PERCH Pneumonia Etiology Research for Child Health	►Standard Operating Procedure◄	
Section: Regulatory	**Version: FINAL**	**Initials: KOB**
Title: Serious Adverse Event Reporting	**Revision Date:** Sept 30, 2011	

THIS SOP WAS DEVELOPED FOR THE PERCH PROJECT, LOCAL ADAPTATIONS MAY APPLY

1.0 Definitions

- CRF – Case Report Form
- DCC – Data Coordinating Center
- IS – Induced Sputum
- LA – Lung Aspirate
- LSM – Local Safety Monitor
- PI – Principal Investigator
- SAE – Serious Adverse Event

2.0 Purpose/Background:

The purpose of this Standard Operating Procedure (SOP) is to outline the processes for reporting serious adverse events associated with the induced sputum and lung aspirate procedure, and any serious, unexpected safety events related to study procedures. This is a study of serious pneumonia in children and we do not plan to report every death to the JHSPH IRB, unless the death meets the definition of an SAE. The PERCH PI will, however, report to the IRB any deaths or other safety events which are considered to be serious and *related to study procedures* and unexpected. Non-serious adverse events will not be reported.

2.1 Adverse Events Related to Induced Sputum and Lung Aspirate Procedures:

Induced Sputum

The optimal diagnostic sample comes directly from the diseased anatomical area and is available on almost every patient that meets the clinical case definition. Conventional methods of investigation, such as blood cultures, nasopharyngeal sampling and blood tests, are not specific to lung pathology; direct analysis of lung material, through lung aspiration or post-mortem dissection are only available on a minority of patients that meet the clinical case definition. In adults the sample that does meet both of the desirable criteria is sputum but children are not able to expectorate sputum. Adults with PCP are also rarely able to produce sputum and at the outset of the HIV epidemic physicians devised a method of sputum induction that allowed adults under investigation for PCP to produce sputum. This procedure was then adapted for use in immunodeficient children with pneumonia and has also been widely used in children with cystic fibrosis and in the assessment of bronchial inflammation in asthma. It has also been used for research into conventional (bacterial) pneumonia but it is not part of routine clinical practice in most countries.

The known safety concern with Induced Sputum is that administration of hypertonic saline by nebuliser can induce bronchospasm or coughing fits either of which may lead to respiratory compromise. In a child with marked hypoxia this could lead to a potentially lethal reduction in oxygen saturation. To avert the risk of bronchospasm the procedure was modified to include pre-medication with inhaled bronchodilator. Coughing is the desired outcome of the procedure and in some cases this may even be therapeutic as the

airways are cleared of mucous plugging. Respiratory compromise is only likely to occur with prolonged coughing.

To make the procedure safer and more widely acceptable the PERCH protocol uses a rapid method, with inhaled bronchodilator, short duration of saline nebuliser and minimal chest handling. The procedure will be standardized across the 7 sites by the PERCH clinical standardization monitor and therefore the study will be able to assess the acceptability, utility and safety of the procedure across a large population (>6,000) broadly representative of the population of children in developing countries.

Lung Aspirate:

Lung aspirates have been and continue to be conducted in clinical management and for research purposes in a limited number of settings around the world, in both developed and developing countries. Lung aspirates can be an important diagnostic tool for children with serious pulmonary disease as it provides a direct sample of the infected lung and often results in a microbiologic diagnosis that otherwise goes undetected.

The primary risks associated with lung aspiration are pneumothorax and hemoptysis. A review of children undergoing lung needle aspiration reported pneumothorax occurred in 27 per 1000 procedures, with chest tube drainage required in 5/1000 (0.5% of those undergoing lung aspirate) (Vuori-Holopainen and Peltola 2001). Serious non-fatal pulmonary haemorrhage is reported to occur at a rate of 1/1500 patients and transient pleural pain in 1/50 (Scott and Hall 1999). In over 6000 procedures in adults and children death was temporally, though not necessarily causally, associated with lung aspiration in 6 patients (1/1000), but the majority of these deaths occurred in historical literature, >30 years old, and could be averted by modern procedural and monitoring techniques(Scott and Hall 1999). These procedures will be done in clinical settings where there is 24 hour physician coverage of a seniority and experience where complications can be treated (e.g. chest tube placement).

To minimize risks and maximize the benefit to subjects enrolled in the PERCH study the following steps will be implemented.

