Patients who are trached on a ventilator are considered “intubated”. Trached patients who wean to CPAP should be considered “extubated” and the date weaned to CPAP used as extubation date.

**10A.1. Extubation:** Indicate whether patient was extubated.

- Select “Yes” and record the date (mm/dd/yy) and time (24 hour clock) patient was initially (first attempt) extubated (sustained > 6 hours).
- Select “No”, if patient self-extubated, and was reintubated within 6 hours.
- Select” No”, if patient was extubated when support was withdrawn or infant died while on mechanical ventilator.

**10A.2. Was Infant reintubated?**

Select Yes or No.

- If Yes, continue to 10A.3
- If No, skip the rest of this page and proceed to Form 11A.

**10A.3 Record of Reintubation(s)**

**10A.3.a.** Record date and time of first reintubation.

Indicate the date(s) (mm/dd/yy) and times (24 hour clock) infant was reintubated and placed back on mechanical ventilation.

10A.3.a.i. Indicate reason(s) the patient required reintubation.  
Select all that apply.

- Failed nasal CPAP
  - Defined as inability to maintain target  $S_pO_2$  85-94% despite NCPAP > 8 cm, nasal ventilation or high flow nasal cannula > 3 liter per minute with  $FIO_2$  > 0.6
  - $PCO_2$  consistently > 70 mmHg
  - pH consistently < 7.15

- Recurrent or severe apnea and bradycardia (requiring bag and mask ventilation) despite maximal caffeine therapy and NCPAP.
- Surgery requiring reintubation for anesthesia and post operative recovery
  
- Other

10A.3.a.ii. Indicate date and time of second extubation

**10A.3.b.** Record date and time of second reintubation

10A.3.b.i. Indicate reason(s) for reintubation. Select all that apply,

10A.3.b.ii Record date and time of second extubation

**10A.3.c.** Record date and time of third reintubation

10A.3.c.i. Indicate reason(s) for reintubation. See above Select all that apply.

10A.3.c.ii Record date of third extubation

**10A.4. Indicate whether additional reintubations and extubations occur.**

- If “Yes”, continue to document in the same manner on Form 10B.

## **Form 10 B: Additional Extubation Data (1 page)**

**10B.1. Indicate whether or not additional reintubations/extubations will be recorded on this form.**

- If “Yes”, use Form 10B.2 through 10B.2.d.ii.as needed to record additional reintubations and extubations which occur after those recorded on Form 10A. Record dates, times and reasons as per instructions for Form10A.
- If “No” is selected, Form 10B is complete. Proceed to Form 11A.

Note: For those patients who have intubations/extubations that exceed the lines available on 10A and 10B, do the following. In order to allow documentation of the final extubation, do not record one, or more, of the interim extubations/reintubations.

You can continue your current process of recording all intubations/extubations on an additional F10B (used as a worksheet). After the final extubation date is known, transcribe the information to a new Form 10B. Do not record some of the interim extubation/reintubations to allow room to record the final extubation on Form B.



## **Form 11 A: Co-Morbidities of Prematurity Post- Dosing Period (Enrollment to Date of Final Study Dosing Procedure + 7 days)**

Co-morbidities occurring during this period must be reported as adverse events (AEs). Certain AEs may also qualify as serious adverse events (SAEs) if they occurred close to dosing. See SAE definitions and AE/SAE reporting Flow Chart on previous pages (31-32). By definition, SAEs will only occur within this time period from the beginning of dosing to 7 days after the final dose was received.

### **11A.1 Neurologic**

This section is designed to capture information about IVH and cystic PVL related to prematurity.

#### **11A.1.a. IVH**

11A.1.a.i. Indicate whether or not the patient has an IVH

- Select “Yes”, if there is radiographic evidence of IVH
- Select “No”, if there is no radiographic evidence of IVH
- Select “Unknown”, if no HUS, MRI or CT performed in the Dosing Period.

11A.1.a.ii. If Yes, indicate how the IVH was determined. Select all that apply. Mark unknown if MRI, HUS or CT scan have not been done.

11A.1.a.iii. If Yes IVH, indicate if IVH is new or worsened

- If Yes, **new or worsened**, enter the worst grade seen, e.g. if grade is defined as Grade 2-3, use the worst grade (indicate Grade 3).
- Grade definitions
  - Grade 1 or 2: Germinal Matrix Bleed or IVH without dilatation;
  - Grade 3 - 4 (IVH with dilatation or parenchymal bleed). Indicate if unilateral Grade 3 or 4 intracranial hemorrhage occurred.
  - Grade 3 - 4 (IVH with dilatation or parenchymal bleed). Any combination of bilateral IVH Grade 3 and or Grade 4 intracranial hemorrhage.
- Routinely, do not say “worsened” unless the IVH grade range has changed (eg: increased from I-II to III-IV). However, contact CCC, if you have questions.
- If Yes, IVH is new or worsened since enrollment, this is an adverse event. Report the AE on Form 13A, 13.A.8.

#### **11A.1.b. Cystic PVL**

This section is designed to capture information about cystic PVL related to prematurity. Cystic PVL must be confirmed by HUS or MRI during the dosing period.

11A.1.b.i. Indicate whether or not the patient has cystic PVL.

- Select “Yes”, if there is radiographic evidence of cystic PVL
- Select “No”, if there is no radiographic evidence of PVL

- Select “Unknown”, if no HUS, MRI or CT performed in the Dosing Period.

11A.1.b.ii. If “Yes”, indicate how cystic PVL was determined. Select all that apply. Mark unknown if HUS, MRI or CT were not done.

11A.1.b.iii. If Yes, indicate if cystic PVL is **new or worsened**.

- Cystic PVL, new or worsened since enrollment, is an adverse event. Report the AE on Form 13A, 13.9.

NOTE: If patient has diagnosis of porencephalic cysts or encephalomalacia during dosing, record on 13A/B as an “Other AE” with the original diagnosis date.

### **11A.1.c. Hydrocephalus requiring a shunt**

This section is designed to capture information about newly diagnosed hydrocephalus related to prematurity.

- Select “Yes”, if infant developed evidence of hydrocephalus that required shunt placement. Hydrocephalus requiring a shunt is an adverse event. Record the AE on Form 13A, 13A.10.
- Select “No”, if no hydrocephalus occurred or degree of hydrocephalus did not require shunt placement. This “No”, includes infants who require periodic taps to relieve pressure, but no shunt performed.

## **11A.2. Gastrointestinal**

This section is designed to capture information about newly diagnosed necrotizing enterocolitis (NEC) and isolated GI perforation.

### **11A.2.a. NEC**

NEC is defined as pneumatosis, hepato-biliary gas, or pneumoperitoneum AND one or more of the following: bilious gastric aspirate or emesis, abdominal distension, or occult or gross blood in stool not from fissure.

11A.2.a.i. Indicate if infant developed NEC since enrollment.

Select one: Yes, No or Unknown

- Select “No”, if NEC was not diagnosed. (*“RULE OUT” OR “PRESUMED” NEC DO NOT QUALIFY . . . indicate “No” NEC.*)
- Select “Yes”, if NEC (according to above definition) was diagnosed during Dosing Period.
- Select “Unknown”, if it is unclear that NEC was diagnosed. (This should rarely occur. If you are unclear, you should talk with your site PI or attending physician.)

11A.2.a.ii. If “Yes” is selected, enter date of definitive NEC diagnosis. Use this same date for reporting AE on 13A, 13A.11.

11A.2.a.iii. NEC Treatment Outcome

Indicate whether or not there was surgical intervention.

- Select “NEC with Surgery”, if patient had NEC that required surgical intervention (This includes peritoneal drain placement).
- Select “NEC without Surgery”, if patient had NEC that only required medical intervention, no surgery (diagnosed, but treated medically).

11A.2.a.iv. If “NEC with Surgery” selected, enter the date of first surgical intervention performed during Dosing Period.

- Record surgery on Form 14: Hospital Course (14A.2)

### **11A.2.b. Isolated GI Perforation without NEC**

11A.2.b.i. Indicate if infant developed a focal GI Perforation without NEC

- Select “Yes”, if focal GI Perforation occurred that required laparotomy.
- Select “Yes”, if focal GI Perforation occurred that required a peritoneal drain without laparotomy.
- Select “No”, if no GI Perforation occurred.
- Select “Unknown”, if it is unclear that GI Perforation was diagnosed. (This should rarely occur. If you are unclear, you should talk with your site PI or attending physician.

11A.2.b.ii. If GI Perforation is “Yes”, Indicate the date that isolated GI Perforation was diagnosed.

- Enter date of laparotomy or drain placement on Form 14: Hospital Course (14A.2). Date of surgery can be in the dosing or discharge period (if delayed).

### **11A.3. Pulmonary**

This section is designed to capture information about pulmonary co-morbidities related to prematurity during the Dosing Period..

#### **11A.3.a. Severe Pulmonary Interstitial Emphysema (PIE)**

- Severe PIE is defined as rupture of air from alveoli or small airways into lung perivascular tissues, characterized by irregular air filled cysts which are lobar, unilateral or bilateral bubbles > 2 mm in size.
- The goal is to record only severe PIE. PIE which is equivocal or controversial should not be counted.
- Severe PIE should only be recorded if it is seen on more than one CXR.

Select Yes, if patient had severe PIE as defined above AND radiological diagnosis of PIE consistent with the severe definition on 2 or more chest x-rays.

- If “Yes”, this is an adverse event. Record the AE on Form 13A.5.

Select “No”, if infant did not have PIE, or if PIE was only mild or moderate.

11A.3.a.i. If “Yes” PIE, enter date of first chest x-ray with diagnosis of severe PIE. (Diagnosis must be supported by findings of severe PIE on at least one additional chest x-ray).

- If PIE was previously diagnosed pre-enrollment and improved so infant was enrolled, and has now worsened again to meet the definition above, the date will be the new date of diagnosis.

**11A.3.b. Severe Pulmonary Hemorrhage:**

Pulmonary hemorrhage is defined as frank bleeding and does not include irritation due to suctioning or infection.

Indicate whether or not patient had severe pulmonary hemorrhage during Dosing Period.

Select “Yes”, if infant had evidence of pulmonary hemorrhage according to the definition above.

- If “Yes”, this is an adverse event. Record the AE on Form 13A.6.

Select “No”, if infant did not have pulmonary hemorrhage as defined above.

11A.3.b.ii. If “Yes”, enter date of diagnosis of severe pulmonary hemorrhage.

- The date of severe pulmonary hemorrhage diagnosis should be recorded within its respective period.

**11A.3.c. Pneumothorax requiring a chest tube**

Record a pneumothorax only if a chest tube is placed during Dosing Period.

Expected pneumothorax with chest tube acquired as a result of clinical interventions such as PDA ligation should not be recorded as a pneumothorax and should not be recorded as an AE or SAE. If you have questions, contact CCC.

Select “Yes”, if infant had evidence of pneumothorax requiring a chest tube.

- If “Yes”, this is an adverse event. Record the AE on Form 13A.7.

Select “No”, if infant did not have a pneumothorax requiring chest tube placement as defined above.

11A.3.c.i. If “Yes”, enter date of diagnosis of pneumothorax requiring chest tube.

- Date of diagnosis will be the date of chest tube insertion, even if it spans two periods.

**11A.3.d. Tracheomalacia (laryngomalacia, bronchomalacia)**

Indicate if tracheomalacia was diagnosed during Dosing Period.

Select “Yes”, if infant developed evidence of tracheomalacia.

- If “Yes”, this is an adverse event. Record the AE on Form 13A.13.

Select “No”, if infant did not have evidence of tracheomalacia.

11A.3.b.ii. If “Yes”, enter date of diagnosis of tracheomalacia.

**11A.3.e. Tracheal Stenosis**

Indicate if tracheal stenosis diagnosis was diagnosed during Dosing Period.

Select “Yes”, if infant had evidence of tracheal stenosis.

- If “Yes”, this is an adverse event. Record the AE on Form 13A.14.

Select “No”, if infant did not have tracheal stenosis.

11A.3.b.ii. If “Yes”, enter date of diagnosis of tracheal stenosis.

**11A.3.f. Vocal Cord Paralysis**

Indicate if vocal cord paralysis was diagnosed during Dosing Period.

Select “Yes”, if infant had evidence of tracheal stenosis.

- If “Yes”, this is an adverse event. Record the AE on Form 13A.14.

Select “No”, if infant did not have tracheal stenosis.

11A.3.b.ii. If “Yes”, enter date of diagnosis of tracheal stenosis.

**11A.4. Cardiovascular**

This section is designed to capture information about cardiovascular co-morbidities related to prematurity during Dosing Period.

**11A.4.a. PDA Requiring Treatment**

Report PDA if it is present and is treated either medically or surgically, during the Dosing Period.

Select “Yes”, if infant received treatment for PDA during the dosing period.

- If “Yes”, this is an adverse event. Record the AE on Form 13A.15.
- On 13A, record the date treatment occurred in the dosing period.

Select “No”, if infant did not have a treated PDA (No PDA or sub-clinical PDA, not requiring treatment).

If “Yes PDA requiring treatment”, record treatment received:

11A.4.a.i. PDA Treated with Indomethacin or Ibuprofen

- Select “Yes” if infant treated with Indomethacin or Ibuprofen.
- Select “No”, if infant was not treated medically
- Select “Unknown” if it is unclear if infant treated medically.

11A.4.a.ii. Ligation

- Select “Yes” if PDA was ligated during Dosing period.
- Select “No”, if PDA was not ligated during Dosing period
- Select “Unknown” if it is unclear if PDA was ligated.

11A.4.a.iii. If Ligation is “Yes”, record date of surgery

- Also record surgery on Form 14A Hospital Course, 14A.2.

Note: If PDA is recorded on form 4 AND is ongoing during the dosing or discharge period (s), it will NOT be recorded on 11A/B unless new treatment for PDA is given during those time periods.

**11A.4.b. Hypotension**

For this study hypotension is defined as requiring vasopressor support for > 24 hours with one of the following treatment regimens to maintain mean blood pressure within normal limits.

- Dopamine > 20 mcg/kg/min > 24 hours
- Addition of a second vasopressor agent and treated > 24 hours (e.g. treatment with dopamine 10 mcg/kg/min plus dobutamine or hydrocortisone added)
- Caveat to the definition above: If death occurred less than (<) 24h post pressor initiation, and infant required either > 20 mcg/kg/min of Dopamine or 2 pressor agents, you should mark "Yes" for this field.

Do not record as “Hypotension” if the above criteria were not met (e.g. infant is on any Dopamine 20 mcg or less).

Indicate whether the infant had hypotension as defined above. Select one: Yes, No or Unknown.

Select “Yes”, if infant required pressor support as defined above.

Select “No”, if infant did not require pressors or treatment did not meet the definition above.

Select “Unknown”, if unable to determine.

11A.4.b.i. If Hypotension “Yes”, did infant receive Dopamine > 20 mcg/kg/minute for > 24 hours? Select Yes, No, or Unknown.

11A.4.b.ii. If Hypotension “Yes”, did infant receive two or more pressor agents for > 24 hours? Select Yes, No, or Unknown.

- Hydrocortisone is considered a second pressor agent when used in conjunction with dopamine/dobutamine

- Report PDA treatment as defined above as an adverse event. Record the AE on Form 13A, 13A.16.
- If the patient experiences more than one discreet episode of hypotension during the study dosing period + 7 days, record additional episodes on Form 13A as “Other”.

#### **11A.4.c. Pulmonary hypertension**

Defined as elevated pulmonary vascular pressure > systemic pressure resulting in right to left shunting and systemic hypoxemia.

Pulmonary hypertension may be diagnosed clinically or by echo, but should be documented in patient medical progress or cardiology consult notes in medical record during the specific dosing period. If PH is diagnosed in the dosing period, it should be recorded on 11A to document it was present. Dates of diagnosed PH recorded on 11A should fall within the dosing period window. PH should then be recorded on 13A with the date diagnosed during that period.

Indicate if pulmonary hypertension was diagnosed.  
Select one: Yes, No or Unknown.

11A.4.c.i. If “Yes”, indicate how diagnosis of pulmonary hypertension was determined (clinical, echocardiogram, unknown).  
Select all that apply.

11A.4.c.ii. If “Yes”, enter date pulmonary hypertension diagnosis first recorded in medical record by attending physician or cardiologist.

- If Yes, this is an adverse event. Record the AE on Form 13A, 13A.17.

Note: If pulmonary hypertension (PH) is recorded on form 4 AND is ongoing during the dosing or discharge period (s), it will also be recorded on 11A/B with the same pre-enrollment diagnosis date. HOWEVER, these PH episodes that were diagnosed pre-enrollment will not be reported on 13A/B, even if the outcome is death.

#### **11A.5. Culture Proven Sepsis**

Report the following as sepsis:

Record all “episodes of infection” resulting in positive bacterial, fungal or viral cultures from blood, CSF, urine or tracheal aspirate that were treated with antibiotics, antifungal or antiviral agents for  $\geq 7$  days. Our intent is to report each, discreet episode of sepsis, not each time a repeat culture from the same episode, remains positive with the same organism. If a culture with a new organism is identified and treated for  $\geq 7$  days, record on 11A.

**11A.5.a.** Indicate if infant had culture positive sepsis (as defined above) during Dosing Period.  
Select one: Yes, No, or Unknown.

- Mark unknown only if unsure of culture results at previous hospital (if transferred).
- If “Yes”, patient had culture proven sepsis as defined above during Dosing Period, record an adverse event on Form 13A, 13A.23.
- Note: If infant was on antibiotics and death due to sepsis occurred without a) a positive culture or b) antibiotics prior to death were given for < 7 days, please mark “Yes”. Talk with CCC about how to record.

For each positive culture treated for > 7 days:

- Indicate the date specimen was drawn
- Indicate the specimen type (blood, CSF, urine or TA) and
- Indicate the type of organism isolated (bacterial, fungal or viral).

Note: If infant has ongoing treatment (in the dosing period) from sepsis episode that began pre-enrollment, do not record sepsis as “yes” during dosing period, unless a “new” episode of sepsis occurs during the dosing period.

#### **11A.5.b. RSV Pneumonia**

Record RSV infections documented with positive culture (or DFA) from tracheal aspirate or nares. Do not record RSV in section 11A.5a.

Select one: Yes, No, or Unknown.

- Mark unknown only if unsure of culture or DFA results at previous hospital (if transferred).

If “Yes”, record the date of first positive RSV culture collected.

- Also record an adverse event on Form 13A, 13A.28.

#### **11.A.6. Ophthalmologic**

Use this section to record eye exams and results.

**11A.6.a.** Indicate whether or not the patient was examined for retinopathy of prematurity (ROP).

Select Yes, No or Unknown.

Select “Yes”, if exam was performed and proceed to 11A.6.a.i.

Select No if exam was not performed or if patient was transferred back to referring hospital before ROP screening exam was performed. (Information from ROP screening examinations performed after discharge from the study hospital will be captured on Form 16A: Discharge Report, Q16A.5.)

11A.6.a.i. If eye exam “Yes”, indicate worst stage observed in either eye.

- Select No ROP if none was observed
- Select the worst stage ROP observed (Stages 1-5) during Dosing Period.
- ROP classified as Stage 1-5, is reportable as an adverse event. Record the AE on Form 13A.



11A.6.a.ii. Indicate if any surgery was performed for ROP (laser, cryo, etc). Select one: Yes, No or Unknown

11A.6.a.iii. Record the date of surgery. Enter surgery on Form 14 Hospital Course, Q14.A.2

Patients receiving Avastin treatment for ROP should have Avastin treatment date recorded as an "Ophthalmologic Surgery OTHER" on Form 14.

## **Form 11 B: Co-Morbidities of Prematurity - Discharge Period - (8 days after final dosing to Discharge)**

Co-morbidities occurring during this period (final dose + 8 days to discharge) must be reported as adverse events (AEs). AEs that occur during the Discharge Period DO NOT qualify as serious adverse events (SAEs).

### **11B.1. Was infant in study hospital after dosing period + 1 day?**

Select "Yes" if infant remained in study hospital after dosing period.

- If "Yes", continue to answer all questions on Form 11B.
- If "No", Form 11B is complete, proceed to Form 12A.
- If Unknown, look further and decide if "Yes" or "No" . . . ☺

### **11B.2 Neurologic**

This section is designed to capture information about IVH and cystic PVL related to prematurity.

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#### **11B.2.a. IVH**

- Select "Yes", if there is radiographic evidence of IVH
- Select "No", if there is no radiographic evidence of IVH
- Select "Unknown", if no HUS, MRI or CT performed in the Discharge Period.

11B.2.ai. If Yes, indicate how the IVH was determined. Select all that apply. Mark unknown if MRI, HUS or CT scan have not been done.

11B.2.a.ii. If Yes IVH, indicate if IVH is new or worsened

- If Yes, **new or worsened**, enter the worst grade seen, e.g. if grade is defined as Grade 2-3, use the worst grade (indicate Grade 3).
- Grade definitions
  - Grade 1 or 2: Germinal Matrix Bleed or IVH without dilatation;
  - Grade 3 - 4 (IVH with dilatation or parenchymal bleed). Indicate if unilateral Grade 3 or 4 intracranial hemorrhage occurred.
  - Grade 3 - 4 (IVH with dilatation or parenchymal bleed). Any combination of bilateral IVH Grade 3 and or Grade 4 intracranial hemorrhage.
- Routinely, do not say "worsened" unless the IVH grade has changed (increased 1 grade). However, contact CCC, if you have questions.
- If Yes, IVH is new or worsened since enrollment, this is an adverse event. Report the AE on Form 13B, 13.B.7.

#### **11B.2.b. Cystic PVL**

This section is designed to capture information about cystic PVL related to prematurity. Cystic PVL must be confirmed by HUS or MRI during the Discharge period.

Indicate whether or not the patient has cystic PVL.

- Select “Yes”, if there is radiographic evidence of cystic PVL
- Select “No”, if there is no radiographic evidence of PVL
- Select “Unknown”, if no HUS, MRI or CT performed in the Discharge Period.

11B.2.b.i. If “Yes”, indicate how cystic PVL was determined.  
Select all that apply. Mark unknown if HUS, MRI or CT were not done.

11B.2.b.ii. If Yes, indicate if cystic PVL is **new or worsened**.

- Cystic PVL, new or worsened since enrollment, is an adverse event. Report the AE on Form 13B, 13B.8.

NOTE: If patient has diagnosis of porencephalic cysts or encephalomalacia during dosing, record on 13B as an “Other AE” with the original diagnosis date.

