A PHASE I/II RANDOMIZED TRIAL OF THE SAFETY AND IMMUNOGENICITY
OF COLD ADAPTED INFLUENZA VACCINE (FLUMIST™)
IN HIV-INFECTED CHILDREN AND ADOLESCENTS

A Multicenter Trial of the Pediatric AIDS Clinical Trials Group

Sponsored by:

The National Institute of Allergy and Infectious Diseases

Pharmaceutical Support Provided by:

MedImmune

IND # ___

The Pediatric ACTG HIV Complications Research Agenda Committee:

Sharon Nachman, M.D., Chair

Protocol Chair: Myron J. Levin, M.D.

Protocol Vice Chairs: Sharon A. Nachman, M.D.
Adriana Weinberg, M.D.

DAIDS Medical Officer: Elizabeth Smith, M.D.

Clinical Trials Specialist: Diane G. Costello, B.S.

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August 13, 2004
PACTG P1057 PROTOCOL TEAM ROSTER

All questions concerning this protocol should be sent via e-mail to actg.teamp1057@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 actg.teamp1057@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail Protocol@tech-res.com, fax: (800) 418-3544, or phone: (301) 897-1707. For enrollment questions, call (716) 834-0900 ext. 301. For SAE questions, e-mail SAE@tech-res.com or call 1 (800) 537-9979 or (301) 897-1709. To order study drug, call the Clinical Research Products Management Center at (301) 294-0741.

Protocol Chair

Myron J. Levin, M.D.
University of Colorado Health Sciences Center
Section of Pediatric Infectious Diseases
Campus Box C227
4200 East Ninth Avenue
Denver, CO 80220-3706
Phone: (303) 315-4620
Fax: (303) 315-7909
E-mail: myron.levin@uchsc.edu

Protocol Vice Chairs (Cont.)

Adriana Weinberg, M.D.
University of Colorado Health Sciences Center
Section of Pediatric Infectious Diseases
Campus Box C227
4200 East Ninth Avenue
Denver, CO 80220-3706
Phone: (303) 315-4624
Fax: (303) 315-6955
E-mail: adriana.weinberg@uchsc.edu

Protocol Vice Chairs

Sharon A. Nachman, M.D.
SUNY at Stony Brook
Health Science Center
T11-080
Stony Brook, NY 11794-8111
Phone: (631) 444-7692
Fax: (631) 444-7292
E-mail: snachman@mail.som.sunysb.edu

DAIDS Medical Officer

Elizabeth Smith, M.D.
Pediatric Medicine Branch
DAIDS, NIAID, NIH, DHHS
Room 5157
6700-B Rockledge Drive MSC 7624
Bethesda, MD 20892-7624
Phone: (301) 402-3226
Fax: (301) 480-4582
E-mail: bs161v@nih.gov
### PACTG P1057 PROTOCOL TEAM ROSTER (Cont.)

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Affiliation</th>
<th>Address</th>
<th>Phone</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICHD Medical Officer</td>
<td>Jennifer S. Read, M.D., M.S., M.P.H.</td>
<td>DTM&amp;H Pediatric, Adolescent, and Maternal AIDS (PAMA) Branch</td>
<td>NICHD, NIH Executive Building, Room 4B11F 6100 Executive Boulevard MSC 7510 Bethesda, MD 20892-7510</td>
<td>(301) 435-6872</td>
<td>(301) 496-8678</td>
<td><a href="mailto:Jennifer_Read@nih.gov">Jennifer_Read@nih.gov</a></td>
</tr>
<tr>
<td>Protocol Data Manager</td>
<td>Barbara Nowak, B.A.</td>
<td>Frontier Science &amp; Technology Research Foundation</td>
<td>4033 Maple Road Amherst, NY 14226-1056</td>
<td>(716) 834-0900 x7233</td>
<td>(716) 834-8675</td>
<td><a href="mailto:nowak.barbara@fstrf.org">nowak.barbara@fstrf.org</a></td>
</tr>
<tr>
<td>Clinical Trials Specialist</td>
<td>Diane G. Costello, B.S.</td>
<td>Pediatric ACTG Operations Center</td>
<td>8757 Georgia Avenue Silver Spring, MD 20910</td>
<td>(301) 628-3559</td>
<td>(301) 628-3304</td>
<td><a href="mailto:dcostello@s-3.com">dcostello@s-3.com</a></td>
</tr>
<tr>
<td>Statistician</td>
<td>Lin-Ye Song, Ph.D.</td>
<td>SDAC, Harvard School of Public Health</td>
<td>651 Huntington Avenue Boston, MA 02115-6017</td>
<td>(617) 432-3867</td>
<td>(617) 432-2843</td>
<td><a href="mailto:song@sdac.harvard.edu">song@sdac.harvard.edu</a></td>
</tr>
<tr>
<td>Protocol Pharmacist</td>
<td>Debra S. Payne, Pharm.D.</td>
<td>Pharmaceutical Affairs Branch</td>
<td>DAIDS, NIAID, NIH 6700-B Rockledge Drive, Suite 4222 MSC 7260 Bethesda, MD 20817-7857</td>
<td>(301) 451-2775</td>
<td>(301) 402-1506</td>
<td><a href="mailto:depayne@niaid.nih.gov">depayne@niaid.nih.gov</a></td>
</tr>
</tbody>
</table>
Protocol Virologist

