A Multicenter Trial of the
International Maternal Pediatric Adolescent AIDS
Clinical Trials Group (IMPAACT)

IMPAACT P1114
A Companion Protocol to CIR Protocol Number: CIR 285

A Phase I Study of the Safety and Immunogenicity of a Single Dose of the
Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine RSV cps2,
Lot RSV#005A, Delivered as Nose Drops to RSV-Seronegative
Infants and Children 6 to 24 Months of Age

BB-IND # 15284

MANUAL OF PROCEDURES (MOP)

MOP Version 1.3
FINAL
20 May 2014
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## SUMMARY OF CHANGES

<table>
<thead>
<tr>
<th>4/18/14</th>
<th>Version 1.1 to 1.2</th>
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<tbody>
<tr>
<td>2.4.2; Appendix I</td>
<td>Revised to make clear that the rectal temperature should be denoted as such in the source documentation</td>
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<tr>
<td>2.4.5.1</td>
<td>Specified the FSTRF Form F1601 (Off study)</td>
</tr>
<tr>
<td>3.3</td>
<td>Revised days when samples may be shipped</td>
</tr>
<tr>
<td>4.2</td>
<td>Removed “and adventitious agents” from the 7th bullet point</td>
</tr>
<tr>
<td>5.5.3</td>
<td>Additional information has been provided re Product Labeling</td>
</tr>
<tr>
<td>5.5.5</td>
<td>Clarified that small gauge needle should be used when preparing vaccine to avoid loss of vaccine</td>
</tr>
<tr>
<td>5.5.8</td>
<td>Clarification of documentation of vaccine temperature dose to be recorded on the VAR</td>
</tr>
<tr>
<td>5.6</td>
<td>Revision to processes for snap freezing</td>
</tr>
<tr>
<td>6.2; table 3</td>
<td>Removed “for Infants and Children in study” from the title of the table</td>
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<tr>
<td>6.3</td>
<td>Clarified that period of reporting of SAEs and LRIs is of events between Day 0 to Day 56.</td>
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<tr>
<td>6.5</td>
<td>New section re “Reporting Events During Surveillance” has been added.</td>
</tr>
<tr>
<td>7.2.2</td>
<td>Reference was added to this section to Appendix IX.</td>
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<tr>
<td>7.3.1</td>
<td>Removed references to labeling with respect to the Sarstedt cryovials</td>
</tr>
<tr>
<td>7.3.2; Appendix IV</td>
<td>Clarified and updated instructions re snap freezing of the nasal washes</td>
</tr>
<tr>
<td>Appendix I</td>
<td>Clarified that flow chart applies to temperatures equal to or greater than 100.0°F</td>
</tr>
<tr>
<td>Appendix V</td>
<td>Renamed “Placebo and Diluent Preparation Form as “Diluent Preparation Form”; updated the form; replaced references throughout the MOP with new title; updated VAR to indicate that current, min and max temps to be recorded are at time of vaccine administration.</td>
</tr>
<tr>
<td>Appendix VIII</td>
<td>Updated instructions and request forms for ordering study products</td>
</tr>
<tr>
<td>Appendix IX</td>
<td>Added new appendix IX: “NW/VTM Specimen Label Cross-reference Log Instructions”</td>
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<thead>
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<th>5/20/2014</th>
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<tr>
<td>4.1</td>
<td>More detail re assuring eligibility have been added to this section</td>
</tr>
<tr>
<td>6.2</td>
<td>A new section 6.2 has been inserted, which summarizes expectations for recording adverse events on CRFs. The remaining sections have been re-numbered; previous section 6.5 has been removed given the overlap with this new section.</td>
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### List of Commonly Used Abbreviations and Definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACTG</td>
<td>AIDS Clinical Trials Group</td>
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<tr>
<td>ACTN</td>
<td>AIDS Clinical Trials Network</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>BLD</td>
<td>Blood</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CIR</td>
<td>Center of Immunization Research</td>
</tr>
<tr>
<td>CRA</td>
<td>Clinical Research Associate</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CSO</td>
<td>Clinical Safety Office</td>
</tr>
<tr>
<td>CTS</td>
<td>Clinical Trials Specialist</td>
</tr>
<tr>
<td>DAERS</td>
<td>DAIDS Expedited Adverse Event Reporting System</td>
</tr>
<tr>
<td>DAIDS</td>
<td>Division of AIDS</td>
</tr>
<tr>
<td>D/C</td>
<td>Discontinue</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Management Center</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>ER</td>
<td>Emergency Room</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FSTRF</td>
<td>Frontier Science &amp; Technology Research Foundation</td>
</tr>
<tr>
<td>GCLP</td>
<td>Good Clinical Laboratory Practice</td>
</tr>
<tr>
<td>HHS</td>
<td>Health and Human Services</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>IATA</td>
<td>International Air Transport Association</td>
</tr>
<tr>
<td>IC</td>
<td>Informed Consent</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>IMPAACT</td>
<td>International Maternal, Pediatric and Adolescent AIDS Clinical Trials</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>JHU</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>L15</td>
<td>L-15 Leibovitz medium</td>
</tr>
<tr>
<td>LDMS</td>
<td>Laboratory Data Management System</td>
</tr>
<tr>
<td>LID</td>
<td>Laboratory of Infectious Diseases</td>
</tr>
<tr>
<td>LIMS</td>
<td>Laboratory Information Management System</td>
</tr>
<tr>
<td>LPC</td>
<td>Laboratory Processing Chart</td>
</tr>
<tr>
<td>LRI</td>
<td>Lower Respiratory Illness</td>
</tr>
<tr>
<td>MD</td>
<td>Medical Doctor</td>
</tr>
<tr>
<td>MOP</td>
<td>Manual of Procedures</td>
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</tbody>
</table>
NIAID National Institute of Allergy and Infectious Diseases
NICHID National Institute of Child Health and Human Development
NIH National Institutes of Health
NON No additive (e.g. serum tubes)
NPW Nasopharyngeal wash
NSC Nomenclature Standards Committee
NW Nasal Wash
OHRP Office for Human Research Protections
OM Otitis Media
PCR Polymerase Chain Reaction
PFU Plaque Forming Units
PI Principal Investigator
PID Patient Identification
PoR Pharmacist of Record
PSE Protocol Specified Event
QA/QC Quality Assurance / Quality Control
RCHSPB Regulatory Compliance and Human Subjects Protection Branch
RLS Ringers Lactate Solution
RSC Regulatory Support Center
RSV Respiratory Syncytial Virus
SAE Serious Adverse Event
SAIC Science Applications International Corporations
SCK Sick
SES Subject Enrollment System
SER Serum
SID Study Identification Number
SIP Site Implementation Plan
SOP Standard Operating Procedures
SWFI Sterile Water for Injection
UP Unanticipated Problem
URI Upper Respiratory Illness
USP US Pharmacopeial Convention
VTM Viral Transport Media
1.0 PROTOCOL OVERVIEW

1.1 Study Design Overview

IMPAACT P1114 is a domestic, multi-center, randomized, double-blind, placebo-controlled study in which RSV seronegative subjects will be randomized in a 2:1 ratio to receive vaccine or placebo, respectively. Placebo recipients are needed in pediatric studies because of the frequent occurrence of mild respiratory and febrile illnesses in young infants and children. For the purpose of this study, “seronegative” will be defined as having serum neutralizing antibody titer to RSV of <1:40. At randomization, subjects will be divided up as follows:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Number*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Vaccine</td>
<td>10^{5.3} PFU</td>
<td>N=34</td>
</tr>
<tr>
<td>2 Placebo</td>
<td>0</td>
<td>N=17</td>
</tr>
</tbody>
</table>

* Together, from IMPAACT P1114 and CIR 285. It is expected that IMPAACT sites will enroll about 36 of 51 subjects, and CIR will enroll about 15 of 51 subjects, but these numbers can vary.

Infants will be randomized to receive 10^{5.3} PFU of vaccine virus or placebo (1x L15). All subjects will be monitored for protocol defined “solicited” adverse events (Solicited AEs) for 28 days following inoculation with investigational product. The infectivity and genetic stability of the vaccine virus will be assessed by obtaining nasal washes for viral culture and quantification during each study visit on days 0, 3, 5, 7, 10, 12, 14, 17, 19, 21, and 28 (± 1 day) post inoculation with investigational product. Blood and nasal wash specimens will be obtained before inoculation and at day 56 after inoculation to assess immune responses to the vaccine. Duration of participation in the initial phase of the study is 56 days. Additionally, children will be assessed for medically attended respiratory or febrile illnesses or otitis media from November 1st through March 31st - the onset to the end of the RSV season following immunization. Thus, the total duration of participation will be up to 365 days, depending upon the time of enrollment relative to the RSV season.

CIR 285 is a separate but almost identical protocol conducted at only the Hopkins site using a different MOP. The schedule of events and case report forms (CRF) for the two studies are identical and all the data will be entered into a single database at Frontier Science (FSTRF). The entire cohort will be analyzed as a single cohort. The directions in this MOP are specifically for IMPAACT sites participating in the protocol.

2.0 PROTOCOL IMPLEMENTATION

2.1 Recruitment of Study Subjects

This is a multi-site study. Subjects will be recruited from outpatient clinics at domestic IMPAACT sites. Each site will determine site specific appropriate recruitment sites and recruitment materials, to be reviewed and approved by site IRBs and by the protocol team through approval of a site implementation plan (SIP).
Study visits, except vaccination, may be performed at one of the clinical sites or as home visits. Vaccination visits must be completed at a clinic/office site where emergency supplies are available.

2.2 Randomization, Stratification

Subjects meeting all the study inclusion criteria and none of the exclusion criteria, from either IMPAACT sites or CIR will be enrolled in IMPAACT P1114 by utilizing the Subject Enrollment System (SES) located on the IMPAACT Data Management Center (DMC) Website at www.fstrf.org.

Subjects will be randomized in a 2:1 ratio to RSV cps2 vs. placebo, using a dynamic permuted blocks method with block size of 6. This will yield approximately 34 vaccinees and 17 placebo recipients. Subjects will be randomized as they become eligible, regardless of the site (IMPAACT or CIR).

2.3 Blinding and Unblinding

Each site will have an unblinded pharmacist who will receive treatment assignments, prepare the vaccine/placebo, and maintain records of each study patient’s treatment. The unblinded pharmacist will not assist in patient assessment or other data collection and will not provide any information about treatment assignment to others at the clinical site.

Vaccine syringes will be labeled, in a blinded fashion, with the subject randomization number, the study number, route of administration, expiration date and time, and initials of pharmacy staff.

Subjects (parents and guardians) and study personnel performing all clinical assessments will remain blinded as to treatment assignment until the end of the RSV season following the subject’s enrollment, when notified by the study team. The IMPAACT Unblinding SOP (# SDM-4001-01) will be followed.

If the need arises to unblind a specific subject's assignment in the event of a serious illness prior to completion of the acute observation phase, the Protocol Chair will make a decision regarding early unblinding in collaboration with the DSMB. The Sponsor and the DSMB Executive Secretary (niaiddsmbia@niaid.nih.gov) will also be notified of the event as specified in section 8.5 of the protocol. The IMPAACT unblinding SOP can be found at https://member.impaactgroup.org/cms/dl/14261.

2.4 General Information Regarding Clinic Visits

2.4.1 Windows for Clinic Visits

- Study inoculation (Day 0) must be completed within 42 days of the screening visit. Please note: Study inoculation (Day 0) should be completed as soon as possible after screening, typically within 30 days of screening. The additional days allowed in the window are intended to be available in extenuating circumstances.
- The Day 3, 5, 7, 10, 12, 14, 17, 19, 21, and 28 visits (clinical assessment and nasal wash) have a window of ±1 day. Please note that contact should be made with the subject on whichever day the subject is not seen in person.
during the time frame of Days 1-29. E.g. if the subject comes in on Day 3, the family should be contacted on Day 4.

- The Day 56 visit (blood draw and nasal wash for immunologic assays) has a window of +7 days and as such, can be performed on Days 56 to Day 63 if this is more convenient.

2.4.2 Temperature Readings

For standardization, the P1114 team requires that temperature readings on the child be taken using a Phillips Sensor Touch or similar temporal artery thermometer. The use of rectal thermometers should be minimized and used only to verify the elevated temporal readings. The method of taking temperature readings should be recorded on the appropriate CRF.

Temperature monitoring occurs daily for days 0-28 after immunization. On days without study visits, the temperatures are recorded by parents. A parental instruction sheet is provided in Appendix I of the MOP.

To briefly describe, the parents/guardians take a temporal temperature 3 times in a row and record the highest temperature. If the highest temperature is less than 100.0°F, parents/guardians should record the temperature in the memory aid and reported to site staff during the daily phone calls for the first 28 days following inoculation.

If the highest temporal temperature is greater than or equal to 100.0°F, then the parents need to obtain a rectal temperature within 20 minutes. If the rectal temperature is less than 100.4°F, the temperature should be recorded in the source documention with a notation of “R” to denote rectal. For the purposes of this study, this is not considered a fever and is not recorded as an AE.

If the rectal temperature is greater than or equal to 100.4°F, then for study purposes, this is considered a fever and a solicited AE and is recorded as such.

If a temporal temperature is greater than or equal to 100.0°F but no rectal temperature is measured, then this is considered a fever and a solicited AE. The temperature is recorded with the exact measure in the source documentation and “T” to denote that it was collected by temporal measurement.
2.4.3 Medications Allowed During the Study

The following must be recorded during the active study period (28 days following inoculation). There are no disallowed medications during the study. The use of prophylactic antipyretics, decongestants, or antihistamines is not permitted during the intensive clinical monitoring period (28 days); however, use of these medications for treatment of symptoms is allowed. The subject’s temperature should always be taken prior to administering any antipyretic medications. The following must be recorded during the active study period:

- Use of prescription, non-prescription and herbal medications
  
  Action: Document in progress notes and complete PE0413 Non Antiretroviral Concomitant Medications/Therapies – III
Minimum documentation must include:
- Name of the medication or treatment
- Dose, Route and Frequency
- Start and Stop Date of medication or treatment
- Indication for medication or treatment

2.4.4 Emergency Plan for After Hours

Study subjects will be informed of the procedures for reaching a study staff member out of normal clinic hours. Each site will have an emergency plan in place for evaluation and management of sick children for after-hours sick visits, as per the Standard of Care at the site. The parent/guardian will be informed of exactly how they would reach medical help in an emergency situation.

