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

IMPAACT 2000
A Companion Protocol to CIR Protocol Number: CIR 291

A Phase I Study of the Safety and Immunogenicity of
Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine
RSV LID ΔM2-2 in RSV-Seronegative Infants and Children

IND # 15713

MANUAL OF PROCEDURES (MOP)

MOP Version 1.3
November 7, 2014
TABLE OF CONTENTS

LIST OF APPENDICES .................................................................................................................. 3
GLOSSARY OF TERMS .................................................................................................................. 4
1.0 PROTOCOL OVERVIEW ........................................................................................................ 6
1.1 Study Design Overview ......................................................................................................... 6

2.0 PROTOCOL IMPLEMENTATION ............................................................................................ 7
2.1 Recruitment of Study Subjects ............................................................................................. 7
2.2 Randomization, Stratification ............................................................................................... 7
2.3 Blinding and Unblinding ........................................................................................................ 7
2.4 General Information Regarding Clinic Visits ...................................................................... 7
2.41 Windows for Clinic Visits .................................................................................................. 7
2.42 Temperature Readings ....................................................................................................... 8
2.43 Data Collection .................................................................................................................. 9
2.44 Expectations for Recording Adverse Event on CRFs .......................................................... 10
2.45 Medications Allowed During the Study ............................................................................. 10
2.46 Emergency Plan for After Hours ....................................................................................... 10
2.47 Subject Withdrawal / Replacement .................................................................................... 10

3.0 SCREENING ........................................................................................................................ 11
3.1 Introduction to the Informed Consent .................................................................................. 11
3.2 Screening & Enrollment ....................................................................................................... 11
3.21 Screening and Enrollment Logs ......................................................................................... 11
3.22 Assignment of Participant ID Numbers (PIDs) .................................................................. 11
3.3 IMPAACT 2000 Screening Procedures .............................................................................. 12

4.0 ENROLLMENT ..................................................................................................................... 13
4.1 Randomization ..................................................................................................................... 13
4.2 Inoculation (Day 0) .............................................................................................................. 13
4.3 Day 0 to Day 28 Visit (Acute Phase) .................................................................................. 14
4.31 Study Days with In-Person Visits ...................................................................................... 14
4.32 Non-visit Contacts Post-Inoculation (Days 0 to 28) .......................................................... 15
4.33 Sick Visits during the Acute Phase .................................................................................... 15
4.4 Day 29 to Day 56 Visit (Post-Acute Phase) .................................................................... 15
4.41 Clinical Assessment and Sick Visits .................................................................................. 15
4.42 Day 56 Visit (+7 Days) ..................................................................................................... 16
4.5 Period after Day 56 Visit until October 31st ..................................................................... 16
4.6 Pre-RSV Season Study Visit (October 1st to 31st) ............................................................. 16
4.7 RSV Season Surveillance (November 1st through March 31st following inoculation) .... 16
4.8 Post-RSV Season Study Visit (April 1st to 30th) ................................................................. 16

5.0 SITE PHARMACY PROCEDURES & VACCINE/PLACEBO PREPARATION .................... 17
5.1 The Study Vaccine - Overview ........................................................................................... 17
5.2 Ordering Vaccine and 2X L-15 Leibovitz Medium ................................................................ 18
5.3 Site Procedures upon Receipt of Vaccine and 2X L-15 Leibovitz Medium ................................ 18
5.4 Pharmacy Procedures – Storage, Preparation & Accountability ....................................... 18
5.41 Storage of the Vaccine ..................................................................................................... 18
5.42 Randomization, Prescribing & Blinding .......................................................................... 19
5.43 Vaccine and Placebo Preparation Guidelines ................................................................... 19
5.44 Preparing the Diluent and Placebo .................................................................................. 21
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.45</td>
<td>Preparing the Vaccine</td>
<td>23</td>
</tr>
<tr>
<td>5.46</td>
<td>Transport of Vaccine/Placebo to the Clinic</td>
<td>25</td>
</tr>
<tr>
<td>5.47</td>
<td>Vaccine/Placebo Chain of Custody Accountability</td>
<td>26</td>
</tr>
<tr>
<td>5.48</td>
<td>Preparation of Vaccine Aliquots for Snap Freezing</td>
<td>26</td>
</tr>
<tr>
<td>5.5</td>
<td>Disposal of Vaccine/Placebo</td>
<td>28</td>
</tr>
<tr>
<td>5.6</td>
<td>Shipping the Diluted &amp; Undiluted Vaccine for Quality Control</td>
<td>28</td>
</tr>
<tr>
<td>5.7</td>
<td>Maintaining the Blind</td>
<td>29</td>
</tr>
<tr>
<td>5.8</td>
<td>Communication with Pharmacy Staff</td>
<td>29</td>
</tr>
<tr>
<td>5.9</td>
<td>Administering the Vaccine/Placebo</td>
<td>30</td>
</tr>
<tr>
<td>5.10</td>
<td>Pharmacy Questions/Problems</td>
<td>30</td>
</tr>
<tr>
<td>6.0</td>
<td>SAFETY SECTION</td>
<td>30</td>
</tr>
<tr>
<td>6.1</td>
<td>Determination of Severity/Grade for Solicited Adverse Events</td>
<td>30</td>
</tr>
<tr>
<td>6.2</td>
<td>Serious Adverse Events (SAE) and Lower Respiratory Illnesses (LRI)</td>
<td>30</td>
</tr>
<tr>
<td>6.3</td>
<td>Unanticipated Problems (UPs)</td>
<td>30</td>
</tr>
<tr>
<td>6.4</td>
<td>Pausing Rules</td>
<td>31</td>
</tr>
<tr>
<td>6.5</td>
<td>Stopping Rules</td>
<td>31</td>
</tr>
<tr>
<td>7.0</td>
<td>SPECIMEN COLLECTION AND PROCESSING</td>
<td>32</td>
</tr>
<tr>
<td>7.1</td>
<td>Introduction</td>
<td>32</td>
</tr>
<tr>
<td>7.2</td>
<td>General Overview and Guidelines</td>
<td>32</td>
</tr>
<tr>
<td>7.21</td>
<td>Specimen Chain of Custody</td>
<td>32</td>
</tr>
<tr>
<td>7.22</td>
<td>Labeling Specimens</td>
<td>33</td>
</tr>
<tr>
<td>7.23</td>
<td>Laboratory Data Management System (LDMS)</td>
<td>33</td>
</tr>
<tr>
<td>7.3</td>
<td>Specimen Collection Procedures</td>
<td>34</td>
</tr>
<tr>
<td>7.31</td>
<td>Collection Supplies for Nasal Washes</td>
<td>34</td>
</tr>
<tr>
<td>7.32</td>
<td>Nasal Wash Collection Procedure</td>
<td>35</td>
</tr>
<tr>
<td>7.33</td>
<td>Requesting Adventitious Virus Assay</td>
<td>36</td>
</tr>
<tr>
<td>7.4</td>
<td>Specimen Processing Procedures (also see LPC)</td>
<td>36</td>
</tr>
<tr>
<td>7.41</td>
<td>Obtaining Protocol-specific Viral Transport Media</td>
<td>36</td>
</tr>
<tr>
<td>7.42</td>
<td>Specimen Processing</td>
<td>37</td>
</tr>
<tr>
<td>7.43</td>
<td>Nasal Wash Processing in the Field</td>
<td>37</td>
</tr>
<tr>
<td>7.5</td>
<td>Additional Resources</td>
<td>38</td>
</tr>
<tr>
<td>8.0</td>
<td>DATA MANAGEMENT</td>
<td>38</td>
</tr>
<tr>
<td>8.1</td>
<td>Responsibilities</td>
<td>38</td>
</tr>
<tr>
<td>8.2</td>
<td>Schedule of Case Report Forms (CRF)</td>
<td>38</td>
</tr>
<tr>
<td>8.3</td>
<td>Data Management Resources</td>
<td>39</td>
</tr>
</tbody>
</table>