- For any other site that will implement the procedure they must have the capacity to management potential complications of lung aspirate at short notice for the 24 hour period following the procedure.
- The Gambian SOP and a training video will be available to all sites, and clinicians will learn the procedure by visiting the Gambian site for a sufficient period to be trained by local experts or by having Gambian physicians travel to the local site for training..
- The standard operating procedure for lung aspirates from the Gambia will be the basis for SOPs at other sites. In general the procedure involves inserting a needle (18 to 23 gauge) over the top of a rib (to avoid infracostal vessels and nerves) into the area of consolidation or maximum physical findings, applying suction to the plunger of the syringe, and maintaining constant suction while withdrawing the needle. The actual lung aspirate takes less than 5 seconds to perform. Chest radiography (1-view or 2-view) and/or physical signs typically determine the site of needle insertion.
- Lung aspiration will only be performed in patients with large peripheral consolidation on chest-xray , distant from great vessels, such that the risk of failing to get a specimen and the risk of inducing haemorrhage are both minimal. Cases with conditions that pre-dispose to complications (i.e. coagulopathy, suspected PCP, chest hyper-expansion, chest cysts or bullae) will be excluded from having this procedure performed.

- Patients will be followed up closely for the 4 hours after the procedure and will be investigated with a chest radiograph if they show signs of clinical deterioration based on the clinical judgment of the physician.
- Performance of chest radiograph will be used to localize the consolidation. Following the procedure CXR will be repeated if clinically indicated. This is rarely needed but will be available at all sites.
- Specimens from lung aspirates will be tested in real time for the microbiologic cause of the pneumonia episode using all assays available at the site. This policy will maximize the opportunity for the subject to derive immediate clinical benefit from the procedure. The principal benefit to children undergoing the procedure is the early (and potentially life-saving) identification of pathogens that are not adequately treated with first line antimicrobial therapy. In developing country settings, using WHO treatment guidelines, these pathogens include *S. aureus*, most pathogenic gram-negative bacilli and tuberculosis. Without accurate diagnosis many of these children will be inadequately treated and a significant proportion will go on to chronic disease (in the case of TB) or death.

2.2 Serious Adverse Events Related to Study Procedures

In addition to SAEs that occur in children who have the induced sputum and lung aspirate procedure, PERCH sites will report study events that are:

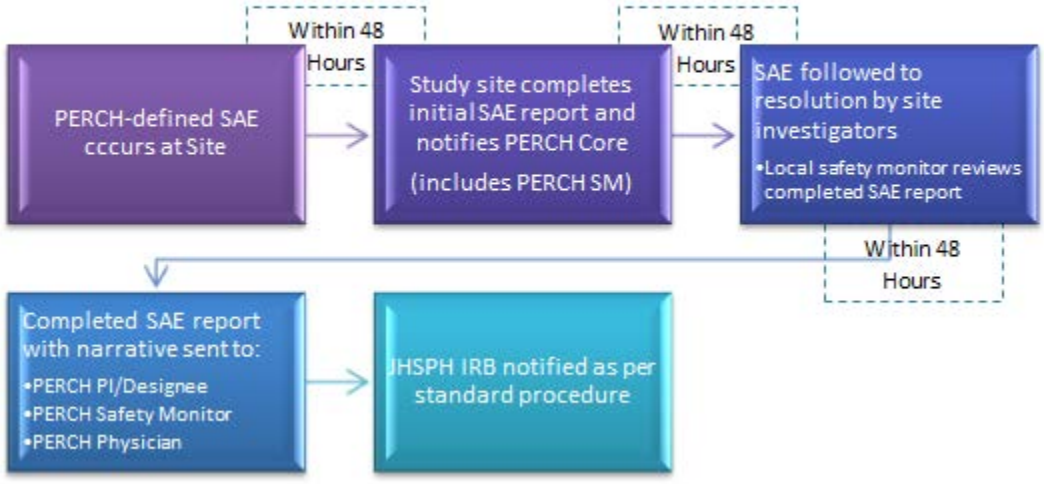
- Serious
- Unexpected
- Related to a study procedure

When SAE defining clinical events occur all attempts will be made to provide stabilization and clinical management to protect the safety and well-being of the child. All SAEs will be followed to resolution.

3.0 Scope/Applicability:

All clinical staff involved in care of PERCH cases should be made aware of the safety reporting mechanism for children who have had an induced sputum/lung aspirate. In addition, the figure below describes who is involved in SAE reporting.

PERCH SAE Reporting



4.0 Prerequisites/Supplies Needed

None

5.0 Roles/Responsibilities

5.1 PERCH-Trained Clinician

Clinicians who are involved in the PERCH study are responsible for reporting any events, as defined in Section 6.0, to the site PI.