2.4.5 Subject Withdrawal / Replacement

Regardless of the reason for withdrawal, study personnel are responsible for identifying all subjects who withdraw and documenting the reason and date of termination.

2.4.5.1 Subject Withdrawal

1. Parents/guardians may withdraw their child from the study at any time. Study personnel should attempt to collect final data from subjects who are withdrawn early. Study personnel will record the date and reason for withdrawal in the subject’s source record, and on the subject case report form. FSTRF Form F1601 Off Study

2. In general, the investigator should not withdraw a subject unless that subject is lost to follow up or is noncompliant with the protocol. Every attempt should be made to collect all data specified by protocol relative to study vaccine received, including post-immunization blood and nasal wash collections. Study personnel will record the date and reason for withdrawal in the subject’s source record, and on the subject case report form.

2.4.5.2 Subject Replacement

Subjects who withdraw early will not be replaced.

3.0 SCREENING

3.1 Introduction to the Informed Consent

Follow the IMPAACT SOP for obtaining and documenting the informed consent (IC) process. See page 18 of the DAIDS Source Documentation Requirements SOP for more information:
http://www3.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/ClinicalSite.htm
3.2 Screening & Enrollment

The study screening and enrollment procedures are described in detail in Sections 5 and 6 of P1114, and summarized in the P1114 Schedule of Evaluations (IMPAACT P1114, Appendix 1A). P1114 is available on the IMPAACT P1114 webpage (www.impaactgroup.org).

3.2.1 Screening and Enrollment Logs

Per the DAIDS policy for Essential Documents, study sites are required to document all screening (including screening failures) and enrollment activity on screening and enrollment logs. Screening and enrollment/randomization logs may be separate or combined. A screened subject is defined as having signed the screening or study consent.

The Screening and Enrollment Logs should be maintained in the Investigator Study Binder. Logs should include the following information:
- Initials of the subject
- PID if patient receives one
- Date screened
- Race
- Gender
- Status of screening, such as pass/fail
- For all screen failures, indicate why the subject is unable to participate
- Date randomized
- If not randomized, indicate reason

For additional information, refer to the NIAID/DAIDS website http://www3.niaid.nih.gov/about/organization/daids/

3.2.2 Assignment of Participant ID Numbers (PID)

The PID is assigned at the site from a list that is generated by the DMC and sent to the sites. If a participant has been on another IMPAACT or ACTG study that PID is carried with them. A new PID number would not be assigned.

3.3 P1114 Screening Procedures

During this initial screening visit, detailed study information will be presented to the parent/guardian. Informed consent for screening and study participation must also be obtained. Screening must occur ≤42 days prior to enrollment (randomization) and vaccine/placebo must be administered within 72 hours of randomization, and within 42 days of screening.

The child’s parent/guardian will be encouraged to ask questions and then complete a multiple-choice comprehension assessment questionnaire (also known as the parent quiz or comprehension quiz) to evaluate consent comprehension. Study staff will use incorrect answers from the questionnaire to identify those areas of the screening informed consent form that need further review with the parent/guardian. This will help ensure that the parent/guardian has sufficient understanding before signing the consent form. The comprehension quiz can be found in Appendix III.
The standardized quiz will be administered to the parent/guardian who is providing the written, informed consent. The quiz can be administered in writing or, if the parent/guardian prefers, the questions may be read aloud to the parent/guardian and their answers provided verbally. If a parent/guardian answers one or more question incorrectly, that area of the consent should be reviewed with the parent/guardian until it is clear that the topic area is understood.

There is no specific quiz score that a parent/guardian must earn for their child to be allowed to enroll, rather, the quiz is meant to identify areas where further teaching is needed to assure full understanding of the consent process.

If the parent/guardian needs additional time to consider the study, another visit will be scheduled and no procedures will be done.

If used, information regarding topical anesthetic medication will be presented and consent will be obtained before anesthetic is applied to several potential sites for the blood draw.

Ensure parent/guardian has authorized or denied authorization for use of samples for future studies.

Provide parent/guardian with a copy of the signed informed consent that they can keep.

If necessary, obtain a HIPAA release from parent or guardian to review the subject’s medical record and obtain the immunization record.

If necessary, ensure parent/guardian has signed medical release to obtain records of any AEs that might occur which necessitate medical record clarification or confirmation. Only those portions of the medical record that are pertinent to the study will be maintained in the study chart.

To ensure the child is in good health and eligible for the study, the following procedures will be completed:

- Obtain medical history and perform complete physical examination.
- If parent/guardian has agreed, apply topical anesthetic cream to potential venipuncture sites, cover with occlusive dressing, and allow it to penetrate skin per manufacturer’s instructions. Use of topical anesthetic cream is optional.
- Remove dressings and obtain approximately 5 mL of blood in a red top (no additive) to:
  - Test for serum antibodies to RSV;
  - Act as a pre-vaccination blood specimen
- Remove anesthetic cream from unused sites, if used
- Schedule a return visit, if needed

**Blood Samples Collected During Screening**

Prior RSV infection status will be determined using this blood sample, therefore, it is important to process and ship the serum as quickly as possible. Screening samples may be shipped to JHU on Mondays, Tuesdays and Wednesdays. There should be no shipment to JHU on Thursday. Serologic testing will be performed on Fridays and results will be emailed to the sites on Tuesdays. During the 2014 enrollment season, serum from the screening visit will be shipped weekly to JHU from each clinical site. Serologic testing will be performed weekly. Results will be sent via email directly to the sites and to the Clinical Trials Specialist (CTS).

Study Staff will notify parents as to whether the subject is eligible for the study.
If the child is confirmed to be RSV seronegative, then he/she should return for the enrollment visit. If the child is confirmed to be RSV seropositive, then he/she is ineligible for enrollment.

4.0 **ENROLLMENT**

4.1 **Randomization**

Sites should err on the side of caution when considering children for participation in P1114. Specifically, prior to randomization:

- Evaluate the child for acute illness. Acute illness is a clear exclusion criterion.
- Evaluate the child not only for evidence of acute illness but also for evidence of any chronic or other illness. As a Phase I study of safety and immunogenicity, P1114 cannot afford to have subjects enrolled who might have conditions that could skew response to the vaccine or make them vulnerable to adverse effects. Rule of thumb: if you find that you will be entering a sign/symptom or diagnosis at baseline, reconsider the child’s eligibility.
- Evaluate the child’s growth. Participants should exhibit normal growth and age-appropriate development.
- Evaluate the child’s current medications. If the child is on any medications, reconsider bullet #2 and the child’s eligibility.
- Contact the P1114 Team ([impaact.teamp1114@fstrf.org](mailto:impaact.teamp1114@fstrf.org)) in the event of any doubts about potential eligibility. As with any message to the P1114 team, be sure to include “P1114” in the subject of the message.

Thereafter:

- Subjects meeting all the study inclusion criteria and none of the exclusion criteria will be enrolled in IMPAACT P1114 by utilizing the Subject Enrollment System (SES) located on the IMPAACT DMC Website at [www.fstrf.org](http://www.fstrf.org).
- Sites are strongly encouraged to schedule this visit within 30 days whenever possible. This visit must occur within 42 days of screening.

4.2 **Vaccination**

- This vaccination will generally occur the same day as randomization, but must occur within 72 hours of randomization. Please note that vaccination must occur within 42 days of screening.
- Complete interim history and focused physical assessment, including check of ears, nose, throat, regional lymph nodes, chest, and heart, concentrating on any acute complaint areas.
- Record any clinical significant findings resulting in medication (prescription or over the counter), MD/ER visit or consultation, hospitalization, event causing study termination or additional events judged to be significant by the Investigator on the appropriate CRFs.
- Review Inclusion and Exclusion criteria (section 5.3 of the protocol) including treatments that could potentially interfere with vaccine-induced immunity (section 5.5 of the protocol).
• Order study vaccine from your site pharmacy, per site SOP.
• Record temporal and/or rectal temperature, heart rate, and respiratory rate.
• Obtain nasal wash for immunologic assays, and for viral culture testing prior to administration of vaccine or placebo (see Section 7.3 of the MOP).
• Administer vaccine/placebo (see Section 5.10 of the MOP).
• Observe for a minimum of 30 minutes after vaccination to evaluate for immediate adverse reactions.
• Record any positive findings on the appropriate CRF.
• Provide parent/guardian with temporal artery thermometer and digital rectal thermometer, and instructions for use (see Appendix I).
• Provide and explain temperature card, solicited AE illness criteria, and study personnel contact information.
• Schedule Day 1 visit and (if non-visit day) Day 2 contacts, as well as Day 3 visit. The Day 3 visit can be scheduled within a ± 1-day window.

4.3 Study Days with in-Person Visits (After vaccination)

After vaccination, in-person visits are scheduled to take place on:
   Day 3 (window of ±1 day)
   Day 5 (window of ±1 day)
   Day 7 (window of ±1 day)
   Day 10 (window of ±1 day)
   Day 12 (window of ±1 day)
   Day 14 (window of ±1 day)
   Day 17 (window of ±1 day)
   Day 19 (window of ±1 day)
   Day 21 (window of ±1 day)
   Day 28 (window of ±1 day)

• At each visit, obtain and record interim history and temperatures since last contact.
• Record temperature, measurement method (temporal and/or rectal), pulse and respirations.
• Perform focused physical assessment, including check of ears, nose, throat, regional lymph nodes, chest and heart, emphasizing assessment for any acute complaints.
• Record any clinical significant findings resulting in medication, (prescription or over the counter), MD/ER visit or consultation, hospitalization, event causing study termination or additional events judged to be significant by the Investigator on the appropriate CRFs.
• Obtain nasal wash for culture of vaccine virus (see Section 7.3 of the MOP). If febrile or respiratory illness criteria are met or suspected, complete adventitious virus assay request form, to be sent to the CIR Research laboratory along with the nasal wash specimen Appendix V.
• Schedule next visit.
- Day 28 visit only - instruct parent/guardian to notify study nurse immediately of any illness that requires medical care, any hospitalization, or any lower respiratory tract illness, including croup, pneumonia, or wheezing that occurs prior to day 56.

4.4 Telephone Contacts Post Immunization
(all non-visit days between Day 1 and 29 after Immunization)

- Obtain interim history and temperature from parent/guardian.
- Record any clinical significant findings resulting in medication changes (prescription or over the counter); MD/ER visit or consultation; hospitalizations or any events causing study termination or additional events judged to be significant by the Investigator on the appropriate case report forms.
- Clarify positive findings to determine need for illness visit.
- Schedule illness visit if child meets criteria for illness per the timeframe as described in section 4.7 of the MOP.
- Confirm next visit.

4.5 Day 56 Visit (+7 Days)

- Obtain and record interim history only for previously unreported SAEs and LRIs for study days 29 to 56.
- Obtain approximately 5 mL of blood for immunologic assays.
- Obtain nasal wash for immunologic assays (see Section 7.3 of the MOP).
- Provide parent/guardian with compensation (as determined by study site). Parents/Guardians will only be compensated for that portion of the study which is completed.
- Review RSV surveillance monitoring instructions with parents.
- Schedule a time window for pre-RSV surveillance blood draw.

4.6 RSV Surveillance Monitoring

- Between October 1st and October 31st of the calendar year in which the child was enrolled, or at day 56 follow-up if after October 1st, obtain approximately 5 mL of blood for pre-RSV season serum antibody specimen detection.
- Obtain and record interim history with weekly reporting. Arrange for study visit within 72 hours if child demonstrates any of the following:
  - Medically attended fever
  - Medically attended upper respiratory illness
  - Medically attended otitis media
  - Medically attended lower respiratory tract illness
- If one of the above events occurs, obtain, within 72 hours of initial report, a nasal wash for RSV culture and testing for adventitious virus (respiratory viruses by multiplex rRT-PCR) (lab assays to be performed by CIR, indicate request for adventitious virus assay request on the sample collection form in Appendix V).
• Between April 1\textsuperscript{st} and April 30\textsuperscript{th}, obtain approximately 5 mL of blood for post-RSV season serum antibody detection.

• Provide parent/guardian with compensation (as determined by site).

• Inform parent/guardian of study randomization, if known.

4.7 Solicited Adverse Event Visit - Protocol Defined Illness Criteria

Solicited AEs are defined as adverse events which may occur after a respiratory viral vaccine and include fever and respiratory symptoms as defined in protocol Appendix 4. Subjects who meet study criteria for Grade 1 solicited adverse events during the acute phase of the study (Days 0-28) will require an unscheduled illness visit within 72 hours of study staff notification of the event. If the reported temperature elevation and/or respiratory tract illness is of grade 2 severity or greater during days 0-28, the subject will be clinically evaluated and will have nasal washes obtained for culture of vaccine virus and testing for adventitious viruses within 48 hours of the time the illness is reported. Subjects with symptoms of lower respiratory tract illness at any time between study days 0 and 56 will be evaluated and tested for vaccine and adventitious viruses within 24 hours of staff notification of the event. All solicited AEs, LRI and SAEs require at least one illness visit within time frame described above. A follow-up adventitious virus culture will be requested if the solicited AE, LRI or SAEs continue at the time of the next routine appointment. Otherwise a second unscheduled illness visit appointment will be completed and an adventitious virus assay will be requested if the solicited AE, LRI or SAE symptoms worsen. All AEs will be followed to resolution by the clinical site or until the site PI deems the event to be chronic or the subject to be stable.

Illness visits must include:

• Obtain and record interim history and temperatures.

• Perform focused physical assessment, including check of ears, nose, throat, regional lymph nodes, chest and heart, emphasizing assessment for any acute complaints.

• Obtain vital signs (temperature, pulse, and respirations) and clinical assessment findings.

• Document history & physical findings in the subject’s study record.

• Record any clinical significant findings resulting in medication, (prescription or over the counter), MD/ER visit or consultation, hospitalization, event causing study termination or additional events judged to be significant by the Investigator on the appropriate case report forms.

