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

DAIDS ES #11948

This file contains the current IMPAACT P1114 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #3, dated 13 January 2015
- Letter of Amendment #1, dated 03 November 2014
- Clarification Memorandum #2, dated 07 April 2014
- Clarification Memorandum #1, dated 14 November 2013
- Protocol Version 1.0, dated 19 August 2013
Clarification Memorandum #3 for:

**IMPAACT P1114**

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

Version 1.0, dated 19 August 2013

**DAIDS ES # 11948**

Clarification Memo Date: 13 January 2015

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**Summary and Rationale of Clarification**

*Fever Grading:* For consistency of data, a note has been added to Table 3 (Fever Grading: Temperature Measurement) specifying that the Fahrenheit scale should be used when recording fever temperatures on case report forms (CRFs) and assigning fever grades.

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**Implementation**

Institutional Review Board (IRB) approval of this Clarification Memorandum (CM) is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs for their information or, if required by the IRBs, for their approval prior to implementation.

The clarification included in this memorandum will be incorporated into the next full protocol amendment.

The detailed modification of the protocol text is indicated below using strikethrough for deletions and bold type for additions.

**Clarification of Temperature Scale for Recording and Grading Fevers**

8.4.2  Fever Grading: Temperature Measurement

**Table 3: P1114-specific Fever Grading: Temperature Measurement for Infants and Children in study***

<table>
<thead>
<tr>
<th>Severity</th>
<th>Defined</th>
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<tbody>
<tr>
<td>Grade (0)</td>
<td>$\geq 100.0^\circ\text{F} \text{ but } &lt;100.4^\circ\text{F}$ ($\geq 37.8^\circ\text{C} \text{ but } &lt;38^\circ\text{C}$) temporal without confirmatory rectal</td>
</tr>
<tr>
<td>Grade (1)</td>
<td>$\geq 100.4^\circ\text{F} \text{ but } \leq 101.4^\circ\text{F}$ ($\geq 38^\circ\text{C} \text{ but } \leq 38.6^\circ\text{C}$)</td>
</tr>
<tr>
<td>Grade (2)</td>
<td>$\geq 101.5^\circ\text{F} \text{ but } \leq 102.4^\circ\text{F}$ ($\geq 38.7^\circ\text{C} \text{ but } \leq 39.1^\circ\text{C}$)</td>
</tr>
<tr>
<td>Grade (3)</td>
<td>$\geq 102.5^\circ\text{F} \text{ but } \leq 104.8^\circ\text{F}$ ($\geq 39.2^\circ\text{C} \text{ but } \leq 40.5^\circ\text{C}$)</td>
</tr>
<tr>
<td>Grade (4)</td>
<td>$\geq 104.9^\circ\text{F}$ ($\geq 40.6^\circ\text{C}$)</td>
</tr>
</tbody>
</table>

*When recording fever temperatures on CRFs and assigning fever grades, the Fahrenheit scale should be used.*
Letter of Amendment #1 for:

IMPAACT P1114
A Phase I Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine RSV cps2, Lot RSV#005A, Delivered as Nose Drops to RSV-Seronegative Infants and Children 6 to 24 Months of Age
Version 1.0, dated 19 August 2013

DAIDS ES # 11948

Letter of Amendment Date: 03 November 2014

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**Information/Instructions to Study Sites from the Division of AIDS**

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1114 study and must be submitted to site Institutional Review Boards (IRBs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining IRB/EC approval and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA, including use of revised site-specific informed consent forms for newly enrolled participants. Unless directed by site IRBs/ECs, re-consenting is not required for current study participants.

Upon receiving IRB approval, study sites must submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1114.

If the IMPAACT P1114 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

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Summary of Modifications and Rationale

1. *Updates to the protocol team roster:* Alexandria DiPerna replaced Barbara Heckman as the Protocol Data Manager, Charlotte Perlowski was added as a Clinical Trials Specialist, and Rachael Henderson was added as a Laboratory Data Manager.

2. *Addition of information to Section 4.2.4.6 regarding early unblinding of a limited group of Protocol Safety Review Team (PSRT) members:* Section 4.2.4.6 has been updated to specify that the Protocol Statistician, Protocol Vice Chair, and the two Scientific Investigators of the Laboratory of Infectious Diseases (LID) will be unblinded at the end of the Post-Acute Phase for the last subject enrolled in each calendar year.

3. *Revision to Section 8.8.2 to indicate that the Protocol Chair is responsible for reporting to the Data and Safety Monitoring Board (DSMB)*

Implementation

Modifications of protocol text are shown below, using strikethrough for deletions and bold type for additions. The individual modifications are presented per the order listed above.

**Revision 1: Updates to the protocol team roster**

*Cover page:*

Clinical Trials Specialists: Megan Valentine, MPA  
Charlotte Perlowski, MSPH

*Protocol team roster:*

**Clinical Trials Specialists**

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**Protocol Data Manager**

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4.2.4.6 Blinding/Unblinding

The vaccine will be prepared as instructed in the site pharmacy with the pharmacist serving as the unblinded dispenser. A copy of the randomization code will be retained by the unblinded dispenser. Without the Protocol Chair’s written request to unblind, the randomization code will not be released to the clinical staff until the end of the RSV season, when notified by the study team. The IMPAACT Unblinding SOP (# SDM-4001-01) will be followed.

If the need arises to unblind a specific subject’s assignment in the event of a serious illness prior to completion of the acute observation phase, the IMPAACT SOP for unblinding will be followed. In the event that unblinding is required, only that specific subject’s assignment will be unblinded. Whenever possible, the Protocol Chair will make a decision regarding early unblinding in collaboration with the DSMB. The Sponsor and the DSMB Executive Secretary will also be notified of the event in real time. We will follow IMPAACT SOP for unblinding if necessary.

A subset of protocol team members limited to the Protocol Statistician, Protocol Vice Chair, and the two Scientific Investigators of the Laboratory of Infectious Diseases will be unblinded at the completion of the Post-Acute Phase of follow-up (Day 56) for the last subject enrolled in each calendar year to enable more efficient and timely study evaluation and planning for appropriate next steps with respect to RSV candidate vaccine development.
Revision 3: Updates to Section 8.8.2

8.8.2 Serious Adverse Event Review

All serious adverse events, LRIs, unanticipated problems and all IND Safety Reports will be reported by the Sponsor Clinical Safety Office Protocol Chair to the DSMB at the same time they are submitted to the IND Sponsor or FDA.
Summary and Rationale of Clarifications

1. **Updates to the NIAID Medical Officer and Clinical Trials Specialist roles:** The NIAID Medical Officer has been updated from Paul Sato to Devasena Gnanashanmugam on both the cover page and in the Protocol Team Roster. The Clinical Trials Specialist has been updated from Mwenda Kudumu to Megan Valentine on both the cover page and in the Protocol Team Roster.

2. **Ordering Vaccine or Placebo:** In section 4.2.4.1, the language that a site must identify an eligible subject before requesting shipment of vaccine/placebo has been clarified to indicate that a site must identify a “potentially” eligible subject prior to requesting shipment of vaccine/placebo. This is consistent with the intent of this section and with the procedures/operations followed for shipment of product since study start.

3. **Inclusion and Exclusion Criteria:** The numbering for individual criteria in section 5.3 has been corrected.

4. **RSV Antibody Testing:** As described in section 4.2.6.1 of Version 1.0 of P1114, the expectation is that nasal washes be obtained at sick visits for RSV viral detection and quantification only, not for RSV antibody testing. To maintain internal consistency, the indication of saving a sample for antibody testing at sick visits was removed from Appendix 1A.

**Implementation**

IRB approval of this CM is not required by the sponsor prior to implementation; however, sites may submit it to the IRBs/ECs for this information or, if required by the IRBs/ECs, for their approval prior to implementation.

The clarifications included in this CM, specified below, will be incorporated into the next full protocol amendment.

Detailed modifications of the protocol text are indicated below using strikethrough for deletions and bold type for additions. The individual modifications are detailed below and presented per the order listed above.
Revision 1: Updates to NIAID Medical Officer and Clinical Trials Specialist roles

Cover page:
NIAID Medical Officer: Paul Sato, MD, MPH Devasena Gnanashanmugam, MD
Clinical Trials Specialist: Mwenda Kudumu Megan Valentine, MPA

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Maternal, Adolescent and Pediatric Research Branch
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Revision 2: Ordering Vaccine or Placebo
4.2.4.1 Study Drug Regimen and Administration

Vaccine: Vaccine virus for this protocol will be stored at an approved NIH repository until the site has identified the first potentially eligible subject. Once the first potentially eligible subject is identified, the site can request shipment of vaccine/placebo for the anticipated number of enrollees.
Revision 3: Inclusion and Exclusion Criteria

5.3.1 Inclusion Criteria

5.23.1.1. As ≥6 to <25 months of age at the time of enrollment/immunization.

5.23.1.2. Parents/guardians who demonstrate their understanding of the study (by taking a multiple choice questionnaire), sign the informed consent, and agree to vaccine administration following detailed explanation of the study.

5.23.1.3. Seronegative for RSV antibody, defined as a serum RSV neutralizing antibody titer <1:40 as determined within 42 days prior to enrollment/immunization.

5.23.1.4. Subject’s history has been reviewed and subject has undergone a physical examination indicating that s/he is in good health.

5.23.1.5. In the view of the site investigator, the subject has received routine immunizations appropriate for their age.

5.23.1.6. Subject is expected to be available for the duration of the study.

5.23.1.7. For children born to HIV-infected women: two negative PCR tests with one collected when >1 month of age and one collected when >4 months old, and no positive HIV PCR test; or two negative HIV antibody tests.

5.3.2 Exclusion Criteria

5.23.2.1. Known or suspected impairment of immunological functions or HIV infection.

5.23.2.2. Receipt of immunosuppressive therapy including systemic corticosteroids within 30 days of study entry. NOTE: Topical steroids, topical antibiotic and topical antifungal medications are acceptable within 24 hours of enrollment. May be reassessed after symptoms have resolved.

5.23.2.3. Bone marrow/solid organ transplant recipients.

5.23.2.4. Major congenital malformations, including congenital cleft palate, cytogenetic abnormalities, or serious chronic disorders.

5.23.2.5. Previous immunization with an RSV vaccine or previous receipt of or planned administration of any anti-RSV antibody product.

5.23.2.6. Previous serious vaccine-associated AE or anaphylactic reaction.

5.23.2.7. Known hypersensitivity to any vaccine component.

5.23.2.8. Lung or heart disease, including any wheezing event or reactive airway disease. Subjects with clinically insignificant cardiac abnormalities requiring no treatment may be enrolled. Subjects who had one episode of wheezing or received bronchodilator therapy for a single episode of illness in the first year of life but who have not had any additional wheezing episodes or bronchodilator therapy for at least 12 months may also be enrolled.

5.23.2.9. Member of a household that includes an infant less than 6 months of age.

5.23.2.10. Member of a household which contains an immunocompromised individuals (including, but not limited to: those with HIV related immunodeficiency, defined as CD4<300, or <15% if <5 years of age, measured within the previous 6 months; or any household members who
have received chemotherapy within the last 12 months). Verbal report is sufficient documentation if the parent/guardian is confident of history.

5.23.2.11. Attends day care with infants less than 6 months of age, and whose parent/guardian is unable or unwilling to suspend daycare for 14 days following immunization. Children who attend facilities that separate children by age and minimize opportunities for transmission of virus through direct physical or aerosol contact are acceptable.

5.23.2.12. Fever (rectal temperature of ≥100.4°F (38°C)), or upper respiratory illness (rhinorrhea, cough, or pharyngitis) or nasal congestion significant enough to interfere with successful vaccination, or otitis media.

5.23.2.13. Subject has received any killed vaccine or live attenuated rotavirus vaccine within the last 2 weeks, any other live vaccine within the last 4 weeks, or gamma globulin (or other antibody products) within the past 3 months or is scheduled to receive any immunization in the 28 days after enrollment.

5.23.2.14. Receipt of another investigational vaccine or investigational drug within 28 days of receiving this investigational RSV vaccine.

5.23.2.15. Subject has received antibiotics or systemic or nasal steroid therapy or other prescription medications for acute illness within 3 days of study entry. Permitted concomitant medications include nutritional supplements, medications for gastroesophageal reflux, eye drops, and topical medications, including (but not limited to) topical steroids, topical antibiotics, and topical antifungal agents.

5.23.2.16. Subject has received salicylate (aspirin) or salicylate-containing products within the past month.

5.23.2.17. Infants born at <37 weeks gestation and less than 1 year of age.

Revision 4: RSV Antibody Testing

APPENDIX 1A: Screening, Acute Phase (Study Days 0 to 28), and Post-Acute Phase (Study Days 29 to 56) SCHEDULE OF EVALUATIONS

See end of document for the LoA #1 update to the Schedule of Evaluations: The “X” in the “Nasal wash for antibody” row and “Sick Visit” column has been removed.
APPENDIX 1A: Screening, Acute Phase (Study Days 0 to 28), and Post-Acute Phase (Study Days 29 to 56)

SCHEDULE OF EVALUATIONS

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<td>Interim History</td>
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<td>Vaccine administered \textsuperscript{2,3}</td>
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<td>Blood for immunologic assays \textsuperscript{5}</td>
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<tr>
<td>Nasal wash for antibody</td>
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<tr>
<td>Nasal wash for viral detection &amp; quantification \textsuperscript{6}</td>
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<td>TOTAL BLOOD VOLUMES \textsuperscript{5}</td>
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\textsuperscript{a} = 7 days,
\textsuperscript{b} = 2 days,
\textsuperscript{c} = 4 days,
\textsuperscript{d} = 1 day,
\textsuperscript{e} = 1 day,
\textsuperscript{f} = 1 day,
\textsuperscript{g} = 1 day,
\textsuperscript{h} = 1 day,
\textsuperscript{i} = 1 day,
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\textsuperscript{k} = 1 day,
\textsuperscript{l} = 1 day,
\textsuperscript{m} = 1 day,
To: IMPAACT Principal Investigators and Study Coordinators at Sites Participating in IMPAACT P1114

From: IMPAACT P1114 Protocol Team

Date: November 14, 2013

Re: Clarification Memo #1 for Protocol P1114, Version 1.0, dated August 19, 2013, entitled "A Phase I Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine RSV cps2, Lot RSV#005A, Delivered as Nose Drops to RSV-Seronegative Infants and Children 6 to 24 Months of Age" (A companion protocol to CIR Protocol Number: CIR285)

This is Clarification Memo #1 for IMPAACT P1114, Version 1.0, dated August 19, 2013. This Memo can be obtained from the P1114 protocol-specific web page (PSWP) (http://www.impaactgroup.org). Enter the Member/MIS area using your individual username and password. Search for the study number. From the P1114 web page you will have the option to click the PSWP tab. The document is located under the section titled Current Protocol Related Documents.

This memo serves to clarify the following:

1. Remove the word “Rectal” from the title of section 8.4.2 on page 47 of the protocol. The correct title for section 8.4.2 is: “Fever Grading: Temperature Measurement”. The fever grading applies to both temporal and rectal temperature readings.

2. Remove the word “Rectal” from the title of table 3 on page 47. The correct title for table 3 is: “P1114-Specific Fever Grading: Temperature Measurement for Infants and Children in study”.

3. Change the definition of Grade (0) in table 3 on page 47 to read:
   ≥ 100.0°F but < 100.4°F (≥ 37.8°C but < 38°C) temporal without confirmatory rectal

4. Clarify protocol’s day 22-27 visit:
   This visit should represent a phone visit on day 22, 23, 24, 25, 26, and 27, not one visit over the course of this time frame.
   In order to address this please do the following:
   a. Complete a phone visit on each day (22, 23, 24, 25, 26, and 27)
   b. Go to the forms management utility on the portal and follow the day 22-27 visit and CRF completions for each of these study visits.
5. Add the following bolded text and parentheses to section 5.2.2.12 on page 37, to clarify that the term “significant enough to interfere with successful vaccination” refers to nasal congestion and not rhinorrhea. The revised section should read:

5.2.2.12 Fever (rectal temperature of ≥100.4°F (38°C)), or upper respiratory illness (rhinorrhea, cough, or pharyngitis), or nasal congestion (that is significant enough to interfere with successful vaccination), or otitis media.

This clarification will be included in the next version of the protocol when it is amended. The CRF will be updated to reflect this information in time for the next enrollment period. Please contact the protocol team at impaact.teamp1114@fstr.org if you have any questions. Thank you for your interest in IMPAACT P1114.

Sincerely,

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

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

Sponsored by:
Regulatory Compliance and Human Subjects Protection Branch (RCHSPB)
Division of Clinical Research (DCR) / Office of the Director (OD)
The National Institute of Allergy and Infectious Diseases (NIAID)
and
The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

IND# 15284

The IMPAACT Vaccines Scientific Committee Chair:
Coleen K. Cunningham, MD

Protocol Chair: Coleen K Cunningham, MD
Protocol Vice Chair: Ruth Karron, MD
NIAID Medical Officer: Paul Sato, MD
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Clinical Trials Specialist: Mwenda Kudumu, BS

Version 1.0
FINAL
August 19, 2013
IMPAACT P1114 PROTOCOL TEAM ROSTER

All questions concerning this protocol should be sent via e-mail to impaact.teamp1114@fstrf.org. Remember to include the subject’s PID when applicable. The appropriate team member will respond to questions via e-mail with a “cc” to impaact.teamp1114@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail protocol@tech-res.com or call 301-897-1707. Protocol registration material should be submitted via the DAIDS Protocol Registration System (DPRS): https://daidses.niaid.nih.gov/protocolregistration or can be sent via e-mail to epr@tech-res.com. For EAE questions, e-mail DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 1-301-897-1709 or fax 1-800-275-7619 or 301-897-1710. For randomization or enrollment questions, contact the Data Management Center at 716-834-0900 or by email at rando.support@fstrf.org.