APPENDIX I ................................................................. 40
APPENDIX II ............................................................. 41
APPENDIX III ............................................................ 42
APPENDIX IV ............................................................ 43
APPENDIX V ............................................................ 44
APPENDIX VI ............................................................ 53
LIST OF APPENDICES

Appendix I  Instructions for Parents/Guardians for Taking Daily Temperatures
Appendix II  Checklist of Required Supplies for Home Visits
Appendix III Template RSV Pediatric Comprehension Assessment (Parent/Guardian Quiz)
Appendix IV  Snap Freezing SOP for Nasal Washes
Appendix V  Preparation and Accountability Documents (blank forms, logs and records)
   • Investigational Drug Packing Slip – Vaccine Aliquots
   • Vaccine Aliquot Log
   • Study Product Accountability Record - RSV
   • Study Product Accountability Record – L-15
   • Diluent Preparation Form
   • Placebo Preparation Form
   • Vaccine Preparation Form
   • IMPAACT 2000 Study Product Administration Record
Appendix VI  NW/VTM Specimen Label Cross-reference Log Instructions

Summary of Changes

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8/21/14</td>
<td>Version 1.0 to 1.1</td>
</tr>
<tr>
<td>3.3</td>
<td>Clarification on notifying JHU re: screening sample shipment and results dissemination timeline</td>
</tr>
<tr>
<td>4.31, 4.33, 7.33</td>
<td>Details added to clarify steps for requesting adventitious virus assay on nasal wash specimens</td>
</tr>
<tr>
<td>8/28/14</td>
<td>Version 1.1 to 1.2</td>
</tr>
<tr>
<td>4.31, 4.33, 7.33</td>
<td>Clarification on shipping times for nasal wash specimens needing adventitious virus assay</td>
</tr>
<tr>
<td>11/07/14</td>
<td>Version 1.2 to 1.3</td>
</tr>
<tr>
<td>5.42, 5.43</td>
<td>Clarification on preparation of study product by designated licensed pharmacy personnel</td>
</tr>
<tr>
<td>5.451</td>
<td>Update on allowable temperature range for water bath</td>
</tr>
<tr>
<td>Appendix V</td>
<td>Space added for additional vaccine vial on Vaccine Preparation Form</td>
</tr>
<tr>
<td>Appendix VI</td>
<td>Study number corrected on Specimen Label Cross-reference Log</td>
</tr>
</tbody>
</table>
### GLOSSARY OF TERMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG</td>
<td>AIDS Clinical Trials Group</td>
</tr>
<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>BSC</td>
<td>Biosafety cabinet</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 for Immunization Research</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRPMC</td>
<td>Clinical Research Products Management Center</td>
</tr>
<tr>
<td>CRS</td>
<td>Clinical research site</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>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, Inc.</td>
</tr>
<tr>
<td>GCLP</td>
<td>Good Clinical Laboratory Practice</td>
</tr>
<tr>
<td>GERD</td>
<td>Gastroesophageal Reflux Disease</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>
</tr>
<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 Adolescent AIDS Clinical Trials Network</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug application</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>JHU</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>L-15</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>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NON</td>
<td>No additive (e.g., serum tubes)</td>
</tr>
<tr>
<td>NPW</td>
<td>Nasopharyngeal wash</td>
</tr>
<tr>
<td>NSC</td>
<td>Nomenclature Standards Committee</td>
</tr>
<tr>
<td>NW</td>
<td>Nasal wash</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>OHRP</td>
<td>Office for Human Research Protections</td>
</tr>
<tr>
<td>OM</td>
<td>Otitis media</td>
</tr>
<tr>
<td>PAB</td>
<td>Pharmaceutical Affairs Branch</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PFU</td>
<td>Plaque forming unit</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PID</td>
<td>Participant identification number</td>
</tr>
<tr>
<td>PoR</td>
<td>Pharmacist of Record</td>
</tr>
<tr>
<td>PSE</td>
<td>Protocol Specified Event</td>
</tr>
<tr>
<td>QA/QC</td>
<td>Quality Assurance/Quality Control</td>
</tr>
<tr>
<td>RCHSPB</td>
<td>Regulatory Compliance and Human Subjects Protection Branch</td>
</tr>
<tr>
<td>RLS</td>
<td>Ringers Lactate Solution</td>
</tr>
<tr>
<td>RSC</td>
<td>Regulatory Support Center</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAIC</td>
<td>Science Applications International Corporations</td>
</tr>
<tr>
<td>SES</td>
<td>Subject Enrollment System</td>
</tr>
<tr>
<td>SER</td>
<td>Serum</td>
</tr>
<tr>
<td>SID</td>
<td>Study identification number</td>
</tr>
<tr>
<td>SOE</td>
<td>Schedule of Evaluations</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SPAR</td>
<td>Study Product Administration Record</td>
</tr>
<tr>
<td>SST</td>
<td>Serum Separator Tube</td>
</tr>
<tr>
<td>SWFI</td>
<td>Sterile water for injection</td>
</tr>
<tr>
<td>UP</td>
<td>Unanticipated Problem</td>
</tr>
<tr>
<td>URI</td>
<td>Upper respiratory illness</td>
</tr>
<tr>
<td>USP</td>
<td>US Pharmacopeial Convention</td>
</tr>
<tr>
<td>VTM</td>
<td>Viral Transport Media</td>
</tr>
</tbody>
</table>
1.0 PROTOCOL OVERVIEW

1.1 Study Design Overview

IMPAACT 2000 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 to distinguish the background respiratory and febrile illnesses that occur in infants and children from those attributable to vaccination. For the purpose of this study, “RSV-seronegative” will be defined as having serum neutralizing antibody titer to RSV of <1:40. At randomization, subjects will be divided as follows:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Number*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Vaccine</td>
<td>$10^{5.0}$ PFU</td>
<td>N=34</td>
</tr>
<tr>
<td>2 Placebo</td>
<td>0</td>
<td>N=17</td>
</tr>
</tbody>
</table>

*From IMPAACT 2000 and CIR 291 combined

Infants will be randomized to receive $10^{5.0}$ PFU of vaccine virus or placebo (1X L-15). 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 (NWs) 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) after inoculation with investigational product. Blood and nasal wash specimens will be obtained before inoculation and at the Day 56 visit after inoculation to assess immune responses to the vaccine.

Duration of participation in the initial phase of the study is 56 days, which consists of an Acute and a Post-Acute Phase. During the Acute Phase (Study Days 0 to 28), participants will be evaluated daily for the first 28 days. During the Post-Acute Phase (Study Day 29 to the Day 56 visit), study participants will be evaluated at Day 29 and the Day 56 visit. Additionally, from the onset to the end of the RSV season following inoculation (November 1st to March 31st), children will be assessed by site study staff through weekly contact to identify medically attended episodes of fever, upper or lower respiratory illnesses, or otitis media (OM).

Participants may have a study visit during the pre-RSV season (between October 1st and 31st) to obtain a blood sample for a pre-RSV season specimen for immunological assays to assess the durability of the vaccine response. Participants will also receive a post-RSV season visit (April 1st to April 30th), to obtain a blood sample to measure RSV immune responses to compare to the pre-RSV season specimen. Therefore, the total duration of participation will be up to 395 days, depending upon the time of enrollment relative to the RSV season.