Paul Palumbo, MD
UMDNJ/New Jersey Medical School
Division of Pulmonary, Allergy, Immunology & Infectious Diseases,
Department of Pediatrics
185 South Orange Avenue, F570A
Newark, NJ 07103-2714
Phone: (973) 972-5066
Fax: (973) 972-6443
E-mail: palumbo@umdnj.edu

Protocol Immunologist

Adriana Weinberg, MD
University of Colorado Health Sciences Center
Section of Pediatric Infectious Diseases
Campus Box C227
4200 East Ninth Avenue
Denver, CO 80220-3706
Phone: (303) 315-4624
Fax: (303) 315-6955
E-mail: adriana.weinberg@uchsc.edu

Laboratory Technologist

David L. Shugarts, M.A.
University of Colorado Health Sciences Center
Infectious Diseases, 168
Campus Box B
4200 East Ninth Avenue
Denver, CO 80262
Phone: (303) 315-1827
Fax: (303) 315-1816
E-mail: david.shugarts@uchsc.edu

Pharmaceutical Company Representatives

Edward M. Connor, M.D.
Senior Vice President, Clinical Development
Chief Medical Officer
MedImmune, Inc.
One MedImmune Way
Gaithersburg, MD 20878-4024
Phone: (301) 398-0000
Fax: (301) 398-9375
E-mail: connore@medimmune.com

Paul Mendelman, M.D.
Vice President and Group Leader,
Infectious Diseases and Vaccines
MedImmune Vaccines, Inc.
297 North Bernado Avenue
Mountain View, CA 94043
Phone: (650) 919-6510
Fax: (650) 919-6686
E-mail: mendelmanp@medimmune.com

Robert Walker, MD
Director, Clinical Development
MedImmune Vaccines, Inc.
297 North Bernado Avenue
Mountain View, CA 94043
Phone: (650) 919-1266
Fax: (650) 919-2495
E-mail: WalkerR@medimmune.com
Community Constituency Group (CCG) Representatives

Brian Feit
HRSA Title IV
Division of Community Based Programs
Comprehensive Family Service Branch, CCG
Parklawn Building, Room 7A-30
5600 Fishers Lane
Rockville, MD 20857
Phone: (301) 443-3478
Fax: (301) 443-1839
E-mail: bfeit@hrsa.gov

Noemi Nagy
31-34 51st Street, #5C
Woodside, NY 11371
Phone: (718) 334-3837
Fax: (718) 334-1064
E-mail: nagyn@nychc.org

Laboratory Data Coordinator

Joanne Schiffhauer, B.S.
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst, NY 14226-1056
Phone: (716) 834-0900 x7337
Fax: (716) 834-8432
E-mail: schiffhauer.joanne@fstrf.org

WESTAT Study Manager

Erin Smith, CCRA
Clinical Research Associate
WESTAT Inc.
1441 West Montgomery Avenue, WB 323
Rockville, MD 20850-3129
Phone: (240) 453-2640
Fax: (240) 453-2720
E-mail: erinsmith@westat.com
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SCHEMA

A PHASE I/II RANDOMIZED TRIAL OF THE SAFETY AND IMMUNOGENICITY OF COLD ADAPTED INFLUENZA VACCINE (FLUMIST™) IN HIV-INFECTED CHILDREN AND ADOLESCENTS

DESIGN: Phase I/II, open label.

SAMPLE SIZE: 300 subjects; 150 per arm. All subjects need to be enrolled between the time the study opens to accrual at PACTG sites and the last date for vaccination because of the changing nature of the influenza vaccines from year to year.

POPULATION: HIV-infected children and adolescents (≥ 5 to < 18 years of age) on a stable HAART regimen for ≥ 16 weeks, with no change in their HAART regimen anticipated. HAART is defined as ≥ 3 antiretroviral drugs (ARVs) from at least two different therapeutic classes or the combination of ZDV/3TC/ABC (Trizivir®).

- HIV-1 plasma RNA < 60,000 copies/mL within 60 days prior to screening.
- CD4+ percentage ≥ 15% (Groups 1 and 2) or ≥ 25% (Group 3) and CD4+ count that meets age-specific criteria for CDC immunological class 2.
- Receipt of inactivated influenza vaccine in at least one of the prior two years.

REGIMEN: All subjects will receive influenza immunization starting as soon as possible in September 2004 and as late as November 19, 2004.

Subjects will be randomly allocated to either study Arm:
- Arm A will receive cold-adapted live attenuated influenza vaccine (FluMist™).
- Arm B will receive inactivated influenza vaccine (IAIV, Fluzone®).