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<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
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<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AGM</td>
<td>African green monkey</td>
</tr>
<tr>
<td>cDNA</td>
<td>complementary deoxyribonucleic acid</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>CRL</td>
<td>Charles River Laboratories</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
</tr>
<tr>
<td>EL</td>
<td>Experimental Lot</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>F protein</td>
<td>fusion protein (of RSV)</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FSTRF</td>
<td>Frontier Science and Technology Research Foundation, Inc</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
</tr>
<tr>
<td>β-HCG</td>
<td>human chorionic gonadotropin</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</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>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IFN</td>
<td>Interferon</td>
</tr>
<tr>
<td>IgA, IgG, IgE</td>
<td>immunoglobulin A, G, E</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>L-15</td>
<td>Leibovitz-15 medium</td>
</tr>
<tr>
<td>LID</td>
<td>Laboratory of Infectious Diseases</td>
</tr>
<tr>
<td>LRI</td>
<td>lower respiratory illness</td>
</tr>
<tr>
<td>LRT</td>
<td>lower respiratory tract</td>
</tr>
<tr>
<td>MOP</td>
<td>Manual of Operations</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>OHHRP</td>
<td>Office for Human Research Protections</td>
</tr>
<tr>
<td>ORF</td>
<td>open reading frame</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>Patient Identification number</td>
</tr>
<tr>
<td>r</td>
<td>Recombinant</td>
</tr>
<tr>
<td>RCHSPB</td>
<td>Regulatory Compliance and Human Subjects Protection Branch</td>
</tr>
<tr>
<td>RSV</td>
<td>respiratory syncytial virus</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SDAC</td>
<td>Statistical &amp; Data Analysis Center, Harvard School of Public Health</td>
</tr>
<tr>
<td>SGH</td>
<td>Syrian golden hamster</td>
</tr>
<tr>
<td>SPG</td>
<td>sucrose-phosphate-glutamate buffer</td>
</tr>
<tr>
<td>SUSARs</td>
<td>Serious, unexpected, suspected adverse reactions</td>
</tr>
<tr>
<td>UP</td>
<td>Unanticipated Problem</td>
</tr>
<tr>
<td>URI</td>
<td>upper respiratory illness</td>
</tr>
<tr>
<td>URT</td>
<td>upper respiratory tract</td>
</tr>
<tr>
<td>wt</td>
<td>wild-type</td>
</tr>
</tbody>
</table>
A Phase I Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-Attenuated Respiratory Syncytial Virus Vaccine RSV cps2, Lot RSV#005A, Delivered as Nose Drops to RSV-Seronegative Infants and Children 6 to 24 Months of Age

1.0 PROTOCOL SUMMARY

Number of Subjects: Approximately 51 healthy RSV-Seronegative Infants and Children ≥6 to <25 months of age.

Study Design: A double-blind, randomized, placebo-controlled study design will be used to evaluate the safety and immunogenicity of the vaccine in seronegative infants and children.

<table>
<thead>
<tr>
<th>Table 1: Immunization Schedule</th>
</tr>
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<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td>Seronegative infants &amp; children ages ≥6 to &lt;25 months</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*plaque forming units

This protocol is a companion study to CIR 285; a study being conducted by the Center for Immunization Research (CIR, Johns Hopkins, Baltimore), and the Laboratory of Infectious Diseases (NIAID, Bethesda). The protocols have identical primary and secondary objectives; immunization schedules; evaluation assays and schedules; safety monitoring and reporting. The protocols will vary slightly in site selection requirements, eligibility requirements and site monitoring. These are all operational issues modified to account for the IMPAACT sites’ operations and infrastructure.

Study Duration: Children will be enrolled in the protocol outside of RSV season (April 1-October 14) and will remain on study until they complete the post RSV season visit between April 1-30, in the calendar year following enrollment. For example, a child enrolled on October 14, 2013 will remain on study approximately 6 months (completing a final visit in April 2014) while a child enrolled April 1, 2014 will remain on study approximately 12 months (completing study in April 2015).

---

1 Seronegativity refers to RSV antibody status throughout the protocol and informed consent documents.
2.0 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Epidemiology, Disease Burden, and the Need for a Vaccine

Human respiratory syncytial virus (RSV) is the most common viral cause of serious acute lower respiratory illness (LRI) in infants and children under 5 years of age worldwide. [1] In the United States alone, RSV is responsible for 75,000-125,000 hospitalizations of infants yearly [2], and worldwide, RSV infects at least 34 million children under 5 years, with an estimated 3.4 million RSV LRI hospitalizations and 66,000 to 199,000 RSV-attributable deaths each year. [1] In temperate climates, annual RSV epidemics occur in late winter and early spring, and nearly all children are infected within the first 2 years of life. RSV illness can range from mild upper respiratory tract illness (URI) including rhinitis, pharyngitis, and coryza to severe LRI including bronchiolitis and pneumonia. Beyond the acute burden of disease caused by LRI, severe RSV disease in infancy may predispose to reactive airways disease during childhood. [3,4]

RSV is an enveloped RNA virus that is a member of the Paramyxoviridae family, genus Pneumovirus. [5] RSV has a single negative-sense strand RNA genome of 15.2 kilobases encoding 10 mRNAs. Each mRNA encodes a single protein, with the exception of the M2 mRNA, which contains 2 overlapping open reading frames (ORFs). The 11 RSV proteins are: the viral RNA-binding nucleocapsid protein N, the phosphoprotein P, the large polymerase protein L, the attachment glycoprotein G, the fusion glycoprotein F, the small hydrophobic surface glycoprotein SH, the internal matrix protein M, the 2 nonstructural proteins NS1 and NS2, and the M2-1 and M2-2 proteins encoded by the M2 mRNA. The gene order is: 3'-NS1-NS2-N-P-M-SH-G-F-M2-L-5'. RSV transcription and genome replication take place exclusively in the cytoplasm and virions form by budding from the apical plasma membrane of respiratory epithelial cells.

Currently, no licensed vaccine against RSV is available, although there is broad consensus that such a vaccine is urgently needed and should be a global health priority. Although passive immunoprophylaxis with the monoclonal RSV neutralizing antibody palivizumab is available for high-risk infants, this approach is not feasible for general use. A formalin-inactivated vaccine against RSV was evaluated clinically in the 1960s and did not confer protection; instead, disease enhancement following infection of vaccinees with wild-type (wt) RSV was observed. [6] Studies in experimental animals established that disease enhancement was specific to non-replicating RSV vaccines and not seen with infectious RSV or replicating vaccine vectors. [5]
Following the failure of the formalin-inactivated RSV vaccine, attempts at developing RSV vaccines at NIAID have focused largely on live-attenuated approaches. [7] Importantly, over a period of over 20 years, a number of live-attenuated investigational RSV vaccines have been evaluated in RSV-naïve infants and children, and enhanced disease following wt RSV infection of vaccinees has not been observed. [8] Apart from the absence of enhanced disease, live-attenuated RSV vaccines have a number of known advantages over non-replicating RSV vaccines: they can be administered intranasally, induce protective mucosal immunity in the respiratory tract as well as systemic immunity, infect in the presence of maternally-derived RSV serum antibody, and are well tolerated and immunogenic when administered to infants as young as 4 weeks of age. [9]

Human RSV has a single serotype with 2 antigenic subgroups, A and B. The 2 subgroups exhibit a 3- to 4-fold reciprocal difference in neutralization by polyclonal convalescent serum. Analysis of glycoprotein-specific responses in infants by enzyme-linked immunosorbent assay (ELISA) with purified F and G glycoproteins showed that the F proteins were 50% related antigenically and the G proteins were 7% related. [10] Consistent with this level of antigenic relatedness, F protein expressed by a recombinant vaccinia virus was equally protective in cotton rats against challenge with either subgroup A or B, whereas the G protein was 13-fold less effective against the heterologous subgroup. [11] Thus, the F protein is responsible for most of the observed cross-subgroup neutralization and protection, and a subgroup A vaccine virus is likely to induce a broad immune response against wt RSV of either subgroup. [11]

The RSV vaccine to be evaluated in this protocol was derived using a recombinant DNA-based technique called reverse genetics. [12] The technique of reverse genetics has been used to produce a number of licensed vaccines; among them, FluMist, the live-attenuated influenza vaccine currently licensed for adults and children. This technique allows de novo recovery of infectious virus entirely from cDNA in a qualified cell substrate under defined conditions. Reverse genetics provides a means to introduce predetermined mutations into the RSV genome via the cDNA intermediate. Specific attenuating mutations were characterized in preclinical studies and combined to achieve the desired level of attenuation of this investigational vaccine. Derivation of vaccine virus from cDNA minimizes the risk of contamination with adventitious agents and helps to keep the passage history brief and well documented. Once recovered, the vaccine virus is propagated in the same manner as a biologically derived virus. As a result of repeated passage and
amplification, the drug substance (clinical trials material) does not contain any recombinant (rDNA). This vaccine is a derivative of strain A2, subgroup A, and is a genetically stabilized version of rA2cp248/404/1030ASH, the most promising live-attenuated RSV vaccine candidate identified to date.

rA2cp248/404/1030ASH contains 5 independent attenuating elements that were identified in biologically-derived viruses or created by reverse genetics and subsequently combined: (i) a set of five amino acid substitutions in the N, F, and L proteins that were identified in a cold-passaged (cp) RSV (V267I in N, E218A and T523I in F, and C319Y and H1690Y in L [13-15]), (ii) "248", an amino acid substitution in the L protein (Q831L [13,16,17]), (iii) "404", a nucleotide substitution at position 9 in the M2 gene start signal [17-19], (iv) "1030", another amino acid substitution in the L protein (Y1321N), and (v) an SH gene deletion (nucleotides 4210-4628) that was slightly attenuating in chimpanzees [1,11,20]. The original “248”, "1030", and “404” designations were based on plaque number during the original isolation of the mutants rather than on sequence position. These mutations have been evaluated in detail, including in studies in seronegative chimpanzees, the only animal model that approaches humans in permissiveness for RSV replication. [13,14,17,21,22] The "248", "404" and "1030" mutations each render RSV temperature sensitive (ts): individually, they shift the shutoff temperature from >40ºC for wild-type (wt) RSV to 38ºC for "248" and "1030" [13,19,22,23] or 37ºC for "404".[22] The cp and ΔSH mutations also are attenuating [20,24], but do not confer a ts phenotype to RSV. The combination of these five independently attenuating elements by reverse genetics resulted in the highly attenuated and highly temperature sensitive vaccine candidate rA2cp248/404/1030ASH, with a shutoff temperature of 35-36ºC.

The original version of the rA2cp248/404/1030ASH vaccine candidate was evaluated in RSV-naïve 1-2 month old infants by Karron et al., 2005 [9], and was well-tolerated, moderately immunogenic, and protective against a second vaccine dose. Analysis of specimens recovered from nasal washes in the days following vaccination showed that approximately one-third of the isolates exhibited a partial loss of the ts phenotype. [9,25] Sequence analysis of a limited number of the recovered isolates identified two types of genetic changes, namely loss of the “248” attenuating assignment (L amino acid 831), or loss of the “1030” mutation (L amino acid 1321), with the majority of the changes involving the latter position. [9,25] The wt assignment at amino acid 1321, tyrosine (TAT), and the ts/attenuating “1030” mutation, asparagine (AAT), differ by a single nucleotide (underlined). In the instances of reversion at this position in
clinical trial specimens, the mutant assignment of asparagine (AAT) was changed to the wt assignment of tyrosine (TAT) in a number of cases, as well as to histidine (CAT) in one case. [9] Reversion to the wt assignment clearly could account for the partial loss of the ts phenotype. The same may also be true for the single instance of change to histidine.

A second version of the rA2cp248/404/1030ΔSH virus is presently being evaluated in a clinical trial by Medimmune, under a Cooperative Research and Development Agreement (CRADA) with LID, NIAID, NIH (ClinicalTrials.gov identifier NCT00767416). This virus was designated MEDI-559 by Medimmune, and hereafter will be called Medi-559. Both the rA2cp248/404/1030ΔSH virus tested by Karron et al. and MEDI-559 contain the cp, 248, 404, 1030, and ΔSH mutations. These two versions differ by 37 point mutations throughout the genome that are silent at the amino acid level and are considered inconsequential (Appendix 3; Table 7). These include differences due to naturally occurring variability in wt virus and in some cases due to the presence or absence of added restriction sites or sequence tags. In addition, the “248” mutation (Q831L) is specified by the codon TTA in MEDI-559 and by the codon CTG in the version of rA2cp248/404/1030ΔSH used in the clinical study described by Karron et al. (Appendix 3; Table 8, [9]) No differences have been identified between the two versions with regard to virus replication, ts and attenuation phenotypes, or other biological properties.

The vaccine virus to be tested under this clinical protocol, designated cps2, contains cp, 248, 404 and 1030 point mutations and has a deleted SH gene. Compared to the rA2cp248/404/1030ΔSH virus, cps2 shows a moderate increase in stabilization of the 248 mutation and complete stabilization of the 1030 mutation. Additional details are provided in Section 2.3.

2.2 Experimental Vaccines against Respiratory Syncytial Virus

Efforts have been directed toward the development of a live-attenuated RSV vaccine because of the advantages of live-attenuated vaccines over inactivated or subunit vaccines, including the ability to: (i) induce the full spectrum of protective immune responses including serum and local antibodies as well as CD4+ and CD8+ T cells and innate immunity; (ii) infect and replicate in the presence of maternal antibody permitting immunization of young infants; and (iii) produce an acute, self-limited, attenuated infection that is well tolerated and readily eliminated from the respiratory tract. Another important advantage is the absence of vaccine-related enhanced disease, as has been confirmed in clinical studies. [8]
Several live-attenuated RSV vaccines have been evaluated in clinical trials in adult and pediatric populations as part of NIAID's ongoing RSV vaccine development program. All of these trials have been published in peer-reviewed journals [9,20,26,27]. Here, only the findings obtained with the two RSV vaccine viruses that are closest to the drug substance to be tested under this clinical protocol will be summarized, i.e., findings from the clinical trials of rA2cp248/404ΔSH and rA2cp248/404/1030ΔSH. Additional details of these studies can be found in the Investigators’ Brochure.

The rA2cp248/404ΔSH and rA2cp248/404/1030ΔSH investigational vaccines share 4 attenuating genetic elements and differ only by a single amino acid substitution in the L polymerase protein (the 1030 substitution) that creates an additional, fifth attenuating element in rA2cp248/404/1030ΔSH. Both vaccines were highly attenuated in adults and RSV seropositive children and were well tolerated and immunogenic in RSV seronegative children. Although both rA2cp248/404ΔSH and rA2cp248/404/1030ΔSH readily infected RSV seronegative children, the level of viral replication differed significantly. The mean peak titer shed by recipients of the $10^{5.0}$ PFU dose of rA2cp248/404ΔSH was approximately 50-fold greater than that shed by recipients of the $10^{5.3}$ PFU dose of rA2cp248/404/1030ΔSH ($10^{4.3}$ vs. $10^{2.5}$ PFU/mL, respectively; $P=0.009$).[9] The replication of rA2cp248/404ΔSH was not significantly different in RSV seronegative children than replication of the previously evaluated cpts248/404 vaccine. Since cpts248/404 was associated with nasal congestion in young infants [26], rA2cp248/404ΔSH was not evaluated in this age cohort. However, compared with the level of replication of rA2cp248/404ΔSH, replication of the rA2cp248/404/1030ΔSH vaccine was restricted in RSV seronegative children (mean peak titer, $10^{4.3}$ vs. $10^{2.5}$ PFU/mL, respectively), indicating that the 1030 mutation had a potent attenuating effect. For this reason, rA2cp248/404/1030ΔSH was subsequently evaluated in 1- to 2-month-old infants.

Although rA2cp248/404/1030ΔSH was well tolerated in infants, only 44% of those who received 2 $10^{5.3}$ PFU doses of vaccine had detectable antibody responses. However, replication of the second dose of vaccine was highly restricted, indicating that protective immunity was induced. [9] These results indicate that rA2cp248/404/1030ΔSH is the first RSV vaccine candidate to be sufficiently attenuated in 1- to 2-month-old infants, the target population for a pediatric RSV vaccine.
As noted above, MedImmune is currently evaluating a second version of the rA2cp248/404/1030∆SH virus called MEDI-559 under a CRADA between MedImmune and the LID/NIAID/NIH. MEDI-559 differs from the rA2cp248/404/1030∆SH virus at 37 nucleotide positions. However, rA2cp248/404/1030∆SH and MEDI-559 have been indistinguishable in preclinical studies, and it is not anticipated that they will differ in genetic stability (see below). MEDI-559 is currently being evaluated in several hundred RSV-naive children 1 to 23 months of age in a Phase 1/2a study conducted by MedImmune (ClinicalTrials.gov Identifier: NCT00767416). Children in this study were randomized 1:1 to receive 3 doses of vaccine or placebo at 0, 2, and 4 months. Data analysis is currently underway.

While the attenuation characteristics of the rA2cp248/404/1030∆SH vaccines are highly desirable, some phenotypic and genetic instability of the original rA2cp248/404/1030∆SH was observed following replication in RSV naïve children. In approximately 30% of the nasal washes obtained from RSV-naive children, subpopulations of viruses were detected that formed plaques at temperatures (35, 36, or 37°C) which were non-permissive for the parent virus. Sequence analysis demonstrated single nucleotide reversions at the 248 or 1030 loci in 6 of 9 specimens tested. For this reason, NIAID scientists have worked to develop a live attenuated RSV candidate vaccine, based on the sequence of MEDI-559, that retains the attenuation properties of the parent virus but exhibits enhanced genetic stability at the 248 and 1030 loci. That virus, designated RSV cps2, is the candidate vaccine to be evaluated under this protocol.

2.3 Vaccine Description

The Drug Substance RSV cps2 described here is a genetically stabilized version of MEDI-559. Compared to MEDI-559, RSV cps2 has 5 nucleotide differences, and one amino acid difference to increase the genetic stability of this vaccine (Appendix 3; Table 7).