CIR 291 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 (CRFs) for the two studies are identical, and all the data will be entered into a single database at Frontier Science & Technology Research Foundation, Inc. (FSTRF). The entire cohort will be analyzed together. The directions in this MOP are specifically intended 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 selected based upon ability to recruit and enroll in respiratory vaccine studies. Each site will identify specific clinics where recruitment will occur. The sites will create recruitment materials that will be reviewed and approved by site Institutional Review Boards (IRBs).

2.2 Randomization, Stratification

Subjects from either IMPAACT sites or Center for Immunization Research (CIR) who meet all the study inclusion criteria and none of the exclusion criteria will be enrolled in IMPAACT 2000 by utilizing the Subject Enrollment System (SES) located on the IMPAACT Data Management Center (DMC) Website at www.fstrf.org.

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 subject’s treatment. The unblinded pharmacist will not assist in subject assessment or other data collection and will not provide any information about treatment assignment to others at the clinical site.

Subjects (parents/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 sites will be notified of treatment assignment by the study team. Sites will share this information with the parents/guardians. The IMPAACT Unblinding Standard Operating Procedure (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 post-RSV season visit, sites should use the Unblinding Request program located below the Utilities category under the IMPAACT tab on the Portal. This program provides a structured method of collecting pertinent information with which the Protocol Chair and specified members of the Protocol Team will make a decision regarding early unblinding in collaboration with the Data Safety Monitoring Board (DSMB). The Sponsor and the DSMB Executive Secretary (niaiddembia@niaid.nih.gov) will also be notified of the event as specified in Section 5.16 of the IMPAACT 2000 protocol, which is available on the IMPAACT webpage (www.impaactnetwork.org).

2.4 General Information Regarding Clinic Visits

2.41 Windows for Clinic Visits

- Study inoculation (Day 0) should ideally occur on the same day as randomization, but the site is allowed up to 3 days after randomization to administer the study product. Inoculation must be completed within 42 days of the screening visit. Please note that study inoculation (Day 0) should be completed as soon as possible after screening, preferably 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 timeframe 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 any day between and including study Day 56 and Day 63. This visit should not be performed before day 56 because this is the minimum desired time for the allowing the immune response to develop.

Note: study visits, except inoculation, may be performed at one of the clinical sites or as home visits. Inoculation visits must be completed at a clinic/office site where emergency supplies are available.

### 2.42 Temperature Readings

The site will provide temporal and rectal thermometers to the families. For standardization, the IMPAACT 2000 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 documented in the participant charts and recorded on the appropriate CRF.

Temperature monitoring occurs daily for Days 0-28 following inoculation. On days without study visits, the temperatures are taken by parents/guardians. A flow sheet for the site staff is in the figure that follows. A parental instruction sheet is provided in Appendix I of the MOP.

Please refer to Table 4, Section 7.152 of the protocol for temperature grading and Table 5, Section 7.2 of the protocol for AE CRF recording requirements.
**Temperature Flow Chart**

Following temporal thermometer manufacturer's instructions, take the temporal temperature THREE times and document the highest temperature, indicate "T"

If >100.0°F

Temporal temperature confirmed by rectal temperature within 20 minutes

Rectal temperature is <100.4°F; document and indicate "R"*

Rectal temperature is ≥100.4°F; document and indicate "R"*

Temporal temperature not confirmed by rectal temperature

Temporal temperature not confirmed by rectal temperature

Study automatically counts this event as fever; indicate "T"**

Rectal temperature is ≥100.4°F; document and indicate "R"*

Perform visit as per protocol SOE and complete the appropriate AE CRF

Does not meet solicited AE criteria

Fever

Solicited AE

*Document in subject study files

---

**2.43 Data Collection**

**2.431 Source Documentation**

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

Symptoms communicated by parents/guardians that would suggest a solicited AE but are not confirmed by clinical assessment or do not meet criteria according to AE definitions in Appendix 4 of the protocol will not be recorded on the CRF; however, they should be included in the subject’s source documentation with a note stating why the symptoms did not need to be recorded on the CRF.
2.44 Expectations for Recording Adverse Event on CRFs

The events to be recorded on CRFs during the various time periods of study participation are defined in Table 5, Section 7.2 of the protocol.

2.45 Medications Allowed During the Study

The following must be recorded during the active study period (28 days following inoculation). 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 PE0414 (2000) Non-Antiretroviral Concomitant Medications/Therapies – IV

Minimum documentation must include:

- Name of the medication or treatment
- Route and frequency
- Start and stop date of medication or treatment
- Indication for medication or treatment

2.46 Emergency Plan for After Hours

The parent/guardian will be informed of exactly how they would reach medical help and the study staff in an emergency situation, including outside 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 per Section 6.15 of the protocol.

2.47 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.

2.471 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

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 the protocol relative to study product received, including post-inoculation blood and nasal wash.

3. Study personnel will document the date and reason for withdrawal in the subject’s source record and record this information on the subject CRF, FSTRF Form F1601 Off Study.
2.472 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:


3.2 Screening & Enrollment

The study screening and enrollment procedures are described in detail in Section 4 of the protocol, and summarized in the Schedule of Evaluations (Appendix 2 of the protocol).

3.21 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 files as per site Standard Operating Procedures. Logs should include the following information:

- Initials of the subject
- Participant ID number (PID) if patient receives one
- Date screened
- Race
- Gender
- Status of screening (e.g., 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/

3.22 Assignment of Participant ID Numbers (PIDs)

The PID is assigned at the site from a list that is generated by the DMC and sent to the sites. If a subject has been on another IMPAACT or ACTG (AIDS Clinical Trials Group) study, that PID is carried with them;
a new PID number would not be assigned for such subjects. (Assignment of Study ID Numbers [SIDs] is addressed in MOP Section 5.42.)

### 3.3 IMPAACT 2000 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.

The child’s parent/guardian will be encouraged to ask questions, and the site will confirm informed consent comprehension using the template quiz provided in Appendix III of the MOP or other, site-specific method. Study staff will use incorrect responses to questions 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 of study procedures before signing the consent form.

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

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, or offer to mail a copy if they prefer.

If necessary, obtain a Health Insurance Portability and Accountability Act (HIPAA) release from parent/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 a complete medical history and perform a physical examination.
- Obtain approximately 5 mL of blood in a red top or Serum Separate Tube (no additive) to be shipped to the JHU laboratory:
- Plan for a return visit for enrollment if eligible.

#### 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 Johns Hopkins University (JHU) on Mondays (1), Tuesdays (2), and Wednesdays (3). Please inform Bhavin Thumar and Kim Wanionek of plans for shipment of specimens no later than the preceding Friday at 2 PM Eastern Time by email: bthumar@jhsph.edu and kwanione@jhsph.edu. In September and October, results will be emailed to the sites and the Clinical Trials Specialist (CTS) on Monday afternoons for samples shipped on (1, 2), and Tuesday afternoons for sample shipped (3). In April through August, results will be emailed to the sites and the Clinical Trials Specialist (CTS) on Tuesday afternoons. There should be no shipment to JHU on Thursdays or Fridays.

Study staff will notify parents/guardians regarding 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.
Note: Because inoculation must occur within 42 days of the screening evaluation, sites are encouraged to schedule randomization and inoculation as soon as possible after eligibility is determined. In this manner, if the inoculation needs to be delayed for some reason (such as acute illness), the site can request team permission to inoculate outside the 3 day window after randomization. No inoculations will be permitted more than 42 days after screening.