• Obtain nasal wash for viral culture and adventitious agents.

• Complete adventitious virus agent assay request located on the P1114 PSWP. Ship sample on the day of collection if possible or on the first allowed shipping day.

• Notify the P1114 team (impaact.teamp1114@fstrf.org) and study sponsor of any LRI or serious adverse events.

• Report SAEs and LRIs in an expedited manner through the DAIDS Expedited Adverse Event Reporting System (DAERS).
5.0 SITE PHARMACY PROCEDURES & VACCINE PREPARATION

5.1 The Study Vaccine - Overview

The clinical lot preparation of RSV cps2 was generated by Charles River Laboratories using the seed virus provided by the NIH. This virus vaccine preparation is stable and potent when stored at a temperature of -80°C ±15°C.

The RSV cps2 clinical lot (Lot RSV#005A) was tested for sterility, infectivity, sequence identity, safety in animals, and the presence of adventitious agents in tissue culture. The clinical lot passed all of these tests. The final vaccine, designated Lot RSV#005A, has a mean infectivity titer of $10^{6.6}$ Plaque Forming Units (PFU) per mL.

A photo of the vial is shown below.

An enlarged example of a final vaccine vial label is shown below.

<table>
<thead>
<tr>
<th>Live Recombinant Respiratory Syncytial Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV cps2</td>
</tr>
<tr>
<td>VERO GROWN VIRUS VACCINE</td>
</tr>
<tr>
<td>CAUTION:NEW DRUG LIMITED BY FEDERAL (USA) LAW</td>
</tr>
<tr>
<td>TO INVESTIGATIONAL USE</td>
</tr>
<tr>
<td>Store at -80°C ± 15°C</td>
</tr>
<tr>
<td>Charles River Laboratories, Malvern, PA</td>
</tr>
</tbody>
</table>

Vaccine Product and Diluent Information

2X L-15 Leibovitz Medium

Diluted on site to make diluent/placebo. Concentrated lot is reserved and stored at Fisher BioServices. A photo of the bottle (content: 100 mL) is below.
Sterile Water for Injection USP

Sterile Water for Injection, USP (SWFI) to dilute the 2X L-15 Leibovitz medium should be provided by the site pharmacy.

RSV cps2

Concentration of the undiluted vaccine is $10^{6.6}$ PFU per mL
Lot is reserved and stored at Fisher BioServices.
Lot RSV #005A

Syringes

CIR at JHU will provide the site pharmacists with autoclaved 1 mL oral amber syringe and tips to be used for the intranasal vaccine dose.

Syringe carrier cases

Sites should order from Borin-Halbich, cat. number 5001B

Empty sterile vials

30 mL empty sterile vials must be provided by the site pharmacy for diluent preparation. Vaccine preparation will require 10 mL or 30 mL empty sterile vials.

5.2 Ordering Vaccine

The study agent for this protocol will be ordered by the site from the Regulatory Compliance and Human Subjects Protection Branch (RCHSPB), and shipped from Fisher BioServices as described below.

- To request study agent for this study, the sites should follow the ‘Instructions for Ordering RSV and L-15 Study Agents’, and complete a Vaccine Request Form, both located in Appendix VIII of the MOP. Please print the form and fill in the information by hand. **Do not make changes to the form.**

- The PI/Pharmacist of Record (PoR) completes section A of this form indicating the desired amount of study agent. For most sites, the initial order will be 10 vials which will be sufficient for five participants. Please place the first order at the same time the site is shipping the first screening blood samples to JHU; this will assure that supplies are received prior to receiving serology results.

- The form is then faxed or scanned and e-mailed to the RCHSPB CRA, below:
  
  RCHSPB CRA: L. Hoopengardner  
  Fax: 1-301-846-6440  
  Phone: 1-301-228-4118  
  e-mail: hoopengardnerl@mail.nih.gov

- Study agents are normally shipped on Monday, Tuesday, or Wednesday, in order to ensure that pharmacy staff members are available at the site to receive the shipment.

- Once the vaccine shipment arrives at the site, the study pharmacist should complete Section D of the form and fax or scan and e-mail to the RCHSPB CRA below to confirm receipt of the shipment:
  
  RCHSPB CRA: L. Hoopengardner  
  Fax: 1-301-846-6440  
  e-mail: hoopengardnerl@mail.nih.gov
The completed form should then be filed in the study product accountability records in the site pharmacy.

5.3 Ordering 2X L-15 Leibovitz Medium (used to make the diluents and the placebo)

The diluent/placebo for this protocol will be ordered from the RCHSPB, and shipped from Fisher BioServices as described below.

- To request 2X L-15 Leibovitz medium for this study, the sites should follow the ‘Instructions for Ordering RSV and L-15 Study Agents’ and complete a L-15 Request Form, both located in Appendix VIII of the MOP. Please print the form and fill in information by hand. **Do not make changes to the form.**

- The PI/PoR completes section A of this form indicating the desired amount of L-15. For most sites, the initial order will be 8 bottles.

- The form is then faxed or scanned and e-mailed to the RCHSPB CRA, below:
  
  **RCHSPB CRA:** L. Hoopengardner  
  Fax: 1-301-846-6440  
  Phone: 1-301-228-4118  
  e-mail: hoopengardnerl@mail.nih.gov

- 2X L-15 Leibovitz medium is normally shipped on a Monday, Tuesday, or a Wednesday, in order to ensure that staff members are available at the site to receive the shipment.

- Once the 2X L-15 Leibovitz medium shipment arrives at the site, the study pharmacist should complete Section D of the form and fax or e-mail to the RCHSPB CRA below to confirm receipt of the shipment.
  
  **RCHSPB CRA:** L. Hoopengardner  
  Fax: 1-301-846-6440  
  e-mail: hoopengardnerl@mail.nih.gov

- The completed form should then be filed with the study product accountability records in the site pharmacy.

5.4 Site Procedures Upon Receipt of Vaccine and 2X L-15 Leibovitz Medium

**NOTE:** The vaccine and the 2X L-15 Leibovitz medium will be shipped separately. Vaccine and 2X L-15 Leibovitz medium are shipped at different temperatures.

- Site pharmacy staff must open the box immediately and follow the instructions contained in the package. This involves inventorying the provided study agent/2X L-15 Leibovitz medium, completion of the Vaccine/L-15 Request Forms and any other forms enclosed in the box.

- The study vaccine must immediately be transferred to the appropriate freezer in order to maintain the specified storage temperature of -80°C ±15°C. The freezer must be in a secure location with limited access.

- The 2X L-15 Leibovitz medium must be transferred to the appropriate refrigerator to maintain storage at 2-8°C. The refrigerator must be in a secure location with limited access. Follow instructions on the forms to fax back or return electronically to RCHSPB and Fisher BioServices. Keep original documents in the pharmacy files.

- Follow instructions included in the shipment to download the TempTale data for review or where to return the TempTale.
• A copy of the TempTale data must be provided to the RCHSPB CRA who will be responsible for notifying the site that the product is acceptable for use.
  o If the pharmacy has the TempTale Manager Desktop software available, the data can be downloaded and forwarded to Lisa Hoopengardner at hoopengardnerl@mail.nih.gov for verification.
  o If the software is not available the TempTale must be returned to Fisher BioServices and it may take several days for the data to be verified.
• Once the RCHSPB CRA has verified the shipment temperature, she will contact the Protocol CTS who will forward the approval to the site.
• Document receipt of the vaccine and the 2X L-15 Leibovitz medium on the appropriate Study Product Accountability Record.
• Any problems that are noted during the receipt process, such as thawing of the vaccine or a cloudy 2X L-15 Leibovitz medium, should be immediately communicated to the RCHSPB CRA.
• It is the responsibility of the site pharmacist to monitor the amount of vaccine and 2X L-15 Leibovitz medium at the site, along with the expiration dates and to request additional products as needed.

5.5 Pharmacy Procedures – Storage, Preparation & Accountability

5.5.1 Storage of the Vaccine

• The RSV cps2 vaccine must remain frozen at -80°C ±15°C until just prior to use. Vaccine must never be refrozen for re-use.
• L-15 Leibovitz medium to be used as diluent/placebo must be stored at 2-8°C in accordance with the manufacturer’s recommendation.
• The sterile water for injection must also be stored in the refrigerator at 2-8°C.
• Vaccine, L-15 Leibovitz medium and SWFI must be opened from new containers for each use. No product should be reused for vaccine or placebo preparation.
• The temperature of the storage refrigerator/freezer must be recorded on a daily basis and equipped with an alarmed temperature monitor that will notify staff in the event of an excursion from the acceptable temperature range.

5.5.2 Randomization, Prescribing & Blinding

• This is a double-blind, placebo-controlled study with a ratio of vaccine to placebo recipients of 2:1.
• When the site is registered, FSTRF will send the site pharmacist the Pharmacist’s Prescription List (SID list) that lists SID’s and the corresponding treatment assignment.
• A SID number will be assigned by FSTRF when the participant is enrolled into the study.
• The research staff must send the site pharmacist a copy of the enrollment confirmation containing the assigned SID number.
• The research staff must also send the pharmacist a prescription for RSV cps2 vaccine or placebo. The prescription must contain the SID and PID of the participant, verification of signed consent, any other information required
by the site and must be signed by an authorized prescriber

- The site pharmacist will use the Pharmacist’s Prescription List to determine if the participant receives active vaccine or placebo.
- The pharmacist should be notified of the date and time the vaccine is to be administered.
- The designated unblinded pharmacist will prepare the vaccine as outlined below.
- The unblinded pharmacist will agree not to reveal the identity of the vaccine/placebo to personnel (e.g. investigator, study nurse, study monitor) involved in the conduct of the study.
- For further information on blinding and unblinding, see section 2.3 of the MOP.

5.5.3 Vaccine and Placebo Preparation Guidelines

- Vaccine and placebo preparation should be performed in a biosafety cabinet (BSC) or isolator, using worker safety protection, aseptic technique procedures and standards applicable to the clinical research site.
- The BSC/isolator should be cleaned before and after vaccine/placebo preparation with a recommended cleaning agent such as CaviCide® followed by 70% isopropyl alcohol or by using the site’s approved procedure to disinfect biosafety cabinets for preparation of live virus components.
- Preparation of all study products must be performed by a pharmacist and double checked by another pharmacy staff member.
- On days that both vaccine and placebo doses are prepared, the placebo doses should be prepared first.
- Two doses should be prepared for each participant. One dose is sent to the clinic for administration to the participant and the other dose should be kept in the pharmacy on wet ice as a backup replacement dose in the event the first syringe is damaged or goes out of temperature range. The study coordinator will contact the site pharmacist if the replacement dose is needed.
- If using an isolator or working in a clean room, to reduce the risk of contamination, put the wet ice into two zip lock bags, and place the bags in a beaker. Spray the outside of the bags, inside and outside of the beaker with isopropyl alcohol. If using a BSC, the ice may be placed outside of the cabinet and the product can be brought out of the cabinet when necessary to place on ice. When using an isolator, the ice container must be placed in the isolator.
- The diluent should be prepared before thawing the vaccine.
- If 2 participants are being dosed within the 4 hour period you may use the same 1X L-15 and vaccine dilution for both participants (always draw up the placebo dose first).
- Vaccine must be administered within 4 hours of removing vaccine from the freezer. However, the expiration time is assigned based on the time the diluent is removed from the refrigerator in order to maintain the blind.
PRODUCT LABELING

- Doing syringes should be labeled with a two part label containing:

  P1114 Intranasal RSV or Placebo
  SID_________PID_________
  Exp:_________@_____:_____  
  Initials:_________/_________

  **These labels can be purchased from Health Care Logistics – item #6028**

- The syringe carrier bag should be labeled with a participant specific label containing the following and any other information required at the site:

  Date dispensed
  Participant Name or Identifiers (per site’s SOP)
  Directions: Instill 0.25 mL in each nostril
  P1114 RSV cps2 10^{5.3} PFU or Placebo nasal vaccine
  0.5mL/syringe
  Expiration Date _____time_____ in 24 hr clock
  Initials of pharmacist preparer and checker
  Authorized prescriber’s name

- The syringe carrier bag should be labeled with an auxiliary label:

  FOR INTRANASAL ADMINISTRATION ONLY

- Vaccine dilution and diluent labels
  "Diluted vaccine 10^{5.3} PFU per 0.5 mL"
  "1X L-15 Diluent"

  The site is responsible for providing and preparing labels for the diluent and the diluted vaccine vial that will remain legible while on wet ice during product preparation.

- After preparing vaccine for administration, the pharmacist will prepare Vaccine Aliquots from the left-over vaccine for freezing and storage- for these aliquots, the site is responsible for providing and preparing labels for the cryovials that will remain legible and attached to the cryovials during transport on dry ice and storage at -80°C ±15°C. The labels must contain:

  RSV cps2 1:10 Diluted
  Site Number
  Date and time aliquots prepared

  RSV cps2 UNDILUTED
  Site Number
  Date and time aliquots prepared

5.5.4 Preparing the Diluent and Placebo

**Product:** 1X L-15 Leibovitz medium (1X L-15) is used as the vaccine diluent and as the placebo for this study. It is prepared by diluting 2X L-15 Leibovitz medium (2X L-15) with sterile water for injection.
Dose of Placebo: The dose of placebo is 0.5 mL of 1X L-15.

Storage of Placebo: 1X L-15 should be kept on wet ice after preparation.

Expiration of Placebo: 4 hours after removal of the 2X L15 from the refrigerator.

Documentation: Use the Diluent Preparation Form to document preparation of the diluent and the placebo vaccine.