We previously described a strategy to increase the phenotypic and genetic stability of attenuating amino acid substitutions that are based on a single nucleotide substitution, such as the “248” and “1030” mutations [23,28]. This strategy is based on increasing the number of nucleotides that must be changed in a given mutant codon in order to achieve reversion to any amino acid that confers phenotypic reversion of attenuation. This recognizes that nucleotide substitution at any single nucleotide position in RNA viruses can occur with at relatively high rate, ~10⁻⁴, thus providing for relatively frequent reversion if only a single nucleotide is involved. However, if reversion at the amino acid level requires changes at two or, preferably, three positions within the codon, the frequency of reversion would be much less: ~10⁻⁸ and ~10⁻¹², respectively. We used this strategy
to increase the genetic and phenotypic stability of the “1030” and "248" mutations of rA2cp248/404/1030ASH [29]. The resulting cDNA derived vaccine RSV cps2 has five nucleotide changes and one amino acid difference compared to MEDI-559 (Appendix 3: Table 7). Compared to MEDI-559, in the RSV cps2 cDNA, the “248” mutation 831L(TTA) was replaced by the codon 831L(TTG), which had been previously shown to confer increased stability [23], and the “1030” mutation involving 1321N(AAT) was replaced by 1321K(AAA). The amino acid assignment 1321K confers an attenuation/temperature sensitivity phenotype to RSV that is comparable to that of the original mutation "1030" mutation 1321N. In addition, a codon that was subject to second site suppressor mutation, S1313 (AGC), was replaced by S1313 (TCA), which was silent at the amino acid level. Virus was readily recovered and readily replicated to titers in excess of $10^7$ plaque forming units per ml at the permissive temperature of 32°C, comparable to rA2cp248/404/1030ASH and to MEDI-559. It maintained a ts phenotype, with a shut-off temperature of 35-36 °C, and an attenuation phenotype in mice.

To generate a cps2 RSV antigenomic cDNA containing the 5 nucleotide changes noted above, the antigenomic cDNA of MEDI-559 was modified by site directed mutagenesis. The resulting plasmid, designated pRSV cps2, was used for the recovery of the drug substance at LID/NIAID/NIH [8]. The RSV cps2 seed virus was derived entirely from cloned plasmid cDNA in qualified Vero cells (BB-MF #13008) by LID/NIAID/NIH. Sequence analysis of the seed virus genome indicated that its consensus sequence perfectly matched that of the pRSV cps2 cDNA.

The seed virus was transferred to Charles River Laboratories (CRL). The seed virus passed pre-production final container testing (Sterility, Mycoplasma, and Bacteriostasis/Fungistasis) and was accepted for manufacturing. For the production of the Final Drug Product at CRL, the 143rd passage of Vero cells (BB-MF #11702; Lot #426068-2) was grown in OptiPRO™ SFM. Antibiotics were not used in any stage of cell passage, virus growth, or vaccine development. The virus-containing supernatant was harvested on day 8 post-infection, and clarified by centrifugation. Intact cells were removed by filtration.

Clarified supernatant in 1x SPG (sucrose, 0.218 M; KH$_2$PO$_4$, 0.0038 M; K$_2$HPO$_4$, 0.0072 M; L-Glutamic Acid, 0.0054 M) was dispensed in 0.6 mL aliquots into labeled 2.0 mL cryogenic vials. Vials are snap-frozen and stored at -80°C ± 15°C.

The Final Drug Product is a concentrated suspension of live recombinant RSV cps2 Vero Grown Virus Vaccine (Lot RSV #005A) in Leibovitz L-
15 Medium containing 1X SPG (sucrose, 0.218 M; KH$_2$PO$_4$, 0.0038 M; K$_2$HPO$_4$, 0.0072 M; L-Glutamic Acid, 0.0054 M). The Final Drug Product has a potency of 6.6 ± 0.1 log$_{10}$ PFU/mL and is diluted to dose on site.

The Final Drug Product, RSV cps2, Lot RSV #005A, passed the required safety tests. Sequence analysis confirmed that the working seed virus and Final Drug Product, RSV Lot #005A, were of identical sequence. RSV cps2, Lot RSV #005A was released by CRL for use as an investigational vaccine.

2.4 Preclinical Studies

Two preparations of the drug substance have been evaluated in preclinical studies. The first preparation, designated Seed Lot, was evaluated in vitro for temperature sensitivity and genetic stability, and in mice and in juvenile chimpanzees for its infectivity and attenuation. The second preparation, designated Clinical Lot (CL; GMP) was evaluated in African Green Monkeys (AGMs) only.

2.4.1 In vitro evaluation of RSV cps2

As noted above, RSV cps2 maintained a ts phenotype, with a shut-off temperature of 35-36ºC, and an attenuation phenotype in mice indistinguishable from that of rA2cp248/404/1030ΔSH. To directly evaluate the increased genetic stability of the RSV cps2 virus, it was subjected to an in vitro stress test in parallel with the rA2cp248/404/1030ΔSH virus that had been tested in a clinical study by Karron et al [9] which had exhibited genetic instability in vaccinees. The two viruses were each passaged in ten parallel cultures for two passages each at 33º, 34º, 35º, 36º, and 37ºC. Note that for these viruses, temperatures of 36ºC and higher are restrictive. Following the final passage, the genome regions containing the "248" and "1030" mutations were subjected to sequence analysis. This analysis showed that the "248" mutation (L protein mutation 831L) sustained mutations in each virus, reverting to the wt assignment of glutamine in 9 out of 10 cultures in the case of the rA2cp248/404/1030ΔSH virus and changing to serine in 6 out of 10 cultures in the case of cps2. This serine assignment at position 831 of the L gene specifies a wt phenotype [23], and therefore represents a reversion. It was not surprising to find reversion at position 831 in both viruses, since it was previously shown that the "248" mutation could not be strongly stabilized [23], and since the stress test involved four passages at restrictive temperatures. Overall, the frequency of reversion at the "248" site
was 90% with rA2 cp248/404/1030ΔSH and 60% with RSV cps2. Of note, a reversion of the "248" mutation alone would yield a virus that maintains a high level of attenuation and temperature sensitivity. With regard to the "1030" mutation (L protein amino acid position 1321), the sequence analysis showed that this mutation in the original rA2cp248/404/1030/ΔSH virus (i.e., not stabilized) completely reverted to the wt assignment of tyrosine, while nine of the ten cultures of RSV cps2 at the restrictive temperatures retained the attenuating assignment of lysine. In the remaining culture, 30% of the culture appeared to have the assignment of arginine. However, this assignment was nonviable when introduced into wt RSV [30], and its presence here may represent nonviable virus that is maintained because the high MOI of infection involved in these low-dilution passages allowed complementation by co-infecting functional virus. Thus, the virus with arginine at this position likely is a defective non-replicating particle. The assignment at position 1313 at RSV cps2 also was confirmed to be completely stable during passage, and no other adventitious mutations were observed. In conclusion, these data showed that (i) the "248" mutation was moderately stabilized, with a reduced frequency of detection of revertants, and (ii) the "1030" mutation was completely stabilized against the generation of viable revertants by the alternative amino acids. This is particularly significant because the "1030" mutation exhibited a several-fold higher level of reversion in the previous clinical trial. [9] Thus, this work showed that RSV cps2 is a version of rA2cp248/404/1030ΔSH with substantially increased genetic stability.

2.4.2 Evaluation of the attenuation phenotype of RSV cps2 in experimental animals.

As noted, the mouse model is commonly used to evaluate the replication of RSV variants. The Seed Lot of RSV cps2 was evaluated for its ability to replicate in the upper and lower respiratory tract (URT and LRT, respectively) of mice in comparison to rA2cp248/404/1030ΔSH [9] and to wt RSV rA2. Compared to wt RSV, replication of the Seed Lot of RSV cps2 and of rA2cp248/404/1030ΔSH were restricted below the level of detection in the URT and LRT of mice, due to the high level of attenuation of these viruses. Thus, both viruses are highly attenuated.

For further comparison, the Seed Lot of RSV cps2 was evaluated in juvenile chimpanzees, which among experimental animals evaluated to
date are the most permissive for RSV replication and have the same body temperature as humans, which is critical for evaluation of viruses with a temperature-sensitive phenotype. It was confirmed that the animals were RSV seronegative. Animals were infected by combined intranasal and intratracheal inoculations of 10⁶ PFU per site, and virus shedding in the respiratory tract was evaluated by taking nasal washes daily for 12 days post-infection, bronchioalveolar lavages (BAL) on days 2, 4, 6, and 8, and tracheal lavages on day 10 and 12. Virus titers were determined by plaque assay on Vero cells at 32°C. There were two or three animals in each group (Appendix 3, Tables 9 and 10). MEDI-559 served as a comparator for RSV cps2, since the first version of rA2cp248/404/1030ΔSH was well-tolerated in 1- to 2-month old infants. [9] The nasal wash data are presented in Appendix 3; Table 9, and the BAL and tracheal lavage data are presented in Table 10. This showed that MEDI-559 replicated at a low level over 8-9 days, with virus being detected primarily in the nasal washes. This is consistent with MEDI-559 being a highly attenuated virus, based on our previous analysis of multiple viruses in the chimpanzee model [14,19,31,32]. Importantly, the RSV cps2 virus also was highly attenuated, comparable to MEDI-559.

In summary, RSV cps2, the Drug Substance of this IND, was found to be temperature sensitive and phenotypically and genetically stable in vitro and in non-human primates. RSV cps2 was attenuated in mice and restricted in replication in the respiratory tract of non-human primates. RSV cps2 was immunogenic in chimpanzees, the best animal model for RSV infection and disease. This indicates that the RSV cps2 virus is suitable for evaluation as candidate RSV vaccine in RSV seronegative infants and children.

2.5 Previous Clinical Experience

The live attenuated recombinant RSV cps2 vaccine virus is being evaluated for the first time in humans. However, as noted above, this vaccine is genetically similar and phenotypically identical to the rA2cp248/404/1030ΔSH vaccine, suggesting that it is likely to be attenuated and well tolerated in seronegative children.[9]

2.6 Clinical Development Plan

The investigational RSV vaccine RSV cps2 will be evaluated in RSV seronegative children ≥6 to <25 months of age. The main purpose of this study is to determine whether RSV cps2 vaccine displays the attenuation
characteristics of the rA2cp248/404/1030ΔSH vaccine, but with enhanced genetic stability.

If the investigational vaccine is found to be well-tolerated, infectious, and immunogenic in seronegative infants and children \( \geq 6 \) to \(<25\) months of age, we would plan for a separate phase I clinical trial in infants \(<6\) months of age, since they are at highest risk for severe RSV-associated LRI and are therefore a target population for a live-attenuated RSV vaccine.

The design of subsequent phase 2 studies in the target population has yet to be determined.

2.7 Participation of Children

The vaccine being tested in this protocol has been designed to be administered to children. The safety of the vaccine will be evaluated in RSV seronegative infants and children \( \geq 6 \) to \(<25\) months of age.

2.8 Statement of Compliance

This trial will be conducted in compliance with the protocol, ICH GCP guidelines, U.S. Food and Drug Administration (FDA) guidelines, and applicable IRB guidelines.

3.0 OBJECTIVES

3.1 Primary Objectives

The safety, infectivity, and immunogenicity of a dose of \( 10^{5.3} \) PFU of RSV cps2 Lot RSV #005A will be evaluated in RSV seronegative children and infants. The primary objectives of this study are the following:

Objective 1. To determine the frequency of vaccine-related solicited adverse events (AEs) and unsolicited adverse events (AEs)

Objective 2. To quantify the amount of vaccine virus shed by each vaccine recipient

Objective 3. To determine the number of vaccinated children and infants infected\(^2\) with RSV cps2

Objective 4. To characterize immune responses to the RSV cps2 vaccine, including quantification of the amount of RSV neutralizing antibody and antibody to the RSV F

\(^2\) Infection is defined as recovery of vaccine virus from a nasal wash and/or a \( \geq 4\)-fold rise in neutralizing antibody titer.
glycoprotein induced by the vaccine

Objective 5. To determine the genetic stability of the 248, 404 and 1030 mutations in vaccine virus recovered from nasal washes at the time of peak viral replication and on the last day of replication

3.2 Secondary Objective

To characterize clinical and immune responses in vaccinated seronegative children who experience subsequent natural infections with wild-type RSV

4.0 STUDY DESIGN SUMMARY

4.1 Summary

The study will be conducted in infants and children at the Johns Hopkins University Center for Immunization Research (CIR) in Baltimore, MD, and at selected IMPAACT sites in the United States. The vaccine will be evaluated in RSV seronegative (i.e. RSV-naïve) 6 to < 25-month-old infants and children. For the purpose of this study, RSV seronegative is defined as having a serum neutralizing antibody titer of <1:40. This definition has been used in previous evaluations of cpts 248/404, rA2cp248/404/ΔSH, and rA2cp248/404/1030ΔSH in children > 6 months of age. [9,26] In previous studies, live-attenuated RSV vaccines were highly restricted in replication and poorly immunogenic in > 6 month-old children with titers ≥1:40, but were far less restricted in replication and highly immunogenic in children with titers <1:40. These data suggest that in 6- to 24-month-old infants and children, this neutralizing antibody cutoff can distinguish effectively between RSV-experienced and RSV-naïve children.

The study will be double-blind, randomized and placebo-controlled. Approximately 51 RSV seronegative subjects will be randomized at a ratio of 2:1 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. Eligible children will be enrolled until October 14th and then will be followed intensely for 56 days and then monitored through the winter RSV season. Enrollment will resume on April 1st of the following year if the study has not fully accrued.
While some children will be enrolled under the companion study CIR285, all data will be entered into the same database and all subjects, regardless of site of enrollment (or protocol version) will contribute to all study analyses.

4.2 Study Procedures

4.2.1 Recruitment and Enrollment

This is a multi-site study. Subjects will be recruited from outpatient clinics at IMPAACT sites selected on the ability to recruit and enroll in respiratory vaccine studies. Each site will identify the specific clinics where recruitment will occur in their Site Implementation Plan (SIP) which will be reviewed and approved by the protocol team. All recruitment materials must be reviewed and approved by site IRBs.

Enrollment will only occur outside RSV season which, for purposes of this protocol, is defined as October 15 - March 31. While RSV season varies somewhat by geographic location, the range used for this study is expected to be broad enough to encompass the season at all participating sites. Enrollment will resume on April 1st of the following year if the study has not fully accrued.

Study visits, except vaccination, may be performed at one of the clinical sites or as home visits. Inoculation visits must be performed at a clinic site where emergency supplies are available.

4.2.2 Screening Procedures, Informed Consent, Pre-Inoculation Blood Specimen

Healthy infants and children may be screened up to 42 days prior to inoculation to determine serologic eligibility. Enrollment cannot occur until the screening sample confirms that the infant is RSV seronegative and he/she meets all other inclusion/exclusion criteria.

To ensure that the child or infant is in good health and eligible for the study, study staff will complete and document all procedures listed in section 5.1.

A study physician, physician assistant, nurse practitioner, or nurse will inform parents or guardians of any significant abnormal
physical findings and will make appropriate referrals back to the child’s primary care giver, if necessary.

4.2.3 Randomization

On the day of the enrollment (randomization visit) the following procedures will be completed:

- Review the study with parent or guardian and make sure questions are answered.
- Obtain medical history and perform focused physical examination.

Subjects meeting all the inclusion and none of the exclusion criteria can be enrolled in IMPAACT P1114 by utilizing the Subject Enrollment System (SES) located on the IMPAACT DMC website and www.fstrf.org. Subjects will be randomized in a 2:1 ratio of RSV cps2 Lot RSV #005A vs. placebo.

- Administer study immunization (Day 0) as outlined in 4.2.4.

Most children will be randomized and received study treatment on the same day (Day 0) but in the event that randomization occurs but vaccine is not administered immediately, the site has up to 72 hours after randomization to complete the immunization. If this occurs, Day 0 corresponds to the day of immunization.

4.2.4 Vaccine Preparation and Administration

On the day of inoculation, a physical examination or assessment will be performed, and, if the subject is healthy, he/she will receive a single dose of RSV cps2 Lot RSV #005A or placebo. Detailed directions for diluting, labeling and transporting study vaccine are provided in the P1114 Manual of Operations (MOP). Briefly, 0.5 mL of vaccine or placebo in a 1 mL syringe that is labeled with PID number, the date, and time of preparation, and with the label: “FOR INTRANASAL ADMINISTRATION ONLY” will be administered intranasally (approximately 0.25 mL per nostril) within 4 hours from the time of removal from the freezer using a needleless 1mL syringe while the subject is supine. There is no nasal preparation prior to administration and subjects will remain supine for approximately 60 seconds following dosing.
All subjects will receive either a dose of $10^{5.3}$ PFU of vaccine virus or placebo. The randomization system at the DMC assigns a PID number upon a successful enrollment. Using the pharmacy list sent at site registration, by the DMC, the site pharmacist will dispense the treatment regimen corresponding to the PID number. To maintain blinding, the pharmacist preparing the vaccine will not be involved in assessing study outcomes. This designated individual will be unblinded and will prepare vaccine to the indicated dose according to the instructions detailed in the MOP.

**4.2.4.1 Supplies**

**Vaccine**

Vaccine virus for this protocol will be stored at an approved NIH repository until the site has identified the first eligible subject. Once the first eligible subject is identified, the site can request shipment of vaccine/placebo for the anticipated number of enrollees. Procedures for ordering and vaccine shipment are in the MOP.

The Final Drug Product vaccine virus is contained in sterile 2.0 mL cryovials, containing 0.6 mL of live recombinant RSV cps2 Vero Grown Virus Vaccine (Lot RSV #005A), with a titer of approximately $10^{6.6}$ PFU/mL. The Drug Product composition is a concentration of RSV cps2 Vero Grown Virus Vaccine in OptiPro SFM with 1X SPG (sucrose, 0.218 M; KH$_2$PO$_4$, 0.0038 M; K$_2$HPO$_4$, 0.0072 M; L-Glutamic Acid, 0.0054 M). The vaccine virus concentrate is diluted to dose by the site pharmacy as outlined in the MOP. The diluted virus vaccine is intended for intranasal administration of a dose of $10^{5.3}$ PFU in a 0.5 mL volume to 6 to < 25 month-old seronegative infants and children.

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**Live Recombinant Respiratory Syncytial Virus RSV cps2 VERO Grown Virus Vaccine**

| CAUTION: NEW DRUG LIMITED BY FEDERAL (USA) LAW TO INVESTIGATIONAL USE | Date: 23MAY2012 |
| Store at –80°C ± 15°C | Vial # XXXX |
| Charles River Laboratories, Malvern, PA | Lot: RSV #005A |
Vaccine will be stored at the site in a locked –80°C (±15°C) freezer until time of use. If the freezer is not in the pharmacy, there must be restricted access to the freezer and the vaccine must be physically separated from other items in the freezer (e.g. separate shelf).