### **11B.2.c. Hydrocephalus requiring a shunt**

This section is designed to capture information about newly diagnosed hydrocephalus related to prematurity.

- Select “Yes”, if infant developed evidence of hydrocephalus that required shunt placement. Hydrocephalus requiring a shunt is an adverse event. Record the AE on Form 13B, 13B.9.
- Select “No”, if no hydrocephalus occurred or degree of hydrocephalus did not require shunt placement. This “No”, includes infants who require periodic taps to relieve pressure, but no shunt performed.

### **11B.3. Gastrointestinal**

This section is designed to capture information about newly diagnosed necrotizing enterocolitis (NEC) and isolated GI perforation.

#### **11B.3.a. NEC**

NEC is defined as pneumatosis, hepato-biliary gas, or pneumoperitoneum AND one or more of the following: bilious gastric aspirate or emesis, abdominal distension, or occult or gross blood in stool not from fissure.

11B.3.a.i. Indicate if infant developed NEC during Discharge Period.  
Select one: Yes, No or Unknown

- Select “Yes”, if NEC (according to above definition) was diagnosed during Dosing Period.
- Select “No”, if NEC was not diagnosed. (*“RULE OUT” OR “PRESUMED” NEC DO NOT QUALIFY . . . indicate “No” NEC.*)
- Select “Unknown”, if it is unclear that NEC was diagnosed. (This should rarely occur. If you are unclear, you should talk with your site PI or attending physician.)

11B.3.a.ii. If "Yes" is selected, enter date of definitive NEC diagnosis. Use this same date for reporting AE on 13B, 13B.10.

11B.3.a.iii. NEC Treatment Outcome

Indicate whether or not there was surgical intervention.

- Select "NEC with Surgery", if patient had NEC that required surgical intervention (This includes peritoneal drain placement).
- Select "NEC without Surgery", if patient had NEC that only required medical intervention, no surgery (diagnosed, but treated medically).

11B.3.a.iv. If "NEC with Surgery" selected, enter the date of first surgical intervention performed during Discharge Period.

- Record surgery on Form 14: Hospital Course (14A.2)

**11B.3.b. Isolated GI Perforation without NEC**

11B.3.b.i. Indicate if infant developed a focal GI Perforation without NEC during Discharge Period.

- Select "Yes", if focal GI Perforation occurred that required laparotomy.
- Select "Yes", if focal GI Perforation occurred that required a peritoneal drain without laparotomy.
- Select "No", if no GI Perforation occurred.
- Select "Unknown", if it is unclear that GI Perforation was diagnosed. (This should rarely occur. If you are unclear, you should talk with your site PI or attending physician.

11B.3.b.ii. If GI Perforation is "Yes", Indicate the date that isolated GI Perforation was diagnosed. GI Perforation is an adverse event. Record the AE on Form 13B, 13B.11.

- Enter date of laparotomy or drain placement on Form 14: Hospital Course (14A.2).

**11B.4. Pulmonary**

This section is designed to capture information about pulmonary co-morbidities related to prematurity during the Discharge Period..

**11B.4.a. Severe Pulmonary Interstitial Emphysema (PIE)**

- Severe PIE is defined as rupture of air from alveoli or small airways into lung perivascular tissues, characterized by irregular air filled cysts which are lobar, unilateral or bilateral bubbles > 2 mm in size.
- The goal is to record only severe PIE. PIE which is equivocal or controversial should not be counted.
- Severe PIE should only be recorded if it is seen on more than one CXR.

Select Yes, if patient had severe PIE as defined above AND radiological diagnosis of PIE consistent with the severe definition on 2 or more chest x-rays before enrollment.

- If “Yes”, this is an adverse event. Record the AE on Form 13B.4

Select “No”, if infant did not have PIE, or if PIE was only mild or moderate.

11B.4.a.i. If “Yes” PIE, enter date of first chest x-ray with diagnosis of severe PIE. (Diagnosis must be supported by findings of severe PIE on at least one additional chest x-ray).

- If PIE is diagnosed as described above during current “discharge” period, or if it is ongoing from “dosing” period, enter the original date of diagnosis.
  - Exception will be that if PIE that was previously diagnosed improves or resolves and then worsens again to meet the definition above, the date will be the new date of diagnosis.

#### **11B.4.b. Severe Pulmonary Hemorrhage:**

Pulmonary hemorrhage is defined as frank bleeding and does not include irritation due to suctioning or infection.

Indicate whether or not patient had severe pulmonary hemorrhage during Discharge Period.

Select “Yes”, if infant had evidence of pulmonary hemorrhage according to the definition above.

- If “Yes”, this is an adverse event. Record the AE on Form 13B, 13B.5.

Select “No”, if infant did not have pulmonary hemorrhage as defined above.

11B.4.b.ii. If “Yes”, enter date of diagnosis of severe pulmonary hemorrhage.

- The date of severe pulmonary hemorrhage diagnosis should be recorded within it’s respective period.

#### **11B.4.c. Pneumothorax requiring a chest tube**

Record a pneumothorax only if a chest tube is placed during Discharge Period.

Expected pneumothorax with chest tube acquired as a result of clinical interventions such as PDA ligation should not be recorded as a pneumothorax and should not be recorded as an AE or SAE. If you have questions, contact CCC.

Select “Yes”, if infant had evidence of pneumothorax requiring a chest tube.

- If “Yes”, this is an adverse event. Record the AE on Form 13B, 13B.6.

Select “No”, if infant did not have a pneumothorax requiring chest tube placement as defined above.

11B.4.c.ii. If “Yes”, enter date of diagnosis of pneumothorax requiring chest tube.

- Date if diagnosis will be the date of chest tube insertion, even if it spans two periods.

**11B.4.d. Tracheomalacia(laryngomalacia, bronchomalacia)**

Indicate if tracheomalacia was diagnosed during Discharge Period.

Select “Yes”, if infant developed evidence of tracheomalacia.

- If “Yes”, this is an adverse event. Record the AE on Form 13B, 13B.12.

Select “No”, if infant did not have evidence of tracheomalacia.

11B.4.d.i. If “Yes”, enter date of diagnosis of tracheomalacia.

**11B.4.e. Tracheal Stenosis**

Indicate if tracheal stenosis diagnosis was diagnosed during Discharge Period.

Select “Yes”, if infant had evidence of tracheal stenosis.

- If “Yes”, this is an adverse event. Record the AE on Form 13B, 13B.13.

Select “No”, if infant did not have tracheal stenosis.

11B.4.e.i. If “Yes”, enter date of diagnosis of tracheal stenosis.

**11B.4.f. Vocal Chord Paralysis**

Indicate if vocal chord paralysis was diagnosed during Discharge Period.

Select “Yes”, if infant had evidence of tracheal stenosis.

- If “Yes”, this is an adverse event. Record the AE on Form 13B, 13B.25.

Select “No”, if infant did not have tracheal stenosis.

11B.4.f.i. If “Yes”, enter date of diagnosis of tracheal stenosis.

**11B.5. Cardiovascular**

This section is designed to capture information about cardiovascular co-morbidities related to prematurity during Discharge Period.

### **11B.5.a. PDA Requiring Treatment**

Report PDA if it is present and is treated either medically or surgically, during the Dosing Period.

Select "Yes", if infant received treatment for PDA during the discharge period.

- If "Yes", this is an adverse event. Record the AE on Form 13B, 13B.14.

Select "No", if infant did not have a treated PDA (No PDA or sub-clinical PDA, not requiring treatment).

If "Yes PDA requiring treatment", record treatment received:

#### 11B.5.a.i. PDA Treated with Indomethacin or Ibuprofen

- Select "Yes" if infant treated with Indomethacin or Ibuprofen.
- Select "No", if infant was not treated medically
- Select "Unknown" if it is unclear if infant treated medically.

#### 11B.5.a.ii. Ligation

- Select "Yes" if PDA was ligated during Discharge period.
- Select "No", if PDA was not ligated during Discharge period
- Select "Unknown" if it is unclear if PDA was ligated.

#### 11B.5.a.iii. If Ligation is "Yes", record date of surgery

- Also record surgery on Form 14A Hospital Course, 14A.2.

Note: If PDA is recorded on form 4 AND is ongoing during the dosing or discharge period (s), it will NOT be recorded on 11A/B unless new treatment for PDA is given during those time periods.

### **11B.5.b. Hypotension**

For this study hypotension is defined as requiring vasopressor support for > 24 hours with one of the following treatment regimens to maintain mean blood pressure within normal limits.

- Dopamine > 20 mcg/kg/min > 24 hours
- Addition of a second vasopressor agent and treated > 24 hours (e.g. treatment with dopamine 10 mcg/kg/min plus dobutamine or hydrocortisone added)
- Caveat to the definition above: If death occurred less than (<) 24h post pressor initiation, and infant required either > 20 mcg/kg/min of Dopamine or 2 pressor agents, you should mark "Yes" for this field.

Do not record as "Hypotension" if the above criteria were not met (e.g. infant is on any Dopamine 20 mcg or less)

Indicate whether the infant had hypotension as defined above during the Discharge period. Select one: Yes, No or Unknown.

Select "Yes", if infant required pressor support as defined above.  
Select "No", if infant did not require pressors or treatment did not meet the definition above.  
Select "Unknown", if unable to determine.

11B.5.b.i. If Hypotension "Yes", did infant receive Dopamine > 20 mcg/kg/minute for > 24 hours? Select Yes, No, or Unknown.

11B.4.b.ii. If Hypotension "Yes", did infant receive two or more pressor agents for > 24 hours? Select Yes, No, or Unknown.

- Hydrocortisone is considered a second pressor agent when used in conjunction with dopamine/dobutamine
- Report PDA treatment as defined above as an adverse event. Record the AE on Form 13B, 13B.15.
- If the patient experiences more than one discreet episode of hypotension during the study dosing period + 7 days, record additional episodes on Form 13A as "Other".

### **11B.5.c. Pulmonary hypertension**

Defined as elevated pulmonary vascular pressure > systemic pressure resulting in right to left shunting and systemic hypoxemia.

Pulmonary hypertension may be diagnosed clinically or by echo, but should be documented in patient medical progress or cardiology consult notes in medical record during the specific dosing period. If PH is diagnosed in the discharge period, it should be recorded on 11B to document it was present. Dates of diagnosed PH recorded on 11B should fall within the discharge period window. PH should then be recorded on 13B with the date diagnosed during that period.

Indicate if pulmonary hypertension was diagnosed.  
Select one: Yes, No or Unknown.

11B.5.c.i. If "Yes", indicate how diagnosis of pulmonary hypertension was determined (clinical, echocardiogram, unknown).  
Select all that apply.

11B.5.c.ii. If "Yes", enter date pulmonary hypertension diagnosis first recorded in medical record by attending physician or cardiologist.

- If Yes, this is an adverse event. Record the AE on Form 13B, 13B.16.

Note: If pulmonary hypertension (PH) is recorded on form 4 AND is ongoing during the dosing or discharge period (s), it will also be recorded on 11A/B with the same pre-enrollment diagnosis date. HOWEVER, these PH episodes that were diagnosed pre-enrollment will not be reported on 13A/B, even if the outcome is death.



### 11.B.6. Ophthalmologic

Use this section to record eye exams and results.

**11B.6.a.** Indicate whether or not the patient was examined for retinopathy of prematurity (ROP).

Select Yes, No or Unkown.

Select "Yes", if exam was performed and proceed to 11A.6.a.i.

Select "No" if exam was not performed or if patient was transferred back to referring hospital before ROP screening exam was performed. (Information from ROP screening examinations performed after discharge from the study hospital will be captured on Form 16A: Discharge Report, Q16A.5.)

11B.6.a.i. If eye exam "Yes", indicate worst stage observed in either eye.

- Select "No ROP" if none was observed
- Select the worst stage ROP observed (Stages 1-5) during Discharge Period.
- ROP classified as Stage 1-5, is reportable as an adverse event. Record the AE on Form 13B, 13B.18.

11B.6.a.ii. Indicate if any surgery was performed for ROP (laser, cryo, etc). Select one: Yes, No or Unknown

11B.6.a.iii. Record date of surgery. Enter surgery on Form 14 Hospital Course, Q14.A.2

Patients receiving Avastin treatment for ROP should have Avastin treatment date recorded as an "Ophthalmologic Surgery OTHER" on Form 14.

### 11A.7. Culture Proven Sepsis

Report the following as sepsis:

Record all "episodes of infection" resulting in positive bacterial, fungal or viral cultures from blood, CSF, urine or tracheal aspirate that were treated with antibiotics, antifungal or antiviral agents for  $\geq 7$  days. Our intent is to report each, discreet episode of sepsis, not each time a repeat culture from the same episode, remains positive with the same organism. If a culture with a new organism is identified and treated for  $\geq 7$  days, record on 11B.

**11B.7.a.** Indicate if infant had culture positive sepsis (as defined above) during Discharge Period.

Select one: Yes, No, or Unknown.

- Mark unknown only if unsure of culture results at previous hospital (if transferred).
- If "Yes", patient had culture proven sepsis as defined above during Discharge Period, record an adverse event on Form 13B,, 13B.19.
- Note: If infant was on antibiotics and death is recorded as due to sepsis but there was a) no positive culture or b) antibiotics prior to death were given for  $< 7$  days, please mark "Yes". Talk with CCC about how to record.

For each positive culture treated for > 7 days:

- Indicate the date specimen was drawn
- Indicate the specimen type (blood, CSF, urine or TA) and
- Indicate the type of organism isolated (bacterial, fungal or viral).

Note: If infant has ongoing treatment (in the discharge period) from sepsis episode that began in the dosing period, do not record sepsis as “yes” during discharge period, unless a “new” episode of sepsis occurs during the discharge period.

**11B.8.b. RSV Pneumonia**

Record RSV infections documented with positive culture (or DFA) from tracheal aspirate or nares. Do not record RSV in sepsis section 11B.7.a.

Select one: Yes, No, or Unknown.

- Mark unknown only if unsure of culture or DFA results at previous hospital (if transferred).

11B.8.b.i. If “Yes”, record the date of first positive RSV culture collected.

- Also record an adverse event on Form 13B, 13B.24.
- If RSV is diagnosed during dosing period and continues into discharge period record “yes” in each period, but record the date of original diagnosis (13A onset date) in 11B/13B.

## **Form 12A BPD Outcomes – 36 weeks PMA (1 page)**

**Determination of BPD status (YES or NO) at 36 weeks  $\pm$  1 week PMA<sup>\*\*\*</sup> is the primary outcome for the TOLSURF Study.**

**When the patient is no longer in your hospital, you should attempt to contact the patient's home or transfer hospital to record respiratory status at 36 weeks. Status at 36 weeks is the primary outcome of the study. Every effort should be made to obtain this information.**

**12A.1. Record date the patient reaches 36 weeks PMA.** Record this information from the actual 36 week PMA date.

- Record the patient's weight and oxygen saturation recorded on that date.<sup>\*\*\*</sup>
- Record the most recent PCO<sub>2</sub> obtained prior to the 36 week PMA date.

<sup>\*\*\*</sup> If you do not have a patient weight on the exact 36-week PMA date, and the patient is still hospitalized, enter the date of the weight obtained closest to 36 weeks PMA.

<sup>\*\*\*</sup> If the patient is discharged earlier than 36 weeks and you cannot contact the family, you should still enter the actual 36 week PMA date. You can use the weight at discharge if it is within 2 weeks of the 36 week date. Also record SpO<sub>2</sub> and the PCO<sub>2</sub> nearest the discharge date (must be within 2 weeks of discharge).

Note: The date for recording the 36-week PMA data should be calculated according to gestational age recorded on Form 1B. If a range is estimated for gestational age, use the lower end of the range. For example, 27-28 weeks should be rounded off to 27 weeks 0 days.

Calculation of 36 weeks PMA Date:

- Using a calendar begin counting on the date of birth using the known gestation (include completed weeks only).
- Count out by weeks until you get to 36 weeks. This is the 36 week PMA date. Example:

Example: If date of birth is 3.24.04 and gestational age is 27 weeks 5 days, then counting forward 9 weeks (36 – 27 = 9) the PMA date is 5.26.04.

### **12A.2. Infant status when 36 weeks PMA ( $\pm$ 1 week).**

Indicate patient's location on the 36 week PMA  $\pm$  1 week date.

Select one option.

- Select Home if patient has been discharged and is at home.
- Select Still in Study Hospital if infant is still an inpatient in a participating study hospital
- Select Transferred to other facility if patient has been transferred from study site hospital(s) to another facility; another tertiary hospital (not a study site); home hospital or rehabilitation center.
- Select Dead if patient expired on or before this date.

- Select dead if patient expired on or before this date. Select BPD “Unknown” for 12A.3.iii. Complete Form 17: Death Report. Skip sections 12B.2.a through 12B.3.iii. Ask PI to complete section 12B.4., sign and initial.

**12A.2.a.** If the patient is alive, indicate status of respiratory support at 36 weeks PMA ( $\pm 1$  week). Be sure to follow and monitor infant respiratory status until end of monitor period (36 + 1 week), in case status changes. Select appropriate bubble to indicate respiratory status on the actual date you evaluate the patient for BPD.

- **Select off continuous respiratory support**, If patient is off all respiratory support (i.e. off CPAP, off supplemental oxygen, off nasal cannula), **Go to Q12A.3.ii. Mark No BPD.**
- **Select mechanical ventilation**, If patient is on conventional or high frequency ventilation (Patient is not eligible for oxygen/flow reduction challenge testing). **Go to Q12A.3.i. Mark Yes BPD.**
- **Select SiPAP, BiPAP or nasal prong ventilation**, if patient is receiving continuous non-invasive bi-level positive airway pressure respiratory support. (Patient is not eligible for oxygen/flow reduction challenge testing) **Go to Q12A.3.i. Mark Yes BPD.**
- **Select nasal CPAP**, if patient is on any continuous single level non-invasive positive airway pressure or nasal cannula flow  $> 4$  lpm (if in room air). (Patient is not eligible for oxygen/flow reduction challenge testing) **Go to Q12A.3.i. Mark Yes BPD.**
- **Select continuous nasal cannula  $>2$  lpm on any oxygen**, if patient requires nasal cannula flows greater than 2 liters and any supplemental oxygen, (Patient is not eligible for oxygen/flow reduction challenge testing) **Go to Q12A.3.i. Mark Yes BPD.**
- **Select continuous nasal cannula  $\leq 2$  lpm flow with oxygen or  $\leq 4$  lpm in room air**, for all those patients who are in low-flow oxygen ( $\leq 2$ lpm) or room air nasal cannula ( $\leq 4$  lpm) These patients need further evaluation to determine BPD status. They should be evaluated for eligibility to receive the O<sub>2</sub>/flow reduction challenge test. Determine the effective oxygen (see MOP Section I-9.0). If effective oxygen is  $\leq 0.30$ , the patient is eligible for oxygen/flow reduction challenge testing.

[Note: The flow definitions for nasal cannula hold, regardless of the device used that is humidified or non-humidified.]

[Note: If the patient has been off all respiratory support for  $\geq 7$  days in the study hospital prior to transfer to the convalescent hospital (OH), and respiratory support is resumed at OH (e.g. nasal cannula oxygen), the

patient should be coded as NO BPD at 36 weeks PMA on Form 12A, regardless of the respiratory support received at the OH.]

[NOTE: If a patient is trached and on positive pressure, mark bubble for appropriate mode of positive pressure being delivered (vent, CPAP, SiPAP).

- However, if the Infant is trached and on supplemental O<sub>2</sub> by trach collar or mask, mark “continuous nasal cannula  $\leq$  2 lpm” and follow arrow to indicate the FiO<sub>2</sub> and literflow (indicate liter flow as 9.99, if 10 or above). Talk with attending physician about appropriateness of doing challenge.
- If the infant is in room air trach mask and only needs the flow for humidity, mark this infant as being in room air “off all support”.]

The oxygen/flow reduction challenge test should be performed on all eligible babies at 36 weeks ( $\pm$  1 week) PMA to determine need for continued respiratory support.

Note: If you miss the window for performing the challenge test

12A.2.a.i. This section is used to document patient eligibility for being challenged with the oxygen/flow reduction test. The patient must be receiving effective oxygen  $\leq$  0.30 (30%) to be eligible for testing. Refer to Oxygen/flow Challenge Procedure f instructions for determining effective oxygen ( MOP Section I , 9.0).

- Enter FiO<sub>2</sub> and liters per minute flow that patient is receiving via nasal cannula.
- Enter effective oxygen calculated using the weight from 12.A.1. and Tables 1 and 2 in the Oxygen/Flow Reduction Challenge procedure.
- Enter unknown if it is not possible to determine the effective oxygen.

12A.2.a.ii. Indicate whether effective oxygen is  $\leq$  0.30 (30%).

- If No, (effective oxygen  $>$  0.30) this patient is not eligible for testing. **Go to Q12A.3.i. Mark Yes BPD.** Select first bubble indicating effective oxygen  $\geq$  0.30.
- If Yes, go to 12A.2.a.iii

12A.2.a.iii. If the patient qualified for testing, indicate if oxygen/flow reduction challenge test was performed at 36 weeks ( $\pm$  1 week) PMA. Select Yes, No or Unknown.

[Note: Prior to testing, notify the attending physician that the patient is due to be tested. Obtain an order to perform the oxygen/flow reduction challenge

[Note: Refer to Oxygen/flow challenge procedure in MOP Section I, 9.0. and follow testing procedure. Use Oxygen/flow challenge data collection worksheet to record raw data during testing procedure (see MOP Appendix IV.). Do not fax the worksheet forms to the DCC. Keep these forms with patient’s study records.]

Select "Yes", if oxygen challenge completed  
**Go to 12.A.2.a.iv.**

Select "No", if oxygen challenge not completed  
**Go to 12.A.2.a.vi.**

Select "Unknown" if you cannot determine if oxygen challenge completed  
**Go to 12.A.3.iii.**

12A.2.a.iv. If Yes, oxygen/flow challenge test was performed, enter date performed (eligible date range is 36-week PMA date  $\pm$  7 days.

12A.2.a.v. Enter result of challenge test.  
Select one:      Passed (Go to 12A.3.ii)  
                         Or  
                         Failed (Go to 12A.3.i)

[Note: If testing was performed, but not as indicated during the 36 weeks ( $\pm$  1 week) PMA interval, this is a protocol violation. Record on Form 19 Protocol Violation: Failure to perform oxygen/flow reduction test as indicated.]