These individuals must:

1. Immediately receive notification from clinical staff of an SAE
2. Report the SAE to the site PI
3. Follow the SAE to resolution

5.2 PERCH Site PI

Dr. _____ Tel: (_)___-_____ Email:_____

The PERCH PIs are responsible for reporting safety events to the following individuals:

1. Local safety monitors
2. PERCH Clinicians (Danny Feikin/Kate O'Brien)
3. A PERCH Project Coordinator (Andrea DeLuca)

The site PI is also ultimately responsible for ensuring that all SAEs are reported within the time periods detailed in Section 3.0, and followed to complete resolution. Any deviation from the reporting scheme in Section 3.0 will be logged as a protocol violation for the site.

5.3 PERCH Local Safety Monitor (LSM):

Dr. _____ Tel: (_)___-_____ Email:_____

This individual is responsible for reviewing safety events at this study site. He/she is responsible for:

1. Receiving notification from PERCH clinical staff of an SAE (within 48 hours of event)
2. The local safety monitor must:
    a. Acknowledge receipt of CRF 16 (SAE Report)
    b. Review SAE report, focusing on the severity and relatedness assessments
    c. Either:
        i. Sign off on the report
        ii. Ask specific questions as needed before signing off on the report
3. Give the completed SAE to the PERCH study coordinator (within four days (96 hours) of event)

5.4 PERCH Safety Monitor

Dr. Julia Kim Email: jukim@jhsph.edu

Dr. Kim is reviewing all of the SAEs reported to the core teamwithin 5 days, or 120 hours, of an event. She will:

1. Receive notification from the core team of an SAE (within 5 days)
2. Review the Case Report Form (CRF) that accompanies the core teamnotification
3. Evaluate the severity and relatedness of the reported CRF

4. Review with the PERCH Co-PI, Dr. Katherine O'Brien, if necessary
5. Work with the core team to ensure that the JHSPH is notified of the eventthe event using their SAE reporting form (within 10 working days of event)

5.5 PERCH Co-PI

Dr. Kate O'Brien Tel: (410) 955-6931 Email: klobrien@jhsph.edu

Dr. O'Brien will be notified of each SAE within 5 days, or 120 hours, of the event.

6.0 Procedural Steps:

1. All children who undergo a lung aspirate or induced sputum will be monitored for *4 hours after procedure*.

2. If any of the following **serious adverse events** occur, they will be reported by clinicians to the site PI, who will in turn notify the core team and the LSM using CRF 16 *within 48 hours of the event*:

   Among children who had a lung aspirate:

   - Death during hospitalization
   - Pneumothorax or significant haemoptysis (>5 mLs) at any time following the procedure, during the hospitalization
   - Clinical deterioration within 4 hours following the lung aspirate procedure defined as:
     - Drop in oxygen saturation to below 92% resulting in increased supply of supplemental oxygen for 10 minutes or more
     - New onset of unconsciousness or prostration
     - worsening of the respiratory condition as evidenced by
       - new requirement for bronchodilator or increased frequency of bronchodilator treatment.

   Among children who had an induced sputum:

   - Death within 4 hours following the procedure
   - Clinical deterioration within 4 hours following the induced sputum procedure defined as:
     - Drop in oxygen saturation to below 92% resulting in increased supply of supplemental oxygen for 10 minutes or more
     - New onset of unconsciousness or prostration
     - Worsening of the respiratory condition as evidenced by:
       - new requirement for bronchodilator or increased frequency of bronchodilator treatment.

3. Any other serious, unexpected, and study-related events will be reported to the site PI, who will in turn notify the core team and LSM using CRF 16 *within 48 hours of the event.*

4. The site PI and team will follow all SAEs to resolution, and will assign severity and relatedness of the SAE using CRF 16.

5. The PERCH safety monitor will review the SAE

6. The core team will report to the JHSPH IRB *within 10 working days of the event; each site is responsible for reporting SAEs according to local ERC guidelines.*

7.0 Record Management

All SAEs should be kept on file at the site, and transmitted electronically using the AdvantageEDC system. The DCC will create monthly cumulative reports of all SAEs and will send to the PERCH Safety Monitor and the PERCH co-PI.

8.0 Quality Assurance

The local safety monitors and PERCH safety monitor should keep under review the accumulating experience of and IS and LA procedures and to protect the interests of the patient-participants in the study by ensuring that the observed risks and benefits provide a net benefit to the child in the investigation and management of his or her disease. If it proves necessary to change practice the Safety Monitors will work with the investigators to define new criteria in the protocol and SOP that retain the balance of benefit.