As described above, the vaccine is supplied as a concentrate that must be diluted to the proper dose prior to administration, using a qualified lot of Leibovitz L-15 medium (a solution with amino acids, sugar and salt) described below. Prior to vaccination, a study Investigator will supply a prescription and a vaccine request form (see the MOP for details) to the pharmacy which will include the protocol number, the vaccine virus name, the lot number, the vaccine titer (concentration), the Investigational New Drug (IND) number, the number of subjects to be vaccinated, and the dilution instructions for the vaccine. As outlined in detail in the MOP, pharmacy personnel will prepare the correct dose of vaccine for each subject in a biosafety hood using aseptic technique. Vaccine will be diluted with a specific lot of Leibovitz L-15 medium that has been safety tested as described in a Master File (BB-MF #12959) that has been submitted to the FDA. The diluted vaccine or placebo will be drawn up to a volume of 0.5 mL in a 1 mL syringe and labeled with the PID number, and with the label: “FOR INTRANASAL ADMINISTRATION ONLY”. The labeled syringes will be transported on wet ice to the vaccination site for administration. Vaccine must be used within 4 hours of being removed from the freezer.

**Placebo**

The vaccine diluent, 1X Leibovitz L-15 medium, is used as the placebo. The study placebo is prepared from a specific lot of concentrated 2X Leibovitz L-15 medium that has been safety tested as described in Master File BB-MF #12959. The concentrated 2X Leibovitz L-15 medium is
also stored at a NIAID-contracted repository and is requested by the pharmacist in the same fashion as the vaccine. Prior to use as vaccine diluent or placebo, 2X Leibovitz medium is mixed 1:1 with sterile water suitable for injection. Vaccine diluent/placebo will be stored at 2°C to 8°C.

4.2.4.2 Vaccine Storage

Vaccine will be stored at the site in a locked freezer until time of use. Vaccine should remain frozen at -80°C ±15°C until just prior to use. Vaccine should never be refrozen for reuse. Once diluted for use, the vaccine must be stored on wet ice and used within 4 hours.

Vaccine diluent/placebo will be stored at 2°C to 8°C. Vaccine and vaccine diluent/placebo should be prepared from new unopened containers for each use. No component should be reused for vaccine or placebo preparation.

4.2.4.3 Vaccine Accountability

The study pharmacist is responsible for maintaining an accurate inventory and accountability record of vaccine supplies for this study. The pharmacist will be responsible for maintaining the blind and pharmacy records will be maintained in the pharmacy only. Partially used vials of vaccine components may not be saved and reused at a later time.

4.2.4.4 Disposition of Used/Unused Supplies

After the pharmacist has diluted the vaccine and drawn up the vaccine into a syringe for administration, they will remove the label from the vaccine vial and place it in the accountability log. In this manner, monitoring personnel will be able to verify the accountability of all vaccine vials used for the study. A sample of undiluted (if available) and diluted vaccine will be aliquoted from vaccine remaining after vaccine has been prepared and delivered to the clinical staff. One 150 microliter aliquot of undiluted leftover vaccine (if available) and three 150 microliter aliquots of diluted leftover vaccine (labeled with diluted/undiluted, date aliquoted and frozen, and PID number) will be frozen (for details, please see MOP) and stored at -80°C (±15),
separate from the study vaccine product in the investigational pharmacy. The aliquots of previously used vaccine (diluted and undiluted) will be batch shipped to Johns Hopkins Bloomberg School of Public Health (see MOP) for re-titration at a later date. Titration of vaccine is done to confirm the titer of the vaccine administered to the subjects. If there is any vaccine left after the syringes have been drawn up and aliquots have been removed for titering, it will be destroyed by pharmacy personnel or sent to the laboratory for destruction. Any unused vaccine will be destroyed by autoclaving or immersion in 10% bleach.

4.2.4.5 Immunization Procedure

All study subjects will receive a single dose of vaccine, administered as nose drops within 3 days (72 hours) of randomization. Vaccine will be kept frozen at -80°C ±15°C until just before use, whereupon it will be thawed and diluted. Vaccine will be kept on wet ice from the time of dilution until delivery to clinical staff for administration. This must occur within 4 hours of thawing. A volume of 0.5 mL will be delivered as nose drops (approximately 0.25 mL per nostril) using a sterile, needle-less 1 mL syringe while the subject is supine. There is no nasal preparation prior to administration and subjects will remain supine for approximately 60 seconds following dosing.

4.2.4.6 Blinding/Unblinding

The vaccine will be prepared as instructed in the site pharmacy with the pharmacist serving as the unblinded dispenser. A copy of the randomization code will be retained by the unblinded dispenser. Without the Protocol Chair’s written request to unblind, the randomization code will not be released to the clinical staff until the end of the RSV season, when notified by the study team. The IMPAACT Unblinding SOP (# SDM-4001-01) will be followed.

If the need arises to unblind a specific subject’s assignment in the event of a serious illness prior to completion of the acute observation phase, the IMPAACT SOP for unblinding will be followed. In the event that unblinding is required, only that specific subject’s assignment will be unblinded. Whenever possible, the Protocol Chair will
make a decision regarding early unblinding in collaboration with the DSMB. The Sponsor and the DSMB Executive Secretary will also be notified of the event in real time. We will follow IMPAACT SOP for unblinding if necessary.

4.2.5 **Randomization and Enrollment**

Approximately 51 seronegative children and infants will be enrolled in the study and will receive either vaccine or placebo in a 2:1 ratio. These numbers were chosen based upon past experience with Phase I evaluation of other live attenuated respiratory virus candidate vaccines [13,14,24]. It is expected that approximately 30 subjects will be enrolled at IMPAACT sites and the remainder will be enrolled at the CIR (Hopkins); however, that distribution may change based on accrual success. Duration of participation in the initial phase of the study is 56 days. Blood and nasal wash specimens will be obtained at day 56 after inoculation to assess immune responses to the vaccine. Additionally, children will be assessed for medically attended respiratory or febrile illnesses or otitis media from the onset to the end of the RSV season following immunization (see Section 7.4). Thus, the duration of participation will be up to 365 days, depending upon the time of enrollment relative to the RSV season.

4.2.6 **Monitoring Methods**

Appendix 1A depicts the schedule of events through day 56 of this study. Appendix 1B depicts the schedule of events during the RSV surveillance season.

Infants and children enrolled in the study will be monitored for the following:

- **Solicited adverse events** which are monitored for 29 days after immunization (Study Day 0-28) and include fever, signs of respiratory illness detailed in Section 8.1.2;
- **Unsolicited adverse events** which are all adverse events that are not included in the solicited adverse events or the serious adverse events (for example illnesses such as vomiting and diarrhea) are monitored for 29 days after enrollment;
- **Serious adverse events** (defined in Section 8.1.3); and **Lower respiratory tract infections** (LRIs), which will be considered protocol-specified adverse events, are both subject to EAE reporting (see Section 8.5) and are monitored and reported for 56 days after enrollment;
Symptomatic, medically attended RSV associated illness will be reported through RSV season.

Solicited adverse events
In addition to checking temperatures on the days of visits, the parent or guardian will daily record and report temperatures and signs of illness to study personnel. For temperature measurements, parents or guardians will be instructed to use a temporal artery thermometer to screen for elevated temporal artery temperatures. This device is used to minimize the number of rectal temperature measurements and has been shown to be an effective screening tool for fever. [24] The parent or guardian will measure temporal artery temperatures 3 consecutive times, following manufacturer’s directions. The highest of the 3 readings will be recorded. Parents or guardians will be asked to verify within 20 minutes any temporal artery temperature of ≥100.0°F with a rectal temperature measurement.[24] Temporal artery and rectal thermometers will be provided to parents or guardians for use during the study. A child will be considered febrile if s/he has a rectal temperature of ≥100.4°F. Temporal temperatures ≥100.0°F that are not confirmed by the parent or guardian with a rectal temperature, will be considered to be solicited AEs for the purposes of this study.

Solicited AEs will be monitored by recording temperature and signs of illness daily for 29 days (the day of inoculation and the following 28 days). A physical examination will be performed on each child or infant on or before inoculation (Day 0). A clinical assessment will be completed during routine visits (Days 3, 5, 7, 10, 12, 14, 17, 19, 21, and 28; each visit ±1 day) after inoculation. This period of follow up is consistent with the duration of shedding of live attenuated respiratory virus vaccines in RSV seronegative infants and children. [13-15,24] On non-visit days, a parent or guardian will record and report temperatures and signs of illness to study personnel. Children or infants with reported illness may have additional visits to assess the severity of the illness, and treatment will be provided for vaccine related illnesses, if necessary. Any illness will be followed until resolution with appropriate clinical and laboratory evaluations.

Serious Adverse events and LRI
On Days 29 through 56, only illness data related to any LRI and to serious adverse events will be recorded. Physical examinations will
be performed and nasal washes will be obtained in the event of a lower respiratory tract illness (for the purposes of this study, all lower respiratory tract illnesses are considered expected protocol specified AEs as described in Section 8.1.3).

**RSV-associated illness**

Infants and children enrolled in this study will also be monitored for symptomatic, medically attended, RSV-associated illness during the RSV season following inoculation. Based on previous data, from Baltimore, regarding the seasonality of RSV (Appendix 5), we will conduct surveillance for RSV-associated disease between November 1st and March 31st. During the surveillance period, all study subjects will be assessed for the occurrence of medically significant RSV disease by monitoring the following illnesses:

- Medically attended fever
- Medically attended upper respiratory illness
- Medically attended lower respiratory illness
- Medically attended otitis media

Fever, upper respiratory illness or otitis media that meet the definition of a SAE, and medically attended lower respiratory illness of any type, regardless of whether it meets the definition of an SAE, will be reported to the sponsor.

Information about these illnesses will be obtained by weekly reporting between study personnel and the subjects’ parent or guardian. If any of the above illnesses are reported, nasal washes for testing for RSV and other respiratory viruses by culture and rRT-PCR will occur within 72 hours of notification.

Blood samples will be obtained to assess the duration of protection and response to wild type (wt) RSV infection before and after the RSV season. For each infant or child in whom the day 56 specimen was obtained prior to October 1st, an additional specimen will be obtained between October 1st and October 31st, which will serve as the pre-RSV season specimen. A post-RSV season specimen will be obtained from each child between April 1st and April 30th. These specimens will allow us to measure antibody responses to wt RSV infection in vaccines and placebo recipients, which will allow us to determine whether the incidence of infection and antibody responses differ between these 2 groups.
4.2.6.1 Duration and Frequency of Clinical Assessment

Clinical data will be collected for approximately 56 days following vaccination. The schedule of study visits is shown in Appendix 1A. A study physician, physician assistant, nurse practitioner, or study nurse will be available by telephone 24 hours a day for consultation with parents or guardians regarding any illnesses that may occur during this period.

Additionally, infants and children may have unscheduled visits during the RSV season if they meet the criteria described in Section 4.2.6 and will also have a post-RSV season blood draw as described in Section 4.2.6.

How quickly the subjects must be seen if they develop a fever or respiratory illness will depend on the timing and the severity of the event. Subjects who meet study criteria for fever or respiratory illness during the acute phase of the study (Days 0-28) will be sampled (nasal wash) within 72 hours of study staff notification of the event. If the reported temperature elevation and/or respiratory tract illness is of grade 2 severity or greater during the acute phase of the study, the subject will be clinically evaluated and will have nasal washes obtained for culture of vaccine virus and testing for adventitious viruses within 48 hours of the time the illness is reported. Subjects with symptoms of lower respiratory tract illness at any time between study days 0 and 56 will be evaluated and tested for vaccine and adventitious viruses within 24 hours of staff notification of the event.

4.2.6.2 Laboratory Evaluation: Virus Detection

Specimens for viral culture and quantification of vaccine virus shedding will be obtained by nasal wash with approximately 20 mL of Ringer’s lactate solution once before and approximately 10 times after inoculation as shown in Appendix 1A. Laboratory testing will be performed at Johns Hopkins by personnel that are not involved with clinical assessment to maintain the blinding of the study.

As noted in Section 4.2.6, nasal wash specimens for detection of respiratory viruses by culture and rRT-PCR
will also be obtained during the RSV season from children who meet the criteria for surveillance sampling.

4.2.6.3 Laboratory Evaluation: Immunologic Assays

Serum specimens (5 mL of blood) will be obtained up to 42 days prior to vaccination and again on Day 56 for measurement of serum antibodies to RSV. As noted in Section 4.2.6, up to 2 additional serum specimens will be obtained: a pre-RSV season specimen between October 1st and October 31st of the calendar year in which the child was enrolled (if the day 56 post-inoculation specimen was obtained prior to October 1st), and a post-RSV season specimen between April 1st and April 30th. This will be used to determine whether a fourfold or greater rise in antibody titer has occurred, which would signify infection with wild-type RSV. This will allow comparison of the rate and severity of significant RSV illness following infection with wild-type virus in vaccine and placebo recipients.

Specimens will be obtained by venipuncture, fingerstick, or heelstick. No more than 20 mL of blood will be taken from study subjects for study purposes for the duration of the study.

Nasal wash specimens for measurement of secretory immunity will be obtained before and approximately 56 days after inoculation. In some instances, these specimens may be generated from the same nasal wash used for viral culture, except that the aliquot for measurement of secretory immunity will not contain viral transport medium. Sera and nasal wash specimens collected during this study will be banked for future use with the consent of the parent/guardian.

4.2.6.4 Research Laboratory Testing

Quantitation of the amount of vaccine virus shed, assays to measure immune responses before and after inoculation, and assessment of nasal washes for adventitious viral agents will be performed at the CIR. Cytokine/chemokine assays may also be performed on nasal washes from subjects infected with vaccine virus if sufficient material is
available. Selected specimens may be sent to LID, NIAID for confirmatory testing.

4.2.7 Plan for Use and Storage of Biological Samples

All specimens collected as part of this study may, with the parent’s or guardian’s permission, be stored for future research as part of CIR (Johns Hopkins) approved biospecimen repository for vaccine research. These samples may be used for future screening for respiratory virus vaccine studies and to learn more about RSV infection and other diseases. These samples will not be sold or used to make commercial products. Genetic tests will not be performed on these samples. Samples will be stored only with the parent’s or guardian’s permission. All samples stored in the repository will be labeled with the PID numbers of the subjects that, by themselves, cannot identify study subjects but are linkable to the study databases generated by the main study. The repository database will contain only the study subjects’ PID numbers. A master log linking the study subjects’ PID numbers is maintained at the individual enrolling site and will not be shared with the protocol team or the laboratory at CIR. Study participants, or their parents/guardians, may withdraw consent for future testing of their specimens at any time.

5.0 SELECTION AND ENROLLMENT OF STUDY SUBJECTS

5.1 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.
Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

5.2 Screening Visit

A screening visit will be scheduled up to 42 days prior to vaccination. During this initial screening visit, the child’s parent or guardian will read the screening or study consent form. The child’s parent or guardian will be encouraged to ask questions. The person obtaining the consent will administer a brief written (no-fail) test to ensure comprehension of the consent material. Answers to the test will be reviewed with the parent or guardian to clarify any incorrect answers. This will help ensure that the parent or guardian has sufficient understanding of the study before the informed consent form is signed. Parents or guardians will also receive a copy of the informed consent form.

The parent or guardian must sign the informed consent form before any study related procedures are performed. The screening process will include a medical history and physical examination. All clinically significant abnormalities will be reviewed with the parent or guardian and referral for follow-up care will be provided, when appropriate.

Screening will also include serum RSV antibody testing. As in previous phase I trials of other live-attenuated RSV vaccines [9,20,26,27] other screening laboratory tests will not be performed on children. Such tests are not routinely performed as part of well-child care since the risk of undiagnosed hepatic, metabolic, and renal diseases is much lower in children than in adults. [33]

During the screening visit the study staff will:
- Explain the study and screening process to parent or guardian and answer any questions.
- Review the informed consent form with the parent or guardian.
- Ensure that the parent or guardian has completed and understood the informed consent form comprehension assessment, signed the informed consent form including sections regarding disposition of specimens, and has received a copy of the informed consent.
- Anesthetic cream may be applied to the planned blood draw site (if desired).
- Elicit a complete medical history including delivery information from parent or guardian.
- Administer a complete physical examination (see Appendix 1A for definition).
- Obtain approximately 5 mL of blood to test for serum antibodies to RSV and act as a pre-inoculation blood specimen.
- If necessary, obtain a HIPAA release from parent or guardian to review the subject’s medical record and obtain the immunization record.
- Schedule a return visit, if needed.

5.3 Inclusion and Exclusion Criteria

To be eligible for this study, infants and children must satisfy all of the following inclusion criteria and none of the exclusion criteria.

5.3.1 Inclusion Criteria

5.2.1.1. ≥6 to <25 months of age at the time of enrollment/immunization.

5.2.1.2. Parents/guardians who demonstrate their understanding of the study (by taking a multiple choice questionnaire), sign the informed consent, and agree to vaccine administration following detailed explanation of the study.

5.2.1.3. Seronegative for RSV antibody, defined as a serum RSV neutralizing antibody titer <1:40 as determined within 42 days prior to enrollment/immunization.

5.2.1.4. Subject’s history has been reviewed and subject has undergone a physical examination indicating that s/he is in good health.

5.2.1.5. In the view of the site investigator, the subject has received routine immunizations appropriate for their age.

5.2.1.6. Subject is expected to be available for the duration of the study.
5.2.1.7. For children born to HIV-infected women: two negative PCR tests with one collected when >1 month of age and one collected when >4 months old, and no positive HIV PCR test; or two negative HIV antibody tests.

5.3.2 Exclusion Criteria

5.2.2.1. Known or suspected impairment of immunological functions or HIV infection.

5.2.2.2. Receipt of immunosuppressive therapy including systemic corticosteroids within 30 days of study entry. NOTE: Topical steroids, topical antibiotic and topical antifungal medications are acceptable within 24 hours of enrollment. May be reassessed after symptoms have resolved.

5.2.2.3. Bone marrow/solid organ transplant recipients.

5.2.2.4. Major congenital malformations, including congenital cleft palate, cytogenetic abnormalities, or serious chronic disorders.

5.2.2.5. Previous immunization with an RSV vaccine or previous receipt of or planned administration of any anti-RSV antibody product.