12A.2.a.vi. If oxygen challenge test was not performed, mark the bubble indicating reason test was not done. Select one of the following:

- Select "Not eligible", if testing was not done because the patient did not qualify for testing.
- Select "Infant at non-study facility", if infant has been transferred to another hospital, or rehab center, or other facility
- Select "Infant discharged home", if infant has been discharged home to parents/foster care.
- Select "Eligible (instudy hospital), but not done" if testing was not done (for any reason) when infant is eligible for challenge and remains in study hospital. Call the CCC Project Director for discussion. This is a serious protocol deviation. Complete a deviation (18.2.a.) and **Go to 12A.3.i.**

### **12A.3. BPD STATUS WHEN 36 WEEKS PMA ( $\pm$ 1 WEEK) FOR SURVIVORS**

Select only one:

- 12A.3.i. Select "Yes BPD" if appropriate and select one qualifying criterion.  
OR
- 12A.3.ii. Select "No BPD" if appropriate and select one qualifying criterion.  
OR

- 12A.3.iii. Mark is BPD status information is unavailable or unknown. This choice should rarely be used if patient survives. If patient expires prior to 36 weeks PMA, mark BPD Status as “Unknown”

[NOTE: If the patient is coded as “Yes BPD” at 36 weeks PMA, he/she should be re-tested at 40 weeks PMA - if still hospitalized in the study hospital and eligible for testing.]

[NOTE: If the patient was coded No BPD at 36 weeks, he/she will remain coded as No BPD at 40 weeks, even if receiving respiratory support. The oxygen/flow reduction challenge test will not be repeated at 40 weeks for patients who were coded as No BPD at 36 weeks PMA.]

[NOTE: If an infant has been on room air without respiratory support for  $\geq 7$  days at study Hospital, is then transferred to a referral center off respiratory support prior to 36 or 40 weeks PMA, will be considered “no BPD” regardless of the level of respiratory support infant is receiving at referral center on 36 or 40 week date.]

**12A.4. Study site PI must review determination of BPD outcome.** Give Form 12A to PI for review. Obtain PI signature and initials.

Mark bubbles to indicate that Form 12A was reviewed, signed and initialed by PI.

If the patient was transferred to a convalescent hospital or discharged home, the PI or site study coordinator should make every effort to determine the amount of respiratory support, if any, the baby is receiving at the 36 and 40 week PMA time points.

- Be sure to fill-in BPD Status bubble, indicating it has been reviewed by PI
- Have PI sign form indicating agreement on BPD status.
- Indicate whether PI signed form “Yes” or “No”
- Insert I initials.

## **Form 12B BPD Outcomes – 40 weeks PMA (2 pages)**

Evaluation of respiratory status is performed again at 40 weeks ( $\pm$  1 week) PMA. If the patient was coded as YES BPD at 36 weeks PMA and remains hospitalized in the study hospital, all of 12B needs to be completed. If patient was coded as NO BPD at 36 weeks, patient will be recorded as NO BPD at 40 weeks and only minimal data at 40 weeks is recorded. Form 12B must be submitted for all patients regardless of whether they remain in the study hospital, are discharged to home or transferred, at 40 weeks PMA.

### **12B.1. Record the Date, Weight, SpO<sub>2</sub> and PCO<sub>2</sub> when 40 weeks PMA**

12B.1.a. Record date the patient reaches 40 weeks PMA for all patients. Record this information from the actual 40 week PMA date. Record the patient's weight on that date.\*\*\*

12B.1.b. Record the patient's weight and oxygen saturation recorded on the 40 week PMA date.\*\*\*

12B.1.c. Record the patient's oxygen saturation recorded on the 40 week PMA date.\*\*\*

12B.1.d. Record the most recent PCO<sub>2</sub> obtained prior to the 40 week PMA date (record only if drawn in the past 2 weeks, otherwise leave Null).

\*\*\* If you do not have a patient weight on the exact 40-week PMA date, and the patient is still hospitalized, enter the date of the weight obtained closest to 40 weeks PMA.

\*\*\*If the patient is discharged earlier than 40 weeks, you should still enter the **actual 40 week PMA date**. You can use the weight at discharge if it is within 2 weeks of the 40 week date. Also record the SpO<sub>2</sub> and the PCO<sub>2</sub> nearest the discharge date (must be within 2 weeks of discharge).

Note: The date for recording the 40 week PMA data should be calculated according to gestational age recorded on Form1B. If a range is estimated for gestational age, use the lower end of the range. For example, 27-28 weeks should be rounded off to 27 weeks 0 days. Calculation of 40 weeks PMA date:

- Using a calendar begin counting on the date of birth using the known gestation (include completed weeks only).
- Count out by weeks until you get to 40 weeks. This is the 40 week PMA date. Example:
  1. Date of birth is 3.24.10 and gestational age is 27 weeks 5 days
  2. Counting forward 9 weeks (40 – 27 = 13) the PMA date is 5.26.10.

**If the patient was transferred to a convalescent hospital or discharged home, the PI or site study coordinator should make every effort to determine the amount of respiratory support, if any, the baby is receiving at the 40 week PMA time point.**



**If the patient is no longer in your hospital, contact the patient's home or transfer hospital to record respiratory status at 40 weeks. Status at 40 weeks is the primary outcome of the study. Every effort should be made to obtain this information.**

## **12B.2 Infant status when 40 weeks PMA ( $\pm$ 1 week)**

Indicate patient's location on the 40 week PMA ( $\pm$  1 week) date. Select one option.

- Select Home if patient has been discharged to home or foster care.
- Select Still in Study Hospital if infant is still an inpatient in a participating study hospital.
- Select Transferred to other facility if patient has been transferred from study site hospital(s) to another facility; another tertiary hospital (not a study site); home hospital or rehabilitation center.
- Select dead if patient expired on or before this date. Select BPD "Unknown" for 12B.3.iii. Complete Form 17: Death Report. Skip sections 12B.2.a through 12B.3.iii. Ask PI to complete section 12B.4., sign and initial.

### **12B.2.a.** Indicate if patient was had BPD at 36 weeks PMA.

- If patient was coded as Yes BPD at 36 weeks, select Yes and go to Q12B.2.b.
- If patient was coded NO BPD at 36 weeks, select No and go to Q12B.3.ii. (Skip sections 12B.2.b. – 12B.2.b.vi.)
- If patient was coded as Unknown BPD at 36 weeks, select Unknown and go to Q12B.3.iii. (Skip sections 12B.2.b. – 12B.2.b.vi.)
  - If patient's respiratory support status is unknown, go to 12B.3.iii. and mark unknown.

### **12B.2.b.** Respiratory status when 40 weeks ( $\pm$ 1 week) PMA

For surviving patients who were coded as Yes BPD at 36 weeks PMA, indicate status of respiratory support at 40 weeks PMA ( $\pm$  1 week). Be sure to follow and monitor infant respiratory status until end of monitor period (40 + 1 week), in case status changes. Select only one bubble to indicate respiratory status on the actual date you evaluate the patient.

- **Select off continuous respiratory support**, If patient is off all respiratory support (i.e. off CPAP, off supplemental oxygen, off nasal cannula), **Go to Q12B.3.ii. Mark No BPD.**
- **Select mechanical ventilation**, If patient is on conventional or high frequency ventilation (Patient is not eligible for oxygen/flow reduction challenge testing). **Go to Q12B3.i. Mark Yes BPD.**

- **Select SiPAP, BiPAP or nasal prong ventilation**, if patient is receiving continuous non-invasive bi-level positive airway pressure respiratory support. (Patient is not eligible for oxygen/flow reduction challenge testing) **Go to Q12B.3.i. Mark Yes BPD.**
- **Select nasal CPAP**, if patient is on any continuous single level non-invasive positive airway pressure or nasal cannula flow > 4 lpm (if in room air). (Patient is not eligible for oxygen/flow reduction challenge testing) **Go to Q12B.3.i. Mark Yes BPD.**
- **Select continuous nasal cannula >2 lpm on any oxygen**, if patient requires nasal cannula flows greater than 2 liters and any supplemental oxygen, (Patient is not eligible for oxygen/flow reduction challenge testing) **Go to Q12B.3.i. Mark Yes BPD.**
- **Select continuous nasal cannula  $\leq$  2 lpm flow with oxygen or  $\leq$  4 lpm in room air**, for all those patients who are in low-flow oxygen ( $\leq$  2lpm) or room air nasal cannula ( $\leq$  4 lpm) These patients need further evaluation to determine BPD status. They should be evaluated for eligibility to receive the O<sub>2</sub>/flow reduction challenge test. Determine the effective oxygen (see MOP Section I-9.0). **If effective oxygen is  $\leq$ 0.30, the patient is eligible for oxygen/flow reduction challenge testing.**

[Note: The flow definitions for nasal cannula hold, regardless of the device used that is humidified or non-humidified.]

[Note: If the patient has been off all respiratory support for  $\geq$  7 days in the study hospital prior to transfer to the convalescent hospital (OH), and respiratory support is resumed at OH (e.g. nasal cannula oxygen), the patient should be coded as NO BPD at 36 weeks PMA on Form 12A, regardless of the respiratory support received at the OH.]

[NOTE: If a patient is trached and on positive pressure, mark bubble for appropriate mode of positive pressure being delivered (vent, CPAP, SiPAP).

- However, if the Infant is trached and on supplemental O<sub>2</sub> by trach collar or mask, mark “continuous nasal cannula  $\leq$  2 lpm” and follow arrow to indicate the FiO<sub>2</sub> and literflow (indicate liter flow as 9.99, if 10 or above). Talk with attending physician about appropriateness of doing challenge.

- If the infant is in room air trach mask and only needs the flow for humidity, mark this infant as being in room air “off all support”.]

[NOTE: If a patient is trached and on positive pressure, mark bubble for appropriate mode of positive pressure being delivered (vent, CPAP, SiPAP).

- However, if the Infant is trached and on supplemental O<sub>2</sub> by trach collar or mask, mark “continuous nasal cannula  $\leq$  2 lpm” and follow arrow to indicate the FiO<sub>2</sub> and literflow (indicate liter flow as 9.99, if 10 or above). Talk with attending physician about appropriateness of doing challenge.

- If the infant is in room air trach mask and only needs the flow for humidity, mark this infant as being in room air “off all support”.]

To determine need for continued respiratory support, the oxygen/flow reduction challenge test should be performed on all babies who were coded as YES BPD at 36 weeks PMA and remain in the study hospital at 40 weeks ( $\pm$  1 week) PMA, and are eligible for testing.

12B.2.b.i. This section is used to document patient eligibility for being challenged with the oxygen/flow reduction test. The patient must be receiving effective oxygen  $\leq$  0.30 (30%) to be eligible for testing. Refer to Oxygen/flow Challenge Procedure f instructions for determining effective oxygen ( MOP Section I , 9.0).

- Enter FiO<sub>2</sub> and liters per minute flow that patient is receiving via nasal cannula.
- Enter effective oxygen calculated using the weight from 12.A.1. and Tables 1 and 2 in the Oxygen/Flow Reduction Challenge procedure.
- Enter unknown if it is not possible to determine the effective oxygen.

12B.2.b.ii. Indicate whether effective oxygen is  $\leq$  0.30 (30%).

- If No, (effective oxygen > 0.30) this patient is not eligible for testing. **Go to Q12B.3.i. Mark Yes BPD.** Select first bubble indicating effective oxygen  $\geq$  0.30.
- If Yes, go to 12A.2.a.iii

12B.2.a.iii. If the patient qualified for testing, indicate if oxygen/flow reduction challenge test was performed at 36 weeks ( $\pm$  1 week) PMA. Select Yes, No or Unknown.

Select “Yes”, if oxygen challenge completed  
**Go to 12.B.2.b.iv.**

Select “No”, if oxygen challenge not completed  
**Go to 12.B.2.b.vi.**

Select “Unknown” if you cannot determine if oxygen challenge completed  
**Go to 12.B.3.iii.**

[Note: Prior to testing, notify the attending physician that the patient is due for testing. Obtain an order to perform the oxygen/flow reduction challenge test.]

[Note: Refer to Oxygen/flow challenge procedure in MOP Section I, 9.0 and follow the testing procedure. Use Oxygen/flow challenge data collection forms (Appendix IV) to record raw data during testing procedure. Record final pass/fail result on last page of data forms. Do not fax these forms to the DCC. File these forms with patient’s study records.]

12B.2.b.iv. If Yes, the oxygen/flow challenge test was performed on appropriate date, enter date the test was performed (eligible date range is 40-week PMA date  $\pm$  7 days.)

12B.2.b.v. Enter result of challenge test.

Select one: Passed (Go to 12B.3.ii)

Or

Failed (Go to 12B.3.i)

[Note: If testing was performed, but not as indicated during the 36 weeks ( $\pm$  1 week) PMA interval, this is a protocol violation. Record on Form 19 Protocol Violation: Failure to perform oxygen/flow reduction test as indicated.]

12B.2.b.vi. If oxygen challenge test was not performed, mark the bubble indicating reason test was not done. Select one of the following:

- Select “Not eligible”, if testing was not done because the patient did not qualify for testing and **Go to 12B.3.i.**
- Select “Infant at non-study facility”, if infant has been transferred to another hospital, or rehab center, or other facility and **Go to 12B.3.i.**
- Select “Infant discharged home”, if infant has been discharged home to parents/foster care and **Go to 12B.3.i.**
- Select “Eligible (in study hospital), but not done” if testing was not done (for any reason) when infant is eligible for challenge and remains in study hospital. Call the CCC Project Director for discussion. This is a serious protocol deviation. Complete a deviation (18.2.a.) and **Go to 12B.3.i.**

[NOTE: If an infant has been on room air without respiratory support for  $\geq$  7 days at study Hospital, is then transferred to a referral center off respiratory support prior to 40 weeks PMA, will be considered “no BPD” regardless of the level of respiratory support infant is receiving at referral center on 40 week date.]

### **12B.3. BPD STATUS WHEN 40 WEEKS PMA ( $\pm$ 1 WEEK) FOR SURVIVORS.**

Select only one:

- 12B.3.i. Yes BPD and select one qualifying criterion.  
OR
- 12B.3.ii. No BPD and select one qualifying criterion.  
OR
- 12B.3.iii. Mark “BPD status information is unavailable or unknown”. This choice should rarely be used if patient survives. If patient expires prior to 40 weeks PMA, mark BPD Status as “Unknown”

**12B.4 PI must review determination of BPD outcome.** Give form 12B to PI for review. Obtain PI signature and initials. Mark bubbles to indicate that Form 12B was reviewed, signed and initialed by PI.

- Be sure to fill-in BPD Status bubble, indicating it has been reviewed by PI
- Have PI sign form indicating agreement on BPD status.
- Indicate whether PI signed form “Yes” or “No”  
Insert initials.

## **Form 13A: Adverse Events Post-Enrollment to Date of Final Dosing Procedure + 7 days (6 pages)**

This form is used to record a summary listing of all adverse events which are newly diagnosed (or in the case of IVH, cystic PVL or severe PIE are new or become worsened) in the period between enrollment and 7 days after the final study drug dosing procedure.

- Adverse events should be recorded as they occur throughout hospitalization in the study hospital.
- Form 13A must be completed for all infants. This summary log of adverse events should be submitted by the sites to the DCC within 2 weeks after the date of the final dosing procedure + 7 days.

Specific co-morbidities of prematurity are pre-printed on Form 13A. These should be recorded as AEs if they occur (or in the case of IVH, cystic PVL or severe PIE, become worsened), during this time period. If additional AEs occur, record them on the lines specifying "Other". Do not record common, expected events such as apnea of prematurity, anemia of prematurity, electrolyte imbalance, temperature instability, gastro-intestinal reflux, etc.

**Selected adverse events (AEs) which are both severe and occur in specified time periods surrounding study drug/sham dosing procedures will also qualify as serious adverse events (SAEs). SAEs should be recorded on both Form 13A and Form 21: Serious Adverse Events.**

The following are defined as serious adverse events:

- **Death occurring between enrollment and  $\leq 7$  days after a study drug/sham dosing is an SAE.** This requires expedited reporting within 72 hours (3 working days).
- **Events listed below beginning  $\leq 4$  hours of a study drug/sham dosing procedure are SAEs.** Report these to the CCC PD within 7 working days.
  - Severe respiratory decompensation defined as increase in respiratory severity score (RSS)  $> 5$  above baseline sustained for  $> 24$  hours (RSS = FIO<sub>2</sub>x MAP).
  - Severe cardiopulmonary decompensation requiring CPR with chest compressions and cardiac medications
- **Events below beginning within 24 hours of a study drug/sham dosing procedure are SAEs.** Report these to the CCC PD within working 7 days.
  - Severe pulmonary hemorrhage
  - Severe PIE
  - Pneumothorax requiring a chest tube

*If the above events occur within the time periods described, they must also be recorded on Form 21: Serious Adverse Events. Each SAE should be recorded on an individual Form 21. When the first SAE is recorded, enter the SAE # 01 in the upper right corner of the banner in the SAE# field. Subsequent SAEs should be reported on additional Forms 21. Enter sequential SAE form numbers in the upper right corner SAE# field, e.g. 02 for the second SAE*

reported, 03 for the third, etc. These numbers should be recorded where requested on form 13A.

If the above events occur outside of the time periods described, the events are not defined as SAEs. They should be reported only as AEs on Form 13A.

**13A.1. Have any adverse events listed on co-morbidities Form 11A, pages 1-6 been newly diagnosed (or in the case of IVH, cystic PVL or severe PIE, become worsened), since enrollment?** If Yes is selected, document the AE(s) on the appropriate lines 13A.3 -13A.29

### **13A.2. Death**

Mark "Death" bubble if death occurred between study enrollment date of final dosing procedure performed + 7 days.

**13A.2.a.** Death occurred  $\leq$  7 days after study drug/sham dosing.

Select Yes, if death occurred  $\leq$  7 days after study drug/sham dosing. Also complete Forms 17 and Form 21. Report to the CCC and DCC within 3 working days.

Select "No". NO, DO NOT SELECT "NO". This is leftover from an earlier version of the dataforms. By definition, if the death bubble is filled in, 13A.2.a has to be "Yes".

- If a death occurs  $>$  7 days after final study drug/sham dosing procedure, the death occurred during the Discharge Period and should not be recorded on this form 13A. It should be recorded on 13B, and therefore is not reportable as a SAE.

### **13A.3. Was there Severe Respiratory Decompensation?**

Mark "Severe respiratory decompensation" bubble if RRS score  $>$  5 above baseline occurred and was sustained for  $>$  24 hours. If Yes, proceed to 13A.3.a.

**13A.3.a.** Indicate whether severe respiratory decompensation occurred  $\leq$  4 hours after a study drug dosing/sham procedure.

If "Yes", Severe respiratory decompensation occurred  $\leq$  4 hours after a study drug dosing/sham procedure, this is reportable as a SAE. Record the SAE on Form 21.

13A.3.a.i. Enter SAE Form #. This is the number entered in the SAE # field in the upper right of the banner on Form 21. If this is the first SAE enter the number 01. Report the SAE within 7 working days.

If "No" Severe Respiratory Decompensation actually occurred  $>$  4 hours after a dosing procedure, fill in the "No" bubble. This will not be reported as an AE.

**13A.4. Severe Cardiopulmonary Decompensation is defined as CPR requiring chest compressions and cardiac medication(s).**

Mark “Severe Cardiopulmonary Decompensation” bubble if the infant required CPR with chest compressions and cardiac medication during the dosing period. Continue to 13A.4.a.

**13A.4.a.** *Indicate whether severe cardiopulmonary decompensation occurred  $\leq$  4 hours after a study drug dosing/sham procedure.*

If “Yes”, CPR occurred  $\leq$  4 hours after a study drug dosing/sham procedure. this is reportable as an AE and SAE.

- Record the Number of the SAE (eg: 001, or 002, etc) in 13A.4.ai.
- Enter the AE as an SAE on form 21, in section 21.3. See Form 21 section of MOP for instructions on completing SAE.

13A.4.a.i. Enter SAE Form #. This is the number entered in the SAE # field in the upper right of the banner on Form 21. Complete and report the SAE within 7 working days.

If “No”, the CPR occurred  $>$  4 hours after a study drug dosing/sham procedure, record the event only as an AE.

- Record AE codes: Using the key at the bottom of Form13A, page 3, indicate the date CPR administered, the severity, relationship to study drug, actions taken, outcome, causality and event type.

**13A.5. Severe PIE**

Mark “PIE” bubble if severe PIE was reported on Form 11A, Q11A.3.a., and it occurred  $\leq$  24 hours after a study drug dosing/sham procedure. Continue to 13A.5.a.

**13A.5.a.** Did PIE occur  $\leq$  24 hours after dosing procedure?

If “Yes”, PIE occurred  $\leq$  24 hours after dosing procedure, this is reportable as an SAE.

- Record the Number of the SAE (eg: 001, or 002, etc) in 13A.4.ai.
- Enter the PIE as an SAE on form 21, in section 21.4. See Form 21 section of MOP for instructions on completing SAE.

13A.5.a.i. Enter SAE Form #. This is the number entered in the SAE # field in the upper right of the banner on Form 21. Complete and report the SAE within 7 working days.

If “No”, PIE occurred  $>$  24 hours after dosing procedure, record the event only as an AE on form 13A.5.a.

- Record AE codes: Using the key at the bottom of Form13A, page 3, indicate the date severe PIE was diagnosed, the severity, relationship to study drug, actions taken, outcome, causality and event type.



### **13A.6. Severe Pulmonary Hemorrhage**

Mark “Severe Pulmonary Hemorrhage” bubble if severe pulmonary hemorrhage was reported on Form 11A, Q11A.3.b. Continue to 13A.6.a.

**13A.6.a.** Did Severe Pulmonary Hemorrhage occur  $\leq$  24 hours after dosing procedure?

If “Yes”, severe pulmonary hemorrhage occurred  $\leq$  24 hours after dosing procedure, this is reportable as an SAE.

- Record the Number of the SAE (eg: 001, or 002, etc) in 13A.6.ai.
- Enter the severe pulmonary hemorrhage as an SAE on form 21, in section 21.5. See Form 21 section of MOP for instructions on completing SAE.

13A.6.a.i. Enter SAE Form #. This is the number entered in the SAE # field in the upper right of the banner on Form 21. Complete and report the SAE within 7 working days.

If “No”, severe pulmonary hemorrhage occurred  $>$  24 hours after dosing procedure, record the event only as an AE on form 13A.6.a.

- Record AE codes: Using the key at the bottom of Form13A, page 3, indicate the date severe PIE was diagnosed, the severity, relationship to study drug, actions taken, outcome, causality and event type.