4.0 ENROLLMENT

4.1 Randomization

Sites should err on the side of caution when considering children for participation in IMPAACT 2000. Specifically, prior to randomization, review the inclusion and exclusion criteria (protocol Sections 4.1), and:

- Prior to randomization evaluate the child for acute illness. Defer randomization if the child is acutely ill.
- Evaluate the child for evidence of any chronic illness. As a Phase I study of safety and immunogenicity, IMPAACT 2000 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. Examples of chronic illnesses that would not be considered exclusionary are as follows:
  - Mild Gastroesophageal Reflux Disease (GERD)
  - Iron deficiency anemia
  - Constipation
  - Other conditions should be reviewed with the protocol team
- 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 regarding evaluation of any chronic illnesses and the child’s eligibility.
- Contact the IMPAACT 2000 Team (impaact.team2000@fstrf.org) if there are any doubts about potential eligibility. As with any message to the IMPAACT 2000 team, be sure to include “IMPAACT 2000” 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 2000 by utilizing the Subject Enrollment System (SES) located on the IMPAACT DMC Website at www.fstrf.org.
  - Sites are strongly encouraged to schedule this visit as soon as eligibility is determine and preferably within 30 days of screening whenever possible; however, inoculation must occur within 42 days of screening.

4.2 Inoculation (Day 0)

- Inoculation will ideally occur the same day as randomization, but must occur within 3 days of randomization. The site may request team permission to inoculate outside the 3 day window if the child develops a temporary acute sign/symptom that excludes participation. Please note that inoculation must occur within 42 days of screening.
• Review inclusion and exclusion criteria (Section 4.1 of the protocol) including treatments that could potentially interfere with vaccine-induced immunity (Section 4.5 of the protocol).

• Complete interim history and clinical assessment as per protocol Appendix 2. Do not inoculate if child has developed signs or symptoms which would be exclusionary. Contact the team in this situation.

• Order study product from your site pharmacy per site SOPs.

• 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 5.9 of the MOP).

• Observe subject for a minimum of 30 minutes after inoculation to evaluate for immediate adverse reactions.

• Provide parent/guardian with temporal artery thermometer and digital rectal thermometer and instructions for use (see Appendix I of the MOP).

• Provide and explain temperature card, solicited AE illness criteria, and study personnel contact information.

• Schedule next visit or contact.

4.3 Day 0 to Day 28 Visit (Acute Phase)

Refer to protocol Table 5 for CRF recording requirements during this period.

4.31 Study Days with In-Person Visits

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

• At each visit, obtain from parent/guardian the subject’s interim history and temperatures since previous day’s contact. Document interim history in the study chart and document the highest temperature measurement, denoting measurement method.

• Perform focused clinical assessment as per protocol Appendix 2.

• 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:
  o An adventitious virus assay request should be sent to JHU. Ship these samples with the next batch to JHU, and include a copy of F3008 (see Section 7.33 of the MOP). However, if illness meets criteria for Pausing and Stopping rules (protocol Section 7.7), the nasal wash must be shipped in real time to the JHU lab.
  o Notify the IMPAACT 2000 team via email (impaact.team2000@fstrf.org) within 24 hours of any SAEs or LRIs.
  o Report SAEs and LRIs in an expedited manner through the DAIDS Adverse Experience Reporting System (DAERS) as per Section 7.3 of the protocol.

• Schedule next routine contact or 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 illness, including croup, pneumonia, or wheezing that occurs prior to the Day 56 visit.
4.32 Non-visit Contacts Post-Inoculation (Days 0 to 28)

- On study days without clinical visits between Day 0 and Day 28, contact with the parent/guardian is required. Obtain and document in study chart the interim history, including medications and highest daily temporal temperature measurement or, if obtained, the highest rectal temperature measurement from parent/guardian. Denote the measurement method.
- Clarify positive findings to determine need for Sick Visit.
- Schedule Sick Visit if child meets criteria for illness per the timeframe as described in Protocol Section 6.15.
- Confirm next contact or visit.

4.33 Sick Visits during the Acute Phase

Solicited AEs are defined as adverse events which may occur after a respiratory viral vaccine and include fever and respiratory symptoms as defined in the protocol Appendix 4. All solicited AEs, lower respiratory illnesses (LRI), and Serious Adverse Events (SAEs) require at least one Sick Visit within timeframe described in Section 6.15 of the protocol. If the solicited AE, LRI, or SAEs continue at the time of the next routine appointment, request an adventitious virus culture on the nasal wash. This occurs at each regular study visit until the solicited AE, LRI, or SAE resolves. A second unscheduled Sick 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 investigator deems the event to be chronic or the subject to be stable.

The following procedures must be completed during Sick Visits:

- Obtain from the parent/guardian and document in study chart the highest temperature measurement and denote measurement method (temporal and/or rectal).
- Perform focused clinical assessment as per protocol Appendix 2.
- Obtain nasal wash for culture of vaccine virus and adventitious agents (see Section 7.3 of the MOP). The nasal wash must be shipped with the next available batch to the JHU lab and an adventitious virus assay requested (see Section 7.33 of the MOP).
- Ship sample on the day of collection (if possible) or on the first allowed shipping day.
- Notify the IMPAACT 2000 team via email (impaact.team2000@fstrf.org) within 24 hours of any SAEs or LRIs.
- Report SAEs and LRIs in an expedited manner through the DAIDS Adverse Experience Reporting System (DAERS) as per Section 7.3 of the protocol.

4.4 Day 29 to Day 56 Visit (Post-Acute Phase)

Refer to protocol Table 5 for CRF recording requirements during this period.

4.41 Clinical Assessment and Sick Visits
During the Post-Acute Phase, parents/guardians will be instructed to monitor their infant/child for fever and symptoms suggestive of LRI or SAE and contact the site if these symptoms are present. Guidelines for clinical assessment and Sick Visits may be found in Section 6.21 of the protocol.

4.42 Day 56 Visit (+7 Days)
- Refer to protocol Table 5 for CRF recording requirements during on this visit.
- Obtain approximately 5 mL of blood for immunologic assays.
- Obtain nasal wash for immunologic assays (see Section 7.3 of the MOP).
- Review RSV surveillance monitoring instructions with parents/guardian.
- Schedule a time window for pre-RSV surveillance blood draw.

4.5 Period after Day 56 Visit until October 31st
Refer to Section 6.3 of the protocol for instructions during this time period.

4.6 Pre-RSV Season Study Visit (October 1st to 31st)
Between October 1st and October 31st of the calendar year in which the child was enrolled, or at the Day 56 Visit if that visit falls after October 1st, obtain approximately 5 mL of blood for pre-RSV season serum antibody specimen detection. If the Day 56 Visit occurs on or after October 1st, the Day 56 Visit specimen may also be used as the pre-RSV season serum antibody specimen.

4.7 RSV Season Surveillance (November 1st through March 31st following inoculation)
- Obtain and record interim history with weekly contact.
- Sick Visit: Arrange for study visit within 3 days of the initial report if child demonstrates any of the following:
  - Medically attended fever
  - Medically attended upper respiratory illness
  - Medically attended otitis media
  - Medically attended lower respiratory illness

  If one of the above events occurs, refer to Appendix 3 of the protocol for appropriate testing during the Sick Visit. Medically attended includes events at which the child is either seen by a medical provider or has an intervention recommended by a medical provider without being seen.

Refer to protocol Table 5 for CRF recording requirements during this period.

4.8 Post-RSV Season Study Visit (April 1st to 30th)
- Obtain approximately 5 mL of blood for post-RSV season serum antibody detection.
- Inform parent/guardian of study randomization, if known.
- Refer to protocol Table 5 for CRF recording requirements during this period.
5.0 SITE PHARMACY PROCEDURES & VACCINE/PLACEBO PREPARATION

5.1 The Study Vaccine - Overview

The clinical lot preparation of RSV LID ΔM2-2 was generated by Charles River Laboratories using the seed virus provided by the National Institutes of Health (NIH). This virus vaccine preparation is stable and potent when stored at a temperature of -80°C ±15°C.