9.0 References

Scott, J. A. and A. J. Hall (1999). "The value and complications of percutaneous transthoracic lung aspiration for the etiologic diagnosis of community-acquired pneumonia." Chest **116**(6): 1716-1732.

Vuori-Holopainen, E. and H. Peltola (2001). "Reappraisal of lung tap: review of an old method for better etiologic diagnosis of childhood pneumonia." Clin Infect Dis **32**(5): 715-726.

PERCH Pneumonia Etiology Research for Child Health	►Standard Operating Procedure◄	
Section: Regulatory	**Version No. 2**	**Initials: ADs**
Title: On-site Monitoring Plan	**Revision Date:** 24 Aug 2011	

1. Definitions

- MOP – Manual of Procedures
- Core Team – as defined in the manual of procedures
- CRF – Case Report Form
- GCP – Good Clinical Practice
- ICH - International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
- On-Site Monitor – Individual at each study site responsible for regular data monitoring
- QI Reports – Quality Indicator Reports
- Protocol deviation – a minor or administrative departure from study procedures (see section 6.2.5 for examples)
- Non-compliance – any study procedure that varies from processes outlined in the Standard Operating Procedures (SOP) that is more than minor or administrative (see section 6.2.6 for examples)

2. Purpose / Background

2.1. Background: The overall purpose of the PERCH Quality Management Plan is to (1) assure that the protocol is followed at all sites in a standardized manner and (2) assure that the data that are collected are accurate. On-site monitoring is essential to both of these objectives.

2.2. Purpose: The purpose of this document is to convey the monitoring principles that should be upheld at each site. **Sites are responsible for developing their own on-site monitoring plans** to assure that the following quality objectives are met:

(1) A complete informed consent document is on file for each study participant

(2) All study patients who meet the PERCH screening trigger during screening hours are in fact screened

(3) Representative controls are recruited

(4) Study specimens are transported and stored appropriately

(5) Source data is transcribed correctly on to CRFs

(6) SAEs are reported appropriately to the correct people within the allotted timeframe

(7) Any deviation from study procedures are reported appropriately (see section 6.

The above objectives reflect essential quality elements of any rigorously conducted study.

3. Scope / Applicability

The SOP applies to all sites.

4. Prerequisites / Supplies Needed

4.1. Prerequisites

- Study team members who are responsible for the collection and the monitoring of study data will have undergone GCP and ethics training.

5. Roles / Responsibilities

5.1. Site Team Monitoring Activities

5.1.1. Each site will be responsible for developing an on-site monitoring plan and for implementing GCP where relevant for a clinical observational study. (**Note: Please record your site's on-site monitoring plan in Appendix A**) This means that not every component of GCP/ICH that applies to a clinical trial will be employed. Each team should assign on-site quality manager(s) who will be responsible for overseeing the following guidelines and requirements:

5.1.2. Guidelines and Requirements by Objective:

Objective	Guideline or Requirement	Report to PERCH Core?	Notes
(1) A complete informed consent document is on file for each study participant	100% monitoring of informed consent documents is required at every site.	No	See section 5.3 for instructions
(2) All study patients who meet the PERCH screening trigger during screening hours are in fact screened	Case screening information must tracked be submitted on a monthly basis to EMMES for QI reports	**Yes**	See CRF 31 (to be submitted monthly)
(3) Representative controls are recruited	Control recruitment Information must tracked and submitted on a monthly basis to EMMES for QI reports	**Yes**	See CRF 31 (to be submitted monthly)
(4) Study specimens are transported and stored appropriately	Systematic or spot checks should be conducted on-site to assure this	No	See section 5.4 for suggestions

Objective	Guideline or Requirement	Report to PERCH Core?	Notes
(5) CRFs are complete, entered in a timely manner, and source data is transcribed correctly on all applicable CRFs	Systematic or spot checks should be conducted on-site to assure this	No	See section 5.5 for suggestions
(6) SAEs are reported appropriately	SAEs must be reported using CRF 16 and according to SOP 4.1	**Yes**	Please reference SOP XX and CRF 16
(7) Protocol deviations and non-compliance events are reported appropriately	Events must be reported using CRF 30	**Yes**	Please reference Section 6.2.5-6 and CRF 30

5.1.3 Instructions for monitoring informed consent documents:

For each informed consent document, the following should be confirmed:

(1) all sections of the consent form are complete and that signatures and dates are present

(2) the date of the signature does not occur after the date of enrollment

(3) the correct version of the consent form is used

(4) the staff person who signed the form was authorized to perform the consenting procedure

5.1.4 Guidelines for assuring that specimens are stored and transported appropriately:

Please refer to the specimen storage requirements in Lab SOP 2.0. It is suggested that a spot check be done routinely to follow the chain of custody from the time of specimen collection to the time of storage in the laboratory.