### **13A.7. Pneumothorax requiring chest tube**

Mark “Pneumothorax requiring chest tube” bubble if patient has a pneumothorax that required a chest tube as defined on Form 11A, Q11A.3.c. Continue to 13A.7.a.

**13A.7.a.** Did Pneumothorax requiring chest tube occur  $\leq$  24 hours after dosing procedure?

If “Yes”, pneumothorax requiring chest tube occurred  $\leq$  24 hours after dosing procedure, this is reportable as an SAE.

- Record the Number of the SAE (eg: 001, or 002, etc) in 13A.7.ai.
- Enter the pneumothorax requiring chest tube as an SAE on form 21, in section 21.6. See Form 21 section of MOP for instructions on completing SAE.

13A.7.a.i. Enter SAE Form #. This is the number entered in the SAE # field in the upper right of the banner on Form 21. Complete and report the SAE within 7 working days.

If “No”, the pneumothorax requiring chest tube actually occurred  $>$  24 hours after dosing procedure, record the event only as an AE on form 13A.7.a.

- Record AE codes: Using the key at the bottom of Form13A, page 3, indicate the date severe PIE was diagnosed, the severity,

relationship to study drug, actions taken, outcome, causality and event type.

- Date if diagnosis will be the date of chest tube insertion, even if it spans two periods.
- If chest tube still in place (ongoing) at end of dosing period, outcome should be unchanged or worsened for 13A.

### **13A.8 IVH**

Mark IVH bubble, if IVH was reported on Form 11A, Q11A.1.a.i., and it is newly diagnosed or worsened since enrollment, this is reportable as an AE.

Record the event date when the new or worsened IVH was diagnosed. Using the key at the bottom of Form 13A, page 3, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.

- If the IVH was diagnosed prior to enrollment and has not increased in severity, do not record an AE.

### **13A.9. Cystic PVL**

Mark “Cystic PVL” bubble, if cystic PVL was reported on Form 11A, Q11A.1.b.i., and it is newly diagnosed or worsened since enrollment, this is reportable as an AE.

- Record the date the new or worsened cystic PVL was diagnosed. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- If cystic PVL was diagnosed prior to enrollment and has not increased in severity, do not record an AE.

### **13A.10. Hydrocephalus requiring shunt**

Mark “hydrocephalus requiring shunt” bubble, if hydrocephalus requiring shunt was reported on Form 11A.1.c. this is reportable as an AE.

- Record the date the hydrocephalus requiring shunt was diagnosed. Using the key at the bottom of the form, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
  - If a shunt is placed in the pre-enrollment period use this pre-enrollment date as the onset date for the shunt for 13A.10.

### **13A.11. NEC**

Mark “NEC” bubble, if NEC was reported on Form 11A.2.a.i, and it is newly diagnosed since enrollment, this is reportable as an AE.

- Record the date NEC was diagnosed. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.

- If NEC was diagnosed prior to enrollment, do not record an AE. Only newly diagnosed episodes of NEC during dosing or discharge periods should be recorded as AE's.

### **13A.12. Isolated GI perforation**

Mark "Isolated GI Perforation" bubble, if isolated GI perforation was reported on Form 11A.2.b.i, and it is newly diagnosed since enrollment, this is reportable as an AE.

- Record the date isolated GI perforation was diagnosed. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- If isolated GI perforation was diagnosed prior to enrollment, do not record an AE.

### **13A.13. Tracheomalacia (laryngomalacia, bronchomalacia)**

Mark "Tracheomalacia" bubble, if tracheomalacia was reported on Form 11A.3.d., and is newly diagnosed since enrollment, this is reportable as an AE.

- Record the date tracheomalacia was diagnosed. Using the key at the bottom of Form 13A, page 3, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- If tracheomalacia was diagnosed prior to enrollment, do not record an AE.
- Tracheomalacia will be reported in the period in which it first was diagnosed. Date of diagnosis will be the original date of diagnosis.

### **13A.14. Tracheal Stenosis**

Mark "Tracheal stenosis" bubble, if tracheal stenosis was reported on Form 11A.3.e., and it is newly diagnosed since enrollment, this is reportable as an AE.

- Record the date tracheal stenosis was diagnosed. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- If tracheal stenosis was diagnosed prior to enrollment, do not record an AE.
- Tracheostenosis will be reported in the period in which it first was diagnosed. Date of diagnosis will be the original date of diagnosis.

### **13A.15. PDA**

Mark "PDA" bubble, if PDA was reported on Form 11A.4.a., and it was treated since enrollment (treatment began during the Dosing Period), this is reportable as an AE.

- Record the date PDA was treated in the dosing period. Record the date of indomethacin/ibuprofen treatment or the date of surgery. Using the key at

the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.

- If PDA was also treated pre enrollment, on 13A, record only the date treatment was given in the dosing period.
- If PDA was present prior to enrollment or diagnosed during the Dosing Period but has not received treatment during the Dosing Period, do not record an AE on 13A.

### **13A.16. Hypotension**

For this study, hypotension is defined as requiring vasopressor support for > 24 hours with one of the following treatment regimens to maintain mean blood pressure within normal limits.

- Dopamine/Dobutamine > 20 mcg/kg/min > 24 hours
- Addition of a second vasopressor agent and treated > 24 hours (e.g. treatment with dopamine 10 mcg/kg/min plus dobutamine or hydrocortisone added)

Mark “Hypotension” bubble, if uncontrolled hypotension, as defined above, was reported on Form 11A.4.b. This is reportable as an AE. Repeated, discreet episodes of uncontrolled hypotension should each be reported individually using lines 13A.28. or 13A.29. as “Other”.

- Record the date uncontrolled hypotension was diagnosed. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- If Hypotension is continuing from the Dosing to Discharge period and the 13A outcome is unchanged or worsened, then the Hypotension date for 13B should be the 13A onset date.

### **13A.17. Pulmonary hypertension**

Mark “Pulmonary Hypertension” if pulmonary hypertension was reported on Form 11A.4.c..This is reportable as an AE.

- Record the date pulmonary hypertension was diagnosed. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- If PH is newly diagnosed in the dosing or discharge period(s), it should be recorded on 11A/B for each period it was present. Dates of newly diagnosed PH recorded on 11AB should fall within the respective period window. PH should then be recorded on 13A/B with the date diagnosed during that period.

### **13A.18. Prolonged bradycardia or oxygen desaturation $\leq$ 4 hours after dosing.**

Prolonged bradycardia is defined as:

- heart rate < 80 for > 60 seconds
- oxygen saturation < 75% for > 60 seconds

Mark the Prolonged bradycardia” bubble, if prolonged bradycardia or oxygen desaturation, as defined above, occurred  $\leq 4$  hours after dosing. This reportable as an AE.

- Record the date of the episode of bradycardia. Using the key at the bottom the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.

### **13A.19. Endotracheal tube problems requiring re-intubation within 4 hours after study drug/sham dosing procedure**

Mark “Endotracheal tube problems” if patient required re-intubation within 4hours after a dosing procedure when the re-intubation is done due to clinical instability or respiratory compromise. This is reportable as an AE.

- Record the date of the re-intubation due to ET tube problems occurring within 4 hours after a study drug/sham dosing procedure. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- These “Endotracheal tube problems” are not elective re-intubations or re-intubations after self-extubation. Elective re-intubations are not AE’s.
- Elective, planned re-intubations should not be done within 4 hours after dosing. However, if a planned re-intubation, not related to problems with the ET tube, does occur (e.g. change of tube size) in this period, do not report this as an AE.
- Clinicians are asked to avoid suctioning the ET tube within 4 hours after a dosing procedure, if possible.

### **13A.20. Problems obtaining TOLSURF Study tracheal aspirate sample**

Mark “Problems obtaining TA sample” if any problems occurred while obtaining tracheal aspirate samples. Examples of such problems include dislodgment of ET tube, accidental extubation, severe bradycardia or oxygen desaturation as defined in 13A.18. above, but occurring in association with the TA sampling procedure. These should be reported as an AE.

- Record the date the problem occurred. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.

### **13A.21. Unexpected adverse event**

Mark “Unexpected Adverse Event”, if an unexpected adverse event occurs during the Dosing Period.

**13A.21.a.** Did an Unexpected Adverse Event occur within 7 days of a study dose and is related or possibly related to study drug administration?

Mark the “Yes” bubble, if the event did occur within 7 days of a study dose and is possibly related to study drug administration. This is reportable as an SAE.

- Record the Number of the SAE (eg: 001, or 002, etc) in 13A.21.ai, where indicated.
- Enter the Unexpected adverse event as an SAE on form 21, in section 21.7. Using the key at the bottom of Form 21, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type. Briefly describe the SAE on Form 21, page 2, Q21.7.a.
- See Form 21 section of MOP for instructions on completing SAE.
- Enter SAE Form #. This is the number entered in the SAE # field in the upper right of the banner on Form 21. Complete and report the SAE within 7 working days.

Mark the “No” bubble, if the event occurred > 7 days after a study dose was given.

- If the adverse event was clearly unrelated to the study and occurred > 7days after a study drug/sham dosing procedure, mark the No bubble.
- Briefly describe the event and record it as an AE only.
- Record the date the problem occurred. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type. Briefly describe the event in the text boxes.

### **13A.22. ROP**

Mark “ROP”, if ROP was reported on Form 11A.6.. ROP is reportable as an AE.

- Record the date the ROP was first diagnosed. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type. ROP requiring surgery should be coded as severe.

### **13A.23. – 13A.27. Sepsis**

Mark “Sepsis”, if Sepsis was reported as “Yes” on Form 11A.5.a. Sepsis is reportable as an AE.

- Record each discreet episode of sepsis reported on Form 11A.5. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- Multiple specimens collected (blood, CSF, UA or TA) during the same 1-3 day period resulting in treatment with ≥ 7 days of antibiotics/antifungals/antivirals, should only be recorded as 1 episode of sepsis on form 13A/B. This is true even if the organisms are different.
- If there were multiple positive cultures for the given episode of sepsis, the date on form 13 should be the earliest of those cultures
- Report each discreet episode of sepsis on individual lines
- Only report NEW episodes of sepsis during the Dosing period. If sepsis was present prior to enrollment do not record an AE on Form 13A.

### **13A.28. RSV Pneumonia**

Mark “RSV Pneumonia” if patient had RSV Pneumonia marked “Yes” on 11A.5.b. or 11B.8.b. This requires a TA culture or DFA collected that was positive for RSV and should be reported as an AE.

- Record the date of the first positive culture. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.

### **13A.29. Vocal chord paralysis**

Mark “Vocal chord paralysis” if patient had Vocal chord paralysis marked “Yes” on 11A.3.f. or 11B.4.f. This diagnosis requires vocal cord paralysis confirmed by bronchoscopy and documented in physician progress notes. This should be reported as an AE.

- Record the date of the first diagnosis. Using the key at the bottom of the page, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- Vocal chord paralysis will be reported in the period in which it first was diagnosed. Date of diagnosis will be the original date of diagnosis.

### **13A.30. – 13A.31 Other Adverse Events**

Mark “Other” adverse events, if additional adverse event(s), not listed above, occur after study enrollment.

- Record the date and a description of the event(s) here. Using the key at the bottom of Form 13A, page 3, indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- When Form 13A, page 6. Fax all pages of Form 13A to the DCC within 2 weeks of the patient’s 36 week PMA date.

## **Form 13B: Adverse Events Occurring between Date of Final Dosing Procedure + 8 days to Discharge from Study Hospital (4 pages)**

This form is used to record a summary listing of adverse events which occur during the period between the final study drug dosing procedure + 8 days and discharge from the study hospital. Form 13B must be completed for all patients. Using the key at the bottom of Form 13B, indicate severity, relationship to study drug, actions taken, outcome, causality and type of event (see CRF Completion Guidelines Section 21.1 for definitions). Fax the form to the DCC within 2 weeks after the patient is discharged from the study hospital.

Specific co-morbidities of prematurity are pre-printed on Form 13B. These must be reported as AEs when they occur (or in the case of IVH, cystic PVL or severe PIE are new or become worsened) between the final study drug dosing procedure + 8 days and discharge from the study hospital. Additional newly diagnosed AEs should be recorded on the lines specifying "Other". Do not record common, expected events such as apnea of prematurity, anemia of prematurity, electrolyte imbalance, temperature instability, gastro-intestinal reflux, etc.

**NOTE: Adverse Events occurring during the Discharge Period should not be reported as SAEs.**

**13B.1. Did Any AE's Occur?:** Have any adverse events listed on co-morbidities Form 11B, pages 1-5 occurred between date of final dosing procedure + 8 days and discharge from the study hospital?

Select one: Yes, No or Unknown. If Yes is selected, document the AE(s) on the appropriate lines 13B.2 -13B.27.

### **13B.2. Death**

Mark "Death" bubble if death occurred between date of final dosing procedure + 8 days and discharge from study hospital. Death during this period is not reportable as a SAE.

- Record the date of death. Using the key at the bottom of the page, indicate severity, relationship to study drug, outcome, causality and event type.
- Complete Form 17: Death Report. Fax CRFs to the DCC within 2 weeks.

### **13B.3. Severe Cardiopulmonary Decompensation**

Mark "Severe Cardiopulmonary Decompensation" bubble if the infant required CPR with chest compressions and cardiac medication if CPR occurred during the Discharge period.



- Record the date of the event. Indicate severity, relationship to study drug, outcome, causality and event type. Severe cardiopulmonary decompensation during the Discharge period is not reportable as an SAE.

#### **13B.4. Severe PIE**

Mark the “Severe PIE” bubble if severe PIE was reported as “Yes” on Form 11B.4.a.

- Record the date of diagnosis or worsened status. Indicate severity, relationship to study drug, outcome, causality and event type. Severe PIE during the Discharge period is not reportable as an SAE.
- If PIE is diagnosed as described above during current “discharge” period, or if it is ongoing from “dosing” period, enter the original date of diagnosis.
  - Exception will be that if PIE that was previously diagnosed improves or resolves and then worsens again to meet the definition above, the date will be the new date of diagnosis.

#### **13B.5. Severe Pulmonary Hemorrhage**

Mark the “Severe Pulmonary Hemorrhage” bubble if frank bleeding from the lungs was reported that was not related to irritation due to suctioning or infection and it occurred during the Discharge period. Severe Pulmonary Hemorrhage should also be marked “Yes” on 11B.4.b.

- Record the date of diagnosis or worsened status. Using the key at the bottom of the page, indicate severity, relationship to study drug, outcome, causality and event type. Severe pulmonary hemorrhage during this period is not reportable as an SAE.

#### **13B.6. Pneumothorax requiring chest tube**

Mark the “Pneumothorax requiring chest tube” bubble if pneumothorax requiring chest tube was reported as “Yes” on Form 11B4.c.

- Record the date of diagnosis or worsened status. Indicate severity, relationship to study drug, outcome, causality and event type.
- Date if diagnosis will be the date of chest tube insertion, even if it spans two periods.
- Outcome for 13B should be resolved (infants do not go home with chest tube).

#### **13B.7. IVH**

Mark the “IVH” bubble if IVH was reported as “Yes” on Form 11B.2.a.

- Record the date the newly diagnosed or worsened IVH was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.

#### **13B.8. Cystic PVL**

Mark the “Cystic PVL” bubble if cystic PVL was reported as “Yes” on Form 11B.2.b.

- Record the date the new or worsened cystic PVL was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.

### **13B.9. Hydrocephalus requiring shunt**

Mark the “Hydrocephalus requiring shunt” bubble if hydrocephalus requiring shunt was reported as “Yes” on Form 11B.2.c.

- Record the date the new or worsened hydrocephalus requiring shunt was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
  - If a shunt is placed in the pre-enrollment period use this pre-enrollment date as the onset date for the shunt for 13B.9.

### **13B.10. NEC**

Mark the “NEC” bubble if NEC was reported as “Yes” on Form 11B.3.a.i..

- Record the date NEC was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- If NEC was diagnosed prior to enrollment, do not record an AE. Only newly diagnosed episodes of NEC during dosing or discharge periods should be recorded as AE’s.
- If both a drain and laparotomy were performed for treatment of NEC, mark the date of the laparotomy as it is the most invasive therapy.

### **13B.11. Isolated GI perforation**

Mark the “Isolated GI perforation” bubble if isolated GI perforation was reported as “Yes” on Form 11B.3.b.i..

- Record the date GI perforation was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.

### **13B.12. Tracheomalacia (laryngomalacia, bronchomalacia)**

Mark the “Tracheomalacia” bubble if tracheomalacia was reported as “Yes” on Form 11B.4.d.

- Record the date tracheomalacia was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- Tracheomalacia will be reported in the period in which it first was diagnosed. Date of diagnosis will be the original date of diagnosis.

### **13B.13. Tracheal Stenosis**

Mark the “Tracheal Stenosis” bubble if tracheal stenosis was reported as “Yes” on Form 11B.4.e..

- Record the date tracheal stenosis was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- Tracheostenosis will be reported in the period in which it first was diagnosed. Date of diagnosis will be the original date of diagnosis.

### **13B.14. PDA Requiring Treatment**

Mark the “PDA requiring treatment” bubble if PDA was reported as “Yes” on Form 11B.5.a.

- Record the date the PDA was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- On 13B, record the date PDA treatment was given as follows:
  - If PDA was only treated during the discharge period, record the date of treatment with indomethacin/ibuprofen or the date of surgery.
  - If PDA was treated during the dosing period and the discharge period and the PDA “Outcome” from 13A was “Resolved”, record the discharge period, treatment date as the date of the PDA 13B AE.
  - If PDA was treated during the dosing period and the discharge period and the PDA “Outcome” from 13A was “Improved”, “Unchanged” or “Worsened”, record the dosing period, treatment date as the date of the PDA 13B AE.

### **13B.15. Hypotension**

Mark the “Hypotension” bubble if hypotension, was reported as “Yes” on Form 11B.5.b.

- Record the date the uncontrolled hypotension episode was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- Repeated, discreet episodes of hypotension (by study definition) should each be reported individually using lines 13B.26. or 13B.27.
- If Hypotension is continuing from the Dosing period and the 13A outcome is unchanged or worsened, then the Hypotension date for 13B should be the 13A onset date.
- If Hypotension occurred in the Dosing period and the 13A outcome was improved or resolved, then the Hypotension date on 13B for this occurrence (in the discharge period), should be the date infant met hypotension criteria in discharge period.

### **13B.16. Pulmonary Hypertension**

Mark the “Pulmonary Hypertension” bubble if pulmonary hypertension was reported as “Yes” on Form 11B.5.c.

- Record the date pulmonary hypertension was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- If Pulmonary Hypertension is continuing from the Pre-Enrollment and dosing period, mark Yes here with the pre-enrollment date. Do not record this continuing pulmonary hypertension on 13A.
- If Pulmonary Hypertension is continuing from the Dosing period, mark Yes here with the dosing period date. PH should then be recorded on 13B with the date diagnosed during the dosing period
- If PH is newly diagnosed in the dosing or discharge period(s), it should be recorded on 11A/B for each period it was present. Dates of newly diagnosed PH recorded on 11AB should fall within the respective period window. PH should then be recorded on 13A/B with the date diagnosed during that period.

### **13B.17. Unexpected adverse event**

Mark the “Unexpected adverse event” bubble if an unexpected adverse event occurred between the date of final dosing procedure + 8 days and discharge from study hospital.

- Record the date the unexpected adverse event occurred or was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- If the unexpected adverse event was present prior to the date of final dosing procedure + 8 days, do not record an AE on Form 13B.

### **13B.18. ROP**

Mark the “ROP” bubble if ROP stage 1-5 was reported on Form 11B.6.a.i.

- Record the date of 1<sup>st</sup> diagnosis. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type. ROP requiring surgery should be coded as severe.
- If ROP was present prior to the date of final dosing procedure + 8 days, ONLY record as an AE on Form 13B if ROP increased in severity from the Dosing period.

### **13B.19. – 13B.23. Sepsis**

Mark the “Sepsis” bubble(s) only if culture proven sepsis episode(s) were reported on Forms 11B.7.

- Record the date(s) the positive blood, CSF or urine culture(s) were collected confirming the newly diagnosed culture proven sepsis episode(s). Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- Multiple specimens collected (blood, CSF, UA or TA) during the same 1-3 day period resulting in treatment with  $\geq 7$  days of antibiotics/antifungals/antivirals, should only be recorded as 1 episode of sepsis on form 13A/B. This is true even if the organisms are different.

- If there were multiple positive cultures for the given episode of sepsis, the date on form 13 should be the earliest of those cultures
- Report each discreet episode on individual lines
- Only report NEW episodes of sepsis during the Discharge period. If sepsis was present prior to the date of the final dosing procedure + 8 days, and is still being treated during discharge period, do not record an AE on Form 13B.
  - For these continuing episodes of sepsis, make sure to complete the final outcome for Sepsis on 13A, when you know the outcome (eg: resolved, death).

#### **13B.24. RSV Pneumonia**

Mark the “RSV Pneumonia” bubble if RSV pneumonia was reported as “Yes” on Form 11B.8.b..

- Record the date RSV pneumonia was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.

#### **13B.25. Vocal Chord Paralysis**

Mark the “Vocal Chord Paralysis” bubble if pulmonary hypertension was reported as “Yes” on Form 11B.4.c.

- Record the date pulmonary hypertension was diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- Vocal chord paralysis will be reported in the period in which it first was diagnosed. Date of diagnosis will be the original date of diagnosis.

#### **13B.26. – 13B.27 Other**

Mark the “Other” bubble if additional adverse event(s), not listed above, occurred or were diagnosed between the date of the final dosing procedure + 8 days and discharge from study hospital.

- Record the date(s) the new AEs were diagnosed. Indicate the severity, relationship to study drug, actions taken, outcome, causality and event type.
- If the “Other” AEs were present prior to the date of the final dosing procedure + 8 days, do not record an AE on Form 13B.

#### **NOTE:**

When Form 13B has been completed, ask the PI to review, sign, date and initial the Form 13B, page 4.

Fax all pages of Form 13B to the DCC within 2 weeks of the patient’s discharge from the study hospital.

## **Forms 14A and 14B: Hospital Course while at Study Hospital (2 pages each)**

The purpose of these forms is to document total parenteral nutrition (TPN), surgeries and blood products received by the patient during hospitalization at the study hospital. Record the therapies received from admission to discharge from the study hospital.