5.5.4.1 Preparing the Diluent:

1. Clean BSC/Isolator with recommended cleaning agent and 70% alcohol.
2. Prepare ice in an appropriate container as described above.
3. Remove 1 new unopened bottle of 2X L-15 from the refrigerator and note the time on the Diluent Preparation Form. Put on wet ice until ready to use.
4. Prepare a label for the diluted 1X L-15 and assign a 4 hour expiration time from the time the 2X L-15 was removed from the refrigerator.
5. Remove enough vials of sterile water for injection from the refrigerator to provide 15 mL.
6. Verify that the products are not expired, opened and the solutions are clear.
7. Gather all supplies needed for preparation, spray outside of containers with 70% isopropyl alcohol and place in BSC/isolator:
   - empty sterile vial large enough to accommodate 30 mL
   - Sterile syringes and needles of appropriate size for 15 mL volumes
   - alcohol pads
   - label for the 1X L-15 vial
   - Sterile water for injection
   - 2X L-15 bottle on wet ice
8. With a syringe, transfer 15 mL of 2X L-15 into the empty sterile vial.
9. Add 15 mL of sterile water for injection to the vial to make 30 mL of 1X L-15 and mix well.
10. Label this vial as 1X L-15 and place on wet ice.
12. Remove the label from the 2XL-15 and place on the Placebo and Diluent Preparation Form.

5.5.4.2 Preparing the Placebo Dose

1. Prepare a 2 part syringe label with the expiration time of 4 hours from when the 2X L-15 was removed from the refrigerator.
2. Label the plastic syringe bags with participant specific labels and expiration time of 4 hours from when the 2X L-15 was removed from the refrigerator. Affix a “FOR INTRanasAL ADMINISTRATION ONLY” label to the bag.
3. Gather all supplies needed for preparation, spray outside of containers with 70% isopropyl alcohol and place in BSC/isolator:
   - 2 sterile 1 mL oral syringes and 2 caps
   - 1 mL sterile syringe(s) and needles
- Alcohol wipes
- Vial of 1X L-15 prepared above on wet ice

4. Draw up excess of 0.5 mL of 1X L-15 into a 1 mL syringe.

5. Transfer the 1X L-15 into the oral syringe and adjust the plunger to deliver 0.5 mL.

6. Cap the dosing syringe with the oral syringe cap and place in the wet ice container.

7. Repeat procedure 4-6 to prepare the back up dose.

8. Label each oral syringe with a two-part label.

9. Place the oral dosing syringe in a syringe carrier case and then put the syringe case in the labeled plastic syringe bag.

10. Put the syringe bag into wet ice, burying it in the ice.

11. Place the labeled backup dose in a zip lock bag and keep it in wet ice until it is determined that a replacement dose is not needed at the clinic.

12. Store and transport the placebo dosing syringe in wet ice until just before administration.


14. Disinfect the BSC/isolator using recommended cleaning agent followed by 70% isopropyl alcohol or follow site’s SOP for cleaning.

### 5.5.5 Preparing the Vaccine

Two vials of undiluted vaccine are always used to prepare the vaccine dose to account for potential differences in titers of the concentrated vaccine. When
manipulating the undiluted vaccine use as small a gauge needle as possible to avoid loss of vaccine in the needle and syringe hub.

Concentration of the undiluted vaccine is $10^{6.6}$ PFU per mL. The frozen vaccine is thawed and diluted with 1X L-15 to a dose of $10^{5.3}$ PFU in 0.5 mL.

Do not thaw this product on the bench top or allow the vial to thaw completely before putting it onto wet ice. RSV is extremely sensitive to freezing and thawing and warm temperature. RSV readily loses infectivity if it is allowed to get warm, or allowed to sit too long unfrozen, or if it is not properly quick-thawed or snap-frozen. Loss of infectivity will affect study results. It is important that RSV be thawed rapidly by transferring vials from a -80°C freezer or from dry ice directly into a 32°C water bath, swirling tubes for 2-2.5 minutes until a small ice pellet is left in the tubes, then transfer tubes to wet ice; please follow instructions below. To “snap freeze” diluted and undiluted vaccine aliquots, follow BioCision CoolBox procedures described in 5.5.8 below.

If the -80 freezer where the RSV vaccine is stored is not right next to where the preparation is being done, the vaccine vials should be transported on dry ice from the freezer to the BSC/isolator.

5.5.5.1 Preparation of the RSV cps2 $10^{5.3}$ PFU per 0.5 mL solution

Use the Vaccine Preparation Form to document preparation

1. Prepare 1 “diluted vaccine $10^{5.3}$ PFU per 0.5 mL” label.
2. Gather all supplies needed for vaccine preparation, spray outside of containers with 70% isopropyl alcohol and place in the BSC/isolator:
   - Vial of 1X L-15 prepared above on wet ice.
   - 10 mL and 1 mL syringes and needles
   - alcohol wipes
   - diluted vaccine vial label
   - 1 sterile vial with sufficient volume to accommodate 10 mL
3. Withdraw 5.4 mL of 1X L-15 and inject into the empty sterile vial.
4. Place the vial in the wet ice container.
5. Remove 2 vials of undiluted vaccine from the -80 freezer. Ensure the vaccine name and lot number is correct.
6. Rapidly, and immediately after removing from -80°C freezer or from dry ice, thaw the 2 vials of undiluted vaccine by swirling vials in a 32°C water bath until a small ice pellet is left in the vial (the presence of a small ice residue ensures that the vaccine did not get too warm), and place thawed vial of vaccine immediately into the wet ice container. Thawing typically takes 2 to 2.5 minutes.
7. Document the time the vaccine was removed from the freezer on the Vaccine Preparation Form and confirm the vaccine name and lot number.

8. Draw up the contents of one vial of undiluted vaccine and transfer into the other vaccine vial using a sterile syringe and a small needle (20G or smaller). Do not use a safety needle because it will not fit into the vial.

9. Cap the vial and swirl the undiluted vaccine vial for 30 seconds to mix.

10. Withdraw 0.6 mL from the vaccine vial with a sterile syringe and a small gauge needle. Cap and place the vaccine vial back into the wet ice container.

11. Add the 0.6 mL to the vial containing the 5.4 mL of 1X L-15.

12. Label this vial - diluted vaccine $10^{5.3}$ PFU per 0.5 mL, swirl to mix and place it into the wet ice container.

13. Save the undiluted vaccine vials in wet ice for aliquoting and snap freezing.

5.5.5.2 Preparation of the diluted RSV cps2 $10^{5.3}$ PFU per 0.5 mL VACCINE DOSE

1. Prepare a 2 part syringe label with the expiration time of 4 hours from when the 2X L-15 was removed from the refrigerator.

2. Label the plastic syringe bags with participant specific labels and expiration time of 4 hours from when the 2X L-15 was removed from the refrigerator. Affix a “FOR INTRanasAL ADMINISTRATION ONLY” label.

3. Gather all supplies needed to prepare the vaccine dose, spray the outside of the containers with 70% isopropyl alcohol and place in the BSC/isolator:
   a. 2 sterile 1 mL oral syringes and caps,
   b. 1 mL syringes/needles
   c. alcohol wipes
   d. diluted vaccine $10^{5.3}$ PFU/0.5 mL prepared above on wet ice

4. Draw up excess of 0.5 mL of the diluted vaccine into a 1 mL sterile syringe.

5. Transfer the diluted vaccine into the oral syringe and adjust the plunger to deliver 0.5 mL.

6. Cap the dosing syringe with the oral syringe cap.

7. Repeat procedure 4-6 to prepare the back up dose.

8. Label each oral syringe with a two-part label.
9. Place the oral dosing syringe in a syringe carrier case and then put the syringe case in the labeled plastic syringe bag.

10. Put the syringe bag into wet ice, burying it in the ice.
11. Place the labeled backup dose in a zip lock bag and keep it in wet ice until it is determined that a replacement dose is not needed at the clinic.
12. Transport and store the vaccine dosing syringe in wet ice until just before administration.
14. Document dispensing on the Study Product Accountability Record

5.5.6 Transport of Vaccine/Placebo to the Clinic

1. Prepare a cooler with wet ice or ice packs to maintain a temperature of 2-8°C and place a min/max thermometer in the cooler.
2. Place the labeled zip lock bag containing the syringe in the syringe carrier in another re-sealable plastic bag and put in the cooler.
3. Record the temperature on the P1114 Vaccine Administration Record when the cooler leaves the pharmacy and reset the min/max thermometer.
4. Note the expiration time along with the signatures of the pharmacy staff.
5. The clinic staff must inspect the contents and sign the the P1114 Vaccine Administration Record when the cooler is received at the clinic along with the signature of the clinic staff receiving the cooler.
6. The dose should be kept in the cooler on wet ice until administered to the participant.
7. The clinic staff must record the current, minimum and maximum temperatures on the P1114 Vaccine Administration Record when the vaccine dose is removed from the cooler for administration to the participant
8. If the temperature in the cooler was not maintained between 2-8°C, contact the pharmacy for a replacement dose.
9. If the syringe is not used it should be returned to the pharmacy for disposal.

5.5.7 Vaccine/Placebo Chain of Custody Accountability

- The unblinded pharmacist completes the appropriate sections of the P1114 Vaccine Administration Record and oversees delivery of the product and the P1114 Vaccine Administration Record to the clinic.
- The physician/study nurse verifies the participant identifiers on the bag and the syringe, as well as the date and time of expiration.
- Upon administration of the dose the 2nd part of the detachable syringe label is attached to a source document by the research nurse.
- Unused syringe(s) and P1114 Vaccine Administration Record are returned to the pharmacy at the completion of vaccination.
- The pharmacist receiving the form and returned syringes (if applicable) completes the bottom portion of the P1114 Vaccine Administration Record.
- A photocopy of the P1114 Vaccine Administration Record remains at the pharmacy.
- The original of the P1114 Vaccine Administration Record is returned to the study coordinator for placement in the study binder or participant’s file.

5.5.8 Preparation of Vaccine Aliquots for Snap Freezing

- As soon as possible after the vaccine doses are dispensed, prepare aliquots of the remaining diluted and undiluted vaccine in Sarstedt 72.694.006 cryovials, following the instructions below.
- All aliquots should be snap frozen and stored at -80°C±15°C until shipped.
- Snap freeze the Sarstedt vials using a CoolBox CF30 system (CoolBox 30 with CoolRack CF30, BioCision, Mill Valley, CA) and dry ice pellets, as described below.
- Store the CoolRack in a -20 freezer when not in use.

1. Fill the CoolBox cavity with dry ice pellets up to the bottom of the finger grip recess.
2. Place the CoolRack directly onto the dry ice. Complete this at least 20 minutes prior to preparing the Sarstedt cryovials for snap freezing, because the CoolRack will need 20 minutes to reach dry ice temperature.
3. Prepare 4 cryovial labels for the Diluted vaccine with date and time aliquoted and frozen, and site number.
4. Prepare 4 cryovial labels for the Undiluted vaccine with date and time aliquoted and site number.
5. Gather 6 Sarstedt vials, two 1mL syringes, small gauge needles and labels and place in the BSC/isolator.
6. Withdraw from the $10^{5.3}$ PFU per 0.5 mL diluted vaccine, 3 aliquots of 0.5 mL and put into 3 Sarstedt vials. Label with Diluted vaccine label.
7. Withdraw all of the liquid from the $10^{6.8}$ PFU/mL undiluted vaccine, and divide it into 3 aliquots of at least 0.15 mL and put into 3 Sarstedt vials. Label with Undiluted vaccine label. If there is not enough vaccine for 3 aliquots of 0.15, then prepare 2 aliquots of 0.15 mL.
8. Ensure that the vials to be snap frozen are tightly sealed. Care must be taken to tighten caps because CO$_2$ from dry ice will affect pH of vial content and inactivate virus.
9. Transfer the Sarstedt cryovials to the CF30 CoolRack in the BioCision CoolBox.

10. Leave the vials in the CoolBox for at least 15 minutes.
11. After the vials are frozen, take them out of the CoolBox and store the frozen vials at -80° C±15°C, separate from the study vaccine product in the Investigational Pharmacy. One aliquot of diluted and undiluted vaccine will be batch shipped to JHU.
12. Allow dry ice to dissipate in the CoolBox. Do not throw dry ice in the sink. Extreme cold (dry ice) will crack the drainage pipe.
13. Disinfect the BSC/isolator using recommended cleaning agent followed by 70% isopropyl alcohol or follow site’s SOP for cleaning.
14. Place the extra aliquot labels on the Vaccine Aliquot Log. Enter stock vial numbers of the vaccine used, SID number(s) of participant(s) receiving the vaccine and your initials.
15. Remove the labels from the original undiluted vaccine vials and place on the Vaccine Preparation Form.

5.6 Disposal of Vaccine/Placebo

1. Any remaining, unused vaccine/placebo syringes should be disposed of by incineration or placing in a solution of 1 part bleach to 9 parts water for 30 minutes and then disposed of as medical waste in accordance with site/institutional/local guidelines.
2. Disposal/destruction of unused vaccine/placebo should be documented on a standard destruction/disposal record used at the site.
3. Disposal of and/or destruction of USED vaccine/placebo vials and needles, syringes, pipettes used in preparation must be in accordance with site/institutional/local guidelines.
4. Expired study product or product remaining at the end of the study should be retained at the site pharmacy until instructions for destruction or return are received from RCHSPB or Fisher BioServices.

5.7 Shipping the Diluted & Undiluted Vaccine for Quality Control

For each participant that received active vaccine, the pharmacy must batch ship 1 aliquot of diluted frozen vaccine and 1 aliquot of undiluted frozen vaccine on dry ice. The first shipment should occur shortly after the first vaccine is prepared. Subsequent batch shipment frequency will be determined and communicated to the site pharmacists.
1. Log out the aliquots to be sent from the Vaccine Aliquot Log by locating the label on the form and writing the date and your initials next to the label. Copy that page of the Vaccine Aliquot Log and include in the shipment.

2. Pack in a cooler with dry ice.

3. Fill out and include in the shipment the Investigational Drug Packing Slip – Vaccine Aliquots.

4. Complete the FedEx Airbill - must fill out section 6, check Yes, Shipper's Declaration NOT required. Check ✓ Dry Ice and indicate quantity of dry ice in Kg.

5. The following labels must be attached to the shipping box:
   - UN3373, Biological Substance, Category B
   - UN1845: Fill in the amount of Dry Ice in Kg

6. Send by FedEx overnight to:

   Bhavin Thumar, MS
   JHU – Bloomberg School of Public Health
   615 N. Wolfe Street, Room E5402
   Baltimore, MD 21205
   (410) 955-7230
   Acct number# 412620290201

5.8 Maintaining the Blind

- Because only the active vaccine is snap frozen, it is important that other study staff not be involved in the snap freezing and shipment from the pharmacy. If the pharmacy gets the dry ice from the lab or the CoolBox from the clinic, in order to maintain the blind, the pharmacy should receive these supplies each day that doses are prepared. The dry ice can be disposed of in the pharmacy if not needed.