5.2.2.6. Previous serious vaccine-associated AE or anaphylactic reaction.

5.2.2.7. Known hypersensitivity to any vaccine component.

5.2.2.8. Lung or heart disease, including any wheezing event or reactive airway disease. Subjects with clinically insignificant cardiac abnormalities requiring no treatment may be enrolled. Subjects who had one episode of wheezing or received bronchodilator therapy for a single episode of illness in the first year of life but who have not had any additional wheezing episodes or bronchodilator therapy for at least 12 months may also be enrolled.

5.2.2.9. Member of a household that includes an infant less than 6 months of age.

5.2.2.10. Member of a household which contains an immunocompromised individuals (including, but not limited to: those with HIV related immunodeficiency, defined as CD4<300, or <15% if <5 years of age, measured within the previous 6 months; or any household members who have received chemotherapy within the last 12 months). Verbal report is sufficient documentation if the parent/guardian is confident of
history.

5.2.2.11. Attends day care with infants less than 6 months of age, and whose parent/guardian is unable or unwilling to suspend daycare for 14 days following immunization. Children who attend facilities that separate children by age and minimize opportunities for transmission of virus through direct physical or aerosol contact are acceptable.

5.2.2.12. Fever (rectal temperature of \( \geq 100.4^\circ\text{F} (38^\circ\text{C}) \)), or upper respiratory illness (rhinorrhea, cough, or pharyngitis) or nasal congestion significant enough to interfere with successful vaccination, or otitis media.

5.2.2.13. Subject has received any killed vaccine or live attenuated rotavirus vaccine within the last 2 weeks, any other live vaccine within the last 4 weeks, or gamma globulin (or other antibody products) within the past 3 months or is scheduled to receive any immunization in the 28 days after enrollment.

5.2.2.14. Receipt of another investigational vaccine or investigational drug within 28 days of receiving this investigational RSV vaccine.

5.2.2.15. Subject has received antibiotics or systemic or nasal steroid therapy or other prescription medications for acute illness within 3 days of study entry. Permitted concomitant medications include nutritional supplements, medications for gastroesophageal reflux, eye drops, and topical medications, including (but not limited to) topical steroids, topical antibiotics, and topical antifungal agents.

5.2.2.16. Subject has received salicylate (aspirin) or salicylate-containing products within the past month.

5.2.2.17. Infants born at \(<37\) weeks gestation and less than 1 year of age.

5.4 Access to Medical Records

If needed, parents or guardians of pediatric subjects will sign a HIPAA medical release prior to vaccination to allow review of birth histories, medical records, and immunization records or if, during the course of the study, AEs 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.
5.5 Treatments that Could Potentially Interfere with Vaccine-Induced Immunity

The following criteria should be checked at the Day 56 follow up visit. If any become applicable during the first 56 days on study, the subject will not be included in the immunogenicity evaluations after the time of exclusion. The subject will, however, be encouraged to remain in the safety evaluation for the duration of the study. These subjects will not be replaced.

- Use of any investigational drug or investigational vaccine other than the study article during the study period
- Chronic (defined as more than 14 days) administration of a dosage equivalent of ≥2 mg/kg of prednisone or a dosage equivalent of ≥20 mg of prednisone for subjects weighing more than 10 kg, or other immune-modifying drugs during the study period
- Receipt of a licensed killed vaccine or live attenuated rotavirus vaccine within 2 weeks of receiving study vaccine or placebo
- Receipt of immunoglobulins and/or any blood products during the entire study
- Receipt of a licensed live virus vaccine, except rotavirus vaccine, within 4 weeks of receiving study vaccine or placebo

5.6 Subject Withdrawal/Termination Criteria

Subjects participating in this study have the right to withdraw from the study at any time. In general, the Investigator will not withdraw a subject unless that subject is lost to follow up or is noncompliant with the protocol. Every attempt will be made to collect all data specified by the protocol relative to study vaccine received, including post-immunization blood and nasal wash collections. Any subject who has received vaccine or placebo will be encouraged to remain in the safety evaluation for the duration of the study.

A subject will not be considered to have completed the trial if any of the following reasons apply:

- Research terminated by Sponsor or PI – applies to the situation where the entire study is terminated by the Sponsor or PI for any reason.
- Withdrawal of consent – applies to a parent/guardian who verbally or in writing withdraws consent to participate in the study for any reason.
- Noncompliant with protocol – applies to a parent/guardian who does not comply with protocol-specific visits or evaluations, on a consistent basis, such that adequate follow-up is not possible and the subject’s safety would be compromised by continuing in the
Subject withdrawal may occur if the PI believes that it is in the best interest of the subject to withdraw the subject.

The study sponsor, the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), the Institutional Review Board (IRB), the Office for Human Research Protections (OHRP), the National Institute of Allergy and Infectious Diseases (NIAID) Intramural Data and Safety Monitoring Board (DSMB), or the United States Food and Drug Administration (FDA) may decide to end the study.

Other – a category used when previous categories do not apply and requires an explanation.

6.0 ENROLLMENT AND INOCULATION (Study Day 0)

For the purposes of this protocol, Day 0 will correspond to day of inoculation with investigational product. Randomization will usually occur on the same day but the site is allowed up to 72 hours after randomization to complete the enrollment visit and immunize.

The following will be performed on study day 0:

1. Review the study and answer any remaining questions.
2. Ensure parent/guardian has authorized or denied authorization for use of samples for future research.
3. If necessary, ensure parent/guardian has signed HIPAA 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.
4. Review history (including birth history and maternal HIV status if known), and complete clinical assessment.
5. Review inclusion and exclusion criteria.
6. Obtain nasal wash for viral culture, antibody assays, and testing for adventitious agents or other measurements of immunity.
7. Record temporal and/or rectal temperature, heart rate, and respiratory rate.
8. Administer vaccine and maintain subject in a supine position for 1 minute.
9. Observe for approximately 30 minutes after inoculation to evaluate for immediate adverse reactions and for immediate hypersensitivity reactions.
11. Provide and explain temperature card, thermometer, illness criteria, and study personnel contact information.
12. Schedule Day 1 and 2 telephone/email contact and Day 3 visit.
7.0 **CLINICAL MONITORING AND EVALUATION**

Study visits, except vaccination, may be performed at one of the clinical sites or as home visits. Vaccination visits must be done at an office site where emergency supplies are available.

7.1 **Visit Days**

(Study Days 3, 5, 7, 10, 12, 14, 17, 19, 21, 28; each visit ±1 day)

- Obtain and record interim history and temporal/rectal temperature from previous days.
- Perform focused clinical assessment emphasizing examination for any acute complaints.
- Record vital signs (temperature, pulse, and respirations) and clinical assessment findings.
- Obtain nasal wash for viral culture and for cytokine/chemokine assays.
- Complete adventitious agent assay request if illness criteria met or suspected.
- Schedule next routine visit.
- Day 28 only - review illness criteria and when to contact study personnel during post-acute phase (Study Days 29 to 56).

7.2 **Non-Visit Days**

(Study Days 1, 2, 4, 6, 8, 9, 11, 13, 15, 16, 18, 20, 22-27; each ±1 day, and Study Day 29 +1 day)

- Via phone or email, obtain and record interim history and temporal/rectal temperature from previous reading.
- Address any concerns and schedule appointment if necessary.

7.3 **Day 56 Visit (+7 Days)**

- Obtain and record interim history for study days 29 to 56.
- Obtain approximately 5 mL of blood for immunologic assays.
- Obtain nasal wash for immunologic assays.
- Provide parent/guardian with compensation (as determined by study site). Parents/Guardians will only be compensated for that portion of the study which is completed.
7.4 RSV Pre and Post season sampling and surveillance during the season following inoculation

- Obtain pre-RSV season serum antibody specimen between October 1st and October 31st of the calendar year in which the child was enrolled, or at day 56 follow-up if after October 1st.
- Obtain and record interim history with weekly reporting. Arrange for study visit if child demonstrates any of the following:
  - Medically attended fever
  - Medically attended upper respiratory illness
  - Medically attended otitis media
  - Medically attended lower respiratory tract illness
- If one of the above events occurs, obtain nasal wash for RSV culture and testing for respiratory viruses by multiplex rRT-PCR within 72 hours of initial report (lab assays to be performed by CIR).
- Obtain post-RSV season serum antibody specimen between April 1st and April 30th.
- Provide parent/guardian with compensation (as determined by site).
- Advise parent/guardian of study randomization, if known.

8.0 ADVERSE EVENT MONITORING

8.1 Definitions

8.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject administered the investigational vaccine or placebo and does not necessarily have a causal relationship with vaccination. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational vaccine whether or not related to it. This includes exacerbation of pre-existing conditions and intercurrent illnesses.

All AEs must be graded for severity and assessed for relationship to the investigational vaccine as described in Section 8.4 of this protocol.

However, for infants and children, the following common events will not be recorded as AEs unless a prescribed concomitant medication is used to treat them: diaper rashes, teething pain, and spitting up.

AEs will be assessed during the acute phase of this study (Days 0 to 28).
8.1.2 Solicited Adverse Events

Solicited adverse events (solicited AEs) are predefined AEs that can occur after vaccine administration. Therefore, all solicited AEs are defined as expected AEs. Solicited AEs will be assessed during the acute phase of this study, days 0 to 28.

For the infants and children enrolled in this study, solicited AEs include the following and may be expected to occur if the vaccine is insufficiently attenuated:

1. Fever
2. Upper respiratory tract illness
   a. Rhinorrhea or,
   b. Pharyngitis or,
   c. Cough without lower respiratory tract illness or,
   d. Hoarseness
3. Otitis Media
4. Change in feeding habits sufficient to warrant contact with health care provider
5. Lower respiratory tract illness
   a. Wheezing or,
   b. Pneumonia or,
   c. Laryngotracheobronchitis (croup) or,
   d. Rhonchi or,
   e. Rales

Definitions of these illnesses are listed in Appendix 4, Table 11.

8.1.3 Serious Adverse Event

A Serious Adverse Event (SAE) is an AE, whether considered related to the investigational vaccine or not, meeting one of the following outcomes:

1. **Death** during the period of protocol-defined surveillance.
2. **Life threatening**: defined as an event that places a subject at immediate risk of death at the time of the event and does not refer to an event that hypothetically might have caused death were it more severe.
3. **Hospitalization** (or prolongation of existing hospitalization): defined as at least an overnight stay in the hospital or emergency ward for treatment that would have
been inappropriate if administered in the outpatient setting.

4. Results in a congenital anomaly or birth defect.

5. Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

6. A medically important event*

*Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious AE (SAE) when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

For the purpose of this study, any lower respiratory tract illness (LRI) as defined in Appendix 4, Table 11, is considered a Protocol Specified Event (PSE), and thus, must also be reported in an expedited manner through the DAIDS Expedited Adverse Event Reporting System (DAERS). An LRI is also an SAE if it meets one or more of the outcomes listed above (1-5).

8.1.4 Study Reporting Period for Adverse Events and Solicited Adverse Events

The reporting period for solicited AEs, other AEs, and concomitant medications is the period immediately following the administration of study dose through the acute monitoring phase, days 0 to 28. SAEs and LRIs will be reported through day 56. AEs will be recorded and assigned a severity grade by study personnel. Assessment of relationship to study vaccine will be determined by the PI, study MD, NP or PA. Monitoring for adverse events ends at the time of completion of the follow up visit, day 56 (+7 days), unless there is an LRI or SAE that has not resolved. All LRIs and SAEs will be followed until satisfactory resolution or until the PI or Sub-investigator deems the event to be chronic or the subject to be stable.

8.2 Assessment of Safety

Safety Monitoring

A P1114 Protocol Safety Review Team (PSRT) will routinely review clinical and laboratory safety data reports prepared by FSTRF. To meet minimum quorum for a safety data review the
PSRT must include (but not limited to) the Protocol Chair or Vice Chair, Data Manager, NIAID/DCR Medical Monitor, DAIDS or NICHD Medical Officer, and the Protocol Statistician. Designees for PSRT members will be allowed in the event of their non-availability for a review. The content, format and frequency of safety monitoring will be agreed upon in advance between the PSRT and FSTRF. Representatives of the product developer may also be included on PSRT discussions, but not in decisions.

The PSRT will convene via teleconference or other means routinely throughout the study to review data relevant to safety monitoring and discuss any safety concerns – at least every two weeks during the active immunization phases, and at least once a month thereafter, as well as on an ad hoc (as needed) basis outside of regularly scheduled calls. The PSRT will also provide rapid consultation to site clinicians regarding toxicity management as needed.

8.2.1 Assessment of Solicited Adverse Events

The primary solicited AEs to be measured are described in Section 8.1.2. Solicited AEs will be analyzed for each subject, taking the pattern of viral shedding into account. Key parameters (e.g., numbers of subjects with fever, cough, otitis media, upper respiratory illness [URI], or lower respiratory illness [LRI]) will be summarized by treatment group at the end of the study.

8.2.2 Solicited Adverse Events Elicited by History

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

8.2.3 Identification of Adverse Events

Assessment of safety will include clinical observations and monitoring of subjects. Subjects will be closely monitored from the time of vaccine administration until the end of the acute monitoring phase, days 0 to 28. All AEs will be recorded,
assigned a severity grade, and assessed for the relationship to study vaccine. A study clinician will perform assessments on Days 0, 3, 5, 7, 10, 12, 14, 17, 19, 21, and 28, with each visit being within ±1 day. A study clinician will also be available by telephone 24 hours a day during this study evaluation period. Transient or mild symptoms, such as rhinorrhea, pharyngitis, hoarseness, or cough that do not meet the solicited AE study definitions (see Appendix 4, Table 1) will not be classified as a solicited AE.

Subjects who meet study criteria for fever or respiratory illness during the acute phase of the study (Days 0-28) will be sampled (nasal wash) within 72 hours of study staff notification of the event. If the reported temperature elevation and/or respiratory tract illness is of grade 2 severity or greater during the acute phase of the study, the subject will be clinically evaluated and will have nasal washes obtained for culture of vaccine virus and testing for adventitious viruses within 48 hours of the time the illness is reported. Subjects with symptoms of lower respiratory tract illness at any time between study days 0 and 56 will be evaluated and tested for vaccine and adventitious viruses within 24 hours of staff notification of the event.

The following common childhood illnesses or events will not be recorded as AEs unless prescribed concomitant medications are given to treat them: diaper rashes, teething pain, and spitting up.

8.2.4 Association with Receipt of Study Vaccine

Study subjects will be considered to have met criteria for a solicited AE if they experience any of the criteria listed in Section 8.1.2.

Subjects will be considered to have a vaccine-associated solicited adverse event if they meet criteria for a solicited AE accompanied by shedding of vaccine virus in the absence of other identifiable agents of respiratory or febrile illness.

All AEs and solicited AEs will have their relationship to study vaccine assessed by the site investigator using the following terms:

Definitely related: Clear-cut temporal association, and no other possible cause.

Probably related: Clear-cut temporal association and a potential alternative cause is not apparent.
Possibly related: Less clear temporal association; other causes also possible.

Probably not related: Temporal association between the AE and the vaccine or the nature of the event is such that the vaccine is not likely to have had any reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible).

Unrelated: The AE is completely independent of vaccine administration, and/or evidence exists that the event is definitely related to another cause.

8.3 Adverse Event Reporting

AEs may be observed by the Investigator, elicited from the parent/guardian or subject, reported on subject’s temperature cards, or volunteered by the parent/guardian or subject. Assessment of safety will include clinical observation and monitoring of hematological, chemical, and immunologic parameters as necessary, and all adverse events (solicited and unsolicited) will be reported on case report forms (CRFs) which are detailed in the MOP.

Requirements, definitions, and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at:

http://rsc.tech-res.com/safetyandpharmacovigilance/.

The DAERS internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/.

For questions about EAE reporting, please contact the RSC at: (DAIDSRSCSafetyOffice@tech-res.com)
The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used by this study.

The study agent for which expedited reporting is required is recombinant live-attenuated respiratory syncytial virus vaccine RSV cps2, lot RSV#005A/placebo.

In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are: lower respiratory tract illness (LRI) as defined in Appendix 4, Table 11.

8.3.1 Medical Follow-up and Details of Adverse Events

Follow-up such as history, physical examination, and laboratory testing and/or treatment may be necessary if a subject experiences an AE. Details of all AEs will be properly recorded in the source documents and CRFs and subsequently reported to LID Investigators and the DSMB in separate semi-annual and annual reports. AEs will be reported to the IRB as defined by the individual IRB policy.

8.4 Determination of Severity

All solicited AEs and fever will be graded using the following protocol-defined grading system:

8.4.1 Solicited AE Grading Tables

Table 2: P1114-specific AE Grading Table for solicited adverse events

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

8.4.2 Fever Grading: Rectal Temperature Measurement

Table 3: P1114-specific Fever Grading: Rectal Temperature Measurement for Infants and Children in study

<table>
<thead>
<tr>
<th>Severity</th>
<th>Defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (0)</td>
<td>&lt; 100.4°F (&lt; 38°C)</td>
</tr>
<tr>
<td>Grade (1)</td>
<td>≥ 100.4°F but ≤ 101.4°F (≥ 38°C but ≤ 38.6°C)</td>
</tr>
<tr>
<td>Grade (2)</td>
<td>≥ 101.5°F but ≤ 102.4°F (≥ 38.7°C but ≤ 39.1°C)</td>
</tr>
<tr>
<td>Grade (3)</td>
<td>≥ 102.5°F but ≤ 104.8°F (≥ 39.2°C but ≤ 40.5°C)</td>
</tr>
<tr>
<td>Grade (4)</td>
<td>≥ 104.9°F (≥ 40.6°C)</td>
</tr>
</tbody>
</table>
8.4.3 All AE other than solicited AE and fever will be assessed for severity by the investigator using the most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), which is available on the RSC website at:

http://rsc.tech-res.com/safetyandpharmacovigilance/.