The RSV LID ΔM2-2 Vero Cell Grown Virus Vaccine (Lot RSV#007A) 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#007A, has a mean infectivity titer of $10^{5.9}$ Plaque Forming Units (PFU) per mL.

An enlarged example of a final vaccine vial label is shown on the following page.

![Vaccine Label Example](image)

**Vaccine Product and Diluent Information**

- **2X L-15 Leibovitz Medium**: Diluted on site to make diluent/placebo. A photo of the bottle (content: 100 mL) is below.

![Leibovitz Medium Bottle](image)

- **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 LID ΔM2-2**: Concentration of the undiluted vaccine is $10^{5.9}$ PFU per mL. Lot RSV #007A

- **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 and 2X L-15 Leibovitz Medium

Clinical research site (CRS) pharmacists can order the vaccine and the 2X L-15 Leibovitz Medium (which is used to make the diluent and placebo) from the CRPMC by following the instructions in Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

5.3 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 in separate packaging, because they must be shipped at different temperatures.

- Site pharmacy staff must open the box immediately and follow the instructions contained in the package. This involves inventorying the study product received.
- 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 in the pharmacy.
- 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 the pharmacy.
- Follow instructions included in the shipment to inform the CRPMC of the condition of the products upon receipt. Return the temperature-monitoring device to the CRPMC.
- If the product is not received under appropriate conditions, it must be quarantined until notified by the CRPMC that the product is acceptable for use or that it must be replaced.
- 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 CRPMC.
- 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 from the CRPMC as needed.

5.4 Pharmacy Procedures – Storage, Preparation & Accountability

5.41 Storage of the Vaccine

- The RSV LID ΔM2-2 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 (SWFI) 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 and freezer must be measured on a daily basis, and there must be an alarmed temperature monitor that will notify staff in the event of an excursion from the acceptable temperature range.

5.42 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 protocol registered, FSTRF will send the site pharmacist the Pharmacist’s Prescription List (SID list) that lists SIDs and the corresponding treatment assignment.
- An 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 LID ΔM2-2 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/placebo is to be administered.
- The designated unblinded licensed pharmacy personnel will prepare the vaccine/placebo as outlined below.
- The designated unblinded licensed pharmacy personnel will agree not to reveal the identity of the vaccine/placebo to personnel (e.g., investigator, study nurse, research assistant) involved in the conduct of the study.
- For further information on blinding and unblinding, see Section 2.3 of the MOP.

5.43 Vaccine and Placebo Preparation Guidelines

- Relevant forms are found in the MOP Appendix V.
- 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 designated licensed pharmacy personnel 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**

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

  IMPAACT 2000 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
  IMPAACT 2000 RSV LID ΔM2-2 10^{5.0} PFU or Placebo nasal vaccine
  0.5mL/syringe
  Expiration Date _____ time_____ in 24 hr clock
  Initials of pharmacy preparer and checker
  Authorized prescriber’s name

- The syringe carrier bag should be labeled with an auxiliary label stating:
  FOR INTRANASAL ADMINISTRATION ONLY

- Vaccine dilution and diluent labels will state:
  “Diluted vaccine 10^{5.0} 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 designated licensed pharmacy personnel will
prepare Vaccine Aliquots from the remaining 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 LID ΔM2-2 1:4 Diluted
Site Number
Date and time aliquots prepared

RSV LID ΔM2-2 UNDILUTED
Site Number
Date and time aliquots prepared

5.44 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 L-15 from the refrigerator.

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

5.441 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 or opened and the solutions are clear.
7. Gather the supplies below that are needed for preparation, spray outside of containers with 70% isopropyl alcohol, and place in BSC/isolator:
   - 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.

5.442 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 procedures 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 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. Maintain 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.

5.45 Preparing the Vaccine

Three 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 $10^{5.9}$ PFU per mL. The frozen vaccine is thawed and diluted with 1X L-15 to a dose of $10^{5.0}$ 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, 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 instructions below. To “snap freeze” diluted and undiluted vaccine aliquots, follow BioCision CoolBox procedures described in Section 5.48 below.

If the -80°C 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.

5.451 Preparation of the RSV LID ΔM2-2 $10^{5.0}$ PFU per 0.5 mL solution

Use the Vaccine Preparation Form to document preparation

1. Prepare 1 label with “diluted vaccine $10^{5.0}$ PFU per 0.5 mL.”

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
   - 3 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 3 mL of 1X L-15 and inject into the empty sterile vial.

4. Place the vial in the wet ice container.

5. Remove 3 vials of undiluted vaccine from the -80°C 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 3 vials of undiluted vaccine by swirling vials in a 32 to 37°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 two vials of undiluted vaccine and transfer into the third 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 1 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 1 mL to the vial containing the 3 mL of 1X L-15.

12. Label this vial with the “diluted vaccine 10^{5.0} PFU per 0.5 mL” label, swirl to mix, and place it into the wet ice container.

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

### 5.452 Preparation of the diluted RSV LID ΔM2-2 10^{5.0} 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 the supplies listed below that are 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 \(10^{5.0}\) 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 procedures 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. Maintain the vaccine dosing syringe in wet ice until just before administration.


### 5.46 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. Document the temperature on the IMPAACT 2000 Study Product Administration Record (SPAR) 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 on the SPAR.

5. The clinic staff must inspect the contents and sign the SPAR 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 document the current, minimum, and maximum temperatures on the SPAR 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.

5.47 Vaccine/Placebo Chain of Custody Accountability

- The unblinded pharmacist completes the appropriate sections of the SPAR and oversees delivery of the product and the SPAR 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 the SPAR 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 SPAR.
- A photocopy of the SPAR remains at the pharmacy.
- The original of the SPAR is returned to the study coordinator for placement in the study binder or subject's study record.

5.48 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 cryo vials, 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 system (CoolBox with CoolRack, BioCision, Mill Valley, CA) and dry ice pellets, as described below.
- Store the CoolRack in a -20°C 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 1 mL syringes, small gauge needles and labels and place in the BSC/isolator.

6. Withdraw from the $10^{5.0}$ 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 $10^{5.9}$ 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 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 freezer. 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.
5.5 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 of and/or destruction of USED AND UNUSED vaccine/placebo vials and needles, syringes, pipettes used in preparation must be in accordance with site/institutional/local guidelines for disposal of Biosafety Level 2 materials.

3. Expired study product or product remaining at the end of the study should be retained at the site pharmacy until instructions for destruction are received from study sponsor, CRPMC, or Pharmaceutical Affairs Branch (PAB).

5.6 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 correct aliquot label on the form and writing the date the sample is sent and your initials. 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 # 4974-1746-5

5.7 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 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.

5.8 Communication with Pharmacy Staff

- Establish a system of communication to inform the pharmacist of each upcoming participant visit prior to the visit (e.g., provide a calendar of visits, weekly emails/phone calls).
- Inform pharmacy staff in a timely manner of any changes to expected visits and/or enrollments (e.g., cancellations, date/time changes, participant eligibility for vaccine).
- 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 IMPAACT 2000 have been added to an “Authorized Prescribers” list provided to the pharmacy staff.
- Ensure all Authorized Prescribers are on the Food and Drug Administration (FDA) Form 1572.
- Ensure that signatures are legible and consistent with original list.
- Update list immediately with any changes (e.g., name changes, additional/departing staff) 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).