STRATIFICATION: Each of the two study arms will be stratified by the following CD4% criteria (50 subjects per group):
- Group 1 = CD4% < 15% at nadir and ≥ 15% at screening
- Group 2 = CD4% ≥ 15 but < 25% at nadir and ≥ 15% at screening
- Group 3 = CD4% ≥ 25% at nadir and ≥ 25% at screening
Nadir is defined as the lowest CD4% ever recorded during the subject’s lifetime. The subject will remain in his/her assigned Group throughout the study for purposes of analysis.

TREATMENT/STUDY DURATION:

After a single immunization on Day 0 subjects will be followed for 6 months.

OBJECTIVES:

Primary

1. To compare the safety of FluMist™ with IAIV in HIV-infected children and adolescents.

2. To compare the immunogenicity of FluMist™ with IAIV in HIV-infected children and adolescents.

3. To determine prevalence and duration of viral shedding of FluMist™ in HIV-infected vaccinees.

Secondary

1. To correlate immune responses and viral shedding with the immunologic Group of the vaccinee (i.e., defined by nadir and current CD4%).

2. Correlate vaccine responses and baseline antibody titer.

3. Determine responses in each Arm and Group after 6 months as a measure of persistence of antibody responses.

4. Correlate immune responses with CD4+ cell count, CD4%, and plasma HIV-1 RNA concentration at the time of immunization.

5. Determine the frequency, duration, and quantity of viral shedding in recipients of FluMist™ (Arm A) as a function of the Group of the vaccinee.

6. Determine the homotypic and heterotypic immune responses in each Arm and Group.

7. Correlate humoral and cellular immune responses.

8. Correlate viral shedding with humoral and mucosal immunity.
1.0 INTRODUCTION

1.1 Background

Influenza virus infections occur commonly in normal children in annual winter-spring epidemics. The resulting illness sometimes consists of mild or inconsequential upper respiratory symptoms, but more significant tracheobronchial involvement is also common. Moreover, bacterial superinfection following influenza is common in children, causing otitis media, sinusitis, and pneumonia (1-4). Influenza has an even greater potential to cause bacterial complications in some HIV-infected children, and is more likely to complicate their routine care during epidemic periods (5, 6). There is also the theoretical possibility that this viral illness will enhance HIV replication by activating CD4+ cells (especially in children with incomplete drug suppression) and thereby will stimulate more rapid HIV disease progression.

The current standard of care is to immunize HIV-infected children with an inactivated influenza vaccine (IAIV). The immunogenicity of this vaccine in HIV-infected adults and children with advanced disease is limited, whereas it is more likely to induce a strong response in those with less advanced HIV disease (7, 8). The efficacy of IAIV in HIV-infected children has not been established.

Side effects that have been reported following FluMist™ administration include runny nose, nasal congestion, cough, irritability, headache, decreased activity, sore throat, muscle aches, low grade fever, chills and vomiting. Due to concerns of shedding vaccine virus, FluMist™ recipients should avoid close contact (e.g., within the same household) with immunocompromised individuals for at least 21 days following vaccination. FluMist™ is contraindicated in children and adolescents receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye syndrome with aspirin and wild-type influenza infection. Systemic reactions such as malaise, fever, and myalgia have been reported following administration of Fluzone® as well as soreness, redness, or swelling at the injection site. Guillain-Barré Syndrome is a risk common to both vaccines. Individuals with a history of hypersensitivity to any component of either vaccine, including eggs or egg products as well as gentamicin, should not receive FluMist™ or Fluzone® (Package Insert for Influenza Virus Vaccine Live, Intranasal FluMist™. MedImmune Vaccines, Inc., 16 June 2003; Package Insert for Influenza Virus Vaccine Fluzone®. Aventis Pasteur Inc., July 2003).

1.2 Rationale

Cold-adapted live attenuated influenza vaccine (FluMist™) is immunogenic and effective in HIV-uninfected children (9-10). In these pediatric studies, influenza-related otitis media was also decreased by FluMist™ (11). FluMist™ is licensed
for children 5 to 17 years of age who are immunocompetent (Package Insert for Influenza Virus Vaccine Live, Intranasal FluMist™. MedImmune Vaccines, Inc., 16 June 2003).

FluMist™ has been safely administered to a small number (n=24) of HIV-infected children (mean age 4.7 years, range 1.0 to 7.9 years) without advanced disease (12). Signs and symptoms in HIV-infected children were similar to those seen in uninfected children after one or more doses of FluMist™ within each HIV status group, and there were no vaccine-related serious adverse events. Similar results were obtained from 57 HIV-infected adults without advanced disease who received FluMist™ (13). Additional safety information in HIV-infected children is desirable.