8.5 Serious Adverse Event Reporting

All LRIs and SAEs will be reviewed by a site physician, recorded in the DAIDS Expedited Adverse Event (EAE) Reporting system, and followed through to resolution by a study physician. All LRIs and SAEs (regardless of their relationship to the study agent) will be reported no later than 3 reporting days after the site becomes aware of the LRI or SAE. “Reporting days” is defined in Version 2.0 of the DAIDS EAE Manual. However, if the event occurs in the 56 days after immunization and meets any protocol pause criteria (an SAE that is possibly, probably, or definitely related to the vaccine virus OR an LRI, OR; a grade 4 fever or any grade 3 or grade 4 solicited AE other than fever), then the site must send an email to the study team within 24 hours of site awareness of the event at: impaact.teamp1114@fstrf.org in addition to completing the DAIDS report within 3 reporting days. The email should describe the LRI or SAE and the plan for follow-up.

LRIs and SAEs will also be reported to local IRBs based on local reporting requirements.

These events will be followed to resolution by the clinical site and reported to the FDA annually.

8.6 Sponsor’s Reporting Responsibilities

Serious, unexpected, suspected adverse reactions (SUSARs) as defined in 21 CFR 312.32 will be reported to the FDA and all participating investigators as IND Safety Reports. The Sponsor will also submit a brief report of the progress of the investigation to the FDA on an annual basis, as defined in 21 CFR 312.33.
8.7 Unanticipated Problems

An Unanticipated Problem (UP) is defined as any incident, experience, or outcome that is:

1. Unexpected in terms of nature, severity, or frequency in relation to
   a. The research procedures that are described in the IRB-approved research protocol and informed consent; or other study documents; and
   b. The characteristics of the subject population being studied; and
2. Possibly, probably, or definitely related to participation in the research; and
3. Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated Problems (UPs) must be reported to the local IRB per their requirements. Non-Serious AEs that are UPs must also be reported to the Sponsor Clinical Safety Office (CSO). Submit the local IRB UP report form to the CSO, at the following address, no later than 7 calendar days of the site investigator awareness of the event.

**SPONSOR CLINICAL SAFETY OFFICE CONTACT INFORMATION:**

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

8.8 Adverse Event Monitoring

8.8.1 Intramural Data and Safety Monitoring Board

The NIAID Intramural DSMB is constituted to review the safety data of Intramural NIAID clinical studies that require DSMB oversight, and consists of experts in infectious diseases, biostatistics, and clinical research. The DSMB will review the protocol prior to opening the study to enrollment. The DSMB will meet at least twice a year to review the completeness of the study data collected, the adherence to the protocol, and AE data. Cumulative safety data will be submitted to the DSMB Executive Secretary for DSMB review. The DSMB Executive Secretary will provide the Protocol Chair with DSMB recommendations.
promptly, and the official DSMB Report will then be provided in a timely fashion through the office of the NIAID Clinical Director. The Protocol Chair will submit the written DSMB recommendations to the sites for distribution to the sites’ IRBs upon receipt.

8.8.2 Serious Adverse Event Review

All serious adverse events, LRIs, unanticipated problems and all IND Safety Reports will be reported by the Sponsor Clinical Safety Office to the DSMB at the same time they are submitted to the IND Sponsor or FDA.

8.9 Pausing and Stopping Rules

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

- An SAE that is possibly, probably, or definitely related to the investigational vaccine or placebo, OR;
- A LRI, OR;
- A grade 4 fever or any grade 3 or grade 4 solicited AE other than fever,

If any of these events occur, the site will report the event (as outlined in section 8.5) AND will notify the team of the event (including a description of the event) via email, at impaact.teamp1114@fstrf.org, within 24 hours of identification of the event. The protocol team will notify all sites to suspend enrollment and immunization. The site reporting the event will complete the event assessment including the collection of viral samples. All respiratory viral samples collected from the child up to that point will be shipped to the Johns Hopkins University laboratory, as soon as possible (see MOP). Study accrual will remain suspended while the SDAC checks treatment assignment and virology studies are started. The DSMB will be informed of the event by the protocol chair and will receive all pertinent data. Follow up visits will continue as outlined in Appendix 1A.

If the event is determined to have occurred in a child who received active vaccine and the event meets one of the following stopping rule criteria, then the event will be reviewed by the DSMB prior to resuming enrollment.
1. One or more subjects experiences a SAE that is determined to be possibly, probably, or definitely related to the vaccine virus, OR
2. One or more subjects develops LRI associated with shedding of vaccine virus at the time of the LRI (even if another pathogen is identified; unless the RSV is confirmed to be wild type), OR
3. One or more subjects develops LRI that is not explained by a diagnosis unrelated to vaccine virus, OR
4. One or more subjects experiences a grade 4 fever or any grade 3 or grade 4 solicited AE other than fever associated with shedding of vaccine virus, OR
5. Any pattern of research laboratory values or clinical symptoms is observed that the protocol team considers as being a significant safety issue for participants.

The DSMB will notify the protocol team if enrollment and immunizations can resume or if the study needs to be stopped. In all cases, once a pause occurs, the sites cannot resume enrollment until notified to do so by the protocol team.

9.0 DATA COLLECTION AND MONITORING

9.1 Source Documentation
Complete source documentation (laboratory test reports, pertinent hospital or medical records, etc.) is required for every study subject for the entire duration of the study. Source documents will be used to record data for subjects enrolled in the study. The Investigator is responsible for the accuracy and completeness of the data reported to the Sponsor in the CRFs. Source documentation will be made available for review or audit by the Sponsor or designee and any applicable Federal authorities.

9.2 Study Documentation
Study-related documentation will be completed as required by the IRB, the Sponsor, and regulatory authorities. Continuing review documentation will be submitted by the Investigator to the IRB on the anniversary date of initial review as specified by the IRB. An annual report will be submitted by the Sponsor to the FDA based on the anniversary date that the IND for the RSV cps2 vaccine went into effect. These reports will provide a brief description of the progress of the investigation as outlined in 21 CFR 312.33, and will include any revisions of the protocol not previously submitted to the FDA.
The Pharmacist will maintain adequate records of the disposition of the investigational product, including dates of receipt and disposition, quantity, and use by subjects. If the study is terminated, suspended, or completed, the Investigator will be notified as to proper disposal of the remaining unused products.

9.3 Retention of Records

Trial-related documents will be maintained by the Investigator for a period of at least 2 years after final marketing approval of the vaccine or, at least 2 years after the formal discontinuation of clinical development of the product (or longer based upon local laws). The Sponsor is required to inform the Investigator as to when such documents need no longer be retained. No study document should be destroyed without prior written agreement between the Sponsor and the PI. Storage of all trial-related documents will be such that confidentiality will be strictly maintained. These records are also to be maintained in compliance with IRB/EC, state, and federal medical records retention requirements, whichever is longest. Should the Investigator wish to assign the study records to another party and/or move them to another location, the Investigator must provide written notification of such intent to the Sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. The Sponsor must be notified in writing and written permission must be received by the site from the Sponsor prior to destruction or relocation of research records.

9.4 Protocol Revisions

No revisions to this protocol will be permitted without documented approval from both the Sponsor and the IRB that granted the original approval for the study. This does not apply to changes made to reduce discomfort or avert risk to study subjects. Furthermore, in the event of a medical emergency, the Investigator shall perform any medical procedures that are deemed medically appropriate. The Investigator must notify the Sponsor and IRB of all such occurrences.

9.5 Clinical Investigator’s Brochure

Investigators will receive the current version of the Clinical Investigator’s Brochure that comprehensively describes all the available preclinical experience with the experimental vaccine. If relevant new information becomes available during the course of the trial, the Investigators will receive a revised Investigator’s Brochure or an amendment to the current version.
9.6 Study Monitoring
The trial will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP), and any applicable regulatory requirement(s). The study site monitoring will be conducted according to the NIAID/DAIDS and NICHD Clinical Research Site Monitoring Guidelines.

10.0 STATISTICAL CONSIDERATIONS
10.1 General Design
The goal of this Phase I vaccine trial is to determine the safety, infectivity, and immunogenicity of the RSV cps2 vaccine candidate in RSV seronegative pediatric subjects. Data from this study and from a companion study of this vaccine conducted at the Center for Immunization Research, Johns Hopkins Bloomberg School of Public Health, will be maintained in the same database and will be analyzed together.

10.2 Description of the Statistical Methods to be Employed
This study, like other Phase I studies, is basically exploratory, rather than confirmatory; its purpose is to assess frequencies of adverse events and patterns of immune responses. Descriptive approaches will be used to meet the protocol objectives as stated in Section 3.0 of this protocol, as well as formal statistical tests as outlined below. Results will be presented in tabular format as well as graphically where appropriate.

10.3 Sample Size Calculations
Approximately 51 seronegative children and infants will be enrolled in the study and will receive either vaccine or placebo in a 2:1 ratio. Assuming an attrition rate of about 10%, approximately 30 vaccines and 15 placebo recipients will provide data for the primary objectives. The sample size was chosen based upon past experience with Phase I evaluation of other live attenuated respiratory virus candidate vaccines [13,14,24]. The 2:1 randomization ratio will be used to maximize the information obtained regarding the response of children to the cps2 vaccine.

Given the small sample size, the study will have limitations with respect to detecting adverse events (AE) and in estimating the proportion of such events in the population represented by the study sample.

The following calculations focus on the assessment of the tolerability of the vaccine (Section 3.1) and in particular, occurrence of LRI, which
occurs very infrequently in children who participate in our studies, but would be considered a sentinel safety event if observed in children infected with vaccine virus. Table 4 shows the probability of observing 0 events within the sample of 30 vaccinees, as well as the probability of observing 2 or more events, under a range of assumptions concerning the true rate of such events in the patient population represented by this sample. From this table, it can be seen that if the true proportion of LRI (or other adverse event) is at least 10%, there is an 82% chance of observing 2 or more events in a group of size 30, and a 96% chance of observing at least a single event.

**Table 4: The Probability of Observing LRI events in Vaccines**

<table>
<thead>
<tr>
<th>True underlying probability of LRI or AEs</th>
<th>Pr (0 events)</th>
<th>Pr (1+ events)</th>
<th>Pr (2+ events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>.01</td>
<td>.74</td>
<td>.26</td>
<td>.04</td>
</tr>
<tr>
<td>.03</td>
<td>.40</td>
<td>.60</td>
<td>.23</td>
</tr>
<tr>
<td>.05</td>
<td>.21</td>
<td>.79</td>
<td>.45</td>
</tr>
<tr>
<td>.1</td>
<td>.04</td>
<td>.96</td>
<td>.82</td>
</tr>
<tr>
<td>.15</td>
<td>.01</td>
<td>.99</td>
<td>.95</td>
</tr>
</tbody>
</table>

Table 5 presents 90% confidence intervals (CI) around potential proportions of LRI or AEs that might be observed in the sample of 30 vaccinees. The CIs around similar proportions in a sample of 15 placebo recipients are also presented. Note that if no LRI or AEs are detected among the 30 vaccinees, we are 90% confident that the true probability of AEs, in the population from which the sample is drawn, is between 0 and 10% (ie. there is only a 5% chance that the true probability of AEs is higher than 10%).

**Table 5: Percent of Subjects Experiencing LRI or AEs with Exact 90% Confidence Intervals**

<table>
<thead>
<tr>
<th>N</th>
<th>% LRI or AEs</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0%</td>
<td>0% --18%</td>
</tr>
<tr>
<td>30</td>
<td>0%</td>
<td>0% --10%</td>
</tr>
<tr>
<td>15</td>
<td>10%</td>
<td>1% --32%</td>
</tr>
<tr>
<td>30</td>
<td>10%</td>
<td>3% --24%</td>
</tr>
<tr>
<td>15</td>
<td>20%</td>
<td>6% --44%</td>
</tr>
<tr>
<td>30</td>
<td>20%</td>
<td>9% --36%</td>
</tr>
<tr>
<td>15</td>
<td>30%</td>
<td>12% --55%</td>
</tr>
<tr>
<td>30</td>
<td>30%</td>
<td>17% --47%</td>
</tr>
</tbody>
</table>
Group sample sizes of 30 in the vaccinated group and 15 in the placebo group would achieve 80% power to detect a difference between the group proportions of about 0.40. The test statistic used is the two-sided Fisher's Exact test. The alpha level of the test was targeted at 0.05. Table 6 presents examples of true group differences which can be detected with 80% power, given the sample sizes.

Table 6: Magnitude of Difference in Responses Detectable with 80% Power

<table>
<thead>
<tr>
<th>Response Proportion in the Placebo Group</th>
<th>Response Proportion in the Vaccinated Group</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>0.45</td>
<td>0.40</td>
</tr>
<tr>
<td>0.1</td>
<td>0.53</td>
<td>0.43</td>
</tr>
<tr>
<td>0.15</td>
<td>0.60</td>
<td>0.45</td>
</tr>
<tr>
<td>0.2</td>
<td>0.66</td>
<td>0.46</td>
</tr>
</tbody>
</table>

10.4 Assessment of Primary Objectives

Safety data from all study participants will be summarized, including data from participants who discontinue study early, or have some missed visits. In the immunogenicity analyses, those who do not provide data for the day 56 follow-up (due to early discontinuation or missed visit) will be treated as “failures” in the analyses. Sensitivity analyses will be performed to check if the results are consistent with those when these participants are excluded.

10.4.1 Primary Objective 1

To determine the frequency of vaccine-related solicited AEs and other AEs.

- Summary of the frequency of solicited AEs and other AEs.
- Line listing of individual clinical solicited AEs and other AEs, graded by severity.

10.4.2 Primary Objective 2

To quantify the amount of vaccine virus shed by each recipient.

- Line listing of the individual peak titer and duration of virus shed by each individual. In addition, the geometric mean peak titer and mean duration of virus shed will be reported.
10.4.3 Primary Objective 3

To determine the number of vaccinated children and infants infected with RSV cps2.
- The proportion of vaccinees who either shed vaccine virus and/or had a fourfold or greater rise in serum antibody titer following vaccination will be presented.

10.4.4 Primary Objective 4

To characterize immune responses to the RSV cps2 vaccine, including quantification of the amount of RSV neutralizing antibody and antibody to the RSV F glycoprotein induced by the vaccine.
- Line listing of the RSV antibody titer pre and post vaccination for each individual subject. In addition, the geometric mean and median antibody titers will be reported.
- Line listing of RSV neutralizing antibody responses by individual.
- Line listing of antibody responses to the RSV F glycoprotein by individual.
- Where appropriate, the Wilcoxon Sum Ranks test will be used to determine significant differences between vaccine and placebo recipients.
- A Fisher’s exact test will be used to determine significant differences between groups with respect to the proportion of subjects that develop 4-fold or greater rises in RSV neutralizing antibody titer following vaccination. These will be the only formal statistical comparisons between the vaccinated and placebo groups.

10.4.5 Primary Objective 5

To determine the genetic stability of the 248, 404 and 1030 mutations in vaccine virus recovered from nasal washes at the time of peak viral replication and on the last day of replication.
- Sequence analysis on vaccine virus isolated from vaccinees at the time of peak shedding and on the final day of shedding will be performed.
10.5 **Assessment of Secondary Objectives**

The secondary objective of this study is to characterize clinical and immune responses in vaccinated seronegative children who experience subsequent natural infections with wild-type RSV. This will be done by:

- Summarizing the frequency of solicited AEs and other AEs for children in whom wt RSV is detected during the surveillance period.
- Listing the RSV antibody titer pre and post the surveillance period for each individual subject. Data will be displayed in tabular format. Geometric mean and median antibody titers will be determined.

10.6 **Outcome Measures**

10.6.1 **Safety**

The primary safety endpoint is the frequency and severity of vaccine-related solicited AEs that occur during the acute monitoring phase of the study (Days 0-28).

10.6.2 **Immunogenicity**

The primary immunogenicity endpoint is the proportion of subjects that develop 4-fold or greater rises in RSV neutralizing antibody titer following vaccination. Antibody responses to the RSV F glycoprotein will also be assessed by ELISA.

10.7 **Monitoring Accrual**

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. The team will monitor feasibility monthly, first based on site registration and then on accrual. Initially, the team will monitor site registration weekly to ensure that an adequate number of sites have registered to complete the protocol. If relatively few of the eligible sites have registered after the protocol has been approved for 1 month, the team will re-assess the feasibility of the protocol and the reasons why sites have not registered, and may amend the protocol accordingly.
11.0 PROTECTION OF HUMAN SUBJECTS

11.1 Institutional Review Board (IRB)

The Investigator at each site will be responsible for obtaining IRB approval for the study. Before the start of the study, the appropriate documents (including but not limited to the protocol, Investigator’s Brochure, informed consent form, information sheets, and advertisements) will be submitted to, and approved by, each site’s local IRB/EC. A copy of the study approval (including approval of the informed consent form) is to be maintained in the Investigator’s study document binder and a copy will be supplied to the Sponsor. During the study, the Investigator is responsible for providing the IRB with all documents subject to review (i.e., protocol amendments, informed consent form updates, advertisements, and any written information that may be provided to the subject’s parents or guardians). Annual reports on the progress of the study will be made to the IRB by the Investigator in accordance with IRB guidelines and government regulations.

11.2 Informed Consent

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirements, Good Clinical Practice, and ethical principles. The written informed consent form must be approved by the IRB prior to its use.

11.3 Risks

Risks to the subjects are associated with venipuncture, nasal wash, and with immunization. These risks are outlined below. The study subject’s family does not pay for the vaccine or research visits including examinations and laboratory tests that are part of this study, including evaluation of illness performed to meet protocol requirements, if any.

11.3.1 Venipuncture

Risks occasionally associated with venipuncture include pain and bruising at the site of venipuncture, lightheadedness, infection, and syncope (rarely).

11.3.2 Nasal Wash

Risks occasionally associated with nasal wash include pain or discomfort, and occasionally epistaxis. Nasal washes are not standard of care in well children and are not usually performed on ill children, although many parents are advised to use saline nose
drops and nasal bulb suction (the 2 components of our nasal wash procedure) to clear a young child’s congested nostrils during an upper respiratory illness.

11.3.3 **Immunization**

If the RSV cps2 vaccine is insufficiently attenuated, subjects could experience rhinorrhea, cough, fever, otitis media, or lower respiratory tract illness. Immediate hypersensitivity reactions including urticaria, anaphylaxis, or other IgE mediated responses are possible, as with any vaccine. As with any investigational vaccine, there is a theoretical possibility of risks about which we have no present knowledge. Parents or guardians will be informed of any such risks should further data become available.