5.9 Administering the Vaccine/Placebo

Note: Inoculation must occur by the expiration time on the syringe label. The expiration time denotes 4 hours from the time study product was removed from freezer or refrigerator.

- Study product will be administered to participants intranasally using a 1 mL oral syringe, which 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/placebo administration for signs and symptoms of local and/or systemic reaction.
- Document any adverse reactions or indicate absence of reaction in the subject's study record.
- Resuscitation equipment, oxygen, and epinephrine 1:1000 (1 mg/mL) must be readily available in case of an anaphylactic reaction.
- Document vaccine/placebo administration on the SPAR and in the study record and record on the appropriate CRF.
5.10 Pharmacy Questions/Problems

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

Ana Martinez, RPh  amartinez@niaid.nih.gov  301-435-3734
Vivian Rexroad, PharmD  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 Section 7 to confirm safety-related requirements.

6.1 Determination of Severity/Grade for Solicited Adverse Events

Solicited adverse events (predefined AEs that can potentially occur after vaccine administration) are highlighted in protocol Section 7.12 (list of solicited AEs) and in protocol Appendix 4 (definitions 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 7.151 and 7.152 and NOT the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table). Events that fail to rise to the level specified in the definitions are recorded but are not reportable as AEs for the purpose of the protocol.

6.2 Serious Adverse Events (SAE) and Lower Respiratory Illnesses (LRI)

The list of serious adverse event outcomes is included in protocol Section 7.13. It includes the typical outcomes seen in most FDA-regulated studies. Additionally, Lower Respiratory 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). For instruction on SAE and LRI reporting, refer to protocol Section 7.3.

Please see protocol Appendix 4 for SAE and LRI definitions.

6.3 Unanticipated Problems (UPs)

The definition of an unanticipated problem (UP) is outlined in protocol Section 7.5. 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 Office for Human Research Protections (OHRP) regulations apply to research conducted or supported by Health and Human Services (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 subjects in the study.

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 after the site investigator becomes aware 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 to:

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 AEs are not reported to the IND Sponsor Clinical Safety Office for this study.

6.4 Pausing Rules

Guidelines for pausing criteria may be reviewed in the protocol Section 7.7. If there is any question as to whether a pausing criterion has been met, clarification MUST be sought immediately from the protocol team via email (impaact.team2000@fstrf.org).

If a site identifies that a **pausing criterion 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.team2000@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.
2. The IMPAACT protocol team will notify all sites to suspend enrollment and inoculations, and FSTRF will close accrual.
3. Site will ship **ALL** respiratory viral samples collected on the subject who 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 as soon as possible because the samples are needed to determine if there are safety concerns (e.g., shedding of vaccine virus). The results assist in determining if the protocol may proceed.
4. All sites will continue to conduct the protocol-specified evaluations on previously enrolled/active subjects.
5. The IMPAACT team will notify sites via email when/if the study enrollment and inoculations may resume. If the study is allowed to resume, accrual will open in FSTRF.

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

6.5 Stopping Rules

A set of 5 stopping rules is noted in protocol Section 7.7. All stopping rule steps are handled internally by the IMPAACT 2000 team. Decisions will be communicated to study sites after review by the team and possibly the DSMB once all data have become available.
7.0 SPECIMEN COLLECTION AND PROCESSING

7.1 Introduction

This section contains instructions related to collection and processing of IMPAACT 2000 specimens. For detailed information on tests and specimens required for each visit, please refer to the Schedule of Evaluations (SOE), protocol Appendix 2.

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 quality assurance/quality control (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 (International Air Transport Association), and ACTG/IMPAACT specimen shipping regulations.

As the transmission of 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:

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 IMPAACT 2000 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.

7.21 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.

7.22 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. The labels used must be capable of being stored at -80°C. Study staff must record the actual specimen collection time on CRF and the tracking forms. See Appendix VI of the MOP.

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.

7.23 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 Manager 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 12:00 AM - 6:00 PM Eastern Time in the US (ET), Monday through Friday. During these business hours, please contact LDMS User Support as follows:

Email: Ldmselp@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 IMPAACT 2000 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>
<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 (no additive) or Serum Separator Tube (SST)</td>
<td>Whole blood</td>
<td>3-5 mL</td>
<td>BLD/NON/SER or BLD/SST/SER</td>
<td></td>
</tr>
</tbody>
</table>

7.31 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 7.41 of the MOP). Thaw VTM in the refrigerator or at room temperature and place into refrigerator immediately thereafter. Transport VTM on wet ice prior to collecting nasal wash.

**NW Collection Supplies:**
- Gloves
- Sterile specimen cup
- Zip lock 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, 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 7.41 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

---

**Table 1. SPECIMEN COLLECTION & TESTING**

- **Collection Supplies for Nasal Washes:**
  - Gloves
  - Sterile specimen cup
  - Zip lock 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, reward, or snack

- **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 7.41 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 “snap 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.
• Portable snap-freezing device
  o BioCision CoolBox 30 with CoolRack CFT30 (BCS-166) or
  o BioCision CoolBox XT with CoolRack CFT24 (BCS-575)
• Day 0 (inoculation day) and the Day 56 Visit: Nunc starfoot vials, external thread, 4.5 mL, manufacturer item number: NUNC 347643, to be used to freeze nasal wash aliquots without VTM for immunology assays
• Nasal wash specimen for immunological testing does not need to be snap-frozen.

7.32 Nasal Wash Collection Procedure

JHU-CIR Pediatric Nasal Wash Instructional Video: http://www.rparedes.com/nasalwash/

• 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, and 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 to minimize 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 mL of VTM
  - If < 4 mL collected, repeat wash.
  - NW specimen for virology culture must be combined with the protocol-supplied VTM immediately, kept on wet ice until freezing, and snap-frozen within 30 minutes of obtaining sample. If sample cannot be transported to the lab to complete processing within 30 minutes, the processing steps (Section 7.4 of MOP) will need to be performed in the field.
- Study Day 0 (inoculation day) and the Day 56 Visit: nasal wash aliquots without VTM for immunology assays are also needed. All remaining nasal wash samples, (after transfer of 6 mL to VTM vial for virology assays, if required) will be aliquoted for immunology assays as described below [Section 7.43, Nasal Wash Processing in the field; the Day 56 Visit], and in the Laboratory Processing Chart (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 zip lock bag prior to setting in wet ice to prevent contact with melting ice.
- Dispose of all collection supplies in biohazard container.

7.33 Requesting Adventitious Virus Assay

In the event that illness criteria are met or suspected during an acute phase in-person visit or during a sick visit, a request for adventitious virus assay is required, and the nasal wash should be sent to JHU with the next available batch. However, if illness meets criteria for Pausing and Stopping Rules (protocol Section 7.7), specimens should be shipped to JHU in real-time. Notify Bhavin Thumar (bthumar@jhsph.edu) and Kim Wanionek (kwanione@jhsph.edu) that a nasal wash specimen is being sent and that an adventitious virus assay is requested on the sample. Include in the email message the PID, date of collection and CRS number. (Include copy of F3008 with shipped samples.)

7.4 Specimen Processing Procedures (also see LPC)

7.41 Obtaining Protocol-specific Viral Transport Media

Viral transport media (VTM) 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 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 ok), VTM has an expiration date 6 months after production. Thaw in refrigerator or at room temperature and place in refrigerator immediately thereafter. 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 Sick 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.