A significant antibody response to at least one influenza virus antigen was observed in 77% of HIV-infected children in the previous small trial (12). HIV-infected children enrolled in PACTG P1057 will be older than those previously studied, and therefore will more likely be seropositive prior to vaccination (more exposure to wild-type influenza and to prior IAIV). Pre-existing immunity will blunt the response to the live vaccine and lower post-vaccination hemagglutination inhibition assay (HAI) responses to FluMist™. In seropositive adults, whether HIV-infected or not, a ≥ 4-fold rise in antibody titer to FluMist™ was observed in less than 10% by strain and their post-vaccination titers did not increase significantly (13). In contrast, pre-existing immunity does not blunt the response to IAIV as immunocompetent vaccinees are likely to have significant post-vaccination serum HAI responses to IAIV (i.e., the majority will have ≥ 4-fold rises or titers ≥ 1:32 or ≥ 1:40). The evaluation of FluMist™ and IAIV will focus on: 1) the number of vaccinees achieving a predefined “protective level” (protective level is not definitively established but many investigators use a titer of 1:32 or 1:40 in the HAI assay as a surrogate for protection); 2) persistence of these responses; 3) induction of specific cell-mediated immunity (CMI); and 4) induction of heterotypic responses. Immune responses to FluMist™ and IAIV in immunocompromised individuals have not been evaluated beyond 28 to 42 days after vaccination. PACTG P1057 will include measurements at 6 months, thereby providing an evaluation of the persistence of immune responses. In addition, the effect of vaccine on influenza-specific mucosal immunity will be evaluated.

FluMist™ is commonly shed following vaccination. The duration and quantity of shedding is of interest for two reasons: 1) it could provide a potential reservoir of virus to revert to wild-type influenza that might be a threat to severely immunocompromised vaccinees; and 2) it might cause primary and secondary infections in severely immunocompromised individuals. In immunocompetent children over 5 years of age, 9% (3/22) had virus isolated 7-10 days after vaccination (Data on File at MedImmune; studies AV002/AV002-2 and DMID 99-012). In contrast to shedding in older children, virus was isolated from
approximately 80% of immunocompetent children < 3 years of age who received FluMist™ (14). However, transmission of vaccine virus from normal children < 3 years of age in a day care center was a rare event (less than 1%) (14), and vaccine viruses isolated in this study retained the vaccine phenotype and genotype - including the single documented vaccine virus that was transmitted (14). Since the attenuation of vaccine strains is related to multiple changes in at least three gene segments, back-mutation to virulence is implausible (11, 15). In a study of age-matched HIV-infected and uninfected children aged 1-7 years, 28% of uninfected children and 13% of HIV-infected children had vaccine virus isolated within the first 10 days after vaccination, and no child, even if HIV-infected, shed virus more than 10 days after vaccination (12). No subject in either group had virus isolated at 28-35 days after vaccination. The titer of shed virus was more than 1000-fold lower than the titer in the vaccine administered. Overall, the available data indicate that shedding is not longer in HIV-infected children than in HIV-uninfected children (12).

FluMist™ has potential advantages for HIV-infected children. These include:
1. FluMist™ is administered intranasally. Therefore, administration is simpler (no injection is required), not painful, and greater acceptability is likely.
2. Because of its intranasal administration, FluMist™ might stimulate greater local and systemic anti-influenza immune responses.
3. Cold-adapted influenza vaccines appear to stimulate better cross-protection against strains not included in the vaccine administered (10, 15-20). In a study of children less than 36 months of age, a single dose of a liquid formulation of the cold-adapted influenza vaccine was 6 times more likely than IAIV to stimulate protective immunity against both the vaccine Type A strain and the Type A drift strain (19).

PACTG P1057 is specifically designed to provide significant new information about the nature of vaccine-induced responses in HIV-infected children at various stages of their HIV disease, and thereby addresses the issue of the nature of immunological reconstitution after HAART. It is the first analysis of responses to a live vaccine administered topically (intranasally) in PACTG subjects receiving HAART and will be the first to assess reconstitution of their CD8-specific responses and mucosal immunity.

2.0 STUDY OBJECTIVES

2.1 Primary

2.11 To compare the safety of FluMist™ with IAIV in HIV-infected children and adolescents.
2.12 To compare the immunogenicity of FluMist™ with IAIV in HIV-infected children and adolescents.

2.13 To determine prevalence and duration of viral shedding of FluMist™ in HIV-infected vaccinees.

2.2 Secondary

2.21 To correlate immune responses and viral shedding with the immunologic Group of the vaccinee (i.e., defined by nadir and current CD4%).

2.22 Correlate vaccine responses and baseline antibody titer.

2.23 Determine responses in each Arm and Group after 6 months as a measure of persistence of antibody responses.

2.24 Correlate immune responses with CD4+ cell count, CD4%, and plasma HIV-1 RNA concentration at the time of immunization.

2.25 Determine the frequency, duration, and quantity of viral shedding in recipients of FluMist™ (Arm A) as a function of the Group of the vaccinee.