### **14A.1. TPN (Total Parental Nutrition)**

**14A.1.a.** Indicate if the patient received TPN during hospitalization at the study hospital. Select Yes or No.

14A.1.a.i. If Yes is selected, enter start date and end date of first TPN course.

- If TPN is interrupted for < 48 hours, then restarted, consider this as one course.
- If interruption is > 48 hours enter date TPN was interrupted as end date.
- If TPN is resumed > 48 hours after it was stopped, record this as a new TPN course with a new start date and end date.
- Record each successive TPN course start and stop dates on lines 14A.1.a.ii. through 14A.1.a.xiv.

### **14A.2. Surgeries**

**14A.2.a.** Indicate if any surgery was performed during hospitalization at the study hospital. Select Yes or No.

14A.2.a.i. If Yes is selected, enter surgery Code\* and date of surgery.

- Record each additional surgery Code and date of surgery on lines 14A.2.a.ii. through 14A.1.a.viii.
- If No is selected, you do not have to send in form 14C.

**14A.2.b.** Indicate whether additional surgeries were performed. Select Yes or No. If Yes, proceed to Form 14C: Additional Surgeries Form to record additional surgeries.

- If No is selected, you do not have to send in form 14C.

Note 1: Central line insertion or removal that requires general anesthesia should be recorded under THORAX, Other (Code 200).

Note 2: Laser surgery, cryosurgery and vitrectomy (surgeries related to ROP) should not be listed as surgeries.

Note 3: If a study patient transfers to another study hospital and has surgery there, record the surgery in 14A.2 (as you respiratory settings on 9A).

Note 4: Patients treated with Avastin or other VEGF product for ROP should have treatment recorded as "Ophthalmic Surgery OTHER" - #103, with treatment date.

**\*Surgery Codes:**

**Head and Neck**

101 Tracheostomy

102 Cricoid split

103 Ophthalmologic surgery OTHER than laser or cryosurgery for ROP (includes Avastin)

104 Cleft lip or palate repair

105 Branchial cleft sinus excision

106 Thyroglossal duct excision

107 Palliative or definitive repair of choanal atresia

108 Mandibular (jaw) distraction

100 Other head and neck surgery requiring general or spinal Anesthesia

**(description required)**

**Thorax**

201 Tracheal Resection

202 Aortopexy

203 Tracheoesophageal atresia and/or fistula repair

204 Thoracoscopy (with or without pleural or lung biopsy)

205 Thoracotomy (with or without pleural or lung biopsy)

206 Thoracotomy (or thoracoscopy) with lobectomy or partial lobectomy

207 Resection of pulmonary sequestration (intrathoracic or extrathoracic)

208 Resection of mediastinal mass

209 Resection of chest wall

210 Bronchoscopy (with or without biopsy)

211 Esophagoscopy (with or without biopsy)

212 Surgery for Congenital Cystic Adenomatoid Malformation of the Lung

213 Lung Transplant

S200 Other thoracic surgery requiring general or spinal anesthesia **(description required)** Enter central line insertions such as Broviac, here.

**Abdomen**

301 Rectal biopsy with or without anoscopy

302 Laparoscopy (diagnostic, with/without biopsy)

303 Laparotomy (diagnostic or exploratory, with/without biopsy)

304 Fundoplication

305 Pyloromyotomy

306 Pyloroplasty

307 Jejunostomy, ileostomy, colostomy for intestinal diversion (with/without bowel resection)

308 Small bowel resection

309 Large bowel resection

310 Duodenal Atresia/Stenosis Repair

311 Jejunal, ileal, or colonic atresia repair (or repair of multiple intestinal atresias)

312 Excision of Meckel's diverticulum

313 Drainage of intra-abdominal abscess (not as primary treatment for NEC, see code

S 333)

314 Surgery for meconium ileus  
 315 Excision of omphalomesenteric duct or duct remnant  
 316 Gastroschisis repair (primary or staged)  
 317 Omphalocele repair (primary or staged)  
 318 Lysis of adhesions without other procedure  
 319 Repair of imperforate anus (with or without vaginal, urethral, or vesicle fistula)  
 320 Pull through for Hirschsprung's disease (any technique)  
 321 Pancreatectomy (partial, near total or total)  
 322 Splenectomy (partial or total)  
 323 Resection of retroperitoneal tumor  
 324 Resection of sacrococcygeal tumor  
 325 Repair of diaphragmatic hernia  
 326 Plication of the diaphragm  
 327 Gastrostomy tube  
 328 Upper endoscopy (stomach or duodenum, with or without biopsy)  
 329 Colonoscopy (with or without biopsy)  
 \*\*330 Takedown of ostomy and/or reanastomosis of bowel (small or large bowel)  
 \*\*331 Ladd's or other procedure for correction of malrotation  
 \*\*332 Appendectomy  
 333 Primary peritoneal drainage for NEC, suspected NEC, or intestinal perforation  
 (If infant  
 subsequently has other applicable surgical procedures, code those also.)  
 334 Anoplasty  
 335 Kasai procedure  
 336 Open liver biopsy  
 300 Other abdominal surgery requiring general or spinal anesthesia (**description  
 required**)

### **Genitourinary**

401 Cystoscopy (diagnostic, with or without biopsy)  
 402 Adrenalectomy  
 403 Nephrectomy  
 404 Nephrostomy  
 405 Urteterostomy  
 406 Resection of urachal cyst  
 407 Cystostomy  
 408 Closure of bladder exstrophy  
 409 Resection of posterior urethral valves  
 410 Inguinal hernia repair  
 411 Orchidopexy  
 412 Orchiectomy  
 413 Drainage of ovarian cyst  
 414 Oophorectomy (partial or complete)  
 416 Pyeloplasty  
 417 Renal Transplant  
 400 Other genitourinary surgery requiring general or spinal anesthesia  
 (**description  
 required**)

### **Open Heart or Vascular Procedures**



- 501 Vascular Ring division
- 502 Repair of coarctation of the aorta
- 503 Repair of major vascular injury
- 504 Repair or palliation of congenital heart disease
- 505 Ligation of Patent Ductus Arteriosus
- 500 Other open heart or vascular surgery requiring general or spinal anesthesia

#### **Diagnostic or interventional cardiac catheterization**

- 601 Diagnostic cardiac catheterization
- 602 Interventional catheterization with balloon septostomy
- 603 Interventional catheterization with aortic valvuloplasty
- 604 Interventional catheterization with pulmonary valvuloplasty
- 600 Other interventional catheterization requiring general or spinal anesthesia  
(description required)

#### **Skin and Soft Tissue**

- S700 Skin or soft tissue surgery requiring general or spinal anesthesia  
(description required)

#### **Musculoskeletal System**

- S800 Other musculoskeletal surgery requiring general or spinal anesthesia  
(description required)

#### **Central Nervous System**

- 901 Ventriculoperitoneal or other ventricular shunt
- 902 External ventricular drain
- 903 Ventricular drain with reservoir
- 904 Myelomeningocele repair
- 900 Other central nervous system surgery requiring general or spinal anaesthesia  
(description required)

#### **Fetal Surgery**

- 1000 Fetal surgery at your hospital (description required)
- 1001 Fetal surgery at another hospital (description required)

#### **Conjoined Twins**

- 1101 Separation of conjoined twins  
Enter date of surgery.

### **14A.3. Transfusions**

Use this section to record all blood products provided by the Blood Bank and received by the patient during hospitalization in study hospital.

- If patients receive more than one transfusion on the same date, record the total number of transfusions received on that date.
- Each individual aliquot of blood product released by the Blood Bank and infused into the patient should be counted as one transfusion.
- An exchange transfusion should be counted as one transfusion. Do not record volumes transfused.

**14A.3.a.** Indicate whether the patient received transfusion(s) as defined above.  
Select Yes or No.

14A.3.a.i. through 14A.3.a.iii. If Yes, the patient was transfused, use these lines to record dates of transfusion(s) and number of transfusion received on each date.

- If No is selected, you do not have to send in form 14B.

**14A.3.b.** Indicate whether additional transfusions were received.  
Select Yes or No. If Yes, proceed to Form 14B.1: Additional Transfusions Form to record further transfusions.

- If No is selected, you do not have to send in form 14C.

14.A.3.b.i. Indicate total number of Forms 14B that were used.

### **14B.1. Additional Transfusions**

If Form(s) 14B will be used to record additional transfusions, enter sequential Additional Transfusion Form number(s) in upper right fields of the banner.

If form 14B is faxed in, the banner information and question 14B1.a must be completed.

**14B.1.a.** Indicate if additional transfusions were administered.  
Select Yes or No.

14B.1.a.i. through 14B.1.a.xv. If “Yes”, use these lines to record additional transfusions.

- At discharge from the study hospital, record the total number of Forms B used on line 14.A.3.b.i.

### **14C.1. Additional Surgeries**

Record additional surgeries that were performed during the hospital stay.

If form 14C is faxed in, the banner information and question 14C1.a must be completed.

**14C.1.a.** Indicate if any additional surgeries were performed.  
Select Yes or No.

14C.1.a.i. through 14B.1.a.xvi. If “Yes”, use these lines to record additional surgery Codes and the date they were performed.

## **Form 15: Medications While at Study Hospital (2 pages)**

This form is used to capture selected medications received by the patient from admission to discharge from the study hospital. Use the following criteria to record Medications:

- If a medication is interrupted for < 48 hours, then resumed, record this as one, continued course.
- If the interruption is > 48 hours, enter the date the medication was stopped.
- If the medication is resumed > 48 hours after it was stopped, record this as a new course with new start and stop dates.
- -If the medication is being continued at discharge, fill in the “Ongoing” bubble and do not enter a stop date.

### **15.1. Systemic Corticosteroids**

Indicate if patient received systemic corticosteroids.

Select Yes, No, or Unknown

**15.1. a-f.** Record start date and stop date(s) of all courses of steroids patient received.

- Select type of corticosteroid. Select one. If more than one type of corticosteroid was received concurrently, enter each type as separate entries on separate lines.
- Select reason(s) corticosteroid was administered. Select all that apply.

### **15.2 Caffeine Administered**

Indicate if patient received caffeine.

Select Yes, No, or Unknown

**15.2.a-f.** Record start and stop date(s) of all courses of caffeine patient received.

- See Clinical Management Guidelines for Caffeine Citrate in Appendix II. If Caffeine administration deviates from Clinical Management Guidelines, report a protocol deviation on Form 18.2.d.

### **15.3. Continuous Infusion Vasopressor(s) Administered**

Indicate if patient received continuous infusion of vasopressor(s) infusion.

Select Yes, No, or Unknown

**15.3. a-g.** Record start and stop date of pressor(s) courses vasopressors (meeting TOLSURF definition) that were administered.

### **15.4 Vitamin A Administered**

Indicate if patient received Vitamin A to prevent BPD.

Select Yes, No, or Unknown

**15.4.a.** If yes, record start and stop date of Vitamin A administration.

If the patient is still receiving Vitamin A when discharged from the study hospital, do not enter a stop date. Select the ongoing bubble.

## **Form 16A: Discharge Report (2 pages)**

Use this form to record information about the patient at discharge or transfer from the study hospital, and final discharge to home. Record the information from each hospital discharge or transfer time point and at final discharge to home.

### **16A.1. Discharged home from study hospital**

**16A.1.a.** Indicate whether patient was discharged (DC) to home or foster care directly from the study hospital.

Select one: Yes or No

If No is selected for Q 16A.1, and the patient was transferred to another hospital or rehabilitation center, proceed to Q16A.2. If the patient expired at the study hospital, proceed to complete Form 17.

If Yes is selected, complete the following:

16A.1.a.i. Enter date of discharge to home or foster care

16A.1.a.ii. Enter weight in grams at the time of discharge (use recorded weight closest to DC date).

16A.1.a.iii. Enter head circumference (nearest 0.5 cm) recorded closest to DC date (within 2 weeks).

16A.1.a.iv. Indicate respiratory support status when discharged home.

Select all that apply.

- Mark in room air if infant is off all respiratory support including room air nasal cannula
- Mark mechanical ventilator w/trach if infant is on a mechanical ventilator via tracheostomy tube.
- Mark oxygen continuously if infant is on continuous O<sub>2</sub> via nasal cannula or trach collar
- Mark Oxygen intermittently if oxygen is not given continuously, (e.g. given only with feedings)

16A.1.a.v. Enter % oxygen saturation (SpO<sub>2</sub>) recorded (when infant in a resting state) closest to the time patient was discharge home.

16A.1.a.vi. Enter the last (most recent) PCO<sub>2</sub> recorded within 2 weeks of DC home.

- PCO<sub>2</sub> may be by arterial, venous or transcutaneous measurement.
- Do not record serum CO<sub>2</sub>.
- Mark as unavailable if not recorded within 2 weeks prior to discharge.

16A.1.a.vii. Indicate all discharge medications prescribed for treatment of BPD. We have recently also added Multivitamin to this list (although not considered “for BPD”). Select all that apply. If none, select None.

The medication list includes:

- Diuretics
- Systemic steroids
- Bronchodilators
- Inhaled steroids
- Multivitamins
- Unavailable
- None
- Other: Describe: \_\_\_\_\_

NOTE: In the case where an infant is transported to another hospital and then the infant returns to study hospital before going home, both 16A.1 and 16A.2 will be completed.

NOTE: In the case where an infant is transported to another hospital and then the infant is discharged home, both 16A.1 and 16A.3 will be completed.

## 16A.2. Discharged to Other Hospital

**16.A.2.a.** Indicate if the infant was discharged to another hospital or rehabilitation center. Select one: Yes or No.

If No is selected for Q 16A.2, you will also answer No to 16A.3.a

If Yes is selected:

16A.2.a.ii. Enter weight in grams recorded at time of DC to other non-study hospital or rehab center.

16A.2.a.iii. Enter head circumference (nearest 0.5 cm) recorded closest to date of DC to other non-study hospital or rehab center.

16A.2.a.iv. Indicate respiratory support status when discharged to other non-study hospital or rehab center. Select all that apply.

- Mark “Off ventilator, CPAP, oxygen, nasal cannula, if patient is off all respiratory support including room air nasal cannula
- Mark “mechanical ventilator” if patient is on conventional ventilation or high frequency ventilation
- Mark “SiPAP, BiPAP, nasal prong ventilation” if patient is on dual pressures administered via nasal prongs or mask.
- Mark “on nasal CPAP” if on nasal CPAP or nasal cannula flow > 4 liters per minute for room air or > 2 lpm on any oxygen.
- Mark continuous nasal cannula if patient is on continuous nasal cannula >2 to 4 lpm in room air or nasal cannula flow ≤ 2 lpm with effective FiO<sub>2</sub> < 0.30 (30%).

16A.2.a.v. If patient is on continuous nasal cannula indicate:

- FiO<sub>2</sub>

- Gas flow in liters per minute
- Effective oxygen
  - For Effective Oxygen levels, refer to Oxygen/flow reduction challenge test procedure in MOP Section I, 9.0.

16A.2.a.vi. Enter % oxygen saturation(SpO2) recorded (when infant in a resting state) closest to the time patient was discharge home.

16A.2.a.vii. Enter the last (most recent) PCO2 recorded within 2 weeks of DC home.

- PCO2 may be by arterial, venous or transcutaneous measurement.
- Do not record serum CO2.
- Mark as unavailable if not recorded within 2 weeks prior to discharge.

### **16A.3. Discharged Home from Other Hospital (OH)**

Complete this section when the infant is discharged to home or foster care from the other, non-study, hospital. The study coordinator or PI should make every attempt to track the patient's progress at the other, non-study hospital. Initially, weekly contact may be sufficient. As the patient nears readiness for discharge to home, more frequent contact may be necessary to capture the required information at discharge. To comply with HIPAA regulations, the other hospital may require that the information is communicated from physician to physician. In this case, the site PI should contact the physician at the other hospital to obtain the information.

**16A.3.a.** Indicate whether patient was discharged to home or foster care directly from another, non-study hospital (OH).

Select one: Yes or No or Unknown

If Yes is selected:

16A.3.a.i. Enter date of discharge to home or foster care from OH.

16A.3.a.ii. Enter weight in grams on discharge home or foster care from OH (use weight recorded closest to discharge date).

16A.3.a.iii. Enter head circumference (nearest 0.5 cm) recorded closest to discharge (within two weeks) from OH date.

16A.3.a.iv. Indicate respiratory support status when discharged home from OH. Select all that apply.

- Mark in room air if infant is off all respiratory support including room air nasal cannula.

16A.3.a.v. Record date patient weaned to room air

- Mark oxygen continuously if infant is on continuous O2 via nasal cannula or trach collar
- Mark Oxygen intermittently if oxygen is not given continuously, e.g. given only with feedings

- Mark mechanical ventilator w/trach if infant is on a mechanical ventilator via tracheostomy tube.
- Mark unavailable if unable to obtain information about respiratory status at discharge from OH to home.

16A.3.a.vi. Enter % oxygen saturation recorded (with infant in a resting state) closest to the time of discharge home.

16A.3.a.vii. Record the last PCO<sub>2</sub> recorded within 2 weeks of DC home. PCO<sub>2</sub> may be by arterial, venous or transcutaneous measurement. Do not record serum CO<sub>2</sub>. Mark as unavailable if not recorded within 2 weeks prior to discharge

16A.3.a.viii. Indicate all discharge medications prescribed for treatment of BPD. We have recently added Multivitamin to this list (although not considered “for BPD”). Select all that apply. If none were prescribed, select None.

The medication list includes:

- Diuretics
- Systemic steroids
- Bronchodilators
- Inhaled steroids
- Multivitamins
- Unavailable
- None

Other: Describe: \_\_\_\_\_

[NOTE: If a patient is trached and on positive pressure, mark bubble for appropriate mode of positive pressure being delivered (vent, CPAP, SiPAP).

- However, if the Infant is trached and on supplemental O<sub>2</sub> by trach collar or mask, mark “continuous nasal cannula ≤ 2 lpm” and follow arrow to indicate the FiO<sub>2</sub> and literflow (indicate liter flow as 9.99, if 10 or above).

- If the infant is in room air trach mask and only needs the flow for humidity, mark this infant as being in room air “off all support”.]

#### 16.A.4. Audiology

Screening test done prior to discharge

**16.4.a.** Indicate if hearing screening test was performed prior to discharge home. Select one: Yes, No or Unknown.

If “Yes”, audiology testing was performed indicate test result for each ear:

16.4.a.i. Right ear:

Select one. Pass, Failed, Refer for additional testing, or not done.

16.4.a.ii. Left ear:

Select one. Pass, Failed, Refer for additional testing, or not done.



### **16.A.5. Ophthalmologic**

This data needs to be filled out for all babies. If ROP screening was performed any time after discharge to another hospital and prior to discharge home, enter that data here. If discharged home directly from study hospital, **ROP data entered into 16.A.5. should match 11B.6.a, as worst stage noted.**

**16A.5.a.** Indicate whether or not the patient was examined for retinopathy of prematurity (ROP) at any time after initial discharge from the study hospital and prior to discharge home. Select one: Yes, No or Unknown

- Select “Yes”, if exam was done and ROP was identified. Proceed to 16B.5.a.i.
- Select “No” if no eye exam was done after initial discharge.
- Select “Unknown” if you do not have information on ROP screening since initial discharge.

16B.5.a.i. If eye exam “Yes”, indicate worst stage observed in either eye.

- Select “No ROP” if no ROP was observed
- Select the worst stage ROP observed in either eye (Stages 1-5) since initial discharge from study hospital.
- ROP classified as Stage 1-5, is reportable as an adverse event. Record the AE on Form 13B, 13B.18, if not reported before.

16B.5.a.ii. Indicate if any surgery was performed for ROP (laser, cryo, etc). Select one: Yes, No or Unknown

16B.5.a.iii. Record the date surgery was performed for ROP (laser, cryo, etc). If surgery done at another hospital, and you have the date of surgery, you can enter the surgery and date on form 14.

Patients receiving Avastin treatment for ROP should have Avastin treatment date recorded as an “Ophthalmologic Surgery OTHER” on Form 14.

## **Form 16B: Hospital Discharge Breathing Outcome Questionnaire (2 pages)**

This scripted questionnaire is used to collect information about the patient's home environment, environmental exposures and family history of respiratory and allergy problems.

The questionnaire should be administered at discharge  $\pm$  2 weeks from the study hospital. Ideally, the questionnaire should be administered in person when parents are visiting the study hospital. If that is not possible, it may be administered by telephone within 2 weeks after discharge from the study hospital.

See Appendix VII for the questionnaire script and more detailed instructions for answering each item on the questionnaire.

- **Family Contact Information:**  
When the questionnaire is administered, contact information should also be collected from the parents or guardian. See Contact Information Forms in MOP Appendix VII. An electronic version will be emailed to the site Study Coordinator. **THE CONTACT INFORMATION FORMS ARE NOT PART OF THE CRF SET. DO NOT FAX THE CONTACT INFORMATION FORMS TO THE DCC.** These forms will contain confidential and protected health information and must be kept securely at the study site.
- If it is permitted by the site IRB and included in the site consent, ask the parents if they are willing to provide Social Security and/or Drivers License numbers. These numbers are collected only to facilitate locating the parents should their contact information change in the future. Inform the parents that **PROVIDING SS AND DL NUMBERS IS OPTIONAL**. If parents decline to provide them, there will be no impact on the infant's participation in the study. A separate page is provided for the SS and DL numbers. The site PI should keep this form securely in a locked file separated from the other study records.

### **16B. The Discharge Questionnaire Intro**

This questionnaire should be administered at the time of discharge from the study hospital  $\pm$  2 weeks. Complete CRF form 16B with data collected from this interview and fax the form into DCC when completed.

Was the interview conducted? Answer Yes or No.

If "Yes", enter the Date the questionnaire was completed.

If "No", Fill in the bubble for the reason why the interview was not conducted.

- Child Died
- Unable to contact family
- Family refused

*Introduction: "Premature babies are more likely than full term babies to have breathing problems after discharge from the intensive care nursery. One of the purposes of this study is to see whether or not the treatment your baby received as part of the TOLSURF Study improves your baby's breathing in the 18-22 months following the baby's due date."*

*As part of this study, we will contact you every 3 months or so to ask you questions about your baby's breathing. The questions will be about your baby's breathing symptoms, such as wheezing and coughing, and about your baby's need for medical visits and treatments for breathing problems.*

*When we contact you, we'd like you to gather any notes, medications or other information about your baby's breathing. We will ask questions about how often your baby has breathing difficulties, including wheezing or coughing, whether your baby visited a doctor's office, emergency room or was hospitalized for breathing problems, and whether your baby has needed breathing medicines or treatments.*

*Right now, we'd like to ask you a few questions about your home and about whether breathing problems run in the family in order to help us understand your baby's breathing and risk for breathing problems at home. We are also going to ask you about the information we need to continue to stay in contact with you while your child remains in the study, including your phone numbers and email addresses and contact information of relatives or friends that will know how to get in touch with you if your contact information changes. As with all information we collect, the answers to these questions will be kept confidential."*

## **16B. Discharge Questionnaire**

Confirm child's name, birth date and sex. The items below are taken from the FU manual and include "script" for the questions being asked.