7.42 Specimen Processing

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

7.43 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 **snap-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 6mL 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 **snap-frozen** within 30 minutes of obtaining specimen.
- Equally divide and aliquot the combined NW and VTM mixture into 7 pre-labeled cryovials. Approximately 1 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.
- Snap freeze specimen aliquots per BioCision Coolbox manufacturer’s -78°C instructions; see Appendix IV of the MOP for snap freezing instructions.
- Day 0 (inoculation day) and the Day 56 Visit: use Nunc starfoot vials, external thread, 4.5 mL, 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. Snap freezing of these aliquots is not required.

- Specimen aliquots must be accompanied by a completed IMPAACT 2000 Specimen Tracking Form.
7.5 Additional Resources

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

AIDS Clinical Trials Network (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 IMPAACT 2000. 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 Schedule of Case Report Forms (CRF)
The IMPAACT 2000 CRF schedule and forms can be found on the FSTRF portal:

- Log in to the FSTRF portal at 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 “IMPAACT 2000” for the CRF schedule and forms
8.3 Data Management Resources

Alex DiPerna, Data Manager
FSTRF
4033 Maple Rd.
Amherst, NY 14226
Phone: (716) 834-0900 ext. 7266
Fax: (716) 834-8675
diperna@fstrf.org

Linda Marillo, Data Manager
FSTRF
4033 Maple Rd.
Amherst, NY 14226
Phone: (716) 834-0900 ext. 7275
Fax: (716) 834-8675
marillo@fstrf.org

For additional queries, you may contact the Randomization Help Desk at 716-834-0900 EXT 7200 or rando.support@fstrf.org.
APPENDIX I

Instructions for Parents/Guardians for Taking Daily Temperatures

Each day for 28 days after receiving the vaccine or placebo, your child will have his/her temperature measured. This will be done by a parent or caregiver on days when your child is not seen by the study staff. During this period, you should not give your child medications such as acetaminophen (Tylenol) or ibuprofen (Motrin) unless he/she has a fever or pain. Please take a temporal temperature of your child 3 times in a row and write down the highest temperature. If the highest temperature is lower than 100.0°F, please write down the temperature on the temperature card. This should be repeated every day.

If the highest temporal temperature is 100.0°F or higher, then you will need to take a rectal temperature. Do this within 20 minutes. If the rectal temperature is lower than 100.4°F, the rectal temperature should be written on the temperature card. Write "R" next to the number to indicate that it was rectal temperature. If the rectal temperature is 100.4°F or higher, contact the study staff to tell them about the fever. [study sites may insert local contact information here.]

Temperature Flow Chart

- Take the temporal temperature, following manufacturer’s instructions, THREE times and write down the highest temperature on the card.

- If 100.0°F or higher
  - Take a rectal temperature. Do this within 20 minutes.

  - If the rectal temperature is lower than 100.4°F
    - No fever
      - Write the rectal temperature on the card

  - If the rectal temperature is 100.4°F or higher
    - Fever
      - Contact study staff and write the rectal temperature on the card
APPENDIX II

Checklist of Required Supplies for Home Visits

a. Nasal Wash - Collection Procedure
   - Disposable gloves
   - Sterile specimen cup with lid
   - Zip lock bag (optional)
   - Specimen label for sterile specimen cup
   - 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 (Study Days 0, 3, 5, 7, 10, 12, 14, 17, 19, 21, 28 each day +/- 1 day and Sick Visits)
   - Disposable gloves
   - Protocol-specific Viral Transport Media – thawed on wet ice
   - 7 x 2 mL cryovials (Sarstedt 72.694.006)
   - Sterile 3 mL syringe or transfer pipette
   - Specimen labels (Appendix VI)
   - Permanent marker (e.g., Sharpie)
   - Two labeled storage boxes
   - Styrofoam box or insulated container (e.g., Igloo) that can vent as the dry ice sublimates (sufficient size to fit coolbox)
   - Dry ice pellets

c. Nasal Wash - Immunology Specimen Processing (Study Days 0 (inoculation day) and the Day 56 Visit)
   - Disposable gloves
   - 5 x 4.5 mL cryovials (Nunc, Starfoot, external thread, NUNC (347643)
   - 3 mL syringe or transfer pipette
   - LDMS labels
   - Permanent marker (e.g., Sharpie)
   - Two storage boxes
   - Styrofoam box or insulated container (e.g., Igloo) that can vent as the dry ice sublimates (sufficient size to fit coolbox)
   - Dry ice pellets

d. Nasal Wash – Snap Freezing
   - Dry ice pellets

e. Coolbox (BioCision CoolBox with CoolRack)

f. Other Supplies for Visit
   - Red-top blood tube or Serum Separator Tube (SST)
   - Syringes and needles
   - Tourniquet
   - Stethoscope
   - Otoscope
   - Gauze, alcohol swabs, and Band-Aids
   - Tongue depressor
### APPENDIX III

**TEMPLATE RSV PEDIATRIC COMPREHENSION ASSESSMENT**

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>What is the name of the vaccine virus your child may receive in this study?</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>How many weeks does your child have to wait between receiving routine vaccinations and the investigational vaccine? (two answers)</td>
<td>1.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.</td>
</tr>
<tr>
<td>3</td>
<td>Presently, is there a vaccine to prevent your child from getting sick with this virus?</td>
<td>☐ YES ☐ NO</td>
</tr>
<tr>
<td>4</td>
<td>What is a placebo?</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>How are we going to give this vaccine or placebo?</td>
<td>☐ NOSE DROPS ☐ MOUTH ☐ SHOT</td>
</tr>
<tr>
<td>6</td>
<td>How many doses of this vaccine or placebo will your child receive?</td>
<td>☐ 1 dose ☐ 2 doses</td>
</tr>
<tr>
<td>7</td>
<td>Is it possible your child could receive placebo?</td>
<td>☐ YES ☐ NO</td>
</tr>
<tr>
<td>8</td>
<td>How many times will we draw blood from your child? (the answer is dependent on the time of year your child enrolls in the study)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>What are 2 risks to drawing blood?</td>
<td>1.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.</td>
</tr>
<tr>
<td>10</td>
<td>Why do we rinse your child’s nose?</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Name 2 reasons your child would not be able to participate in this study?</td>
<td>1.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.</td>
</tr>
<tr>
<td>12</td>
<td>What is the benefit of receiving this vaccine?</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Can your child get illnesses from other germs during the study?</td>
<td>☐ YES ☐ NO</td>
</tr>
<tr>
<td>14</td>
<td>Do you understand the study that your child is about to begin?</td>
<td>☐ YES ☐ NO</td>
</tr>
<tr>
<td>15</td>
<td>Do you have any questions?</td>
<td>☐ YES ☐ NO</td>
</tr>
<tr>
<td></td>
<td>If “yes”, were your questions answered?</td>
<td>☐ YES ☐ NO</td>
</tr>
</tbody>
</table>

---

**Reviewed by:**

Parent/Guardian Signature: ___________________________ Date: ____________

Study Staff Signature: ___________________________ Date: ____________
APPENDIX IV

Snap Freezing SOP for Nasal Washes

Materials:
CoolBox CF30 system (CoolBox with CoolRack, 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 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 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 sublimates, creating pressure inside a sealed container. Maintain in a well-ventilated area.
   a) Be sure to provide lab with a completed IMPAACT 2000 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
- IMPAACT 2000 Study Product Administration Record (SPAR)
INVESTIGATIONAL DRUG PACKING SLIP – VACCINE ALIQUOTS

Study Name: IMPAACT 2000
A Phase I Study of the Safety and Immunogenicity of Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine RSV LID ΔM2-2 in RSV-Seronegative Infants and Children