- Because it will take longer to prepare the vaccine dose than the placebo dose the pharmacy should hold the placebo dose in the pharmacy longer to match the time it would take to prepare an active vaccine dose.

5.9 Communication with Pharmacy Staff

- Establish a system of communication to inform the Pharmacist of each upcoming participant visit prior to the visit (i.e. provide a calendar of visits, weekly emails/phone calls, etc.)

- Inform Pharmacy staff in a timely manner of any changes to expected visits and/or enrollments (i.e. cancellations, date/time changes, participant eligibility for vaccine, etc)

- On day of expected visit, provide confirmation to Pharmacy staff that participant has arrived as scheduled, either by phone, email or in person.

- Ensure that all Authorized Prescribers for P1114 have been added to an “Authorized Prescribers” list provided to the Pharmacy staff.

- Ensure all Authorized Prescribers are on the FDA Form 1572.

- Ensure that signatures are legible and consistent with original list.

- Update list immediately with any changes (name changes, additional/departing staff, etc) and provide to Pharmacy staff.

- Meet all local regulations for writing prescriptions.

- Ensure all relevant information, in accordance with local regulations, is included on prescription.

- Include PID/SID number on prescription.
• Confirm that the informed consent has been signed by the participant and that this has been documented on the prescription, as per site procedures (if applicable).

5.10 Administering the Vaccine/placebo

NOTE: Vaccine must be administered by the expiration time on the syringe label

• Vaccine will be administered to participants intra-nasally using a 1 mL oral syringe. Following on-site dilution, the final vaccine preparation will contain $10^{5.3}$ PFU per 0.5 mL. Syringe must be maintained on ice until immediately before use. Do not warm.
• Position participant in the supine position (lying down).
• Administer approximately 0.25 mL to each nostril.
• Have the participant remain in this position for 1 minute after administration of the study product.
• Discard the empty dosing syringe in accordance with site/institutional/local guidelines for disposal of medical waste.
• Participants must be monitored by qualified staff for a minimum of 30 minutes following vaccine administration, for signs and symptoms of local and/or systemic reaction.
• Record any adverse reactions on the Adverse Event page of the study record, or indicate absence of reaction in the study record.
• Resuscitation equipment, oxygen and epinephrine 1:1000 (1 mg/mL) must be readily available in case of an anaphylactic reaction.
• Document vaccine administration on the P1114 Vaccine Administration Record, in the study record and case report form.

5.11 Pharmacy Questions / Problems

For questions regarding preparation or storage of the vaccine or diluent (placebo), please contact:

Ana Martinez, RPh  
amatinez@niaid.nih.gov  
301-435-3734

Vivian Rexroad, Pharm D  
vrexroa@jhmi.edu  
410-955-4505

Bhavin Thumar, MS  
bthumar@jhsph.edu  
410-955-7230

6.0 SAFETY SECTION

The safety section of the MOP only contains information that is atypical for an IMPAACT study or it summarizes information to enhance understanding of the protocol. Please refer to the protocol to confirm safety related requirements.

6.1 Adverse Events (AEs)

The protocol definition of an adverse event is:

An adverse event (AE) is any untoward medical occurrence in a subject administered the investigational vaccine or placebo and does not necessarily have a causal relationship with vaccination. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational vaccine whether or not related to it. This includes exacerbation of pre-existing conditions and intercurrent illnesses.
However, there are 3 exceptions to what will be considered an adverse event for this trial. The following types of events will NOT be considered adverse events and will NOT be recorded as adverse events on the case report form for this study:

1. Diaper rashes, teething pain, and spitting up will NOT be recorded as AEs unless a prescribed concomitant medication is used to treat them.

2. Transient or mild solicited AE symptoms, such as rhinorrhea, pharyngitis, hoarseness, or cough that do not meet the solicited AE study definitions (see protocol Appendix 4, Table 11) will NOT be recorded as adverse events.

3. Solicited AEs elicited by history that are not confirmed by clinical assessment will NOT be recorded as adverse events if they are reported to have occurred on the same days on which the subject has clinical assessments performed. Solicited AEs elicited by history on days without visits will be counted only if they meet the definition of illness (for example, both rhinorrhea and cough must each occur on 2 consecutive days to meet the definition of illness). See protocol Appendix 4, Table 11 for the definitions of these solicited AEs.

6.2 Summary of Expectations For Recording Adverse Event on CRFs

The events to be recorded on CRFs during the various time periods of study participation are defined below:

Study Days 0 to 28
- (Acute Phase): all solicited AEs (see protocol Appendix 4/Table 11) and all unsolicited AEs, except diaper rash, teething pain and spitting up that do not require a prescribed concomitant medication (see protocol section 8.1.1) and all serious adverse events (SAEs) will be recorded on CRFs

Study Days 29 to 56
- (Post-acute Phase): LRI solicited events (see protocol Appendix 4/Table 11) and all SAEs will be recorded on CRFs

Study Day 57 until October 31st
- (between Post-acute phase and RSV Surveillance): No recording of solicited AEs, unsolicited AEs, or SAEs on CRFs is expected

November 1st through March 31st
- (Surveillance Period for RSV-associated Disease During RSV Season): Record serious adverse events and the following RSV-associated illnesses (see protocol section 4.2.6/"RSV-associated illness") on CRFs if they occur between November 1st and March 31st:
  - Medically attended fever
  - Medically attended upper respiratory illness (URI)
  - Medically attended otitis media
  - Medically attended lower respiratory illness (LRI)
April 1st through April 30th Study Day 57 until October 31
- (post- RSV Surveillance): No recording of solicited AEs, unsolicited AEs, or SAEs on CRFs is expected

6.3 Determination of Severity/Grade for Solicited Adverse Events

Solicited adverse events (predefined AEs that can potentially occur after vaccine administration) are highlighted in section 8.1.2 (list of solicited AEs) of the protocol and in protocol Appendix 4, Table 11 (definition of solicited AEs). It is important to be familiar with the “solicited adverse events” for this study because they will be graded according to the criteria outlined in protocol sections 8.4.1 and 8.4.2 and NOT the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table).

From Protocol Section 8.4.1:
Table 2: P1114 specific AE Grading Table for solicited adverse events

<table>
<thead>
<tr>
<th>Severity</th>
<th>Defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (0) None</td>
<td>None</td>
</tr>
<tr>
<td>Grade (1) Mild</td>
<td>No medical intervention required; may include over-the-counter medications managed by the subject or caregiver for treatment of symptoms</td>
</tr>
<tr>
<td>Grade (2) Moderate</td>
<td>Outpatient medical intervention by a health care provider required; may include use of over-the-counter and/or prescription medications.</td>
</tr>
<tr>
<td>Grade (3) Severe</td>
<td>Prolonged medical intervention and/or hospitalization required</td>
</tr>
<tr>
<td>Grade (4) Life-threatening</td>
<td>Life-threatening illness requiring hospitalization with intensive care</td>
</tr>
</tbody>
</table>

From Protocol Section 8.4.2:
Table 3: P1114 specific Fever Grading: Temperature Measurement

<table>
<thead>
<tr>
<th>Severity</th>
<th>Defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (0)</td>
<td>&lt;100.4°F (&lt;38°C)</td>
</tr>
<tr>
<td>Grade (1)</td>
<td>≥100.4°F but ≤101.4°F (≥38°C but ≤38.6°C)</td>
</tr>
<tr>
<td>Grade (2)</td>
<td>≥101.5°F but ≤102.4°F (≥38.7°C but ≤39.1°C)</td>
</tr>
<tr>
<td>Grade (3)</td>
<td>≥102.5°F but ≤104.8°F (≥39.2°C but ≤40.5°C)</td>
</tr>
<tr>
<td>Grade (4)</td>
<td>≥104.9°F (≥40.6°C)</td>
</tr>
</tbody>
</table>

All AEs other than solicited AE and fever will be assessed for severity by the investigator using the most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), which is available on the RSC website at: http://rsc.tech-res.com/safetyandpharmacovigilance/.

6.4 Serious Adverse Events (SAE) and Lower Respiratory Tract Illnesses (LRI)

The list of serious adverse event outcomes is included in protocol section 8.1.3. It includes the typical outcomes seen in most FDA regulated studies. Additionally, Lower Respiratory Tract Illness (LRI) is considered a Protocol Specified Event (PSE) for this study and must be reported in an expedited manner via the DAIDS Expedited Adverse Event Reporting System (DAERS) in the same timeframe as SAEs which is 3 working days of the study site’s awareness of the SAE or LRI that occur from Day 0 to Day 56.

An LRI includes:
- Wheezing, OR
6.5 **Unanticipated Problems (UPs)**

The definition of a UP is outlined in protocol section 8.7. The concept of UP reporting may be new to some sites so a general UP regulatory background is provided below:

**UP Regulatory Background:**

UPs must be reported to an IRB as required by 45 CFR 46 (OHRP) and 21 CFR 312.66 (FDA). The OHRP regulations apply to research conducted or supported by the HHS. The 21 CFR 312.66 FDA regulation applies to research conducted under an Investigational New Drug application (IND). Therefore, if a study is conducted and/or supported by HHS and/or it is under an FDA IND, UPs must be reported to all IRBs/ethics committees (ECs) involved in the oversight of participants on the trial.

In general, there are 2 types of UPs. One type of UP originates as an adverse event and the other type of UP does not originate as an adverse event. IRBs generally require that all UPs be reported to them. Please refer to the local IRB UP reporting requirements to determine how and when to report UPs. In addition, the IND Sponsor of this study requires non-serious AEs that are also UPs be reported to the Sponsor Clinical Safety Office no later than 7 calendar days of the site investigator awareness of the event. To report UPs to the IND Sponsor Clinical Safety Office, submit the local IRB UP report form via e-mail or fax:

**RCHSPB Clinical Safety Office**

5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301
Fax: 301-846-6224
E-mail: rchpsafety@mail.nih.gov

UPs that do not originate as adverse events are not reported to the IND Sponsor Clinical Safety Office for this study.

6.6 **Pausing Rules**

Per protocol section 8.9: If any of the following occur in a child during the 56 days after s/he receives investigational vaccine or placebo, additional study vaccinations will be temporarily suspended at all sites:

- An SAE that is possibly, probably, or definitely related to the investigational vaccine or placebo, OR;
- A lower respiratory tract illness (LRI) [as defined in protocol Appendix 4/Table 11], OR;
- A grade 4 fever or any grade 3 or grade 4 solicited AE other than fever,
If a site identifies that a pausing criteria has been met, the following steps will be followed:

1. Site will notify the IMPAACT team of the event (including a description of the event) via email, at impaact.teamp1114@fstrf.org, within 24 hours of identification of the event. The site should also determine if the local IRB requires reporting for a study pause and report SAEs and LRIs via the DAERS reporting system if that's the type of event that triggered the pause.

2. The IMPAACT protocol team will notify all sites to suspend enrollment and immunizations and FSTRF will close accrual.

3. Site will ship ALL respiratory viral samples collected on the subject that experienced the event that met pausing criteria. Samples must be sent to the Johns Hopkins University Laboratory as soon as possible. See MOP section 7.0 for further directions about sending samples. It is important that the samples be sent a.s.a.p. because the samples need to be run to determine if there are safety concerns (e.g., shedding of vaccine virus). The results are used to determine if the protocol may proceed or not.

4. All sites will continue to conduct the protocol specified evaluations on previously enrolled/active subjects.

5. The IMPAACT team will notify sites when/if the study enrollment may resume. If the study is allowed to resume, accrual will open in FSTRF.

It’s imperative that sites follow the pausing steps so that the pausing event can be assessed expeditiously and not delay further enrollment if possible.

6.7 Stopping Rules

A set of 5 stopping rules is noted in the protocol section 8.9. All stopping rule steps are handled internally by the IMPAACT Team. Sites must follow the pausing rule steps noted in section 6.5 in the MOP. If a study subject experiences an event associated with a pausing rule, the subject’s randomization status may be unblinded to a limited number of individuals within the IMPAACT team. If the subject received study vaccine and meets any of the 5 stopping rules, the Data and Safety Monitoring Board will review the event and determine if the protocol can resume enrollment.

7.0 SPECIMEN COLLECTION and PROCESSING

7.1 Introduction

This section contains instructions related to collection and processing of P1114 specimens. For detailed information on tests and specimens required for each visit, please refer to the Schedule of Evaluations (SOE), Appendix 1 of the P1114 protocol (www.impaactgroup.org)

All protocol required laboratory testing will be done at JHU. Regardless of where tests are performed, personnel who collect specimens and/or perform assays must be trained in proper collection, handling, testing and associated QA/QC procedures prior to performing the tests for study purposes. Training documentation must be available for inspection at any time.
All laboratory activities should be conducted in accordance with accepted Good Clinical Laboratory Practice (GCLP), the IMPAACT and ACTG Network Laboratory Joint Laboratory Manual and site-specific Standard Operating Procedures (SOPs) for proper collection, processing, labeling, and transport of specimens. Transport of all specimens must comply with federal, state, local, IATA and ACTG/IMPAACT specimen shipping regulations.

As the transmission of HIV and other blood-borne diseases can occur through contact with contaminated needles, blood and blood products, appropriate precautions should be employed by all personnel when drawing blood and handling clinical specimens for this study in both the clinical and laboratory setting, as recommended by the Centers for Disease Control and Prevention (CDC). Respiratory infections may be transmitted by droplet aerosolization and fomites. All study staff should take appropriate precautions when collecting and handling biological specimens. Guidance on Universal Precautions/Body Substance Isolation is available from the US Centers for Disease Control and Prevention:

http://www.cdc.gov/ncidod/dhqp/bp_universal_precautions.html
http://www.cdc.gov/ncidod/dhqp/gl_isolation_standard.html

Additional laboratory reference information can be found in the joint ACTG/IMPAACT Laboratory Manual, which is available at:

http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx

7.2 General Overview and Guidelines

Key elements of specimen management include collection, transport, storage and shipping. Also essential for clinical trials is a Chain of Custody that refers to the tracking of specimens and results.