2.26 Determine the homotypic and heterotypic immune responses in each Arm and Group.

2.27 Correlate humoral and cellular immune responses.

2.28 Correlate viral shedding with humoral and mucosal immunity.

3.0 STUDY DESIGN

PACTG P1057 is a Phase I/II randomized, open label study designed to evaluate the safety, immunogenicity, and shedding of vaccine strain virus in HIV-infected children and adolescents immunized with FluMist™. An additional goal is to determine if safety, immunogenicity, and shedding varies as a function of prior immune deficits and immune status at the time of vaccination.

The study will enroll 300 HIV-infected children and adolescents ≥ 5 years to < 18 years of age who have been on a stable HAART regimen for ≥ 16 weeks with no change in HAART anticipated. Plasma HIV-1 RNA concentration must be < 60,000 copies/mL within 60 days prior to screening, the CD4+ percentage ≥ 15% (Groups 1 and 2) or ≥ 25% (Group 3) and the subject must have a CD4+ count that meets age-specific criteria
for CDC immunological class 2. These inclusion criteria for HIV status were chosen because in two other trials using live virus vaccines (PACTG 265 and PACTG P1024), they were used without the occurrence of any vaccine-related serious adverse events.

To avoid the need for two doses of either inactivated or live vaccine in the initial phase of the study, subjects must be previously primed with IAIV in at least one of the prior two years. In previously influenza virus-naïve children, current recommendations call for the use of either IAIV or FluMist™ as the priming dose for a second FluMist™ vaccination (3).

- Subjects will be randomly assigned to one of two arms (n=150 in each arm); subjects in Arm A will receive FluMist™ and those enrolled in Arm B will receive IAIV (Fluzone®). The vaccination period will begin as soon as possible in September 2004; the actual date is ultimately dependent upon the availability of the vaccines. Sites will continue to vaccinate subjects through November 19, 2004. Historically, the influenza epidemic has generally not occurred prior to January 1. However, the 2003 flu epidemic began much earlier – November to December. The date of November 19th was chosen in anticipation of allowing 2 weeks for an immune response to be present by the time influenza infection is present in the community.

Each arm will be stratified according to CD4% to three groups (n = 50 in each group):
- Group 1 = CD4% <15% at nadir and ≥ 15% at screening
- Group 2 = CD4% ≥ 15 but < 25% at nadir and ≥ 15% at screening
- Group 3 = CD4% ≥ 25% at nadir and ≥ 25% at screening.

Nadir is defined as the lowest CD4% ever recorded during the subject’s lifetime. The subject will remain in his/her assigned group throughout the study for purposes of analysis.

These immunologically defined groups are being used because preliminary results from PACTG 1024 indicate both immunologic nadir and current immune status influence the response to immunogens in HIV-infected children who are stable on HAART (21, 22). Although it is possible to define other immunologic groups, the groups chosen for this protocol reflect the availability of potential vaccinees within the PACTG based on numbers derived from a large, long-term follow-up study (PACTG 219C).

**Laboratory evaluations:**

Specimens to be collected according to the Schedule of Evaluations (Appendix I).

For all subjects:
- Plasma HIV-1 RNA concentration, CD4+ count and CD4%. Note that the screening HIV-1 RNA assay is to be performed only if there is inadequate
documentation (as defined in 4.16) of HIV status and/or no plasma HIV-1 RNA results within 60 days prior to screening.

- Serum HAI anti-influenza antibody against the vaccine strains and to selected drifted influenza strains.
- Serum neutralizing antibody using a microneutralization assay against the vaccine strain and to selected drifted influenza strains.
- Salivary IgG and IgA anti-influenza antibody to the vaccine strains and to selected drifted influenza strains.

For the first 25 subjects in each Group in each Arm (150 total):
- ELISPOT determination of CMI to the vaccine antigens and a non-vaccine influenza antigen.

For subjects in Arm A:
- Influenza virus shedding measured from nasal swabs at 3, 14, and 28 days after vaccination with FluMist™. Viral harvests of all positive cultures will be stored frozen and shipped with the original nasal specimen aliquots to MedImmune Vaccines, Inc. Strain-specific isolates from Day 14 or 28 (the last positive sample) will be subtyped, genotyped, and phenotyped by MedImmune Vaccines, Inc. The amount of virus in an aliquot from the original nasal specimen will be determined quantitatively by MedImmune Vaccines, Inc.

Clinical evaluations:

Please refer to Toxicity Management (section 6.1). Briefly:

- All unplanned health care provider visits in the first 28 days post-vaccination will be reported on the appropriate CRF.

- A Vaccination Report Card will be maintained by the subject and/or their caretaker for 28 days post vaccination (see section 6.1). The Report Card is to be used solely as a memory aid for the participant and will NOT be utilized as a source document. Therefore, it will NOT be collected by the site at the end of the 28-day period.

- All subjects or their caretakers will be contacted by telephone on Days 7 and 21 post-vaccination to inquire about adverse events, obtain the information written on the Vaccination Report Card and to remind them to maintain the Card for the first 28 days ONLY. In addition, those subjects on Arm B (IAIV) will be contacted by phone on Days 3 and 14 post-vaccination to obtain this information, since they will not be seen in clinic on those days. Subjects on Arm A (FluMist™) will be seen in clinic on those days.