In the process, the following should be confirmed:

(1) The specimen was maintained under appropriate temperatures and timeframes as per SOP 2.0

To follow the complete specimen chain of custody, the following may be required:

(1) Specimen collection CRFs
(2) Specimen transport logs (site specific)
(3) Laboratory reception logs (site specific)
(4) Laboratory reception CRF
(5) Freezer and Refrigerator temperature logs (site-specific)
(6) Other site specific documents or databases, as appropriate

5.1.5 Guidelines for Assuring that CRFs are complete and that source data are appropriately transcribed on to CRFs/eCRFs:

Source documents and other study records should be maintained for future reference if needed. Source documents may be hospital records from which data is transcribed, or laboratory log books that are used to capture PERCH laboratory results. For sites that first complete a paper CRF, the paper CRF will serve as a source document. Through systematic checks, the on-site quality manager(s) should verify that the data recorded on the CRFs are complete, consistent with the source documents, and have been signed by a supervisor. This check should include screening CRFs for cases and controls who are not enrolled in the study, either because they are ineligible or refuse enrolment after screening. The timing of data entry into the EMMES system should also be periodically reviewed, to assure that there is not a significant delay between data capture and entry.

*Note: All CRFs, including laboratory as well as clinical CRFs, should be periodically examined for accuracy and completeness ad described above.

5.2 Core Team Monitoring Activities

During Core Team site visits the following monitoring will be carried out. Remote monitoring of data will also be done using the EMMES data system.

5.2.1 Case assessment and enrollment will be monitored to ensure that PERCH is enrolling representative, non-biased severe and very severe pneumonia cases at the study facilities. Hospital or clinic log books, where available, will be used in addition to data collection forms to assess quality indicators for case enrollment.

5.2.2 Control enrollment will be monitored to ensure that representative, non-biased PERCH controls are being enrolled from the hospital catchment area. Quality indicators will assess (a) whether controls are being successfully enrolled in adequate numbers at each site and (b) whether the cases and controls are frequency matched by age and season.

5.2.3 Review systems for replacing updating paper versions of CRFs (where paper forms are being used).

5.2.4 The PERCH core team will be responsible for monitoring a percentage of the items being monitored by the on-site quality manager as described in section 6 above.

- 5.2.4.1 A random selection of 20 case consent forms
- 5.2.4.2 A random selection of 20 control consent forms
- 5.2.4.3 A random selection of 20 case CRFs and 10 control CRFs will be monitored against key variable fields
- 5.2.4.4 A random selection of 10 screening forms from non-enrolled participants will be monitored for accuracy
- 5.2.4.5 A random selection of 5 cases and 5 controls will have specimen transport and custody chain monitored
- 5.2.4.6 Hospital and screening logs will be reviewed for missed cases

5.3. Reporting Deviations from Study SOPs

PERCH is responsible for collecting information on any study process or event that departs from the descriptions in the site standard operating procedures (SOPs). Study deviations are those events that are minor or administrative and do not affect the well-being of the PERCH participant. These are to be reported on a yearly basis to the JHSPH IRB. Sites using the AdvantageEDC system can select a description of the protocol deviation from a code list and report anything that has occurred that can be considered as *minor* and *administrative.*

- Using the incorrect version of study documents
- Consent is missing signature/dates
- Participant is visited outside of timeframe outlined in SOP

5.4 Non-compliance

Departures from study procedures that are more than administrative or minor and may affect a PERCH participant's well-being must be reported to the JHSPH IRB in real time. For sites using the AdvantageEDC system, they can reference the code list on CRF 30 and will be automatically prompted to fill out the details needed for a real-time report. Examples include:

- Not reporting SAEs according to details outlined in the SOP
- Not reporting test results that have clinical care implications
- Not having complete consent on file for a study participant
- A child does not meet eligibility criteria but has been enrolled

6. Record Management

7.1. All sites should be able to produce either the source documentation used to capture a data point, or a copy of the source document. On-site monitoring will be documented on report templates.