**16B.1.:** Record who is providing information on the child (select one).

Select: Mother, Father, Grandparent, Foster Parent, or Other

*"To confirm who I'm speaking with, what is your relationship to the baby?"*

Every effort should be made to interview the primary caretaker. The caretaker needs to live with the child.

**16B.2.:** Record how many people live in the home (select one).

Select: 2-3, 4-6, 7-20, or > 10.

*"How many people normally live in your home including your baby? When counting the total number, include anyone who lives in your home at least six months of the year."*

**16B.2a.:** Record how many children < 5 years live in the home (select one).

Select: None, 1-2, 3-5, 6-8, >8

*"Are there any other children younger than 5 (other than your baby) that live in the home with you? How many other children?"*

**16B.3.:** Are there any pets that live in the home (select all that apply)?

Select: None, Dog, Cat, Other furry animal, Fish, Birds, Other (describe).

*"Do you have any pets currently? For example, a dog, cat, birds, fish, or others? What are they?"* Select all that apply. Write in additional animals concisely (e.g., "reptiles" to describe snake + turtle).

**16B.4.:** What do you feed your child? (check one).

Select: Breast milk only, Formula only, Breast milk and formula, no enteral feedings, or other. *"What type of milk does your child take? Breastmilk only, formula only, or a combination of both?"*

Select one. If infant is taking only breast milk that is either sometimes or consistently fortified with formula powder, record "Breastmilk only". If child is not taking enteral feeds (e.g., TPN-only), record "no enteral feeds". Note typographical error on CRF version 1, "no external feeds", which should be marked if no enteral feeds.

**16B.5.:** Will the child receive any care outside the home in the next year?

Select Yes or No.

*“Will your child receive any care outside the home in the next year?”*

**16B.5.a.:** If yes, *“Who will provide the care?”*

Select all that apply: Relatives, Daycare, Friends, or Other.

**16B.5.b.:** If Yes, will other children be present at the outside care site?

Select Yes or No.

*“Are there other children that are not siblings present at the outside care site?”*

**16B.6:** Explain child’s exposure to smoking.

**16B.6.a.:** Describe smoking exposure. Choose best statement. *“Which of the following statements best describes the situation regarding smoking in your child’s home?”*

- *Smoking is allowed in any room in the home,*
- *Smoking is limited to part of the house where the child will rarely go,*
- *Occasionally, there is smoking inside the house (visitor, family member), or*
- *There is no smoking inside the house at all”*

**16B.6.b.:** Dose either parent smoke?

Select Yes, No, or Unknown.

16B.6.bi: If yes: *“Can you estimate the total number of cigarettes smoked per day by both parents?”*

Select one: < 5, 5-10, 10-20, > one pack per day, unknown.

Prompt for best estimate. May prompt with options if unable to supply number.

**16B.6.c.:** Provide the total number of people who smoke in the house (select one).

Select: None, 1-2, >2 or unknown

*“Altogether, how many people who live in the house smoke?”*

Any smoker counts, whether they smoke in the home, outside the home or at some distant location.

**16B.6.d.:** Will the child travel in a care where someone smokes?

Select: Yes, No or unknown.

*“Will your child travel at least once a week in a vehicle that someone smokes in, even if they only smoke in it when the child is not in the car?”*

**16B.7:** Record what breathing or allergy problems run in the family.

*“Please tell us what breathing and allergy problems run in your child’s family.”*

For each of the items below (a thru c) chose on of the following:

- Asthma/recurrent lung infections
- Allergies (allergies/hayfever)
- Medication allergies
- Eczema
- Other
- None.

**16B.7a.:** Biological Parents (one or both- select all that apply)

*“For the biological parents (mother and father): asthma/recurrent lung infections, allergies/hay fever, medication allergies, eczema”*

**16B.7.b.:** Grandparents (one or both – select all that apply)

*“For the grandparents: asthma/recurrent lung infections, allergies/hay fever, medication allergies, eczema”*

**16B.7.c.:** Siblings (one or both – select all that apply)

*“For the grandparents: asthma/recurrent lung infections, allergies/hay fever, medication allergies, eczema”*

**16B.8.:** Provide additional information on baby’s background.

*“Please tell us more about your baby’s background.”*

**16B.8.a.:** Record mother’s education.

*“What is the mother’s level of education?”*

Select one:

- Some education, high school not completed
- High School graduate
- Some college
- College graduate
- Graduate study (post college, advanced study/degree)
- Unknown/Unavailable

**16B.8.b.:** Record father’s education.

*“What is the father’s level of education?”*

Select one:

- Some education, high school not completed
- High School graduate
- Some college
- College graduate
- Graduate study (post college, advanced study/degree)
- Unknown/Unavailable

**16B.8.c.:** Record how child’s health care will be paid for.

*“How will your child’s health care be paid for?”*

Select one:

- Private insurance,
- Medicaid/public insurance,
- No insurance (self pay)

## **Form 17: Death Report (2 pages)**

This form is used to record whether the patient survived or died. For all deaths, please send a copy of the attending physician's discharge note, if available. Block out all personal identifiers and protected health information. Write the study screening ID, secondary ID and randomization numbers on the copy of the discharge note.

### **17.1 Indicate if patient died.**

Select one: Yes, No or Unknown.

If "No or Unknown" is selected, skip the next questions and proceed to the bottom of Form 17 page 2. The PI must still sign and date Form 17.

If "Yes" is selected, proceed with questions 17.1.a – 17.7.b.

**17.1.a.** Record the date of death

**17.1b.** Indicate how many days after the last study drug/sham dosing procedure the death occurred.

- Mark " $\leq 7$  days", if death occurred less than or equal to 7 days after a study drug/sham dosing procedure.
  - Death in this time period is a SAE that required expedited reporting.
  - If death occurred between enrollment and the date of final dosing procedure + 7 days, confirm that death has been recorded on Form 13A: Adverse Events and on Form 21: Serious Adverse Events, that the CCC project Director has been notified and forms faxed to the DCC within 3 working days.
- Mark " $> 7$  days or Unknown", if death occurred 8 days or more after a study drug/sham dosing procedure, or on an unknown date.
  - If death occurred between the date of final dosing procedure + 8 days and discharge from the study hospital or other hospital, confirm that the death has been recorded on Form 13B: Adverse Events.
  - Death in this time period must be reported as an adverse event, but not as a serious adverse event. Do not enter death occurring in this time period as a SAE on Form 21.

### **17.2. Where did the infant die?**

Indicate whether the infant died (select one):

- Study hospital
- Home
- Other Hospital

### 17.3. Primary cause of death

Record the primary cause of death. Primary cause of death must be verified by the Attending Physician. If death is unexplained, mark unknown.

Select only one of the following:

- Sepsis
- Respiratory disease
- Pulmonary hypertension
- Pulmonary hemorrhage
- Cardiopulmonary arrest
- IVH
- NEC
- Other (if “Other” is selected, record reason in text boxes)
- Unknown

### 17.4. Secondary cause(s) of death

Record the secondary cause(s) of death. Secondary cause(s) of death must be verified by the Attending Physician. If death is unexplained, mark unknown.

Select all that apply:

- Sepsis
- Respiratory disease
- Pulmonary hypertension
- Pulmonary hemorrhage
- Cardiopulmonary arrest
- IVH
- NEC
- Other (if “Other” is selected, record reason in text boxes)
- Unknown

### 17.5. Was life support withdrawn?

Indicate if physician note states that life support was withdrawn.

Select one: Yes, No or Unknown.

### 17.6. What is the relationship of death to study drug/sham?

If death occurred while in hospital, mark relationship between study drug/sham and death as recorded on Form 13A.(Dosing Period) or 13 B (Discharge Period), or on Form 21: Serious Adverse Events.

- Mark not related if it would be impossible to imagine a relationship with study drug/sham administration or TA procedures (e.g., error in clinical care is made which causes adverse event and results in incident report being filed at institution).
- Mark unlikely if it is difficult to conceive of a relationship between adverse event and study drug/sham administration or TA procedures. And, the patient's underlying condition provides a more likely explanation.
- Mark possibly related if it is plausible that adverse event was related to study drug/sham administration or TA procedures. However, the AE . might also be

seen in a patient who did not receive study drug/sham administration or TA procedures.

- Mark probably related if death coincides with study drug/sham administration or TA procedures. Or, death has no other explanation given the patient's clinical state.
- Mark definitely related only if death is associated with study drug/sham administration or TA procedures and cannot reasonably be explained by the patient's underlying condition or a clinical error.

**17.6.a.** Indicate if death was expected or unexpected.

Select one.

- Mark expected if death may be reasonably anticipated to occur as part of the normal disease process or progression.
- Mark unexpected if death exceeds the nature, severity, or frequency described in the current IRB application including the protocol, consent form and Infasurf package insert, or if due to an overdose of study medication, or if due to a deviation from the IRB approved study protocol.

### **17.7 Was an autopsy performed?**

Indicate if an autopsy was performed. Select one: Yes, No or Unknown.

- Mark Yes if autopsy was performed
- Mark No if autopsy was not performed
- Mark unknown if this information is not available

***If autopsy was performed, answer the following:***

**17.7.a.** Record the date of the autopsy

**17.7.b.** Record a brief description of autopsy findings including primary cause of death and findings related to pulmonary and/or brain pathology.

### **PI Signature:**

**Study site principal investigator must review, sign, date and initial Form 17.** Mark Yes or No bubble to indicate that Form 17 has been signed and initialed by PI.



## Protocol Deviations and Violations

These forms are used to notify the CCC and DCC staff of a problem or error that occurs during performance of the study protocol. They should not be viewed as punitive. The information serves both to update the study staff on the status of individual patients as well as to identify potential problem areas in carrying out the study and perhaps preventing future deviations or violations at other sites. The information may also help explain aberrant clinical or laboratory data.

### **Form 18: Protocol Deviations (2 pages)**

Protocol deviations include

- Failure to perform oxygen challenge
- Administration of iNO not in accordance with the NO CLD protocol
- Deviations from clinical management guidelines

Every patient must have Form 18 completed. If no protocol deviations occur, complete Q18.1 and have the PI review, sign, initial and date the form at the bottom of page 2.

Enter 01 in the PD Tracking # fields in the upper right corner of the banner on pages 1 and 2, whether or not a deviation occurred. Submit the form with the completed CRF when the patient is discharged.

If protocol deviations do occur, each time there is a deviation, complete a new Form 18. Enter a protocol deviation tracking form number (PD Tracking #) in the upper right corner of the banner on pages 1 and 2.

- One Form 18 should be submitted for each protocol deviation “category”.
  - If a patient received multiple courses of iNO outside the NO-CLD protocol, you would complete only one deviation for this.
- Enter sequential protocol deviation tracking form numbers (PD Tracking #) each time a protocol deviation category is recorded on a new Form 18 (e.g.01, 02, 03, etc).
- The same PD Tracking # must not be used on more than one set of Forms.
- Fax the completed, signed forms to the DCC at 1-866-226-4607 within 1 week of discharge from the study hospital

#### **18.1. Were there any protocol deviations:**

Indicate if there has been a protocol deviation. Select one: Yes, No or Unknown

- If No is selected, obtain PI signature, initials and date at the bottom of page 2.
- If Yes is selected, complete Form 18 providing information about the deviation that occurred.
- If Unknown is selected, did medical records burn down??? The PI will still need to sign and verify “Unknown”

## **18.2 What is the protocol deviation?**

Fill-in the bubbles of any deviation that occurred.

### **18.2.a.** Failure to perform the oxygen reduction challenge when indicated.

Record a protocol deviation if the patient meets criteria to be eligible for the oxygen/flow reduction challenge test, but does not have the test performed. The oxygen/flow reduction challenge test will only be performed at the study hospital. Record a protocol deviation only if the patient remains in the study hospital, was eligible for testing, but did not receive the testing at 36 weeks  $\pm$  1 week PMA.

Oxygen at 36 weeks is the primary outcome of the study. Every effort should be made to perform the O<sub>2</sub> challenge when a patient qualifies.

- Describe why the oxygen reduction challenge was not done in the study hospital, when indicated.

### **18.2.b.** iNO administration deviated from NO-CLD protocol during iNO treatment. (see NO CLD protocol in Box 1 at the top of Form 6)

Mark this bubble if iNO administration deviated from the NO-CLD iNO dosing schedule during initial iNO treatment (20ppm-10ppm-5ppm-2ppm-Off).

- Record highest concentration of iNO administered during the period of iNO protocol deviation.
- Record the date the highest concentration of iNO, which deviated from the NO CLD protocol was started (after study enrollment)
- Record the end date of the highest iNO concentration, administered which deviated from the NO CLD protocol (after study enrollment)

### **18.2.c.** Additional iNO administered after completing iNO course per NO CLD protocol (see NO CLD protocol in Box 1 at the top of Form 6)

Mark this bubble if iNO was administered after completion of the NO-CLD Dosing schedule.

NOTE: We are most interested in knowing the length of time the baby received the highest dose of iNO off-protocol. Be sure to accurately record the dates below.

- Record highest concentration of iNO administered after completion iNO course per NO CLD protocol
- Record the start date of the highest concentration of iNO administered after completion iNO course per NO CLD protocol
- Record the end date of the highest concentration of iNO administered after completion iNO course per NO CLD protocol

### **18.2.d.** Deviation from Clinical Management Guidelines (No longer recorded as of 4/2011)

See MOP Appendix II for detailed Clinical Management Guidelines

Note: Do NOT record deviations from iNO treatment schedule in 18.2.d

**18.2.e.** Other Protocol Deviation

Mark this bubble if there were other deviations from the study protocol.

**18.2.e.i.** Briefly describe any other protocol deviation in the text boxes.  
Record date of the protocol deviation.

**PI Signature:**

The site PI must review, sign, initial and date this form before it is submitted to the Project Director and faxed to the DCC.

Mark the bubble indicating if the PI signed, initialed and dated From 18.

## **Form 19: Protocol Violations (2 pages)**

Protocol violations require completion of Form 19 for each violation. Using a laser printer, print multiple Forms 19 as needed.

Protocol violations include

- Study inclusion criteria not met at study entry
- Study exclusion criteria were present at study entry
- Consent was not obtained in accordance with IRB guidelines
- Unblinding of study personnel occurred
- Study drug dosing error occurred
- Patient withdrew from entire study (consent withdrawn)
- iNO was not administered at all
- Open label surfactant was administered

Every patient must have Form 19 completed. If no protocol violations occur, complete Q19.1 and have the PI review, sign, initial and date the form at the bottom of page 2.

Enter 01 in the PD Tracking # fields in the upper right corner of the banner on pages 1 and 2, whether or not a violation occurred. Submit the form with the completed CRF when the patient is discharged.

If protocol violation does occur, each time there is a new violation category, complete a new Form 19. Enter a protocol violation tracking form number (PD Tracking #) in the upper right corner of the banner on pages 1 and 2.

- One Form 19 should be submitted for each protocol violation “category”.
  - If a patient received multiple doses of open label surfactant, you would complete only one violation for these doses.
- Enter sequential protocol violation tracking form numbers (PD Tracking #) each time a protocol violation is recorded on a new Form 19 (e.g. 01, 02, 03, etc).
- The same PD Tracking # must not be used on more than one set of Forms.
- Fax the completed, signed forms to the DCC at 1-866-226-4607 within 1 week of discharge from the study hospital

If there have been no protocol violations, it is not necessary to fax Form 19 to the Project Director. Do fax form 19 to the DCC with the other CRFs within 2 weeks after discharge.

### **19.1. Were there any protocol violations?**

Select one: Yes, No or Unknown.

- If No is selected, obtain PI signature, initials and date at the bottom of page 2 and proceed to Form 20.
- If Yes is selected, complete Form 19 providing information about the violation that occurred. Ask PI to review, sign, initial and date at the bottom of page 2.
- If Unknown is selected, did your electronic medical record crash?? The PI will still need to sign and verify “Unknown”

## 19.2 What is the nature of the protocol violation?

Select all that apply.

### 19.2.a. Patient was randomized but all inclusion criteria were not met.

Mark this bubble if patient did not meet inclusion criteria, but was still enrolled. Select all that apply.

- Gestational age was greater than 28 weeks, 0 days
- Chronological age was < DOL 7 or > DOL14 at randomization
- Patient was not intubated and mechanically ventilated
- There was a plan to treat with iNO at the time of randomization, but the iNO was never started

19.2.a.i. Record date of protocol violation

### 19.2.b. Patient was randomized but one or more exclusion criteria were present.

Mark this bubble if patient was randomized but had exclusion criteria present. Select all that apply:

- Serious congenital malformations, defined as
  - life threatening,
  - have the potential to effect pulmonary development
  - have inherent adverse pulmonary consequence,
  - effect, or have the potential to effect, neurodevelopment.
- Chromosomal abnormalities
- Life expectancy < 7 days from enrollment; withdrawal of support planned
- Clinically Unstable at time of randomization
  - Active Pneumothorax with chest tube
  - Active Pulmonary Hemorrhage
  - Uncontrolled hypotension requiring more than 20 mc/kg/min Dopamine or 2 pressor agents for > 24 hours
  - Acute NEC – less than 24 hours from diagnosis or surgery
  - Untreated culture positive sepsis (<6h)
  - Respiratory severity score (RSS) >14
  - Clinical team feels infant would not tolerate dosing procedure
- Bilateral Grade 4 intracranial hemorrhage
- Patient received the first dose of study drug sooner than 48 hours after the last dose of clinically indicated early surfactant.
- Patient enrolled even though ability to determine BPD outcome endpoint at 36 weeks PMA is thought to be unlikely.

19.2.b.i. Record date of protocol violation (use date randomized).

**19.2.c.** Consent to participate and/or HIPAA consent were not obtained in accordance with local RB requirements. Examples: consent obtained after initiation of study activities; consent or HIPAA authorization not obtained

- Record date when the consent related violation occurred.

**19.2.d.** Unblinding of study personnel.

The only persons who are unblinded to treatment assignment at the clinical site are the investigational drug pharmacist(s) and the persons who perform the study drug/sham dosing procedure (study RT/RN). It is a protocol violation if other study personnel become unblinded to the study treatment assignment (Infasurf or sham).

- Record date unblinding of study personnel occurred.

**19.2.e. Study drug administration error**

Any error in administration of the study drug/sham procedures #1- #5 is a protocol violation. Such errors include, but are not limited to, dose not administered (assumes patient is intubated), dose not administered correctly, wrong treatment assignment administered, wrong dose, wrong timing, etc.

- Indicate the Dose where the error occurred (1,2,3,4, or 5)
- Record date study drug administration error occurred.

**Study drug administration errors must be reported within 3 working days. Notify the Project Director at 415-516-4617. Complete Form 19 and fax to the Project Director at 415-514-6353 and to the DCC at 1-866-226-4607 within 3 working days.**

**19.2.f. Withdrawal from entire study (consent withdrawn-data collection stopped).**

Withdrawal from all aspects of study participation in the study (including dosing and data collection) is a protocol violation. If the patient is withdrawn from the study, notify the CCC Project Director. Infants withdrawn from the study by the Study PI or the parents is NOT a Violation. Clinical attending physicians should always consult with the Study PI prior to withdrawing patient. If withdrawal is confirmed by CCC:

- Record date patient was withdrawn from study activities and complete
- Form 20 Record the protocol deviation as "Other" on Form 18.

**19.2.g. Inhaled nitric oxide not administered**

Failure to administration iNO to an enrolled patient is a protocol violation.

- Record date failure to administer iNO occurred (use randomization date)

Note: Administration of iNO outside the guidelines of the NO CLD protocol should be reported only as a protocol deviation, not a protocol violation.

**19.2.i. Open label surfactant administered**

If the attending physician deems that the patient would benefit from late doses of surfactant, the following procedures must be followed:

- Decision must be approved by the site PI and reported to the Project Director at 415-516-4617 within 3 working days.
- Surfactant will not be furnished free for this use
- **DO NOT UNBLIND** - continue the study protocol as appropriate
- Continue collecting TA/urine samples, data collection, AE/SAE reporting as per study protocol
- Report a protocol violation

- Record date open label surfactant administration occurred. If subsequent open label doses are administered, record as subsequent protocol violations.

**PI Signature:**

The site PI must review, sign, initial and date Form 19.

Fax Form 19 for this protocol violation to the Project Director at 415-514-6353 and to the DCC at 1-866-226-4607.

## **Form 20: Early Termination/Permanent Discontinuation of Study Medication (1 page)**

This form is used to record early discontinuation of study procedures. The patient might have all study procedures terminated early. Or, only study drug dosing/sham procedures are discontinued early, but some of the other study activities are continued (data collection, TA and/or urine sampling, oxygen/flow reduction testing, etc.).

Infants who do not complete all study doses due to instability, extubation, but continue in the study for data and Follow-Up, are NOT considered early termination.

Do not report Terminations on Deviation (CRF 18) or Violation (CRF 19) Forms.

Patients who die, should not be considered as terminating study early or discontinuing study.

### **20.1 Indicate whether there has been early discontinuation of any or all study participation.**

Select one: Yes, No or Unknown

If Yes is selected, proceed to Q20.1.a.

#### **20.1.a.** What was discontinued? Select only one bubble.

- Mark the left bubble if study drug/sham dosing has been discontinued early, but the patient remains in the study for data collection, or,
- Mark the right bubble if all study activities have been discontinued early.
- Complete the rest of this page.

20.1.a.i. If only dosing procedures are discontinued, indicate the reasons study drug/sham dosing was terminated early. Select all that apply.

- Parent request
- Adverse Event
- Serious Adverse Event
- Protocol Violation or lack of compliance
- Physician request
- If reason is not listed, select the "Other" bubble and use text box to describe the reason(s).

20.1.a.ii. Record date study drug/sham procedure was discontinued

Note: If study drug is discontinued, iNO needs to be weaned off and stopped as quickly as possible. If clinical team feels the patient needs iNO, they need to switch to commercial gas and delivery device.