11.4 **Benefits**

Subjects may not receive any direct vaccine-related benefit from enrollment in this study. It is possible that some children who receive vaccine may be protected against infections with RSV that circulates in the community. It is hoped that information gained in this study will contribute to the development of a safe and effective vaccine for the prevention of illness associated with infection by RSV.

11.5 **Compensation**

Compensation will be provided to the child’s parent/guardian based on each site’s standard. The amount must be reviewed and approved by each sites’ IRB. Compensation will only be provided for those portions of the study that are completed. Compensation will be in accordance with each institution’s IRB policies.

11.6 **Confidentiality**

All study-related information will be stored securely at the study site. All subject information will be stored in locked areas with access limited to study staff. All laboratory specimens, reports, and forms for study data collection, specimen processing, and vaccine administration will be identified by coded number only to maintain subject confidentiality. Data entry will be done by coded number and information will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link PID numbers to other identifying information will be stored in a locked area with limited access. Subjects’ study information will not be released without the written permission of the subject, except as necessary for monitoring by the Sponsor and/or its
contractors, the Office for Human Research Protections (OHRP), and the FDA.

12.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health. All infectious specimens will be transported using packaging mandated in Title 42 of the Code of Federal Regulations, Part 72 (42CFR72) and in accordance with individual carrier guidelines (e.g., Federal Express, Airborne Express).
13.0 REFERENCES


5. Collins PL, Murphy BR. Vaccines against Human Respiratory Syncytial Virus. Respiratory Syncytial Virus 14, 233-278. 2007. Ref Type: Abstract


19. Whitehead SS, Firestone CY, Collins PL, Murphy BR: A single nucleotide substitution in the transcription start signal of the M2 gene of respiratory syncytial virus vaccine candidate cpts248/404 is the major determinant of the


31. Teng MN, Whitehead SS, Bermingham A, St CM, Elkins WR, Murphy BR et al.: **Recombinant respiratory syncytial virus that does not express the NS1 or M2-2 protein is highly attenuated and immunogenic in chimpanzees.** *J Virol* 2000, **74**: 9317-9321.


APPENDIX 1A: Screening, Acute Phase (Study Days 0 to 28), and Post-Acute Phase (Study Days 29 to 56)

SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>Day Number</th>
<th>2'</th>
<th>3</th>
<th>4'</th>
<th>5</th>
<th>6'</th>
<th>7</th>
<th>8'</th>
<th>9'</th>
<th>10</th>
<th>11'</th>
<th>12</th>
<th>13'</th>
<th>14'</th>
<th>15'</th>
<th>16'</th>
<th>17'</th>
<th>18'</th>
<th>19</th>
<th>20'</th>
<th>21</th>
<th>22-27</th>
<th>28</th>
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<th>6</th>
<th>Sick Visit*</th>
<th>Early DC</th>
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<td>±1 d</td>
<td>±1 d</td>
<td>±1 d</td>
<td>±1 d</td>
<td>±1 d</td>
<td>±1 d</td>
<td>±1 d</td>
<td>±1 d</td>
<td>±1 d</td>
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</table>

- 65 -
APPENDIX 1A: Screening, Acute Phase (Study Days 0 to 28), and Post-Acute Phase (Study Days 29 to 56)

SCHEDULE OF EVALUATIONS (continued)

Footnotes

1. Window for this visit is up to 42 days prior to vaccination (Day 0). Day 0 should occur within 72 hours of randomization per section 4.2.4.5
2. Nasal vaccine is to be administered within 4 hours after pharmacy preparation. Residual vaccine stored by pharmacist staff. See Manual of Operation (MOP).
3. Vaccine administered after Day 0 nasal wash obtained and within 4 hours after pharmacy removes study product from freezer/refrigerator (see MOP).
4. If in-person visit is moved by ±1 day then telephone report is moved to replace the original visit date. Interval, non-study immunizations will be recorded on concomitant medications CRF.
5. Clinical assessment includes interim history, focused clinical examination, vital signs (temperature, pulse, respirations). On Study Visit 28d also review with parent/guardian illness criteria and when to contact study personnel during Study Days 29-56.
6. Nasal wash for viral culture for RSV sent to central laboratory. If illness criteria met, complete adventitious agent assay request for rRT/PCR for adventitious agents (see MOP).
7. Non-Visit Day (Study Day 1, 2, 4, 6, 8, 9, 11, 13, 15, 16, 18, 20, 22-27, 29) information collected by telephone or email contact.
8. Subjects who meet study criteria for fever or respiratory illness during the acute phase of the study (Days 0-28) will be sampled (nasal wash) within 72 hours of study staff notification of the event. For additional details see Section 4.2.6.1 and the MOP.
9. Medical history including demographics, prior diagnoses, current medications, signs and symptoms. Complete physical exam including temperature, heart rate, respiratory rate, blood pressure, weight, length, head circumference, HEENT (Head, Ears, Eyes, Nose, Throat), lungs, heart, abdomen, musculo-skeletal, skin, and age-appropriate neurological exam.
APPENDIX 1B: RSV Pre and Post Season Sampling and Seasonal Surveillance

The following schedule is to be used for patient evaluations and visits for all participants during RSV Season (Nov 1 to March 31).

**SCHEDULE OF EVALUATIONS**

<table>
<thead>
<tr>
<th></th>
<th>Pre-RSV season¹</th>
<th>Weekly report²</th>
<th>Sick Visit³</th>
<th>Post-RSV season</th>
<th>Early DC</th>
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<tbody>
<tr>
<td>Visit Windows</td>
<td>Oct 1st to Oct 31st</td>
<td>Nov 1st to Mar 31st</td>
<td>Apr 1st to Apr 30th</td>
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<td>Interim history</td>
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<td>Nasal wash for viral detection &amp; quantification⁴</td>
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<td>TOTAL BLOOD VOLUMES</td>
<td>5mL</td>
<td></td>
<td>5mL</td>
<td>5mL</td>
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</tbody>
</table>

Footnotes

1. Visit and sample not required if Study Day 56 occurs on or after October 1st.
2. Telephone, email or in person contact weekly to obtain interim history and arrange for study visit if child meets illness criteria for Sick Visit.
3. Study visit within 72 hours if child has a medically attended illness of the following types: fever, upper or lower respiratory illness, or otitis media occurring between November 1st until March 31st.
4. Nasal wash for viral culture for RSV and respiratory viruses by multiplex rRT-PCR within 72 hours of initial report. Sample will be shipped to central laboratory (see MOP).
APPENDIX 2: Planned Laboratory Testing

<table>
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<tr>
<th>Specimen</th>
<th>Assay</th>
<th>Investigator / Lab</th>
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<td>Serum</td>
<td>Immunologic assays</td>
<td>Karron/CIR</td>
</tr>
<tr>
<td>Nasal wash</td>
<td>viral detection &amp; quantification and/or rtPCR for adventitious agents</td>
<td>Karron/CIR</td>
</tr>
<tr>
<td>Nasal Wash</td>
<td>Immunologic assays</td>
<td>Karron/CIR</td>
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<td>Residual vaccine</td>
<td>viral detection &amp; quantification</td>
<td>Karron/CIR</td>
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NOTE: Addresses can be found in the MOP and the LPC
APPENDIX 3: Tables referenced in the background section

Table 7: Comparison of Genomic Sequences of rA2cp248/404/1030ΔSH, MEDI-559, and RSV cps2, Lot RSV#005A

<table>
<thead>
<tr>
<th>Gene Region</th>
<th>RSV Nucleotide (cDNA)</th>
<th>Encoded Amino Acid, Position in ORF</th>
<th>Notes</th>
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<td>MEDI-559&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
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<td>P</td>
<td>2999</td>
<td>A G G</td>
<td>P218</td>
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<td>A G G</td>
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Table 7 (continued):  Comparison of Genomic Sequences of rA2cp248/404/1030ΔSH, MEDI-559, and RSV cps2, Lot RSV#005A

<table>
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<th>Gene Region</th>
<th>RSV Nucleotide (cDNA)(^1)</th>
<th>Encoded Amino Acid, Position in ORF</th>
<th>Notes</th>
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</table>

\(^1\) Genomic position in reference to wt RSV strain A2. The original recombinant RSV backbone \(^2\) contains a single nucleotide insertion at position 1099, and the rA2cp248/404/1030ΔSH cDNA contains in addition the 419 nt-deletion of the SH gene (M74568 nt 4212–4630), but for simplicity the numbering of all sequence positions is based on the complete sequence of biologically-derived strain A2 (Genbank accession number M74568). All sequences are positive-sense.

\(^2\) rA2cp248/404/1030ΔSH, Karron et al., 2005 \(^9\)

\(^3\) MEDI-559, ClinicalTrials.gov Identifier NCT00767416

\(^4\) Drug substance of this IND; rA2cp248/404/1030ΔSH, genetically stabilized version RSV cps2

\(^5\) ncr, non-coding region

\(^6\) GE, Gene end signal

\(^7\) ig, intergenic region

\(^8\) "248" mutation. L831, Codon CTG in rA2cp248/404/1030ΔSH (Karron et al., 2005), TTA in MEDI-559, and stabilized version TTG \(^12\) in RSV cps2

\(^9\) 5 nucleotide changes and one amino acid difference between MEDI-559 and RSV cps2 shaded in light grey

\(^10\) Second site compensatory mutation at position 1313, codon AGC in rA2cp248/404/1030ΔSH (Karron et al., 2005) and in MEDI-559, and genetically stabilized version TCA in RSV cps2.

\(^11\) "1030" mutation. N1321, codon AAT in rA2cp248/404/1030ΔSH (Karron et al., 2005) and in MEDI-559, and genetically stabilized version K1321, codon AAA, in RSV cps2.
Table 8: Stability of L protein codons 831 and 1321 in rA2cp248/404/1030/ΔSH [11] and RSV cps2 after passage at restrictive temperatures

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<th>Codon 1321 (&quot;1030&quot; mutation)</th>
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<tbody>
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<td>% cultures with codon revertants&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
</tr>
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<td>TTG L</td>
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</tr>
<tr>
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</tbody>
</table>

<sup>a</sup>Ten replicate 25 cm<sup>2</sup> flasks of HEp-2 cells were infected with the indicated virus at an MOI of 0.1 PFU/cell at 33°C. Virus was harvested between 5 and 7 days post-infection, serially passaged again at 33°C, and serially passaged twice at 34°C, 35°C, 36°C, and 37°C, for a total of ten passages, each by transferring 1 ml (out of a total of 5 ml) of supernatant to a fresh 25 cm<sup>2</sup> flask of HEp-2 cells. In parallel, two control flasks per mutant were passaged ten times at the permissive temperature of 32°C. For each passage, aliquots were frozen for titration and genotype analysis. Genotype analysis was done after the 10th passage from a 2921 bp PCR fragment of the RSV genome (nt 12271-15191; Genbank accession number M74568) which was partially sequenced. No mutations were detected in the 32°C controls (not shown).

<sup>b</sup>% of cultures with detectable revertants.

<sup>c</sup>Observed codon sequence when mutations were detected: mixtures are indicated in bracket. Nt changes are underlined.

<sup>d</sup>Amino acid coding when mutations were detected; colon indicates a mixed population of the specified amino acids. Amino acid changes are underlined.

<sup>e</sup>In cultures with mixed populations, % of subpopulations with reversions were estimated from sequencing chromatograms. Averages and standard deviation SD from cultures with mixed populations are shown.

<sup>f</sup>rA2cp248/404/1030ΔSH virus that had previously been analyzed in clinical studies by Karron et al [11].

<sup>g</sup>The stabilized codon 1321K (AAA) was used together with codon S1313(TCA); this latter site was completely stable (not shown).
Table 9: Viral Titers of Nasal Wash Samples from Chimpanzees Inoculated with the RSV Vaccine Candidates Medi-559 or cps2

<table>
<thead>
<tr>
<th>RSV Vaccine Candidate</th>
<th>Chimp ID</th>
<th>NW virus titer (log_{10}PFU/mL) on indicated days</th>
<th>Duration of Shedding</th>
<th>Peak Virus Titer</th>
<th>Sum of Daily Titers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1 2 3 4 5 6 7 8 9 10 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEDI-559</td>
<td>A8A007</td>
<td>1.5 - 1.8 - 1.8 1.8 2.6 1.5 1.0 -</td>
<td>9</td>
<td>2.6</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td>A8A008</td>
<td>1.9 - 2.4 2.7 2.8 2.6 2.9 2.4 - -</td>
<td>8</td>
<td>2.9</td>
<td>22.5</td>
</tr>
<tr>
<td>Mean:</td>
<td></td>
<td>8.5 2.7 19.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV cps2</td>
<td>A9A002</td>
<td>- - - - - - - - - - - -</td>
<td>8</td>
<td>3.3</td>
<td>22.4</td>
</tr>
<tr>
<td></td>
<td>4X0533</td>
<td>- - - - - - - - - - - -</td>
<td>8</td>
<td>4.6</td>
<td>21.9</td>
</tr>
<tr>
<td>Mean:</td>
<td></td>
<td>8.3 3.6 20.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Chimpanzees were inoculated by the combined intranasal and intratraceal routes with 10^6 PFU of the indicated virus in a 1 mL inoculum per site (total dose 2 x 10^6 PFU per animal).

b Nasal wash was performed with 3 mL of Lactated Ringer’s solution per nostril. Virus titrations were performed on Vero cells at 32°C. The lower limit of detection was 1.0 log_{10} PFU/mL of nasal wash solution. Samples with no detectable virus are represented as “-“.

The period of days from the first to the last day on which virus was detected, including negative days (if any) in between.

d The sum of daily titers is used as an estimate for the magnitude of shedding (area under the curve). A value of 0.7 was used for samples with no detectable virus.
Table 10: Viral Titers of Bronchoalveolar and Tracheal Lavage Samples from Chimpanzees Inoculated with Medi-559 or cps2a

<table>
<thead>
<tr>
<th>RSV Vaccine candidate</th>
<th>Chimpanzee ID</th>
<th>Bronchoalveolar/Tracheal Lavage virus titer (log_{10}PFU/mL) on indicated daysb</th>
<th>Duration of Sheddingc</th>
<th>Peak virus titer</th>
<th>Sum of daily titersd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 4 6 8 10 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEDI-559</td>
<td>A8A007</td>
<td>2.7 - - - - -</td>
<td>1</td>
<td>2.7</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>A8A008</td>
<td>- - - - - -</td>
<td>0</td>
<td>1.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Mean:</td>
<td></td>
<td>0.5 1.8 5.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV cps2</td>
<td>A8A009</td>
<td>- - - - - -</td>
<td>0</td>
<td>1.0</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>A9A002</td>
<td>- 1.9 3.7 - -</td>
<td>3</td>
<td>3.7</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>4X0533</td>
<td>- 1.0 - 1.6 -</td>
<td>5</td>
<td>1.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Mean:</td>
<td></td>
<td>4.0 2.1 6.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Chimpanzees were inoculated by the combined intranasal and intratracheal routes with 10^6 PFU of the indicated virus in a 1 mL inoculum per site (total dose 2 x 10^6 PFU per animal).
b On Days 2, 4, 6, and 8, bronchoalveolar lavage was performed with 6 mL of PBS; on Days 10 and 12, tracheal lavage was done using 3 mL of PBS per animal. Virus titrations were performed on Vero cells at 32°C. The lower limit of detection was 1.0 log_{10} PFU/mL of lavage solution. Samples with no detectable virus are represented as “-“.
c The period of days from the first to the last day on which virus was detected, including negative days (if any) in between.
d The sum of daily titers is used as an estimate for the magnitude of shedding (area under the curve). A value of 0.7 was used for samples with no detectable virus.
## APPENDIX 4: Definitions of Solicited Adverse Events

### Table 11: Definitions of Solicited Adverse Events (Solicited AEs)

<table>
<thead>
<tr>
<th>Event</th>
<th>Defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Temporal temperatures ≥100.0°F unconfirmed by rectal temp -or- Rectal temperature of ≥100.4°F</td>
</tr>
<tr>
<td>Acute Otitis Media#</td>
<td>Loss of tympanic membrane landmarks, accompanied by erythema and loss of mobility. May or may not be associated with fever or other respiratory symptoms. Confirmed with tympanometry if possible.</td>
</tr>
<tr>
<td>Change in Feeding</td>
<td>Change in feeding habits sufficient to warrant contact with health care provider</td>
</tr>
<tr>
<td><strong>Upper Respiratory Tract Illness</strong></td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>Two or more consecutive days of clear or purulent discharge from the nares not associated with crying, change of room temperature, or eating and drinking.</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>Two or more consecutive days of pharyngeal erythema accompanied by exudate, and/or enlarged tender lymph nodes. May be associated with sore throat, or painful or difficulty swallowing.</td>
</tr>
<tr>
<td>Cough without Lower Respiratory Tract Illness</td>
<td>Two or more consecutive days of 3 or more episodes of cough during a 15 minute timed observation period, in the absence of signs or symptoms suggestive of lower respiratory infection. Not associated with eating, drinking or choking.</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>An unnaturally deep or rough quality of voice, noted by research staff, subject, or parent or guardian.</td>
</tr>
<tr>
<td><strong>Lower Respiratory Tract Illness</strong></td>
<td></td>
</tr>
<tr>
<td>Wheezing*+</td>
<td>Sustained, high pitched, musical breath sounds, especially during the expiratory phase, which do not clear with cough.</td>
</tr>
<tr>
<td>Pneumonia*+</td>
<td>Rales and crackles, originating in the lower respiratory tract, usually accompanied by tachypnea, which do not clear with cough. May be confirmed by x-ray showing areas of consolidation.</td>
</tr>
<tr>
<td>Laryngotracheobronchitis (croup)*+</td>
<td>Barking cough, hoarseness, and inspiratory stridor</td>
</tr>
<tr>
<td>Rhonchi*+</td>
<td>Coarse breath sounds which are not transmitted noises from the upper airway and do not clear with cough.</td>
</tr>
<tr>
<td>Rales*</td>
<td>Abnormal lung sound heard through a stethoscope. Rales may be sibilant (whistling), dry (crackling) or wet (more sloshy) depending on the amount and density of fluid refluxing back and forth in the air passages.</td>
</tr>
</tbody>
</table>

# Diagnosis must be made by a medical professional
* Must be sustained over 20 minutes.
+ Diagnosis must be made by a medical professional and confirmed by a second medical professional, if possible.
APPENDIX 5:  RSV Seasonality in Baltimore

All specimens collected and tested at Johns Hopkins Hospital
APPENDIX 6: INFORMED CONSENT

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP
(IMPAACT)

For protocol: P1114
A Phase I Study of the Safety and Immunogenicity of a Single Dose of the Recombinant Live-
Attenuated Respiratory Syncytial Virus Vaccine RSV cps2,
Lot RSV#005A, Delivered as Nose Drops to RSV-Seronegative
Infants and Children 6 to 24 Months of Age
Version 1.0, dated August 19, 2013

SHORT TITLE FOR IMPAACT P1114: Safety and Immunogenicity of a Single Dose of the RSV
cps2 Vaccine

INTRODUCTION
You are being asked to allow your infant/child to take part in this research study to test a vaccine to
prevent Respiratory Syncytial Virus (RSV) illness in infants and children. This study is sponsored by
the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name
of Principal Investigator). Before you decide if you want your child to be a part of this study, we want
you to know about the study.