It is essential that all staff collecting P1114 specimens have been trained in proper collection techniques, container types, and any special requirements. Specimens must be transported within predefined time limits to the laboratory under proper conditions. The remainder of this section provides information intended to standardize specimen collection and laboratory procedures across sites.

7.2.1 Specimen Chain of Custody

All IMPAACT sites must have a Standard Operating Procedure (SOP) for Chain of Custody in place. The Chain of Custody must track when specimens are transferred between clinics, processing units, and laboratories. Internal movements of specimens within the same laboratory do not need to be tracked. Laboratories with Laboratory Information Management Systems (LIMS) or the Laboratory Data Management System (LDMS) may be able to track most Chain of Custody information electronically. Tracking forms with specific information must accompany specimens. Required information includes the following: the PID/SID, collection time and date, and visit code for each specimen. Subject names or initials may NOT be used on research samples or the accompanying tracking forms.

7.2.2 Labeling Specimens

All samples collected at a study visit must be labeled at the time of collection with labels containing the PID, visit number, and collection date. Study staff must
write the actual specimen collection time on CRF and the tracking forms. See Appendix IX.

All samples must be entered into the LDMS system. The actual collection time from the CRF will be entered into the LDMS system. Information on the CRF must match the information on the tracking forms and in the LDMS.

7.2.3 Laboratory Data Management System (LDMS)

The LDMS must be used at all sites to track the collection, storage, and shipment of the laboratory specimens. Detailed instructions for use of the LDMS are available at: http://www.fstrf.org/ldms

All sites should upgrade to the most current version of the LDMS as soon as possible. For supported label and printer options, refer to the product listing documents located on the LDMS Documentation page on the FSTRF portal. Contact LDMS user support for further information.

Questions about LDMS, shipping and storage for this protocol should be raised with the Laboratory Data Coordinators at FSTRF:

Heather Sprenger, FSTRF
Phone: (716) 834-0900, extension 7262
Email: sprenger@fstrf.org

24-Hour LDMS User Support

Technical support is also available from LDMS User Support. Usual business hours from LDMS user support are 12 AM - 6:00 PM Eastern Time in the US (ET) Monday through Friday. During business hours, please contact LDMS User support as follows:

Email: Ldmshelp@fstrf.org
Phone: (716) 834-0900, extension 7311

Off-Hours Contact Information

If you are locked out of your LDMS or are experiencing errors that prevent you from completing your LDMS lab work during off-hours, page LDMS User Support using the LDMS Web Pager utility on the FSTRF portal.

Additional Resources:
LDMS website:
http://www.fstrf.org/ldms/

FSTRF portal:
http://www.fstrf.org/portal/

7.3 Specimen Collection Procedures

Table 1 outlines all samples required by the P1114 protocol. The table identifies the type of collection tube, the amount and type of specimen to be processed and stored, and the required tests.
Table 1. SPECIMEN COLLECTION & TESTING

<table>
<thead>
<tr>
<th>Assay / Procedure</th>
<th>Collection Container</th>
<th>Specimen Type</th>
<th>Specimen Volume</th>
<th>LDMS Aliquot Code</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIROLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal wash viral detection &amp; quantification</td>
<td>Sterile specimen cup</td>
<td>Nasal Wash</td>
<td>6mL</td>
<td>NPW/RLS/npw/vtm</td>
<td>Viral detection &amp; quantification and/or rtPCR for adventitious agents</td>
</tr>
<tr>
<td><strong>IMMUNOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal wash for antibody</td>
<td>Sterile specimen cup</td>
<td>Nasal Wash</td>
<td>Approx. 6-10mL</td>
<td>NPW/RLS/NPW</td>
<td>Immunologic assays</td>
</tr>
<tr>
<td>Immunologic assays</td>
<td>Red top tube</td>
<td>Whole blood</td>
<td>3-5 mL</td>
<td>BLD/NON/SER</td>
<td></td>
</tr>
<tr>
<td>(no additive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7.3.1 Collection Supplies for Nasal Washes

**Note:** Before collecting nasal wash, ensure that protocol-specific cold (2-8°C) Viral Transport Media (VTM) is on hand. (Instruction in section 7.4.1). Take care to thaw and transfer VTM on wet ice prior to collecting nasal wash.

**NW Collection Supplies:**
Gloves  
Sterile specimen cup  
Ziplock bag (optional)  
Labels and indelible ink pen  
Nasal Wash Solution – Sterile Lactated Ringers 15-20mL  
Paper towel or tissue  
Sterile nasal bulb syringe  
Wet ice  
Biohazard container  
Sticker or reward or snack  

If NW sample processing is to be performed in the field rather than in the lab, additional processing supplies will be required:
• Protocol-specific Viral Transport Media (VTM); keep frozen VTM vials on dry ice during off-site trips; once thawed, keep on wet ice. Do not refreeze (see section 7.4.1 of the MOP). Thaw VTM and put on wet ice (2-8°C) prior to collection of nasal wash specimen.
• (7) Sarstedt (72.694.006) cryovials  
• (2) Disposable sterile individually packaged transfer pipettes or (2) 3cc Syringes  
• Insulated container with dry ice (pellets preferred) for “flash freezing” the aliquots and transporting to the lab for storage. Note: this container must be able to “breathe” as the dry ice sublimates creating pressure inside a sealed container. Maintain in a well-ventilated area.  
• Biocision CoolBox 30 with CoolRack CF30 portable freezing device  
• Day 0 (inoculation day) and day 56 (+ 7): Nunc starfoot vials, external thread, 4.5 mL, Fisher Scientific, product number: 12-565-299, to be used to freeze nasal wash aliquots without VTM for immunology assays
7.3.2 Nasal Wash Collection Procedure

- Assemble required nasal wash supplies as above.
- If the nasal wash solution (sterile lactated ringers) is stored in the refrigerator, remove solution from refrigerator 15-30 minutes before use.
- Pour 15–20 mL of the nasal wash solution into a sterile specimen cup.
- Label outside of sterile container with subject number (PID), date, visit ID.
- Position subject in sitting position in an adult’s lap in chair.
- Have parent/guardian hug child with one arm holding both of child’s arms at his/her sides.
- Instruct parent/guardian to place other hand on child’s forehead and gently position child’s head facing forward and back of head against parent/guardian’s chest.
- Instruct parent/guardian to sit slightly forward so child’s neck does not flex back as this may cause the child to swallow some of the nasal wash (NW) solution.
- Place paper towel in front of subject.
- Draw entire volume of NW solution into sterile bulb syringe by compressing and releasing bulb to create a vacuum.
- Gently place tip of bulb syringe in opening of one nostril.
- Place sterile specimen cup under both nostrils.
- Assist child to position head forward minimizing solution draining to back of throat. Gently compress the bulb syringe to expel the rinsing solution.
- Gently release pressure on bulb syringe to collect effluent from around the bulb syringe and from nostril.
- If the child is able to cooperate, have him/her tip head forward to help expel solution.
- Wipe the child’s face and nose with paper tissue.
- If age appropriate, provide a snack (cookies, crackers, candy, or lollipop etc) to help remove NW solution taste from mouth.
- Study days 0,3,5,7,10,12,14,17,19,21,28 and sick visit study days: Immediately after nasal wash collection, using a sterile transfer pipette or 3cc-syringe, transfer 6 mL of nasal wash effluent into a vial containing 1.5 mL cold (2-8°C) viral transport media (VTM). Store on wet ice.
  - If only 5 mL collected, only use 1.25 mL of VTM
  - If only 4 mL collected, only use 1.0 mL of VTM
  - If < 4 mL collected, repeat wash.
- NW specimen for virology culture must be combined with the protocol-supplied VTM immediately, and snap frozen within 30 minutes of obtaining sample. VTM containing NW must be stored on wet ice. If sample cannot be transported to the lab for processing within 30 minutes, the processing steps (Section 7.4 of MOP) will need to be performed in the field.
- Study days 0 and 56 (+ 7): Nasal wash aliquots without VTM for immunology assays are also needed. All remaining nasal wash sample, (after transfer of 6 mL to VTM vial for virology assays, if required) will be aliquoted for immunology assays as described below [Section 7.4.3, Nasal Wash Processing in the field; Day 56 (+7)], and in the LPC. Replace cap tightly on specimen cup and position cup with NW sample in wet ice or refrigerator until ready to aliquot samples for immunology assays. NOTE: Do not ‘bury’ the cup in the ice; sites should avoid getting any water contamination around the lid of the cup. Suggestion: Cup may be sealed in a ziplock bag prior to setting in wet ice to prevent contact with melting ice.
- Dispose of all collection supplies in biohazard container.
7.4 Specimen Processing Procedures (also see LPC)

7.4.1 Obtaining Protocol-specific Viral Transport Media

Viral transport media will be provided by Bhavin Thumar at JHU – his contact information is below:

Phone: (410) 955-7230
Fax: (443) 287-3167
Email: bthumar@jhsph.edu

Site must obtain protocol-specific viral transport media (VTM) prior to the entry visit. Request sufficient VTM to process your subject’s protocol-required nasal washes. VTM is shipped on dry ice. Upon receipt, immediately transfer the VTM to a -20°C freezer; when stored at -20°C, (colder if ok) VTM has an expiration date 6 months after production. Thaw on wet ice, and note date of thawing on vials. Once thawed, VTM can be stored at 2-8°C for up to two weeks. Do not refreeze.

During outpatient visits, keep frozen VTM on dry ice; once thawed, keep on wet ice. Do not refreeze.

Monitor your stock of VTM as there may be extra nasal washes if the participant has “illness” visits. It is the responsibility of the site to monitor the amount of VTM at the site, along with the expiration date, and request additional product as needed. Other commercial VTM reagents cannot be substituted for the protocol-specific VTM. If the nasal wash is being processed by the lab, the site must ensure that the processing lab has the protocol specific VTM.

7.4.2 Specimen Processing

For serum and nasal wash processing in the laboratory, please refer to the Laboratory Processing Chart (LPC) which is located on the P1114 IMPAACT webpage (www.impaaactgroup.org).

7.4.3 Nasal Wash Processing in the Field

RSV loses infectivity if it is allowed to sit too long in nasal wash fluid without VTM. RSV also loses infectivity if freezing is not performed rapidly (“snap freezing”). To avoid loss of virus titer, nasal washes for viral culture and PCR must be mixed with VTM immediately, kept on wet ice (2-8°C), and processed and flash frozen within 30 minutes of collection. This time constraint may necessitate processing and freezing the nasal wash at the collection site.

- Immediately after nasal wash collection, using a sterile transfer pipette or 3cc-syringe, transfer 6 mL of nasal wash effluent into a tube containing 1.5mL cold (2-8°C) viral transport media (VTM).
- Gently mix contents to assure even distribution of specimen in VTM. Store on wet ice (2-8°C). NOTE: Nasal Wash specimen for virology must be mixed with transport media immediately, and aliquoted and flash frozen within 30 minutes of obtaining specimen.
• Equally divide and aliquot the combined NW and VTM mixture into 7 pre-labeled cryovials. Approximately 1.0 mL of sample should be added to each cryovial.

• Seal tightly with caps. Extra care must be taken to tighten caps because CO₂ from dry ice will affect VTM pH and inactivate virus.

• Flash freeze specimen aliquots per Biocision Coolbox 30 manufacturer’s -78°C instructions; see Appendix IV for snap freezing instructions.

• Day 0 (inoculation day) and 56 (+ 7): Use Nunc starfoot vials, external thread, 4.5 mL, Fisher Scientific, product number: 12-565-299, pre-labeled with LDMS labels, to freeze nasal wash aliquots without VTM for immunology assays. Aliquot the nasal wash fluid into 2 aliquots of approximately 2-4 mL. If volume exceeds 8 mL, prepare additional 2-4 mL aliquots. Flash freezing of these aliquots is not required.

• Specimen aliquots must be accompanied by a completed P1114 Specimen Tracking Form.

7.5 Additional Resources
ACTG/IMPAACT Laboratory Manual: http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx

ACTN Specimen Processing Guide: http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx

ACTN Guidelines for Shipping Diagnostic Specimens: http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx

ACTN Guidelines for Shipping Infectious Substances: http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx
8.0 DATA MANAGEMENT

8.1 Responsibilities

FSTRF will be acting as the data management center for P1114. FSTRF will be used to enroll and randomize the subjects into the study. Additionally FSTRF will liaise with the JHU team and will act as the intermediary for sending and receiving responses to queries.

8.2 Source Documents

Demographic, sample collection, clinical examination, and AE data must be collected and recorded directly on chart documents or investigator spreadsheets, and maintained as source documents. Appropriate source documentation must be available for all data entered into the CRFs.

All documentation must be made available to the Sponsor’s monitor at scheduled monitoring visits.

8.3 Schedule of Case Report Forms (CRF)

The P1114 CRF schedule and forms can be found on the FSTRF portal:

- Log in to the FSTRF portal at [www.fstrf.org](http://www.fstrf.org)
- Go to IMPAACT
- Under the “Case Report Forms” tab select “Forms Management Utility”
- In the “Forms Management Utility” use the drop downs to select “P1114” for the CRF schedule and forms

8.4 Data Management Resources

Barb Heckman, IMPAACT Data Manager
FSTRF
4033 Maple Rd.
Amherst, NY 14226
Phone: (716) 834-0900 ext. 7231
Fax: (716) 834-8675
bheckman@fstrf.org

For additional queries, you may contact the Randomization Help Desk at 716-834-0900 EXT 7200 or email rando.support@fstrf.org
APPENDIX I
Instructions for Parents/Guardians for Taking Daily Temperatures

Temperature monitoring occurs daily for 28 days following inoculation. To briefly describe, the parents/guardians take a temporal temperature 3 times in a row and record the highest temperature. If the highest temperature is less than 100.0°F, parents/guardians should record the temperature in the memory aid. This should be repeated every day.