- Lower respiratory illnesses will be assessed for virologic etiology with culture and/or rapid diagnostic tests (see section 6.1).
• SAEs and additional safety information to include any significant new medical conditions (e.g., diabetes, auto-immune disease, chronic fatigue syndrome etc.) will be obtained from all subjects during the Day 42 phone contact and the 6-month clinic visit.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.11 Age ≥ 5 and < 18 years.

4.12 On stable HAART regimen for ≥ 16 weeks. (HAART defined as ≥ 3 antiretrovirals from at least 2 different therapeutic classes or Trizivir®); no changes in therapy anticipated.

4.13 A minimum at screening of a CD4+ percent ≥ 15% (for Groups 1 and 2) and ≥ 25% (for Group 3). In addition, a CD4+ count that meets age-specific criteria for CDC immunological class 2.

4.14 Plasma HIV-1 RNA concentration < 60,000 copies/mL within 60 days prior to screening.

4.15 Receipt of IAIV in at least one of the prior two years. The purpose of this criterion is to focus the study on previously primed children, and thereby avoid the need for two doses of either inactivated or live vaccine in the immunization phase of the study.
• Prior vaccination is to be documented by review of written medical records or immunization card and noted accordingly on the appropriate CRF.

4.16 A confirmed diagnosis of HIV-1 infection defined as two positive assays from two different samples. The two results may be in any combination of the following:
• Age > 4 weeks: HIV p24 antigen detection
• Age > 18 months: licensed ELISA with confirmatory Western Blot
• At any age: HIV-1 culture, HIV-1 DNA PCR, HIV-1 plasma RNA ≥ 10,000 copies/mL
• One of the two results must be from an assay done in an ACTG-certified laboratory which is approved to perform the assay for protocol testing (CLIA or equivalent plus DAIDS VQA-approved laboratories).
4.17 Subject or parent or legal guardian able and willing to provide signed informed consent.

4.18 Subject or parent or legal guardian available by telephone for purposes of communication with study staff.

4.2 Exclusion Criteria

4.21 Any immunosuppressive or immunomodulatory therapy within 60 days prior to immunization or immunological testing.

4.22 Any aspirin or aspirin-containing therapy at the time of vaccination or planned for 42 days after immunization.

4.23 Any history of hypersensitivity to any component of IAIV or FluMist™, including eggs, egg products, gentamicin or thimerosal.

4.24 Prior history of Guillain-Barré Syndrome.

4.25 Receipt of:
- any inactivated vaccine within 14 days prior to the study vaccination;
- any live vaccine within 30 days prior to the study vaccination;
- or plans to receive any vaccine within the 30 days following the study vaccination;
- any additional influenza vaccine for the duration of the study (through the final 6-month visit).

4.26 Prophylactic use of drugs with anti-influenza activity as listed in 4.6 (amantadine, rimantadine, zanamivir, oseltamivir).

4.27 Chronic pulmonary disease, obstructive or restrictive, that is ≥ moderate in severity based on clinical assessment by the site medical staff and available pulmonary function tests.

4.28 Cardiopulmonary disease affecting normal childhood activity.

4.29 Medically-diagnosed wheezing, bronchodilator use, or steroid use (systemic or inhaled) within the previous 42 days by parent/guardian report or chart review (e.g., children with recent persistent asthma are excluded).

4.291 A medical illness believed by the site investigator to be associated with suppression of T-cell mediated cellular immunity (such as lupus erythematosus or Hodgkin’s Disease; chemotherapy for a malignancy or
autoimmune illness in the prior 3 months; or prednisone (or equivalent) 20mg/kg/day within the 2 weeks prior to study vaccination).

4.292 Pregnancy, or for biologically capable women (e.g., menses within the last year) an unwillingness to continue acceptable birth control, including abstinence, for 3 months following vaccination.

- Acceptable birth control is determined by the subject’s HAART regimen and treatment with a protease inhibitor (PI) or efavirenz, but options may include: the use of a condom, diaphragm, cervical cap, intrauterine device (IUD), oral contraceptives or depoprogesterone, Norplant, the “Patch” or abstinence.

- Pregnancy status is established by asking the subject and recording the response. There is no pregnancy test performed until the actual day of vaccination.

4.293 Breast-feeding or lactating female subjects.

4.294 Household member who in the opinion of the site investigator is severely immunosuppressed (recent chemotherapy; prednisone (or equivalent) ≥ 20 mg/kg/day for 2 weeks before the subject is to receive study vaccine, or organ transplantation).

- An HIV-infected household member with CD4 percentage < 15% or CD4+ count < 200 cells/mm³ would exclude the individual from study participation.
- Note: CD4+ status is historical information and not being obtained by testing of the family member.

4.295 Receipt of any blood product within 3 months prior to vaccination or expected receipt during the study, inclusive of the 6-month follow-up period.

4.296 Any condition that in the opinion of the investigator would interfere with the interpretation or evaluation of the vaccine.