20.1.b.i. If ALL study activities discontinued, including TA/ urine samples and data collection, indicate reason(s). Select all that apply:

- Consent withdrawn
- Physician request



- If reason is not listed, mark 'other' and describe reason(s) in text box.

20.1.b.ii. Record the date that all study procedures were discontinued.

**PI Signature:**

Give the completed Form 20 to the PI to review, sign, date, and initial.

**Review: Adverse Event and Serious Adverse Event Reporting Guidelines**

**Adverse Events that are Serious Adverse Events (SAEs)**

These events are defined as SAEs only if they occur between study dosing time plus 7 days)

1. Death within 7 days after study drug/sham procedure (requires 72 hour expedited reporting)
2. Beginning within 4 hours dosing:
  - a. Severe cardiopulmonary decompensation requiring CPR with cardiac medication and chest compressions
  - b. Increase in RSS >5 sustained for >24 hours
3. Beginning within 24 hrs of dosing:
  - a. Severe pulmonary hemorrhage
  - b. Severe PIE
  - c. Pneumothorax requiring chest tube
4. Unexpected and related to study drug administration

**Adverse Events that are not SAE's**

1. Death >7 d after dosing protocol (also fill out death form)
2. Problems with obtaining tracheal aspirate samples
3. Within 4 h of dosing procedure (separate confidential form completed by dosing team).
  - a. Prolonged (>60 seconds)bradycardia/desaturation
  - b. Endotracheal tube problems requiring reintubation
4. CPR requiring cardiac meds/compressions
5. Hypotension requiring vasopressor support for > 24 h
6. Co-Morbidities occurring after enrollment in study (details are described in CRF and MOP)
  - a. Neurologic (IVH, PVL, hydrocephalus)
  - b. GI (NEC, perforation, surgery)
  - c. Pulmonary (PIE, pulmonary hemorrhage, pneumothorax, tracheomalacia, stenosis, vocal cord paralysis)
  - d. Cardiovascular (PDA - with or without surgery, pulmonary hypertension)
  - e. Sepsis (bacterial, fungal, viral)
  - f. ROP (any ROP diagnosed)
  - g. RSV pneumonia
7. Unexpected adverse events (medication errors, catheter complications etc)

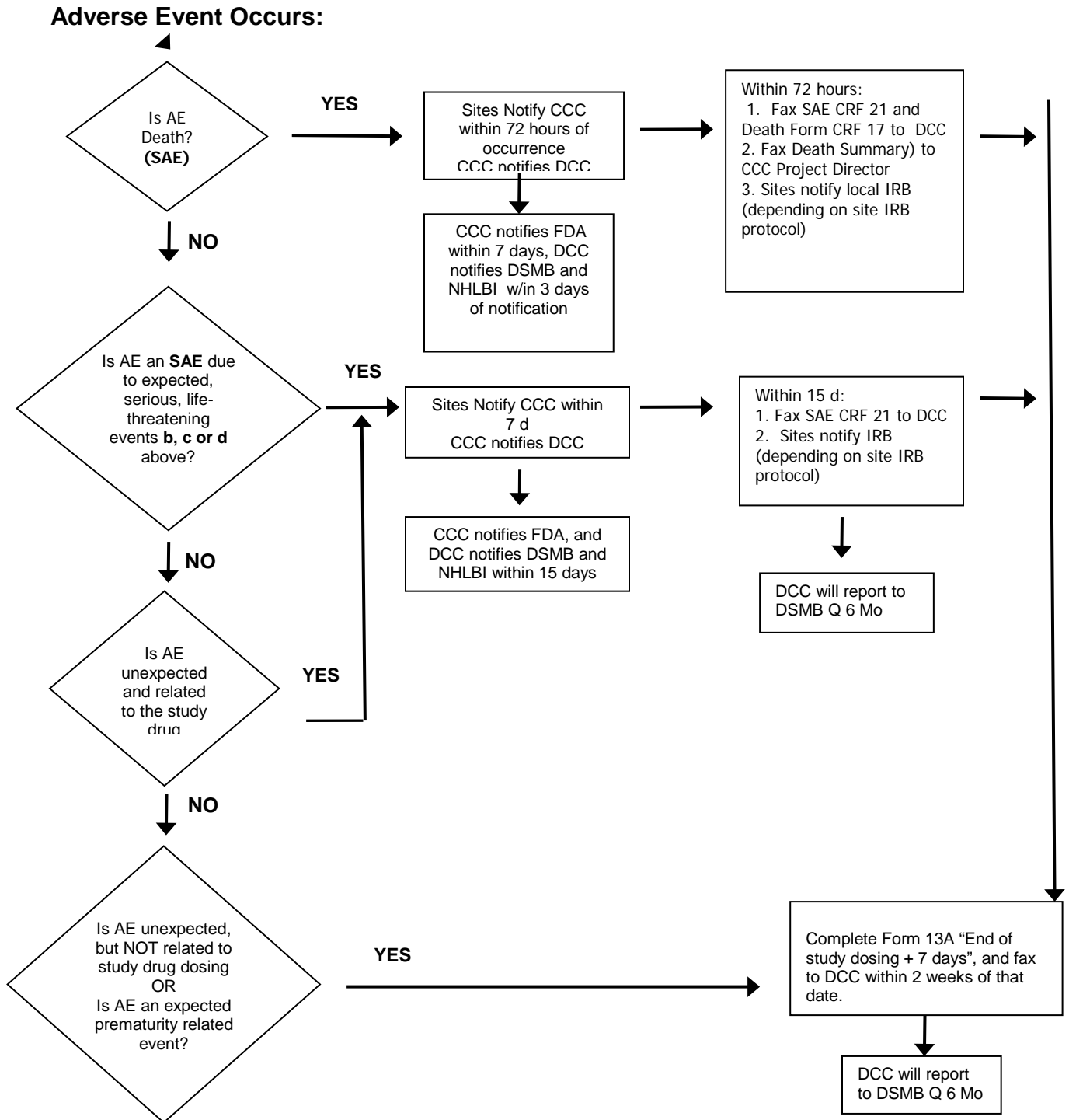
**NOT TO BE CONSIDERED AEs** – common problems encountered in the clinical care of these infants such as feeding intolerance, or electrolyte imbalance will not be considered AEs

**AE/SAE Reporting Timeline**

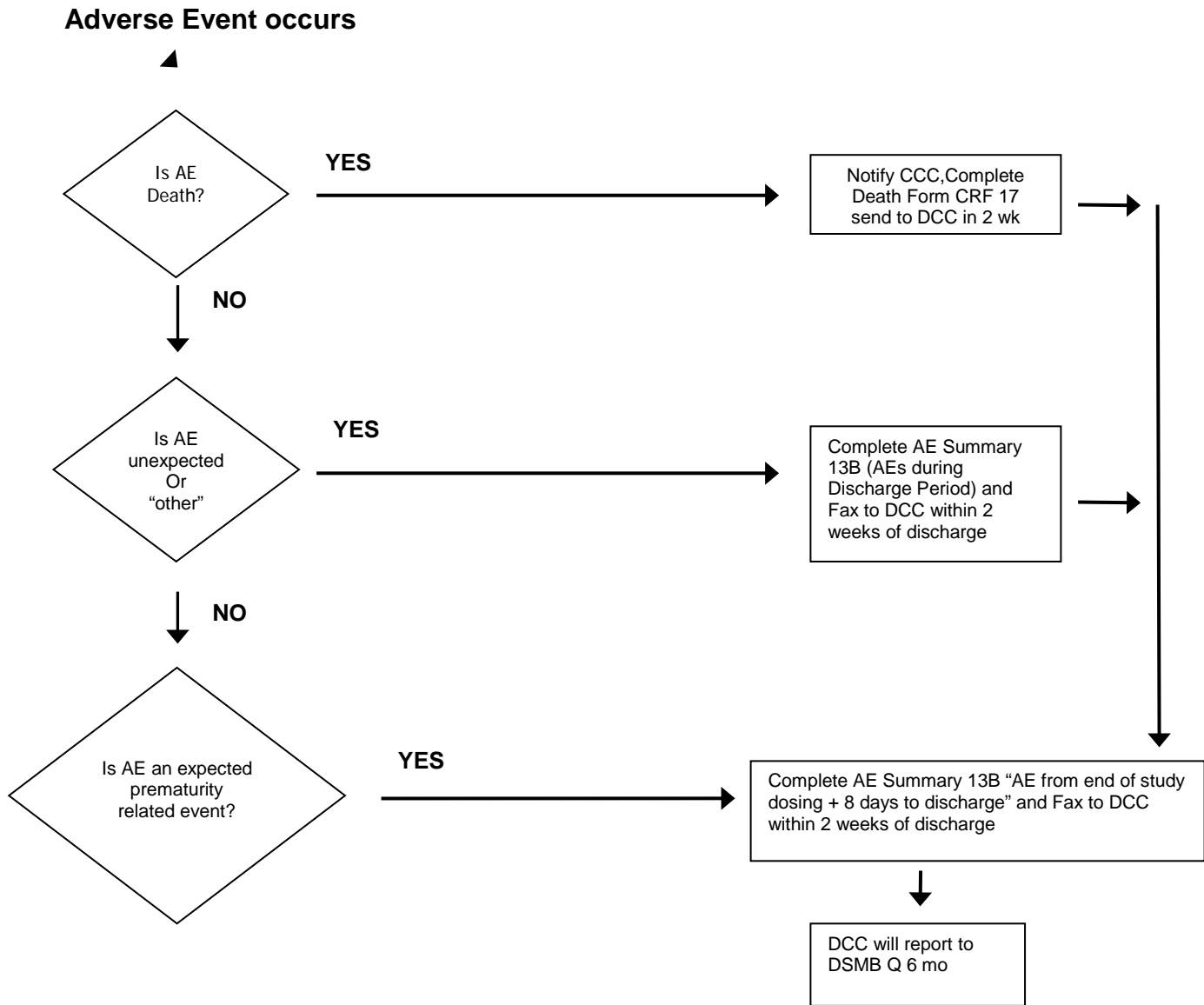
SAE's include the following events:

- a) death if it occurs between enrollment and 1 week (7 days) after dosing completed:
- b) severe respiratory decompensation requiring CPR with chest compressions/cardiac meds within 4 hours of dosing
- c) Increase in RSS >5 from baseline sustained for >24 hours
- d) severe pulmonary hemorrhage, severe PIE, or pneumothorax within 24 hours of dosing
- e) unexpected and related to study drug administration

**SCHEMATIC FOR EVENTS THAT OCCUR BETWEEN ENROLLMENT AND 7 DAYS AFTER DOSING COMPLETED:**



**EVENT OCCURS > 7 DAYS AFTER DOSING COMPLETED:**



**Fax and contact numbers for SAE reporting:**

- Notify Nancy Newton, CCC Study Project Director
  - Cell phone: 415.516.4617
  - Pager: 415.443.4190
  - Fax: 415.514.6353
- Fax SAE Form 21 teleform to the DCC at 1-866-226-4607

## **Form 21: Serious Adverse Events (4 pages)**

Serious adverse events require timely reporting to the site PI, the CCC Project Director (PD) and the DCC. Refer to the Serious Adverse Event/Adverse Event Reporting Flowchart in MOP Section II.10.0 for reporting requirements.

- Fax Form 21 to the CCC Project Director at 415-514-6353 and to the DCC at 1-866-226-4607
- Notify your site IRB according to local IRB requirements

See CRF Completion Guidelines Section 21.1 for definitions of severity, relationship to study drug, actions taken, outcome, causality and type of event.

This form is used to record all serious adverse events (SAEs) that occur after administration of study drug/sham procedures. Selected adverse events (AEs) which are both severe and occur in specified time periods surrounding study drug/sham dosing procedures also qualify as serious adverse events (SAEs). SAEs should be recorded on both Form 13A; Adverse Events during Dosing Period, Post-Enrollment to Date of Final Dosing + 7 Days and on Form 21: Serious Adverse Events.:

Each SAE should be recorded on a separate Form 21 with an individual SAE number. Serious adverse events require timely reporting to the site PI, the CCC and the DCC. Refer to MOP Section II.10.0 Serious Adverse Event/Adverse Event Flowchart for the reporting algorithm.

- Each time a serious adverse event occurs, fax a completed Form 21 to the office of the CCC Project Director, Nancy Newton, at 415-514-6353 and to the DCC at 1-866-226-4607 within 3 working days.
- Enter a unique SAE form number (SAE #) in the upper right corner of the banner. One Form 21 should be submitted for each SAE.
- If more than one set of Form 21 is submitted, enter sequential SAE # each time a SAE form is submitted (i.e. 01, 02, 03 etc.).
- The same SAE # must not be used on more than one set of Form 21.

The following are defined as serious adverse events:

**Death occurring between enrollment and  $\leq 7$  days after a study drug/sham dosing procedure.** Death during this time period requires expedited reporting within 72 hours (3 working days). Report the death to the site PI and the CCC Project Director. Complete Form 17: Death Report and Form 21: Serious Adverse Events and fax to the Project Director at 415-514-6353 and to the DCC at 1-866-226-4607 within 3 working days.

- Events listed below that **occur  $\leq 4$  hours** of a study drug/sham dosing procedure. Requires reporting within 7 days.
  - Severe respiratory decompensation defined as increase in respiratory severity score (RSS)  $> 5$  above baseline sustained for  $> 24$  hours (RSS = FIO<sub>2</sub>x MAP).
  - Severe cardiopulmonary decompensation requiring CPR with chest compressions and cardiac medications
- Events listed below that **occur within 24 hours** after a study drug/sham dosing

procedure. Requires reporting within 7 days.

- Severe PIE
- Severe pulmonary hemorrhage
- Pneumothorax requiring a chest tube
- Unexpected adverse event (that is felt to be related to study drug administration.)

If the above events occur outside of the time periods described, the events are not defined as SAEs. They should be reported only as AEs on Forms 13A and/or 13B.

### **21.1 Has a serious adverse event occurred since administration of study drug/sham?**

Select “Yes” or “No”.

If “No”, complete form with PI review, signature, initials and date on page 4.

If “Yes”, mark yes and proceed to Q 21.1. through 21.7. and record descriptions in 21.1a thru 21.7a.

- Identify SAE(s) that occurred by marking specific bubble(s).
- When recording SAE refer to the instructions below for reporting severity, relationship to study drug, action taken, outcome, causality and type of event.

### **Severity, Relationship to Study Drug, Action Taken, Outcome, Causality And Type of Event**

- Indicate if reported to IRB, no or yes.
- Record the date of the SAE
- Severity

Indicate the SAE level of severity from list

- Enter 1 for mild: defined as a problem unlikely to have an effect on the hospital course of the infant.
  - Enter 2 for moderate: defined as a problem that might have an impact on the infant’s hospital course (e.g., PDA opens and requires ligation).
  - Enter 3 for severe: defined as an adverse event likely to prolong infant’s hospital course.
  - Enter 4 for life-threatening: defined as an event that may result in death or certainly will prolong the infant’s hospitalization (e.g., NEC with perforation requiring surgery).
  - Enter 8 if severity is unavailable or unknown
- Relationship to study drug  
Indicate if the SAE was a result of administration of the study drug/ sham. This relationship must be determined by the principle investigator at study the site.
    - Enter 1 for not related if it would be impossible to imagine a relationship with Infasurf (e.g., error in clinical care is made which causes adverse event and results in incident report being filed at institution).
    - Enter 2 for unlikely if it is difficult to conceive of a relationship between adverse event and Infasurf and infant’s underlying condition is a better explanation.
    - Enter 3 for possible if it is plausible that adverse event was related to Infasurf. However, the AE might also be seen in an infant that did not receive Infasurf.
    - Enter 4 for probably if the adverse event that coincides with the delivery of Infasurf or has no other explanation in infant’s clinical state.

- Enter 5 for definitely related only for adverse event that is associated with Infasurf treatment and cannot reasonably be explained by the infant's underlying condition.
  - Enter 8 if information is unavailable
- Action Taken
 

Indicate action taken in response to the SAE.

    - Enter 1 for N/A if no action was taken
    - Enter 2 if study drug was discontinued (i.e. complete dose not given or subsequent dose not given)
    - Enter 3 if standard care was administered
    - Enter 8 if action is unavailable or unknown
- Outcome
 

Use this column to indicate outcome

    - Enter 1 if the SAE was resolved and the infant recovered from adverse event regardless of whether adverse event felt to be related to study drug/sham or any action was taken (e.g., infant has sepsis, is treated and recovers).
    - Enter 2 for improved if infant's clinical condition improves following adverse event regardless of relationship to study drug/sham.
    - Enter 3 for unchanged for adverse event where clinical condition remains unchanged (e.g., infant develops Grade II IVH after study drug/sham procedure and is unchanged at discharge).
    - Enter 4 for worsened for infant who has a worse outcome (prolonged hospitalization, chronic illness) as a result of serious adverse event -regardless of relationship to study drug/sham (e.g., infant develops NEC requiring surgery and has short bowel syndrome requiring prolonged TPN).
    - Enter 5 for DEATH. Enter 8 if outcome is unavailable or unknown
- Causality
 

Use this column to indicate suspected etiology of event.

    - Enter 1 if the SAE was not related to the study drug/sham.
    - Enter 2 if etiology of the SAE was due to Concomitant medications given to the infant.
    - Enter 3 if etiology of event was due to the patient's underlying disease or condition. (e.g., infant develops Grade II IVH after study drug/sham procedure and is unchanged at discharge).
    - Enter 4 if etiology of event was due to study drug/sham dosing
    - Enter 5 if etiology of event is UNKNOWN. NOTIFY site IRB per site IRB guidelines and Project Director within 72 HOURS.
    - Enter 6 if etiology of even is other than those listed above.
- Type of AE/SAE
    - Mark expected if the adverse event may be reasonably anticipated to occur as a result of the study procedures or study participation and should thus be described in the research proposal, the informed consent document and Infasurf package insert, or is part of the normal disease process or progression.
    - Mark unexpected if the adverse event exceeds the nature, severity, or frequency described in the current IRB application including the protocol, consent form and Infasurf package insert. An unexpected AE also includes any AE that meets any of the following criteria:
      - Results in subject withdrawal from study participation
      - Due to an overdose of study medication
      - Due to a deviation from the IRB approved study protocol

Use the narrative section of Form 21 to record a brief description of each Serious Adverse Event.

21.1.a. Death

21.2.a. Severe Respiratory Decompensation

21.3.a. Severe Cardiopulmonary Decompensation

21.4.a. Severe Pulmonary Hemorrhage

21.5.a. Severe PIE

21.6.a. Pneumothorax

21.7.a. unexpected serious adverse event related to and occurring within 7 days of study drug/sham procedure

**PI Signature:**

Principal Investigator MUST review, sign, date and initial all Forms 21 prior to submission to the DCC submitted.

NOTE: Submit Form 21 each time an SAE occurs (enter sequential SAE numbers in upper banner beginning with "001"). If there were no SAE's, submit with forms 11A and 13A at the end of the dosing period (enter "001" as SAE number, for DCC tracking purposes).

Questions? Contact:

Nancy Newton MS, RN  
Project Director, TOLSURF Study  
UCSF Department of Pediatrics  
Campus Box 0560  
185 Berry Street, Lobby 5, Suite 5700  
San Francisco, CA 94107  
Office: 415.514.6257  
Mobile: 415.516.4617  
Pager: 415.443.4190  
Fax: 415.514.6353  
[newtonn@peds.ucsf.edu](mailto:newtonn@peds.ucsf.edu)

Jeanette Asselin MS, RRT  
Project Clinical Coordinator, TOLSURF Study  
Neonatal-Pediatric Research Group  
Children's Hospital and Research Center Oakland  
747 52<sup>nd</sup> Street  
Oakland, CA 94609  
Office: 510.428.3763  
Cell: 510.813.1177  
Fax: 510.450.5896  
Pager: 510.539.3953  
[jasselin@mail.cho.org](mailto:jasselin@mail.cho.org)

## **7C. DOSING INTOLERANCE DURING STUDY DRUG/SHAM DOSING PROCEDURE FORM**

This form is to be completed by the unblinded dosing team (RT/ RN) after the dosing procedure to document patient tolerance of the dosing intervention. This form is confidential and should not be shown to any blinded clinical or study personnel.

Each of the 5 dosing procedures should be documented on it's own specific page. All 5 pages should be completed whether a dose is given or not. Make copies of all 5 pages and then mail to the DCC in the envelopes provided.

**7C.1. Number of Study Drug Dose/Sham:** These bubbles (1 through 5) will be pre-filled. Use the appropriate page for the dose you are administering.

**7C.1.a.** Was the study drug dose/sham administered? Indicate Yes or No by filling in the appropriate bubble. If dosing procedure was initiated, and any part of dose was administered, check "yes".

If "yes" is chosen, complete the following:

7C.1.a.i. Record the dosing procedure start date and time. This is the time the screen is placed around bed and the dosing procedure begins.

7C.1.a.ii. Record the dosing procedure end date and time. This is the time dosing is complete and the screen is removed from the bedside.

Dosing Tolerance:

Fill in the appropriate bubble "Yes, No, or Unknown" to indicate if patient had evidence of:

7C.1.a.iii. Desaturation less than 75% for greater than 60 seconds..

7C.1.a.v. Bradycardia less than 80 for greater than 60 seconds.

7C.1.a.iv. Patient required reintubation during dosing procedure.

**Unblinded RT/RN MUST complete, sign, date and initial all Dosing Tolerance Forms (7C) prior to mailing to the DCC.**

Once this Dosing Tolerance Form is completed. Place in envelope provided and seal for safekeeping until all doses have been administered (or dosing is completed).

All dosing Tolerance Forms must be sent in, even if doses not administered.