This is a consent form. It gives you information about this study. The clinical research staff will talk
with you about this information. You are free to ask questions about this study at any time. If you
agree to allow your child to take part in this study, you will be asked to sign this consent form. You
will get a copy to keep.

WHY IS THIS STUDY BEING DONE?
The study is being done to look at the safety (side effects) and antibody (germ fighters) response of
infants and children to a single dose of a vaccine against a virus called respiratory syncytial virus or
RSV. The study will measure the amount of virus that sheds (comes) from each child receiving the
vaccine. It will tell us how many vaccinated infants and children became infected with RSV and how
stable and strong the vaccine remained throughout the study. This research study is testing an
experimental vaccine. This vaccine has not been licensed by the U.S. Food and Drug Administration
(FDA).

RSV is a virus (germ) that can cause breathing problems in children. Symptoms of infection with RSV
may include:
• Fever
• Runny nose
• Sore throat
• Ear infection
• Cough
• Croup (barky cough with hoarseness)
RSV can cause serious lung infections such as pneumonia and wheezing. At this time, there is no approved vaccine to prevent RSV illness.

Doctors who develop vaccines at the NIH have made a vaccine that may help prevent RSV illness in babies and children. A live virus vaccine contains a weakened, live virus that is designed to help your body develop an immune response without you developing symptoms of the disease it is intended to prevent. The investigational RSV vaccine to be used in this study contains a live, weakened form of the virus, and is given as nose drops.

We are asking you to allow your child to participate in this study. If you agree, we will give your child either 1 dose of study vaccine or 1 dose of placebo (nose drops of a “pretend” vaccine made from fluid similar to salt water, with no vaccine in it). The clinical team will not know whether your child received vaccine or placebo until your child has completed the study. This is the first time this study vaccine will be evaluated in humans. About 51 children who have not already had an illness caused by RSV virus will take part in the study. Your child was chosen to be in this study because your child is between 6 and < 25 months of age and isn’t known to have had an infection or illness caused by RSV.

WHAT DOES MY CHILD HAVE TO DO IF HE/SHE IS IN THIS STUDY?
The vaccine/placebo will be given to your child by squirting it up their nose like nose drops. The amount is very small, less than one tenth of a teaspoon. Your child will need to lie down on his/her back for one minute after receiving the vaccine/placebo. Approximately 2 of each 3 enrolled children will receive the RSV vaccine and approximately 1 of the 3 enrolled children will receive nose drops without vaccine (placebo). Whether your child receives the study vaccine or nose drops without the vaccine (placebo) will be decided by chance (like tossing dice). Neither you nor the study doctors or study nurses will know whether your child received the study vaccine or placebo until the study ends. However, this information is available to the study doctor if needed in an emergency.

If you agree to allow your child to take part in this study, you will be asked some questions to be sure your child can participate in this study.

Your child cannot take part in this study if he or she already has antibodies against RSV, or lives in a house with people with weak immune systems. Your child cannot take part in this study if he or she lives with or is in a daycare room with babies younger than 6 months of age, unless you are willing to keep your child out of daycare for 14 days after your child receives vaccine or placebo. Your child should not receive routine immunizations for at least 28 days after receiving the investigational study vaccine. We ask that your child does not take part in any other experimental vaccine or drug studies for 8 weeks after they receive vaccine or placebo. We will ask you to review and sign this study consent prior to your child's immunization. At that time, we will ask you to answer questions to see how well you understand the study.

Your child will be followed closely for about 8 weeks after receiving vaccine or placebo. During this part of the study, there will be about 12 visits and 19 non-visit day reports to the clinical research staff. Your child will also be followed from November 1st until March 31st (the winter season after your child receives vaccine or placebo). During this winter surveillance period, we will contact you each week to ask about your child's health, and arrange for follow-up visits if necessary.
Your child will participate in this study until April of the year following enrollment. Study visits will last about 30 minutes, except on the day when your child is screened and on the day your child is given the study vaccine; those 2 visits may take about 1 hour each.

- If your child has RSV symptoms, he or she might need to be seen for an evaluation, sometimes as quickly as within 24 hours.

- All study visits, except the visit where your child receives vaccine or placebo, may take place at your home, at your child's pediatric practice, or at one of the IMPAACT sites. The visit where your child receives vaccine or placebo must take place at your child's pediatric practice or at one of the IMPAACT sites where emergency equipment is available.

- For temperature measurements, parents or guardians will be instructed to use a temporal artery thermometer to screen for elevated temporal artery temperatures. This device is used to minimize the number of rectal temperature measurements and has been shown to be an effective screening tool for fever. [24] The parent or guardian will measure temporal artery temperatures 3 consecutive times, following manufacturer’s directions. The highest of the 3 readings will be recorded. Parents or guardians will be asked to verify within 20 minutes any temporal artery temperature of ≥100.0°F with a rectal temperature measurement.[24] Temporal artery and rectal thermometers will be provided to parents or guardians for use during the study.

Screening Visit
The screening visit is to find out if your child may enter the study. It will take about 1 hour and will include:

- reviewing and signing the study consent form;
- completing a comprehension assessment;
- completing your child's medical history and physical examination. If the physical examination results are not normal, the clinical research staff will tell you and refer your child for follow-up care with your child's primary medical provider;
- answering questions about the health of your child and people living in your house;
- collecting a small amount of blood (about 1 teaspoon) to test for antibodies (germ fighters) against RSV;
- if requested, giving written permission to review you and your child’s medical records;
- if your child is found to be eligible for the study, you will be asked to return for a series of study visits, beginning with a vaccination visit.

Vaccination Visit
At the Day 0 visit, your child will receive 1 dose of study vaccine or placebo given as nose drops using a small syringe without a needle. Your child will be lying on his or her back while we give the nose drops and will remain lying down for about 1 minute afterwards.

- Your child will have a nasal wash using salt water (less than 2 tablespoons), before the study vaccine or placebo is given to check for other viruses and to check for antibodies in the nose.
- After the nose drops are given, we will watch your child in the clinic for 30 minutes.
We will give you a temperature card listing dates of the remaining visits and non-visit reporting days. Each visit will take about 30 minutes and we will:
  o Check your child’s temperature, pulse, and breathing rate.
  o Do a brief clinical assessment.
  o Ask about your child’s health since the last visit.
  o Give your child a nasal wash using salt water (less than 2 tablespoons) to check for study vaccine and other viruses. During the nasal wash we will squirt salt water drops into your child’s nose using a nasal bulb.

Monitoring for 56 Days After Vaccination
  • Your child will have study visits on Days 3, 5, 7, 10, 12, 14, 17, 19, 21, and 28 each ± 1 day) after the study vaccine or placebo is given. There will also be non-visit day reporting to the study nurse on Days 1, 2, 4, 6, 8, 9, 11, 13, 15, 16, 18, 20, 22-27. Your child will have a follow-up visit about 56 days after the study nose drops were given. At this visit, we will take a small amount of blood (about 1 teaspoon) from your child’s vein to measure antibodies in the blood. We will also give your child a nasal wash using salt water (less than 2 tablespoons) to check for study vaccine and antibodies in the nose. At the Day 0 visit, you will be given a temporal artery thermometer, a rectal thermometer and a temperature card to record your child’s temperature daily for 29 days (including vaccination day), and at any other time you are concerned about fever.
  • You will be asked to contact the study nurse daily to report temperatures and any illness your child has during the study.
  • We also ask you to call us right away to report any illness that your child has from the day he or she receives the nose drops up to the follow-up visit (8 weeks).
  • A study nurse or study doctor will be available by telephone to answer your questions 24 hours a day during the first 56 days, then available during working hours from Day 57 through the winter RSV season.
  • If your child becomes ill, you may be asked to bring him or her to the clinic for an examination, sometimes as quickly as within 24 hours. We may do a nasal wash at that time to look for the RSV vaccine virus or any other virus that may be in your child's nose.

Monitoring During RSV Season
  • Your child will also be followed during the winter RSV season (November 1 - March 31) after receiving the study nose drops. We will be in contact with you each week to inquire about your child's health. If your child has a fever and/or a respiratory illness that requires medical care, or an ear infection, we will schedule a visit to obtain a nasal wash.
  • We will collect a small amount of blood (about 1 teaspoon) once before and about 1 teaspoon, once after the winter surveillance period (November 1 through March 31) to measure antibody responses to wild-type RSV infection.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
There will be about 51 children taking part in this study.
HOW LONG WILL MY CHILD BE IN THIS STUDY?
Your child will be in this study through April, which is between 7 and 12 months, depending on which month of the year he/she is enrolled.

WHAT ARE THE RISKS OF THE STUDY?
Risks of the Study Vaccine
- If the study vaccine is not weakened enough, it may cause a runny nose, sore throat, cough, or other signs of a cold. It is also possible that it may cause a sinus infection, croup, ear infection, fever, wheezing or pneumonia (infection of the lungs). In another study, a few more children who received a similar RSV vaccine had an episode of wheezing compared to children who received placebo, but there was no evidence that the wheezing was caused by the vaccine. When we have evaluated similar vaccines we have not observed an increase in wheezing.
- Study investigators have used the same placebo for studies of RSV, parainfluenza, and influenza vaccines in several hundred children over the past 20 years. They have noted no adverse events associated with the use of this placebo.
- There is no specific medicine to treat RSV illness. If any symptoms occur, your child will receive prompt medical care.
- This is an investigational live virus vaccine that may include material that has not been identified.
- There may be other side effects of the study vaccine that are not yet known. If new information about possible side effects of this study vaccine becomes available, we will let you know.
- It is possible that the study vaccine virus could be spread from your child to other people in the home or daycare and may make them sick. We have not seen this type of spread when other vaccines like this one were studied.
- The vaccine could cause a severe allergic reaction. A severe reaction can cause hives, throat swelling, rapid heart rate, weakness, difficulty breathing, and death. Such reactions are rare.
- Your child may catch other germs that may cause illness during or after the study.

Risks of Nasal Washes
Nasal washes may cause brief discomfort like the feeling of getting salt water in the nose and may rarely cause a nosebleed.

Risks of Having Blood Drawn
Blood drawing can cause bleeding, pain, bruising, or infection at the place where the blood is taken. Sometimes, blood drawing can cause your child to feel lightheaded or to faint. It sometimes takes more than 1 try to get blood from a small child.

WHY WOULD THE DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?
The study doctors or the sponsor have the right to end your child's participation in the study at any time without your consent for any of the following reasons:

- It would be dangerous for your child to continue;
- You do not follow study procedures as directed by the study doctors;
New information becomes available regarding the safety of the study vaccine;

If it is in your child's best interest;

You do not consent to continue in the study after being told of changes in the research that may affect your child;

The study sponsor, the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), the Institutional Review Board (IRB), the Office for Human Research Protections (OHRP), the National Institute of Allergy and Infectious Diseases (NIAID) Intramural Data and Safety Monitoring Board (DSMB), or the United States Food and Drug Administration (FDA) decide to end the study (A DSMB is an independent committee that monitors the safety of the research. An IRB is a committee that watches over the safety and rights of research subjects.).

WHAT HAPPENS IF MY CHILD IS INJURED?
If your child suffers physical injury from this study, the study doctor will provide or will refer your child for immediate medical treatment. The study doctor will also provide referrals to appropriate health care facilities. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). No financial compensation by the doctors that gave you the vaccine will be made for any discomfort suffered because of participation in this study. You will not be giving up any of your legal rights by signing this consent form.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
- If your child receives the live virus study vaccine, he or she may be protected against illness from 1 type of RSV germ that occurs in the community, but this cannot be guaranteed.
- Since your child may receive the placebo and not the study vaccine, he or she may receive no benefit.
- Your child's involvement in the study may help find a vaccine that works well to prevent serious RSV illness. Such a vaccine may be of future benefit to babies and children in this country and in the rest of the world.

WHAT OTHER CHOICES DO I/DOES MY CHILD HAVE BESIDES THIS STUDY?
There are no licensed vaccines to protect against RSV illness at this time. There is no other similar study or licensed vaccine that we can offer your child. You may choose to not allow your child to take part in this study.

WHAT ABOUT CONFIDENTIALITY?
Your child's name, birth date, and social security number are not routinely given to anyone unless required by law. All of the information you give us during this study will be put in locked file cabinets and/or on password-protected computer files. The only people who will have access to this information will be those who are involved in the study.

There will be people involved in the study who need to see your child’s health information. These people may include the researchers, study and laboratory personnel, and other research clinical research
staff. Others who may see your information are the groups of people who make sure that the study is being done as it should: Hospital Institutional Review Boards (IRBs), the Center for Immunization Research (CIR), the National Institute of Allergy and Infectious Diseases (NIAID; NIH) Intramural Data and Safety Monitoring Board and others who need to see your information to make sure that the study is going as planned.

Other groups of people who may be involved in the study and may need to see your child’s information are:

- The government agency “Office for Human Research Protections,” that makes sure that we are conducting the research as planned, and the U.S. Food and Drug Administration (FDA)
- The sponsor of the study and people that the sponsor may contract with for the study such as study monitors.

At the end of the study, whatever we learn from the research may be used in a medical journal or used for teaching. Your child’s name or other details about your child’s health will not be used in a manner such that anyone can personally identify your child.

**WHAT ARE THE COSTS TO ME?**

There are no costs to you or your child for him/her being in the study. The costs for study vaccines, study visits or study procedures are covered by the sponsor (NIH/NIAID). However, taking part in this study may lead to added costs to you or your child and your/your child’s insurance company if medical complications arise or if your child’s doctor decides extra tests are needed. In some cases it is possible that your/your child’s insurance company will not pay for these costs because your child is taking part in a research study.

**WILL MY CHILD RECEIVE ANY COMPENSATION?**

You will be paid for your child's participation in this study at the Day 56 follow-up visit at the following rate: site insert their payment.

You will also be paid during the winter RSV surveillance period as follows: site insert their rate

If you stop your child from taking part in the study early, you will only be paid for the days of the study that your child completed. Your child may also receive age appropriate books or small toys. If needed, bus tokens or parking passes will be given to you.

You may be required to provide your Social Security number to be paid. If your payment for study participation exceeds $600 per year, this information must be reported to the Internal Revenue Service.

**WHAT ARE MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?**

Taking part in this study is completely voluntary. You may choose not to have your child take part in this study or leave this study at any time. Your decision will not have any impact on your child’s participation in other studies and will not result in any penalty or loss of benefits to which you or your child are otherwise entitled.
A study physician, physician assistant, nurse practitioner, or study nurse will inform you of any significant abnormal physical findings and will make appropriate referrals back to your child’s primary care giver, if necessary.

We will tell you about new information from this or other studies that may affect your child’s health, welfare or willingness to stay in this study. You may be asked to sign a revised consent form if this occurs. If you want the results of the study, let the clinical research staff know.

At the end of the study, you will be told in writing whether your child was given the vaccine or the placebo

WHAT ARE MY RESPONSIBILITIES?

- If you decide to withdraw your child from the study early, we ask that you notify the study nurse or study doctor.
- If your child comes off the study early, we will ask you to bring him or her into the clinic for an early discontinuation visit so that we can do a final blood draw (about 1 teaspoon) and nasal wash.
- Any child who has received the study vaccine will be encouraged to remain in the study so that safety information can be collected.
- It is important that you do not enroll your child in other studies where your child receives vaccines or medications while in this study.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- Insert name of the investigator or other study staff
- telephone number of above

For questions about your child’s rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

STORAGE OF SPECIMENS

If you agree, any unused blood or nasal wash samples taken from your child will be stored indefinitely once this study is complete. This unused blood and nasal wash samples may be used for future laboratory studies to learn more about RSV and other viruses. This information may lead to other new virus vaccines in the future.

- Your child’s unused blood or nasal wash samples, if any, will be used only for laboratory studies and will not be sold or used directly to make products that will be for sale.
- No human genetic tests will be done on your child’s samples.
- The samples will be coded so that your child’s name cannot be easily identified.
- Reports about studies done with your child’s unused samples will not be put in your child’s health or study records.
• There will be no direct benefit to your child in using the samples as noted, but from studying the unused samples of children taking part in the studies, we may learn more about the RSV germ or other viruses that cause illness in children.

• Results from future studies using your child’s unused samples may be included in medical papers and meeting reports, but your child’s name will not be used.

You can change your mind at any time about allowing your child’s unused samples to be used for future laboratory studies. If you do, contact the study doctor or study nurse and let them know. Then the samples will no longer be used for laboratory studies and will be destroyed.

SPECIMEN STORAGE PERMISSION
Your choice will not have any effect on your child’s taking part in this study.

I will allow the use of my child’s identifiable unused blood or nasal wash samples to be stored indefinitely and to be used in future laboratory studies for the purposes described above. (Please check one and initial below)

Yes:  Initials __________  Date __________

No:  Initials __________  Date __________

If NO, your child’s study samples will be destroyed after the study is completed.
SIGNATURE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Study Participant’s Name (print)

Participant’s Legal Guardian (print)  
Legal Guardian’s Signature and Date

Clinical Research Staff Conducting Consent Discussion (print)  
Clinical Research Staff Signature and Date

Witness’ Name (print)  
(As appropriate)  
Witness’s Signature and Date

Second parent or guardian’s Name  
(As appropriate)  
Signature and Date