Appendix A: On Site Monitoring Plan

The on-site monitor(s) is/are:

Mr/Ms/Dr. _____	Tel: (_)___-_____	Email:_____
Mr/Ms/Dr. _____	Tel: (_)___-_____	Email:_____
Mr/Ms/Dr. _____	Tel: (_)___-_____	Email:_____
Mr/Ms/Dr. _____	Tel: (_)___-_____	Email:_____

Objective	Description of site plan:
(1) A complete informed consent document is on file for each study participant	
(2) All study patients who meet the PERCH screening trigger during screening hours are in fact screened	
(3) Representative controls are recruited	
(4) Study specimens are transported and stored appropriately	
(5) Source data is transcribed correctly on all CRFs	

(6) SAEs are reported appropriately	
(7) Protocol deviations and non-compliance events are reported appropriately	

PERCH Pneumonia Etiology Research for Child Health	►Standard Operating Procedure◄
Section: Regulatory	**Version: FINAL** **Author: A DeLuca**
Regulatory Documents	**Revision Date:** June 1, 2011

1. Definitions

1.1. Specific to this SOP

1.1.1. **Delegation Log** is a spreadsheet that details members of the PERCH study team, and who has been authorized (either through specific training or other processes) to do study procedures

1.1.2.**Signature Sheet** lists PERCH staff members who may be signing study forms and houses their signatures

1.2. Abbreviations

1.2.1.**GCP** is Good Clinical Practice

2. Purpose / Background

2.1. The purpose of this SOP is to describe the procedures required for ensuring that all required PERCH documents are kept on file and match the regulatory binder kept in Baltimore by the PERCH core team. It also details the process for notifying the core team of changes to regulatory documents, and how to manage version control.

2.2. Background. Although PERCH is a observational epidemiological study, principals of GCP apply whenever relevant. The Core team in Baltimore will maintain the necessary regulatory documents according to JHSPH policies and local ethics committee requirements at each of the sites.

3. Scope / Applicability

3.1. This SOP is intended for study coordinators and all study staff that participate in the maintenance of study and regulatory documents.

4. Prerequisites / Supplies Needed

4.1. List of Regulatory Documents:

PERCH Regulatory Binder Contents

I. Study Protocol (current version)

II. Informed Consent* (current versions)
   a. Cases
   b. Controls
   *Note that sites must use the version of the informed consent document with the JHSPH IRB logo

III. Protocol Deviations
   a. List of protocol deviations and actions taken

IV. IRB Documentation
   a. Approval Letters
   b. Study Amendments
   c. Communications with JHSPH IRB

d. Communications with Local ERCs

V. Severe Adverse Event Reports
   a. Individual CRFs
   b. Cumulative monthly reports

VI. Recruitment Materials
   a. Flyers
   b. Information Sheets
   c. Posters
   d. Etc.

VII. Laboratory Certification

VIII. Ethics Training Certificates and CVs of Key Investigators

IX. Delegation Log

X. Signature Sheet

5. Roles / Responsibilities

5.1. Each project site coordinator is responsible for maintaining a binder that includes all of the documentation listed above.

6. Procedural Steps

6.1. This list of regulatory documents is the *minimum* required by the JHSPH IRB in case of an audit. You are welcome to include any additional sections as required by your local ethics committee. All documents in the regulatory binder at your site need to match an identical binder that will be kept by the PERCH core team. Please send additions to andeluca@jhsph.edu any time a document is added to your binder.

6.2. Any documents that have been approved by your local ethics board should be dated and stamped. Any changes to the protocol/informed consent documents require an amendment and must be submitted through the JHSPH IRB as well as your ethics committee. These changes MUST be communicated to the PERCH core team, and all documents need to pass through all required IRB approvals before being used with study participants.

6.3. Please email all documents for steps 6.1 and 6.2 to andeluca@jhsph.edu and perchreg@jhsph.edu. Please ensure that you receive a 'Confirmation of Receipt' email within 72 hours of sending in your document. If you do not receive this email, assume that your documents have not been received, and re-send.

7. Record Management (Version Control)

7.1. SOPs and CRFs will follow the same version control plan. Before the start of enrollment, all versions will be noted as Version 1.0 After the start of enrollment, any minor revisions will require a numbering change after the decimal point (i.e. Version 1.1, Version 1.2, etc). Any *major* revisions will require a numbering change before the decimal point (i.e. Version 2.0, Version 3.0, etc). Any time a revision is made, a version number change should be made, and a new date entered in to both the document title and in the footer of the document (please use the date format YYYMMDD).

8. Quality Assurance / Quality Control

8.1. TBD

9. References