# IV. Appendices

## **APPENDIX A. Participating Sites**

- 01 University of California San Francisco Children's Hospital, San Francisco, CA
- 02 Children's Hospital and Research Center, Oakland, CA\*
- 03 Alta Bates Summit Medical Center, Berkeley, CA\*
- 04 Children's Mercy Hospital, Kansas City, MO,
- 05 Women and Children's Hospital of Buffalo, Buffalo, NY
- 06 Children's Memorial Hospital, Chicago, IL\*
- 07 Northwestern Prentice Women's Hospital, Chicago, IL,\*
- 08 Baylor Texas Children's Hospital, Houston Texas
- 09 Stony Brook University Hospital, Stony Brook, NY
- 10 University of Washington, Seattle, WA
- 11 University of Texas Houston, Houston, TX
- 12 Wolfson Children's, Jacksonville, FL\*
- 13 Shands Hospital, Jacksonville, FL\*
- 14 Wake Forest University – Brenner Hospital, Winston Salem, NC\*
- 15 Wake Forest University – Forsyth Hospital, Winston Salem, NC\*
- 16 Children's Hospital and Clinics of Minnesota, St Paul, MN
- 17 University of Minnesota Children's Hospital, Minneapolis, MN
- 18 Medical University of South Carolina Children's Hospital (MUSC), Charleston, SC
- 19 UT Memphis, Memphis, TN
- 20 University of Minnesota, St Paul, MN
- 21 All Children's Hospital, St Perersburg, FL

\*= 2 hospitals involved in one city

## **APPENDIX B. Clinical Management Guidelines**

### **I. Guidelines for ventilation & oxygenation**

Oxygen saturation limits (until 32 weeks' PMA)

1. Target saturations 85-94%
2. Set saturation monitor limits (depending on individual center saturation targets)
3. Lower: 80-85%
4. Upper: 92-95%

Mechanical ventilation guidelines—conventional ventilation

1. Appropriate PEEP to maintain lung inflation. Usually 5-7 cmH<sub>2</sub>O.
2. Tidal volume 3-7 mL/kg (usually 4-6)
3. PCO<sub>2</sub> target 45-70 mmHg
4. pH target ≥ 7.15 (most want >7.20)

Suggested criteria for reintubation (until 32 weeks' PMA)

**Note: some patients, particularly if unstable or with increased work of breathing may be re-intubated earlier**

1. Inability to maintain target saturation despite NCPAP > 8, nasal ventilation or high flow nasal cannula > 3 liters per minute with FIO<sub>2</sub> > 0.6
2. PCO<sub>2</sub> consistently > 70 mmHg
3. pH consistently < 7.15
4. Recurrent or severe (requiring bag mask ventilation) apnea despite maximal caffeine therapy and NCPAP

### **II. Guidelines for caffeine citrate use**

Caffeine citrate therapy should be considered for infants with gestational age less than 31 weeks, who are less than 10 days of age and require mechanical ventilation or CPAP, for the following indications: apnea prophylaxis, apnea treatment, facilitation of extubation.

Recommended regimens

1. Caffeine citrate IV/PO load 20 mg/kg/dose x1
2. Caffeine citrate maintenance IV/PO 5-10 mg/kg/dose once daily until 32-34 weeks post menstrual age even if infant remains intubated.

Considerations

1. If central apnea occurs / persists on caffeine therapy and other causes of apnea have been ruled out, then caffeine dose may be adjusted by increasing the maintenance dose by 1-3 mg/kg/dose (if HR < 180) to a maximum maintenance dose of 10 mg/kg/dose. In addition, one may also consider an additional caffeine bolus of 10mg/kg. When adjusting caffeine dose, give the bolus immediately regardless of timing of the last maintenance dose. Base timing of subsequent doses from the time the bolus is administered.

2. Schmidt B et al. Caffeine therapy for apnea of prematurity. NEJM 2006; 354:2112-2121.

3. Davis PG, Schmidt B, Roberts RS, Doyle LW, Asztalos E, Haslam R, Sinha S, Tin W; for the Caffeine for Apnea of Prematurity Trial Group. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. J Pediatr. 2009 Nov 17. [Epub ahead of print]

### **III. Guidelines for glucocorticoids for lung disease**

Potential candidates for initiation of glucocorticoids—***try to avoid administration!***

1. Infants at least 2 weeks of age
2. Other therapies optimized
3.  $RSS \geq 7$  ( $RSS = MAP \times FiO_2$ )
4. No contraindications to glucocorticoid therapy
  - a. indomethacin exposure within 48h
  - b. Systemic hypertension
  - c. Active infection with < 24 hours of appropriate antibiotics

Regimen guidelines (**short course**)

1. Hydrocortisone (total dose 5 mg/kg)
  - Day 1 – 3 mg/kg/d divided q 12h
  - Day 2 – 1.5 mg/kg/d divided q 12h
  - Day 3 – 0.5 mg/kg/d divided q 12h
2. Dexamethasone (total dose 0.45 mg/kg = HC 6.75-9 mg/kg (15 – 20x))
  - Day 1 – 0.2mg/kg/d divided q12h
  - Day 2 – 0.15 mg/kg/d divided q12h
  - Day 3 – 0.1 mg/kg/d divided q12h

Regimen guidelines (**long course**)

**Note: Discontinue or rapid taper ( $\frac{1}{2}$  dose x 24h,  $\frac{1}{4}$  dose x 24h then off) if no response after 48h. Response defined as ability to wean ventilator and oxygen.**

1. Hydrocortisone (total dose 15 mg)
  - Day 1-3 – 3 mg/kg/d divided q 12h
  - Day 4-6 – 1.5 mg/kg/d divided q 12h
  - Day 7-9 – 0.5 mg/kg/d divided q 12h
2. Dexamethasone (total dose 0.89 mg/kg = HC 13.35-17.8 mg/kg (15-20x))
  - Day 1-3 – 0.15 mg/kg divided q 12h
  - Day 4-6 – 0.1 mg/kg/d divided q 12h
  - Day 7-8 – 0.05 mg/kg/d divided q 12h
  - Day 9-10 – 0.02 mg/kg/d divided q 12h

Considerations

1. If infant requires surgery while on steroid course, consider stress dose hydrocortisone 2-4 mg/kg/d divided q 6-12h x 24h
2. If infant develops hypotension or other signs of adrenal insufficiency after completion of steroid course, go back on most recent dose x 24h, then taper to  $\frac{1}{2}$  dose x 24h and then  $\frac{1}{4}$  dose x 24h
  1. May repeat short course at 7-10d if infant meets criteria

#### **IV. Guidelines for glucocorticoids for hypotension**

Potential candidates for initiation of glucocorticoids for hypotension.

1. Inadequate response to vasopressor therapy (dopamine  $\geq$  20 mcg/kg/min  $\pm$  dobutamine or epinephrine) with *either*:
  - a. persistent hypotension despite fluid resuscitation, or
  - b. inability to wean medications for > 48h
2. No contraindications to glucocorticoid therapy
  - a. Indomethacin exposure within 48h
  - b. Active infection with < 24 hours of appropriate antibiotics

##### Regimen guidelines

1. Hydrocortisone (total dose 5 mg/kg). Some infants may respond to initial 1-2 doses, making further dosing unnecessary.

Day 1 – 1-2 mg/kg/d divided q 8-12h

Day 2 – 1 mg/kg/d divided q 8-12h

Day 3 – 0.5 mg/kg/d divided q 12h

##### Considerations

1. If infant requires surgery while on steroid course, consider stress dose hydrocortisone 2-4 mg/kg/d divided q 6-12h x 24h
2. If infant develops hypotension or other signs of adrenal insufficiency after completion of steroid course, go back on most recent dose x 24h, then taper to  $\frac{1}{2}$  dose x 24h and then  $\frac{1}{4}$  dose x 24h, then discontinue.

#### **V. Guidelines for Vitamin A therapy (if being used)**

Candidates for initiation of Vitamin A

1. All infants < 1000 g birth weight
2. Infants 1000-1250 g birth weight if ventilated > 24h

##### Dosing regimen

5000 Units IM every M, W, F x 4 weeks

May be discontinued prior to 4 weeks of treatment if infant reaches full enteral feeds (150 mL/kg of premature formula or fortified breast milk or 120 mL/kg of premature formula with 1 mL/d Poly-Vi-Sol)

Vitamin A use should be consistent among all infants at any site.

**APPENDIX C. Worksheet for Oxygen/Flow Reduction Challenge**

## **APPENDIX D. Pharmacy Guidelines**

### **Treatment of Late Surfactant to Prevent BPD The TOLSURF Study**

Pharmacy Study Guidelines – 3/4/10

Thank you for assisting with this study. This is a controlled trial of late surfactant for prevention of bronchopulmonary dysplasia in premature infants ventilated between 7 and 14 days of life. Infants will be randomized to receive either study surfactant (Infasurf® dosed at 3 mL/kg), or placebo (a sham procedure with no manipulation of the patient). The dosing schedule is 0 hrs (at study entry), then every 2-3 days for a total of 5 doses (if patient remains intubated). If the infant is deemed clinically unstable dosing will be delayed. When the infant is considered stable by the clinical team, dosing will be resumed on the every 2-3 day schedule until a maximum of 5 doses have been given.

Before enrollment begins at your site, you will receive the TOLSURF Study “Randomization Log” in a sealed envelope and a template letter for ordering study Infasurf® from the Clinical Coordinating Center (CCC) pharmacist at UCSF. Please use only the Infasurf® supplied by UCSF.

Once parental consent is obtained, your site study coordinator will receive a study Randomization ID # from the Clinical Coordinating Center (CCC) at UCSF. Randomization ID’s are 6-digit numbers, “00-00-00”. The first 2 digits reflect your site ID number, the second 2 digits reflect the consecutive number from “Stratification Cohort”, and the third 2 digits reflect the infant’s birth status: singletons will be “01”, second infant enrolled of twins will be “02” and the third infant enrolled of triplets will be “03”.

#### **Pharmacy Order**

A pharmacy order will then be written that identifies patient as a TOLSURF Study patient. Order should include:

- Order for “Study Surfactant”
- Infant’s Randomization ID #
- Infant’s gestational age
- Infant’s current weight

#### **Randomization Log**

Randomization treatment group codes were created by the Data Coordinating Center (DCC) study statistician. Electronic copies are stored in a password-protected, non-network computer. A paper copy is filed in a sealed envelope and stored in a locked cabinet at the UCSF DCC.

The site-specific pharmacist will receive the randomization key (unblinded treatment assignments) for that hospital in a sealed envelope via FedEx from the DCC.

Refer to the TOLSURF “Randomization Log” for study group assignment. Randomization Tables are identified by gestational age stratification:

## **Stratification**

1. Stratified by gestational age

- Gestation Age 26-28 weeks randomization numbers will range \_\_:01:\_\_ to \_\_:48:\_\_

- Gestation Age < 26 weeks randomization numbers will range \_\_:49:\_\_ to \_\_:99:\_\_

2. Within stratification, infants will be assigned Group A or Group B (randomization key will be sent separately to the site pharmacists).

3. Randomization Log was created to accommodate singletons, twins or triplets enrolled in the study.

- **Siblings from multiple births will be given the same study treatment**

(e.g.: sibling 2 and 3 will receive randomization group of sibling 1).

4. Locate patient Randomization ID on your Randomization Tables. Record Infasurf® Lot # (or “N/A” if sham) and date dispensed.

An Investigational Drug Inventory Log will be provided for invoicing receipt of study drug (Infasurf®).

## **Drawing up Study Drug**

Study drug doses are to be divided into two syringes of Infasurf® (1.5 mL/kg each). Sham syringes should also be divided into two syringes of AIR (1.5 ml/kg in each). Prepare the Infasurf® or “sham” syringes and place them in an opaque envelope. Unblinded dosing personnel will pick up the envelope and take it to the bedside.

## **Pharmacy Binder**

You will receive a TOLSURF Pharmacy Study Binder containing:

1. Pharmacy Study Guidelines
2. Infasurf Package Insert
3. Transferred Patients Log (for use if you are a referral center and have another TOLSURF site in your city between which patients might be transferred)
4. Template Letter for ordering Infasurf® supply from Scott Fields, the investigational drug pharmacist at UCSF.
5. Additional indexed tab sections will be included for filing the:
  - protocol and consent approved by your site IRB
  - Copies of the signed consents for your enrolled subjects (as appropriate).
  - \*Randomization Key
  - \*Randomization Log

\* Randomization Log and Randomization Key will be sent by the DCC in a sealed envelope by Fed Ex to the research pharmacist at the study sites.

## **Transferred Infants**

Several of the study sites\* may receive transferred infants who were randomized at another study hospital. For these patients, a “Transferred Patients Log” is provided.



The Pharmacy order for these patients will identify a different site than you have on your Randomization Logs.

For transferred patients, the study coordinator will give you contact information for the referring hospital pharmacy. Please call the referring hospital pharmacist to obtain the previously assigned randomization assignment. Do not enter these patients on the Randomization Log at your hospital. The patient's original randomization number should be recorded on your Transferred Patient's.

- On "Transferred Patients Log" record patient Randomization ID from the referring center, Infasurf® Lot # (or "N/A" if placebo), and date dispensed.

\* Oakland Children's/Alta Bates, Chicago Children's Memorial/Northwestern Prentiss, Wake Forest Brenner-Baptist/Forsyth, Jacksonville Wolfson/Shands

**Randomization Description from Protocol 6.1.1:**

5.3 Randomization. Randomization tables will be prepared by the DCC and sent to the Pharmacist at the sites. This study has been designed to allow for randomization 8 AM to 5 PM during week days. The site coordinator will phone the Project Director and confirm that the infant meets the eligibility criteria and determine if the infant is part of a multiple birth. If eligibility is confirmed, a randomization ID number will be assigned to the patient and instructions given to the site to enroll the infant. The physician will write the order for respiratory therapy to begin iNO (if not already started) and to the pharmacy to assign the next treatment to the infant. The Project Director will complete an entry on her log giving the date, time, patient ID, randomization number, etc. These can later be confirmed against the clinical center records. Only the pharmacist and dosing RRT/RN will be unblinded to treatment assignment. Patients will be stratified by gestational age (<26 and 26-28w) and by site and randomized to one of two groups: a) iNO with sham instillation and b) iNO and Infasurf®. To ensure balance within clinical centers and with respect to the key prognostic variable, gestational age, the randomization will be implemented using randomly permuted blocks of length 4 and 8, randomly varying, to ensure approximate balance at every time point and to make successive assignments harder to guess. The sequence of assignments for each site and stratum will be prepared in advance by the DCC. Since we have found that parents of multiple births who participate in a clinical study have a strong preference that each of their children receives the same treatment, in this trial, the first infant will be randomized according to the permuted block design. Subsequent infants from a multiple birth will be assigned to the same treatment group as the first infant. This is equivalent to randomizing the mother and will be accounted for in the analysis as described below.

There is one person at the DCC who is unblinded to randomization and treatment arm assignment. For questions of this nature contact Lisa Palermo: [Palermo@psg.ucsf.edu](mailto:Palermo@psg.ucsf.edu), the study statistician.

For questions contact Nancy Newton, Project Director or Jeanette Asselin, Project Coordinator

Nancy Newton MS, RN  
Office: 415.514.6257  
Cell: 415.516.4617  
Pager: 415-443-4190

Jeanette Asselin MS, RRT  
Office: 510.428.3763  
Cell: 510.813.1177

**APPENDIX E. Discharge Breathing Outcome Questionnaire Script and Contact Information Forms**

**TOLSURF CONTACT INFORMATION FORM**

Baby's Name	AKA	Screening ID #	Secondary ID	Randomization #

**DO NOT FAX TO THE DCC**

Collect this contact information from parent/guardian at time of discharge from study hospital. This confidential information should be kept in a locked file and office and should not leave your Institution.

**Family Contact Information:**

Parent #1 name: \_\_\_\_\_  
First Last (if single) AKA Last (if married)

Relationship to baby: \_\_\_\_\_

Address: \_\_\_\_\_  
Street Apt. #

\_\_\_\_\_ City State Zip Code

Home phone #: \_\_\_\_\_ Work phone #: \_\_\_\_\_

Cell phone #: \_\_\_\_\_ Email: \_\_\_\_\_

Parent #2 name: \_\_\_\_\_  
First Last

Relationship to baby: \_\_\_\_\_

Address: \_\_\_\_\_  
Street Apt. #

\_\_\_\_\_ City State Zip Code

Home phone #: \_\_\_\_\_ Work phone #: \_\_\_\_\_

Cell phone #: \_\_\_\_\_ Email: \_\_\_\_\_

**Alternate Contacts (family/friends who will know how to reach you over the next 2 years):**

Grandparent #1 name: \_\_\_\_\_  
First Last

Parent of: \_\_\_\_\_

Address: \_\_\_\_\_  
Street Apt. #

\_\_\_\_\_ City State Zip Code

Home phone #: \_\_\_\_\_ Work phone #: \_\_\_\_\_

Cell phone #: \_\_\_\_\_ Email: \_\_\_\_\_

(continued on page 2)

**APPENDIX F. Sample CRF and Dosing Tolerance Form**

**ATTENTION: THIS FORM CONTAINS UNBLINDED INFORMATION**

**TOLSURF** DO NOT FAX THIS FORM TO THE DCC.

THIS FORM IS TO BE MAILED TO THE DCC. SEE MOP FOR HANDLING INSTRUCTIONS REGARDING THIS FORM.

**DOSING INTOLERANCE DURING STUDY  
DRUG/SHAM DOSING PROCEDURE**

Screening ID #	Secondary ID	Randomization #
□□ : □□	□□□□	□□ : □□ : □□

Page □ of 5

This form is to be completed during the dosing procedure, by the unblinded dosing RT or RN. Data on this form should NOT be shown to anyone who is blinded. Please follow your site's procedures regarding the handling of the form. (see MOP)

EACH DOSING PROCEDURE IS DOCUMENTED ON ITS OWN PAGE AND ALL 5 PAGES OF THIS FORM MUST BE COMPLETED.

7C.1. **STUDY DRUG DOSE #/SHAM:**     #1    #2    #3    #4    #5

7C.1.a. Was this study drug dose/sham administered?     Yes    No    Unknown

7C.1.a.i. Dosing procedure Start Date/Time:	□□ / □□ / □□	□□ : □□
	Month   Day   Year	24 hour clock
7C.1.a.ii. Dosing procedure End Date/Time:	□□ / □□ / □□	□□ : □□
	Month   Day   Year	24 hour clock
<b>Report dosing intolerance during this study drug/sham dosing procedure below :</b>		
7C.1.a.iii. Desaturation < 75% for > 60 sec	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	
7C.1.a.v. Bradycardia <80 for >60 sec	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	
7C.1.a.vi. Required reintubation	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown	

\_\_\_\_\_  
Signature of Unblinded RT or RN

Form signed?    Yes    No

Unblinded RT or  
RN Initials:    □□

□□ / □□ / □□  
Date of signature (mm/dd/yy)

TOLSURF [DRC] v1.0, 01/08/10

# APPENDIX G. CRF Faxing Schedule and Log

Study ID: \_\_\_\_\_

**Make a copy of this form for each patient.** Order of CRFs to fax is listed by when they are due, not by CRF number. Fax the entire original CRF packet to the UCSF/CCC fax # below. Try to keep multiple pages in CRF section sets in numerical order when faxing. To insure timely data entry and safety evaluation and reporting, CRFs should be faxed at the times listed below. Keep this log up-to-date. Original forms should stay on site at the study hospital.

Fax the forms to DCC (no cover sheet!) to: 1-866-226-4607

* CRF	When CRF Due to be Faxed to DCC	Date Fax'd DCC	Initials
1 CRF 1A	Fax completed Forms 1A weekly (Fax to DCC 1 <sup>st</sup> , for all enrolled babies)		
1 CRF1B	Fax within 24-48 hours of patient enrollment		
2 CRF2-5	Fax within 2 weeks of enrollment		
2 CRF 7A	Fax within 1 week of <u>initial</u> study drug/sham dosing procedure		
2 CRF 7B (2 thru 5)	Fax Forms 7B pages 2 - 5 within 1 week after <u>final</u> dosing procedure		
3 CRF 11A	Fax within 1 week of the date of "last study drug dose + 7 days".		
3 CRF 13 A	- 13A.2: If death is ≤ 7 days of study drug dosing procedure, fax within 72 hours. - 13A.3 and 13A.4: If severe respiratory or cardioplumunary decompensation occurs ≤ 4 hours of study drug/sham dosing procedure, fax within 2 weeks of event. - 13A.5 – 13A.7 : if severe PIE, Pulmonary hemorrhage or ptx requiring chest tube occur ≤ 24 hours of study drug/sham dosing procedure, fax within 2 weeks of event. If other adverse event (AE) is unexpected and related to study drug, fax within 2 weeks. - If other AE is expected and prematurity related, fax within 1-2 weeks of the date of "last study drug dosing + 7 days".		
3 CRF 21 (SAE)	Fax 1 <sup>st</sup> to Project Manager at 415-514-6353 at the time of event, then to DCC within 48 hours. If no SAE's, Fax to DCC with 11A and 13A.		
4 CRF 6	Fax within 1 week of iNO discontinuation date		
4 CRF 8 (pgs1-11)	Fax when Study Day 31 completed (within 1 week of completion)		
5 CRF 12 A	Fax within 1 week of date infant reaches 36 weeks PMA (obtain information from convalescent hospital if patient has been transferred)		
5 CRF 12 B	Fax within 1 week of 40 weeks PMA date (obtain information from convalescent hospital if patient has been transferred)		
6 CRF9A (pgs 1-10)	Fax when Study Day 120 completed (within 1 week of completion)		
6 CRF 9B	Fax within 2 weeks of patient DC/transfer from study hospital		
6 CRF 10A and 10B	Fax within 2 weeks of patient DC/ransfer from study hospital		
6 CRF 11B	Fax within 2 weeks after discharge from study hospital.		
6 CRF 13 B	13B.2: Fax AE report of death within 1 week 13B.3 – 13B.26: Fax report of all other AEs within 1-2 weeks of discharge.		
6 CRF's 14-16	Fax within 2 weeks of DC to home from study or convalescent hospital		
6 CRF 17	If death occurs ≤ 7 days after study drug/sham dosing procedure, fax within 72 hours If death occurs >7 days after study drug/sham dosing procedure, fax within 1 week or ASAP after data completed		
6 CRF 18	Fax within 1 week of DC/transfer from study hospital		
6 CRF 19	Notify Project Director 415-514-6257 within 3 working days of event, then fax within 1 week of discharge from study hospital		
6 CRF 20	Fax 1 <sup>st</sup> to Project Manager at 415-514-6353 at the time of event, then to DCC within 48 hours. If no, fax at discharge.		
CRF 25	<i>Comments Form. Fax to Project Manager at 415-514-6353 within 1 week of discharge. FAX CRF 25 to the DCC at discharge.</i>		
7 CRF 23	<i>Discharge questionnaires at 3,6,9,12,and 18 months. Fax within 1 week of each completion.</i>		
8 CRF 24	<i>Followup Neurologic Exams at 12,and 24 months. Fax within 1 week of each completion.</i>		

- Faxing instructions:
- Orient all forms with tops up. Feed the tops of the forms into the fax machine.
  - No cover sheet. Feed forms into the fax machine face up or down as appropriate
  - Do NOT fax lab reports or any examiner visit notes.

- \* = Faxing order