If the highest temporal temperature is greater than or equal to 100.0°F, then the parents/guardians need to obtain a rectal temperature. If the rectal temperature is less than 100.4°F, the temperature should be recorded in the source documentation with a notation of “R” to denote rectal. For the purposes of this study, this is not considered a fever and is not recorded as an SAE.

If the rectal temperature is greater than or equal to 100.4°F, then for study purposes, this is considered a fever and a solicited AE and is recorded as such.

If a temporal temperature is greater than or equal to 100°F but no rectal temperature is measured, then this is considered a fever and a solicited AE. The temperature is recorded in the source documentation with the exact measure and “T” to denote how it was collected.

Temperature Flow Chart

```
Take the temporal temperature, following manufacturer's instructions, THREE times and record the highest temperature

If greater than or equal to 100.0°F

Repeat the temperature rectally within 20 minutes

Rectal temperature is less than 100.4°F

No fever

Parent record in memory aid

Rectal temperature is greater than or equal to 100.4°F

Fever

Parent notify study personnel
```
APPENDIX II

Checklist of Required Supplies for Home Visits

a. Nasal Wash - Collection Procedure
   - Disposable gloves
   - Sterile specimen cup with lid
   - Ziplock bag (optional)
   - Specimen labels
   - Nasal wash solution – 15-20cc Lactated Ringers Solution
   - Paper towels
   - Sterile nasal bulb syringe (1oz)
   - Wet ice
   - Biohazard container
   - Sticker, reward or snack

b. Nasal Wash – Virology Specimen Processing
   - Disposable gloves
   - Protocol-specific Viral Transport Media – thawed on wet ice
   - 7 x 2.0 mL PP cryovials (Sarstedt 72.694.006)
   - 3mL syringe or transfer pipette
   - Specimen labels (Appendix IX)
   - Permanent marker “Sharpie”
   - Two storage boxes
   - Styrofoam box or insulated container (e.g. Igloo) which can vent as the dry ice sublimates (sufficient size to fit coolbox)
   - Dry ice pellets

c. Day 0 (inoculation day) and 56 (+ 7) – Immunology Specimen Processing
   - Disposable gloves
   - 5 x 4.5 mL PP cryovials (Nunc, Starfoot, external thread, Fisher Scientific # 12-565-299)
   - 10 mL syringe or transfer pipette
   - LDMS labels
   - Permanent marker “Sharpie”
   - Two storage boxes
   - Styrofoam box or insulated container (e.g. Igloo) which can vent as the dry ice sublimates (sufficient size to fit coolbox)
   - Dry ice pellets

d. Nasal Wash – Snap Freezing
   - Dry ice pellets
   - Coolbox (Biocision CoolBox 30 with CoolRack CF-30 system item #BCS-135)
e. Other Supplies for Visit
   - Red top blood tube
   - Syringes and needles
   - Tourniquet
   - Anesthetic cream, if used
   - Stethoscope
   - Otoscope
   - Gauze, alcohol swabs and Band-Aids
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<td>1. What is the name of the study your child is being enrolled in?</td>
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<td>2. How many weeks does your child have to wait between receiving routine vaccinations and the investigational vaccine?</td>
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<td>3. Presently, is there a vaccine to prevent your child from getting sick with this virus?</td>
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<td>N</td>
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<td>4. What is a placebo?</td>
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<td>5. How are we going to give this vaccine or placebo?</td>
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<td>6. How many doses of this vaccine or placebo will your child receive?</td>
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<td>7. Is it possible your child could receive placebo?</td>
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<td>8. How many times will we draw blood from your child?</td>
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<td>10. Why do we rinse your child's nose?</td>
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<td>11. Name 2 reasons your child would not be able to participate in this study?</td>
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<td>12. What is the benefit of receiving this vaccine?</td>
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<td>13. Can your child get illnesses from other germs during the study?</td>
<td>Y</td>
<td>N</td>
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<td>14. Do you understand the study that your child is about to begin?</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>15. Do you have any questions?</td>
<td>Y</td>
<td>N</td>
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</table>

If "yes", were your questions answered?  

Parent’s Signature  
Date  
Reviewed by:  
Study Staff Signature  
Date
APPENDIX IV

Snap Freezing SOP for Nasal Washes

Materials:
CoolBox CF30 system (CoolBox 30 with CF-30 CoolRack, BCS-135, BioCision, Mill Valley, CA)
Dry ice pellets

NOTE: RSV is extremely sensitive to freezing and thawing and warm temperature. RSV readily loses infectivity if it is allowed to get warm, or allowed to sit too long unfrozen, or if it is not properly quick-thawed or snap-frozen. Loss of infectivity will affect study results. Please follow these instructions carefully when snap freezing nasal washes.

Note: Keep CF30 CoolRack at -20°C freezer when not in use.

1. Fill the CoolBox cavity with dry ice pellets up to the bottom of the finger grip recesses.
2. Place the CF30 CoolRack directly onto the dry ice. Complete this at least 20 minutes prior to the availability of cryovials for snap freezing, because CoolRack will need 20 minutes to reach dry ice temperature.
3. Ensure that the cryovials to be snap frozen are tightly sealed. Care must be taken to tighten caps because CO₂ from dry ice will affect pH of vial content and inactivate virus.
4. Transfer cryovials to CoolBox. Samples must remain in the CoolBox for 15 minutes to snap freeze properly.
5. The cryovials can be transported in CoolBox with dry ice pellets, or transferred to an insulated container with dry ice pellets. Note: this container must be able to “breathe” as the dry ice sublimes, creating pressure inside a sealed container. Maintain in a well-ventilated area.
   a) Be sure to provide lab with a completed P1114 Specimen Tracking Form. The lab will need the processing times completed on the tracking form.
   b) The lab will log samples into the LDMS, including the sample collection time from the Specimen Tracking Form.
   c) Samples are to be stored in a -80°C (± 15°C) freezer, and then shipped to JHU for testing.
6. Allow dry ice to dissipate in the impervious container. Do not throw dry ice in the sink. Extreme cold (dry ice) will crack the drainage pipe.
APPENDIX V

PREPARATION AND ACCOUNTABILITY DOCUMENTS

- Investigational Drug Packing Slip – Vaccine Aliquots
- Vaccine Aliquot Log
- Study Product Accountability Record - RSV
- Study Product Accountability Record – L-15
- Placebo and Diluent Preparation Form
- Placebo Preparation Form
- Vaccine Preparation Form
- P1114 Vaccine Administration Record
INVESTIGATIONAL DRUG PACKING SLIP – VACCINE ALIQUOTS

Study Name: IMPAACT P1114

A Phase I Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine RSV cps2, Lot RSV#005A, Delivered as Nose Drops to RSV-Seronegative Infants and Children 6 to 24 Months of Age

Ship To: JHU
Bloomberg School of Public Health
Room E5402
615 N. Wolfe Street
Baltimore, MD 21205

Attention: Bhavin Thumar, MS

Shipped By: ____________________________________________

Site Number/PI _________________________________________

Comments: __________________________________________

Storage Instruction: ~ FROZEN ~ Shipped on Dry Ice

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<tr>
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<tr>
<td>RSV cps2 Vaccine – Diluted</td>
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<td>RSV#005A</td>
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PLEASE inventory, inspect and verify the contents for completeness and satisfactory condition.

Received by: ___________________________ Date arrived: ________________

Shipment complete and received in satisfactory condition ☐ YES ☐ NO

Any discrepancies ☐ YES ☐ NO
Vaccine Aliquot Log  
IMPAACT P1114  
SITE: ____________

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# Study Product Accountability Record

**Division of AIDS (DAIDS)**
**National Institutes of Allergy and Infectious Diseases (NIAID)**

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<th>Clinical Research Site Number</th>
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<td>IMPAACT P1114</td>
<td>Live Recombinant Respiratory Syncytial Virus Vaccine, RSV cps2</td>
<td>$10^{6.6}$ PFU per mL nasal solution</td>
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<td>0.6 mL/vial</td>
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<td>ongoing retesting</td>
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*Note: Expiration dates may not be available for all study products.*

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* Note: Expiration dates may not be available for all study products.

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</tr>
</tbody>
</table>
Diluent Preparation Form

Participant Identifier: _______________ SID: _______________ PID: _______________
Participant Identifier: _______________ SID: _______________ PID: _______________
Participant Identifier: _______________ SID: _______________ PID: _______________
Participant Identifier: _______________ SID: _______________ PID: _______________

Study Number: IMPAACT P1114

Date and Time 2X L-15 Leibovitz medium taken out of the refrigerator:

Date (MM/DD/YYYY) @ Time 24-Hr (HH:MM)

Vaccine Diluent and Placebo Used for this study: 1X L-15

1. 2X L-15 w/o Glutamine and Phenol red (100mL)
   Lonza, Walkersville, MD
   (Lot is reserved and stored at Fisher BioSciences)
   Lot: ______________________ Exp: _______________

2. Sterile Water for Inj. USP __________ mL vial
   Lot: ______________________ Exp: _______________

Signature of Pharmacist Preparing Diluent Preparation
Date

Signature of Pharmacy Staff Checking Diluent Preparation
Date

Place Label of 2X L-15
IF PARTICIPANT IS RANDOMIZED TO RECEIVE PLACEBO COMPLETE THE FOLLOWING:

Placebo Preparation Form

Placebo Name: 1X L-15 Study # IMPAACT P1114

Participant Identifier: _______________________ SID: _____________________

PID: _______________________ Preparation Date: _______________________

______________________________________________________________
Signature of Pharmacist Preparing Placebo Dose Date

______________________________________________________________
Signature of Pharmacy Staff Checking Placebo Dose Date
IF PARTICIPANT IS RANDOMIZED TO RECEIVE ACTIVE COMPLETE THE FOLLOWING:

Vaccine Preparation Form

Vaccine Name: RSV cps2  Study # IMPAACT P1114
Lot #: RSV #005A  Titer: \(10^{6.6}\) PFU/mL

Confirm vaccine name and lot # from vaccine vial: □ __________ □ __________

Participant Identifier: ___________________ SID: __________________

PID: ___________________ Preparation Date: __________________

Date and Time vaccine taken out from \(-80^\circ\)C freezer:

\[
\begin{array}{cccc}
\text{Date} & @ & \text{Time 24-Hr} & \text{Vaccine Vial Number} & \text{Vaccine Vial Number} \\
\text{MM/DD/YYYY} & \text{HH:MM} & & \\
\end{array}
\]

Signature of pharmacist preparing vaccine dose ________________ Date ________________

Name of pharmacy staff checking vaccine dose ________________ Date ________________

Place Vaccine Vial Label  Place Vaccine Vial Label
# P1114 Vaccine Administration Record

<table>
<thead>
<tr>
<th>Section 1: Completed by Pharmacy Personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Name or Matching Placebo: <strong>RSV cps2 vaccine or 1X L-15</strong></td>
</tr>
<tr>
<td>Vaccine lot: LOT RSV#005A</td>
</tr>
<tr>
<td>Study #: IMPAACT P1114</td>
</tr>
<tr>
<td>Expiration time of vaccine/placebo:</td>
</tr>
<tr>
<td>Date@@@Time (24-hour clock):</td>
</tr>
<tr>
<td>Signature of Pharmacist Preparing Vaccine:</td>
</tr>
<tr>
<td>I have checked the preparation and documentation of this dispensing:</td>
</tr>
<tr>
<td>Signature of Pharmacy Personnel Checking Vaccine:</td>
</tr>
<tr>
<td>Temperature leaving Pharmacy: __________ °C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section 2: Completed by Clinical Personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of Stock Vaccine: <strong>10^6.6 PFU/mL</strong></td>
</tr>
<tr>
<td>Dilution of Stock to Achieve Dose: <strong>1:10</strong></td>
</tr>
<tr>
<td>Dose of Vaccine: <strong>10^5.3 TCID&lt;sub&gt;50&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td>Volume of Dose: <strong>0.5 mL</strong></td>
</tr>
<tr>
<td>Route of Inoculation: <strong>Intranasal</strong></td>
</tr>
<tr>
<td># of Syringes Received: ________</td>
</tr>
<tr>
<td>Signature of Clinician Accepting Vaccine:</td>
</tr>
<tr>
<td>Temperatures prior to vaccine administration:</td>
</tr>
<tr>
<td>current: __________ °C</td>
</tr>
<tr>
<td>minimum: __________ °C</td>
</tr>
<tr>
<td>maximum: __________ °C</td>
</tr>
</tbody>
</table>

**NOTE:** If temperature is not between 2-8°C please contact the pharmacy for a replacement dose.

<table>
<thead>
<tr>
<th>Section 3: Participant Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>PID #</td>
</tr>
</tbody>
</table>

**Completed by Pharmacy Personnel**

**Completed by Clinical Personnel**

<table>
<thead>
<tr>
<th>Section 4: Completed by Pharmacy Personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Syringes Returned: ________</td>
</tr>
<tr>
<td>Signature of Pharmacy Personnel Accepting Syringes and/or Form:</td>
</tr>
<tr>
<td>Date: ________</td>
</tr>
</tbody>
</table>

**Disposition Code:**
- A=Administered
- R=Returned to Pharmacy

*Original - STUDY BINDER*  *Copy - PHARMACY*
APPENDIX VI

P1114 and CIR 285 Basic Safety Reporting Flow Diagram

Adverse Event (AE)
Identified per protocol definition in section 8.1.1

Enter AE on the Adverse Event Log on either PE6832 or PE6852

Is the AE also a serious adverse event (SAE) or lower respiratory tract illness (LRI)?
[see protocol section 8.1.3, 8.1.4 & Appendix 4, Table 11]

No STOP
Yes Report SAEs and LRIIs within 3 working days in the DAERS online system. Also report to the local IRB if required.

Is the AE also an Unanticipated Problem (UP)?
[See protocol section 8.7]

No STOP
Yes Report UPs that are also AEs to the IND sponsor (RCHSPB) using the local IRB form. See sponsor contact info in protocol section 8.7. UPs that are not AEs are NOT sent to the IND sponsor. Report UPs to IRB if required.