4.3 Vaccination Eligibility Criteria

Subjects must continue to meet the criteria as specified in 4.1, 4.2 and 4.6. In addition, the following must be met for the administration of either FluMist™ or Fluzone® on Day 0:
4.31 Negative pregnancy test. All participants biologically capable of becoming pregnant (menses within the last year) must have a negative urine pregnancy test performed on the day of vaccination (Day 0) and the results verified by the site staff prior to administration of vaccine.

4.32 Absence of significant fever (T > 101°F; rectal reading preferred) or intercurrent illness (as determined by the site investigator) within 72 hours prior to vaccination.
- Neither vaccine should be administered until 3 days after fever and/or symptoms have subsided.
- In the event a subject presents with an intercurrent illness or significant fever at the time of vaccination, the 72 hour window between Entry and vaccination (Day 0) will be extended to 7 days. This is to allow for the resolution of the fever and/or symptoms and the additional 3 days to pass before vaccine may be administered. Sites are to notify the protocol team should this be necessary (actg.teamp1057@fstrf.org).
- If the 7 days are insufficient, the subject must come off study having never received vaccine. The protocol team is to be notified of such an event (actg.teamp1057@fstrf.org).

4.4 Concomitant Medications

For all medications (including over-the-counter cold medications and nasal sprays) taken from screening visit through the 28-day post-vaccination follow-up period: the start and stop dates of the medication(s), and the reason(s) for administration (pre-existing condition or prophylaxis) will be recorded on the appropriate CRF.

4.5 Allowed Medications

Non-steroidal anti-inflammatory agents such as ibuprofen (Advil®) and acetaminophen (Tylenol®) may be taken to relieve pain and fever.

4.6 Disallowed Medications

Any vaccine administered within the time constraints as described in 4.25.

Aspirin (acetylsalicylic acid) and aspirin-containing products within 42 days after vaccination with FluMist™.
- These are prohibited because of the association of Reye Syndrome with aspirin and aspirin-containing therapy and wild-type influenza infection in children.
The following antivirals are disallowed for the first 28 days post-vaccination.

- Amantadine (Symmetrel®)
- Rimantidine (Flumadine®)
- Zanamivir (Relenza®)
- Oseltamivir (Tamiflu®)

However, these antiviral agents may be used for treatment in the immediate post-vaccination period for a lower respiratory tract infection based upon investigator discretion.

Any intranasal medication for 1 hour before and 1 hour after receiving FluMist™.

### 4.7 Enrollment Procedures

Subjects meeting the inclusion/exclusion criteria can be enrolled in PACTG P1057 by the SDAC/DMC (Statistical Data Analysis Center/Data Management Center) enrollment screens. All screening evaluations should be completed within 14 days prior to study entry. Entry evaluations must be completed within 72 hours prior to vaccination with the exception as noted in 4.32.

- Please note that there are specific eligibility criteria that must be met the day of vaccination in order for either vaccine to be administered (see section 4.3).

The vaccination period is anticipated to begin with availability of the designated vaccines at PACTG sites in September 2004 and continue until November 19, 2004.

Sites must be registered with and approved by the DAIDS Regulatory Compliance Center Protocol Registration Office before subjects can be enrolled in this study.

### 4.8 Co-Enrollment Guidelines

Co-enrollment is permitted except for protocols that would violate the exclusion criteria. All co-enrollments require the assent of the protocol chairs of PACTG P1057 and the co-enrollment protocols. Co-enrollment in PACTG 219C (Pediatric Late Outcomes Protocol) is encouraged.

### 5.0 STUDY TREATMENT

#### 5.1 Vaccine Regimens, Administration, and Duration
No antiretroviral study drugs will be supplied as a part of this study. Enrolled subjects must be currently receiving a stable HAART regimen consisting of at least three antiretroviral agents, from at least two of the available therapeutic classes or the combination of ZDV/3TC/ABC (Trizivir®), as chosen by their primary care provider, for ≥ 16 weeks prior to screening.

Influenza Virus Vaccine Live, Intranasal (FluMist™) or Influenza Virus Vaccine, Intramuscular (IAIV) will be administered as a single dose in September 2004 through November 19, 2004.

5.11 Regimen

- Arm A: Influenza Virus Vaccine Live, Intranasal, (FluMist™) 0.5 mL (0.25 mL per nostril),
- Arm B: Influenza Viral Vaccine, Intramuscular, (IAIV) 0.5 mL in the deltoid muscle region,

5.12 Administration

After vaccination, all participants will be observed for approximately 15 minutes. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected adverse reaction. Adequate treatment provisions, including epinephrine, will be available for immediate use in case of anaphylactic reaction.

5.121 Influenza Virus Vaccine Live, Intranasal (FluMist™), will be administered as a single dose of 0.5 mL (0.25 mL per nostril) intranasally at study entry. Do not administer parenterally.