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

**Ship Date:**

**Date vaccine Prepared:**

**Attention:**
Bhavin Thumar, MS

**Shipped By:**

**Site Number/Investigator:**

**Comments:**

**Storage Instruction:** ~ FROZEN ~ Shipped on Dry Ice

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>PID</th>
<th>Stock Vial Numbers</th>
<th>LOT #</th>
<th>Number of vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV LID ΔM2-2 Vaccine – Undiluted</td>
<td></td>
<td></td>
<td>RSV#007A</td>
<td></td>
</tr>
<tr>
<td>RSV LID ΔM2-2 Vaccine – Diluted</td>
<td></td>
<td></td>
<td>RSV#007A</td>
<td></td>
</tr>
</tbody>
</table>

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 2000**

**SITE: _____________**

<table>
<thead>
<tr>
<th>Label Sample</th>
<th># Aliquots Frozen</th>
<th>SID(s) Vaccinated</th>
<th>Initials</th>
<th>Date sample sent to Johns Hopkins</th>
<th>Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stock Vial #s:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stock Vial #s:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stock Vial #s:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stock Vial #s:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stock Vial #s:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stock Vial #s:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study Product Accountability Record

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

<table>
<thead>
<tr>
<th>Clinical Research Site Name</th>
<th>Clinical Research Site Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator of Record Name</td>
<td>Investigator Number</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Study Product Name</th>
<th>Strength and Dosage Form</th>
<th>NSC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPAACT 2000</td>
<td>Live Recombinant Respiratory Syncytial Virus Vaccine, RSV LID ΔM2-2</td>
<td>$10^{5.9}$ PFU per mL nasal solution</td>
<td>*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Package Size</th>
<th>Manufacturer</th>
<th>Lot Number</th>
<th>Storage Temperature</th>
<th>Expiration Date*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6 mL/vial</td>
<td>Charles River Laboratories</td>
<td>RSV #007A</td>
<td>$-80 +/- 15^\circ C$</td>
<td>ongoing retesting</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Patient Identifier (Initials or SID)</th>
<th>PID</th>
<th>DOSE # mL used for preparation</th>
<th># vials Dispensed or Received</th>
<th>Balance Forward</th>
<th>R.Ph. Initials</th>
<th>Second Check Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study Product Accountability Record
Division of AIDS (DAIDS)
National Institutes of Allergy and Infectious Diseases (NIAID)

<table>
<thead>
<tr>
<th>Clinical Research Site Name</th>
<th>Clinical Research Site Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator of Record Name</td>
<td>Investigator Number</td>
</tr>
<tr>
<td>Protocol Number</td>
<td>Study Product Name</td>
</tr>
<tr>
<td>IMPAACT 2000</td>
<td>2X L-15 Leibovitz medium</td>
</tr>
<tr>
<td></td>
<td>Strength and Dosage Form</td>
</tr>
<tr>
<td></td>
<td>2X L-15 Leibovitz medium</td>
</tr>
<tr>
<td></td>
<td>NSC Number</td>
</tr>
<tr>
<td>Package Size</td>
<td>Manufacturer</td>
</tr>
<tr>
<td>100 mL/bottle</td>
<td>Lonza</td>
</tr>
<tr>
<td>Lot Number</td>
<td>0000372724</td>
</tr>
<tr>
<td>Storage Temperature</td>
<td>2-8°C</td>
</tr>
<tr>
<td>Expiration Date</td>
<td>23 Feb 2015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>Patient Identifier (Initials or SID)</th>
<th>PID</th>
<th>DOSE # mL used for preparation</th>
<th># bottles Dispensed or Received</th>
<th>Balance Forward</th>
<th>R.Ph. Initials</th>
<th>Second Check Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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 2000

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

_____/_____/____ @ ____________
(MM/DD/YYYY) (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: ______________________ Exp: ______________________

2. Sterile Water for Injection 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 2000

Participant Identifier: _________________________ SID: _________________________
PID: _________________________ Preparation Date: _________________________

________________________________________  Date
Signature of Pharmacist Preparing Placebo Dose

________________________________________  Date
Signature of Pharmacy Staff Checking Placebo Dose
IF PARTICIPANT IS RANDOMIZED TO RECEIVE VACCINE, COMPLETE THE FOLLOWING:

Vaccine Preparation Form

Vaccine Name: RSV LID ΔM2-2  Study # IMPAACT 2000
Lot #: RSV #007A  Titer: 10^{5.9} PFU/mL

Confirm vaccine name and lot # from vaccine vial: ☐ ___________ ☐ ___________ initials initials

Participant Identifier: _______________________ SID: ____________________

PID: _______________________ Preparation Date: ______________________

Date and Time vaccine taken out from -80°C freezer:

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

Vaccine Vial Number  Vaccine Vial Number  Vaccine Vial Number

Signature of pharmacist preparing vaccine dose ____________________________ Date

Name of pharmacy staff checking vaccine dose ____________________________ Date

Place Vaccine Vial Label  Place Vaccine Vial Label

Place Vaccine Vial Label
### IMPAACT 2000 Study Product Administration Record

<table>
<thead>
<tr>
<th>Vaccine Name or Matching Placebo:</th>
<th>RSV LID ΔM2-2 vaccine or 1X L-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study #: IMPAACT 2000 IND #:</td>
<td>15713</td>
</tr>
</tbody>
</table>

#### Section 1: Completed by Pharmacy Personnel

**Expiration time of Study Product:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Time (24-hour clock)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Signature of Pharmacist Preparing Study Product**

*I have checked the preparation and documentation of this dispensing:*

**Signature of Pharmacy Personnel Checking Study Product**

**Temperature leaving pharmacy:**

<table>
<thead>
<tr>
<th>°C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

#### Section 2: Completed by Clinical Personnel

**Total Volume of Dose:** 0.5 mL

**Route of Inoculation:** Intranasal

**# of Syringes Received:**

**Signature of Clinician Accepting Study Product**

**Temperatures prior to administration of study product:**

- Current: __________ °C
- Minimum: __________ °C
- Maximum: __________ °C

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

#### Section 3: Participant Identifier

<table>
<thead>
<tr>
<th>PID #</th>
<th>Date Given</th>
<th>Study Product Given By (Signature)</th>
<th>Signature below Ensures Correlation between Participant Identifier &amp; PID #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Disposition of Study Product**

- A=Administered
- R=Returned to Pharmacy

#### Section 4: Completed by Pharmacy Personnel

**# of Syringes Returned:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Time (24-hour clock)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Signature of Pharmacy Personnel Accepting Syringes and/or Form**

**Date**

**Disposition Code:**

- Original - STUDY BINDER
- Copy - PHARMACY
APPENDIX VI

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 #: IMPAACT 2000
   - Specimen Date
   - Study Day
   - Specimen type: NW/VTM
   - Vial #1, 2, 3, 4, 5, 6, 7
   - Note: Each specimen aliquot will be numbered with a unique vial #1-7. Seven (7) aliquots of NW with VTM for each visit day are required.

2. Print two 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 snap freezing, document 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 IMPAACT 2000 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>PID #</th>
<th>IMPAACT 2000</th>
<th>Specimen Date</th>
<th>Study Day</th>
<th>Specimen Type</th>
<th>Vial #5</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>
<th>Pre-printed Specimen Label</th>
<th>LDMS Label</th>
</tr>
</thead>
</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>PID #</th>
<th>IMPAACT 2000</th>
<th>Specimen Date</th>
<th>Study Day</th>
<th>Specimen Type</th>
<th>Vial #5</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>
</table>

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

<table>
<thead>
<tr>
<th>PID #</th>
<th>IMPAACT 2000</th>
<th>Specimen Date</th>
<th>Study Day</th>
<th>Specimen Type</th>
<th>Vial #5</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>
</table>

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