Does the AE, SAE or LRI trigger pausing rules? [See protocol section 8.9]

No STOP
Yes Notify the IMPAACT team within 24 hrs. E-mail a summary to the IMPAACT team at impact.teamp1114@fstrf.org. Report pause to IRB if required.
### APPENDIX VII: P1114 Events Reporting Table

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Reporting Timeframe</th>
<th>Directions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event (AE)</strong></td>
<td>Day 0 through day 28 (acute monitoring phase)</td>
<td>Enter adverse events in the Adverse Event Log in FSTRF. Determine if the adverse event also meets the definition/criteria of any event listed below (i.e., SAE, LRI, Pausing/stopping rule or UP).</td>
</tr>
<tr>
<td>[definition in protocol section 8.1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*3 types of events that will NOT be recorded as AEs for this protocol:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) For infants and children, the following common events will not be recorded as AEs unless a prescribed concomitant medication is used to treat them: diaper rashes, teething pain, and spitting up. [Reference: protocol section 8.1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Transient or mild symptoms, such as rhinorrhea, pharyngitis, hoarseness, or cough that do not meet the solicited AE study definitions (see Appendix 4, Table 11) will not be classified as an AE. [Reference: protocol section 8.2.3]</td>
<td></td>
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</tr>
<tr>
<td>3) Solicited AEs elicited by history that are not confirmed by clinical assessment will not be counted if they are reported to have occurred on the same days on which the subject has clinical assessments performed. Solicited AEs elicited by history on days without visits will be counted only if they meet the definition of illness (for example, both rhinorrhea and cough must each occur on 2 consecutive days to meet the definition of illness). [Reference: protocol section 8.2.2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious Adverse Event (SAE) and Lower Respiratory Tract Illness (LRI)</strong></td>
<td>Day 0 through day 56</td>
<td>Report SAEs and LRIs (also referred to as a Protocol Specified Event (PSE) for this study) via the DAERS online reporting system within 3 working days of site awareness of the event. In addition, all LRIs and some SAEs trigger pausing/stopping rules. See pausing and stopping rules section below. All LRIs and SAEs will be followed until satisfactory resolution or until the PI or sub-investigator deems the event to be chronic or the subject is stable. Report SAE/LRI/PSEs per local IRB requirements.</td>
</tr>
<tr>
<td>[SAE definition in protocol section 8.1.3 and LRI definition in Appendix 4, Table 11]</td>
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</tr>
<tr>
<td>Type of Event</td>
<td>Reporting Timeframe</td>
<td>Directions</td>
</tr>
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<td>-------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| **Pausing and Stopping Rules**            | Day 0 through day 56| If a site identifies that a pausing/stopping criteria has been met:  
Site will notify the IMPAACT team of the event (including a description of the event) via email, at impaact.teamp1114@fstrf.org, within 24 hours of identification of the event. Site should also determine if the local IRB requires reporting for pausing/stopping rule trigger.  
The IMPAACT protocol team will notify all sites to suspend enrollment and immunizations and FSTRF will close accrual.  
Site will ship all respiratory viral samples collected on the subject that experienced the pausing/stopping rule event, to the Johns Hopkins University Laboratory as soon as possible. See MOP section 7.0.  
All sites will continue to conduct the protocol specified evaluations on previously enrolled/active subjects.  
The IMPAACT team will notify sites when/if the study enrollment may resume.|
| **Pausing Rules:**                         |                     |  
- An SAE that is possibly, probably, or definitely related to the investigational vaccine or placebo, OR;  
- A LRI, OR;  
- A grade 4 fever or any grade 3 or grade 4 solicited AE other than fever |
| **Stopping rules**                         |                     |  
Stopping rules apply to subjects who have been unblinded and receive study agent. The IMPAACT team will notify sites of appropriate action(s) after a Data and Safety Monitoring Board review. |
| **Unanticipated Problems (UP)**           | Day 0 through day 56| Non-serious AEs that are Unanticipated Problems must be reported to the IND Sponsor Clinical Safety Office no later than 7 calendar days from the site awareness of the event. See directions in protocol section 8.7. UPs that are not AEs are NOT reported to the IND Sponsor Clinical Safety Office.  
Report UPs to local IRBs as required. |
APPENDIX VIII

Instructions for Ordering RSV and L-15 Study Agents

DATE: March 13, 2014

FROM: Lisa Hoopengardner, RCHSPP/SAIC-Frederick, Inc.

SUBJECT: Protocol IMPAACT P1114: “A Phase I Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine RSV cps2, Lot RSV#005A, Delivered as Nose Drops to RSV-Seronegative Infants and Children 6 to 24 Months of Age” Study Agent Request Process

Sites should use the Investigational Study Agent Request Form provided to request the RSV cps2 study agent and the L-15 Request Form to request 2X L-15 Leibovitz Medium. To initiate the initial study agent shipment, the sites should complete Section A. of the forms after they have identified a potential subject and sent the serum sample to Johns Hopkins University for RSV antibody screening. Per the LID Sponsor Representative, Dr. Ulla Buchholz, the sites should request 10 vials of study agent and 8 bottles of 2X L-15 medium at the time of initial shipment. After completing this section, the sites should fax the forms to Lisa Hoopengardner's attention at 301-846-6440 or scan and email at hoopengardnerl@mail.nih.gov. These forms will then be processed through Fisher BioServices for shipment of the drug and 2X L-15 medium. Please note that it will take approximately 1 week from the time Fisher receives the request to shipment. Since the two products are shipped at different temperatures, there will be a separate package for the drug and another package for the medium. Upon receipt of the shipments, the site should complete Section D of both forms and fax the completed form to Lisa Hoopengardner (301-846-6440) or scan and email at hoopengardnerl@mail.nih.gov. In addition, each shipment should contain a TempTale that should be shipped back to Fisher to verify that the shipment stayed within the desired range. Included in the shipment will be instructions on where to send the TempTale.

If the site has the TempTale Manager Desktop software available at their site, they should use the software to download the TempTale information. The shipment information can then be forwarded to Lisa Hoopengardner (hoopengardnerl@mail.nih.gov) for verification.

If a site does not have access to the TempTale Manager Desktop software, they will not be able to begin using the agents until RCHSPP is able to verify the temperature range of the shipment. This can take additional days while the device is returned to Fisher.

Once Lisa Hoopengardner is able to verify the shipment temperature, she will then contact John Tierney and Megan Valentine to notify them if the shipments are acceptable for use. Ms. Valentine will then forward this information to the sites. Only after receiving the information that the TempTale results are acceptable may sites use the study agent or 2X L-15 medium.
RCHSPP/SAIC-Frederick, Inc. Vaccine Request Form

Protocol IMPAACT P114: “A Phase I Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine RSV cps2, Lot RSV#005A, Delivered as Nose Drops to RSV-Seronegative Infants and Children 6 to 24 Months of Age”

Vaccine Request
A. Complete the section below and fax to RCHSPP (Attention: L. Hoopengardner, Fax #: 301-846-6440).

Protocol #: IMPAACT 1114

Agent Requested: RSV cps2 (532238), 2 ML EACH

# of Vials Requested:

Shipment Conditions (Check all applicable boxes):

☒ Dry Ice ☐ Refrigerated Gel Packs ☐ Frozen Gel Packs ☒ Temperature Monitor

Site P.I.: P.I. Signature: Date:

Site Number: Anticipated Vaccination Date:

Recipient Name: Recipient E-mail:

Shipping address: Attention:

Investigational Agent Shipment
C. Complete the section below and send with vaccine to shipping address listed above.

Number of vials shipped: Lot #: Shipment date:

Fisher BioServices Signature Date Time shipped

Investigational Agent Receipt Verification
D. Complete the section below upon receipt and fax this form to RCHSPP (Attention: L. Hoopengardner, Fax #: 301-846-6440).

Number of vials received: Temperature of shipment received:

Received on dry ice: Yes ☐ No ☐

Signature of receipt Date of receipt Time of receipt

Important: Please note that Fisher BioServices Personnel will send completed shipping temperature logs to the CRA at RCHSPP/SAIC-Frederick, Inc. After reviewing this temperature information, the CRA will inform the site of the acceptability of the shipment.
**L-15 Request Form**

Protocol IMPAACT P1114: ‘A Phase I Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine RSV cps2, Lot RSV#005A, Delivered as Nose Drops to RSV-Seronegative Infants and Children 6 to 24 Months of Age’

<table>
<thead>
<tr>
<th>L-15 Request</th>
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<tbody>
<tr>
<td>A. Complete the section below and fax to RCHSPP (Attention: Lisa Hoopengardner Fax #: 301-846-6440).</td>
</tr>
<tr>
<td>Agent requested: 2X L-15 w/o L-Gln or Phenol Red (12-669E) Number of bottles requested: [ ]</td>
</tr>
<tr>
<td>Lot #: 0000372724, expires 2/23/2015 Fisher#: SAC7-1766</td>
</tr>
<tr>
<td>Shipment Conditions (Check all applicable boxes):</td>
</tr>
<tr>
<td>☒ Refrigerated Gel Pack ☒ Temperature Monitor ☐ Other: [ ]</td>
</tr>
<tr>
<td>Site P.I.: [ ] P.I. Signature: [ ] Date: [ ]</td>
</tr>
<tr>
<td>Site Number: [ ]</td>
</tr>
<tr>
<td>Recipient Name: [ ] Recipient E-mail: [ ]</td>
</tr>
<tr>
<td>Shipping address: Attention: [ ]</td>
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</tbody>
</table>

**RCHSPP/SAIC-Frederick, Inc. Signature/Approval**

B. Complete the section below and fax to Fisher BioServices (Fax #: (301) 294-4024).

| CTM Approval [ ] Date [ ] |
| RA Approval [ ] Date [ ] |

**L-15 Shipment**

C. Complete the section below and send with L-15 to shipping address listed above.

| Number of bottles shipped: [ ] Lot #: [ ] Shipment date: [ ] |
| Fisher BioServices Signature [ ] Date [ ] Time shipped [ ] |

**L-15 Shipment Verification**

D. Complete the section below upon receipt and fax this form to RCHSPP (Attention: Lisa Hoopengardner, Fax #: 301-846-6440).

| Number of vials received: [ ] Date shipment received: [ ] Shipment temp: [ ] |
| Signature of receipt [ ] Date [ ] Time of receipt [ ] |

Important: Please note that Fisher BioServices Personnel will send completed shipping temperature logs to RCHSPP/SAIC-Frederick, Inc. After reviewing this temperature information, the CRA will inform the site of the acceptability of the shipment.

RCHSPP 3/12/14
APPENDIX IX

NW/VTM Specimen Label Cross-reference Log Instructions

Rationale:
1. To maintain nasal wash virology specimen integrity, sample must be snap frozen within 30 minutes and
2. To allow study staff the ability to label specimen tubes one or more days prior to collection and snap freezing

Procedure:
1. Create non-LDMS specimen label to include the following information:
   - PID #
   - Protocol # : P1114
   - Specimen Date
   - Study Day
   - Specimen type : NW/VTM
   - Vial # 1,2,3,4,5,6,7
   Note: Each specimen aliquot will be numbered with an unique vial # 1-7.
   Seven (7) aliquots of NW with VTM for each visit day are required.

2. Print 2 copies of the created labels.
3. Place one label on individual vial prior to adding sample to the vial.
4. Place second label on Specimen Label Cross-reference Log (attached below).
5. After sample collection and flash freezing, record the approximate specimen amount for each vial on the Specimen Label Cross-reference Log.
6. Deliver specimen to lab with Specimen Label Cross-reference Log and the completed f3008 CRF.
7. Lab will enter information into LDMS system and print one LDMS label for each aliquot.
8. Lab will place LDMS label on Specimen Label Cross-reference Log (tubes will not be relabeled).
9. Lab will detach bottom portion of the Specimen Label Cross-reference Log and send with shipment of vials #1, 2, 3, and 4. Lab will include f3008 CRF with this shipment.
10. Lab will keep top portion of the Specimen Label Cross-reference Log in the lab where the specimens are stored and then include with shipment of vials # 5, 6 and 7, when those are shipped to testing lab (see P1114 LPC).

NW & Serum Antibody Specimen Labeling Instructions

NW for antibody and serum antibody do not need to be snap frozen thus the LDMS label can be placed on the aliquots at the time of sample processing.
# Specimen Label Cross-reference Log for NPW/RLS/NPW/VTM

<table>
<thead>
<tr>
<th>Pre-printed Specimen Label</th>
<th>LDMS Label</th>
<th>Pre-printed Specimen Label</th>
<th>LDMS Label</th>
<th>Pre-printed Specimen Label</th>
<th>LDMS Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>PID # P1114</td>
<td>Specimen Date</td>
<td>PID # P1114</td>
<td>Specimen Date</td>
<td>PID # P1114</td>
<td>Specimen Date</td>
</tr>
<tr>
<td>Specimen Type Vial #5</td>
<td>Study Day</td>
<td>Specimen Type Vial #6</td>
<td>Study Day</td>
<td>Specimen Type Vial #7</td>
<td>Study Day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vial # 5 amount___________</th>
<th>Vial # 6 amount___________</th>
<th>Vial # 7 amount___________</th>
</tr>
</thead>
</table>

Detach and send with corresponding specimen shipment

<table>
<thead>
<tr>
<th>Pre-printed Specimen Label</th>
<th>LDMS Label</th>
<th>Pre-printed Specimen Label</th>
<th>LDMS Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>PID # P1114</td>
<td>Specimen Date</td>
<td>PID # P1114</td>
<td>Specimen Date</td>
</tr>
<tr>
<td>Specimen Type Vial #3</td>
<td>Study Day</td>
<td>Specimen Type Vial #4</td>
<td>Study Day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vial # 3 amount___________</th>
<th>Vial # 4 amount___________</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Pre-printed Specimen Label</th>
<th>LDMS Label</th>
<th>Pre-printed Specimen Label</th>
<th>LDMS Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>PID # P1114</td>
<td>Specimen Date</td>
<td>PID # P1114</td>
<td>Specimen Date</td>
</tr>
<tr>
<td>Specimen Type Vial #1</td>
<td>Study Day</td>
<td>Specimen Type Vial #2</td>
<td>Study Day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vial # 1 amount___________</th>
<th>Vial # 2 amount___________</th>
</tr>
</thead>
</table>