Directions for Use of the Influenza Virus Vaccine Live, Intranasal (FluMist™):

- Thaw Influenza Virus Vaccine Live, Intranasal, immediately prior to administration by holding the sprayer in the palm of the hand FOR 5 MINUTES, and supporting the plunger rod with the thumb to prevent it from falling out. Do not roll the sprayer or depress the plunger.
- Remove the rubber tip protector.
- Seat the subject in an upright position, with head tilted slightly back, and insert the tip of the sprayer just inside the nostril.
- Depress the plunger to administer the first half dose of approximately 0.25 mL.
• Remove the dose-divider clip from the plunger.
• Insert the tip of the sprayer just inside the other/opposite nostril. Depress the plunger to administer the remaining second half dose of approximately 0.25 mL of the vaccine.

5.122 Influenza Virus Vaccine, Intramuscular (IAIV), will be administered as a single dose of 0.5 mL intramuscularly, in the deltoid muscle region per the manufacturer’s instructions.

5.2 Study Treatment Formulation

*Influenza Virus Vaccine Live, Intranasal (FluMist™)* is a live trivalent nasally administered vaccine intended for active immunization for the prevention of influenza. Each 0.5 mL dose is formulated to contain $10^{6.5-7.5}$ TCID$_{50}$ (median tissue culture infectious dose) of live attenuated influenza virus reassortants of the strains A/New Caledonia/20/99 (H1N1), A/Wyoming/3/2003 (H3N2), and B/Jilin/20/2003 as recommended by the U.S. Public Health Service (USPHS) for the 2004/2005 season. It is supplied as single dose, 0.5 mL prefilled sprayer. Influenza Virus Vaccine Live, Intranasal MUST BE STORED AT -15°C (5°F) OR BELOW. DO NOT REFREEZE the product. Thawed Influenza Virus Vaccine Live, Intranasal may be stored refrigerated (2-8°C) for up to 24 hours before use. Note: the Influenza Virus Vaccine Live, Intranasal vaccine will be stored and shipped to each site at -70°C. Once the Influenza Virus Vaccine Live, Intranasal has been stored at any temperature above -70°C it CANNOT be returned to -70°C.

Storage of Influenza Virus Vaccine Live, Intranasal in a frost-free freezer should be avoided because the temperature could cycle above -15°C (5°F) and can therefore, negatively impact the stability of the product. If a frost-free freezer is the only means available to store the product a Freezer Box for the freezer must be ordered from the Clinical Research Products Management Center (see section 5.3) to ensure proper maintenance of product temperature. The approximate dimensions of the Freezer Box are: 14 ¾” L x 9 9/16” W x 8 3/8” H. The Freezer Box should be placed in the freezer in a horizontal position, with the latch facing forwards.

*Influenza Viral Vaccine, Intramuscular (Fluzone®, IAIV)* is a sterile suspension prepared from influenza viruses propagated in fertilized chicken eggs. Fluzone® has been standardized according to USPHS requirements for the 2004-2005 influenza season. It is formulated to contain 45 micrograms (µg) of hemagglutinin (HA) per 0.5 mL dose of the recommended three prototype strains (15 µg of HA per strain). It is supplied as a single dose, 0.5 mL prefilled syringe. Fluzone® must be stored between 2° - 8°C (35° - 46°F). DO NOT USE FLUZONE® IF IT HAS BEEN FROZEN. Potency is destroyed by freezing.
5.3 Study Agents Supply, Distribution, and Pharmacy

Influenza Virus Vaccine Live, Intranasal (FluMist™) will be provided by MedImmune Vaccines Inc.

Influenza Viral Vaccine, Intramuscular (Fluzone®, IAIV) will be provided for the Pediatric AIDS Clinical Trials Group (PACTG) from Aventis by MedImmune Vaccines, Inc.

Study agents will be available through the NIAID Clinical Research Products Management Center. The Pediatric AIDS Clinical Trials Unit (PACTU) pharmacist can obtain the study agents for the protocol by following the instructions in the manual "Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks" in the section Study Product Control.

The NIAID Clinical Research Products Management Center will NOT provide HAART, syringes, or supplies for administration of vaccines as part of this study.

The PACTU pharmacist is required to maintain complete records of all study medication(s) received from the NIAID Clinical Research Products Management Center and subsequently dispensed. All unused study medication must be returned to the NIAID Clinical Research Products Management Center after the study is completed or terminated. The procedures to be followed are given in the manual, "Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks Group" in the section Study Product Control.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

The Division of AIDS standardized Toxicity Table for Grading Severity of Pediatric Adverse Experiences (>3mos April 1994), will be used for grading toxicities (toxicity table is available at http://rcc.tech-res-intl.com).

The supplemental grading scales in:

*Appendix II (Supplemental Toxicity Table for Pulmonary/Respiratory Symptoms)*, and

*Appendix III (Supplemental Toxicity Table for Vaccine-Related Toxicities Occurring Within 28 Days of Vaccination)*

supercede the Division of AIDS Toxicity Table when grading these specific toxicities.
In addition, all subjects regardless of vaccine received, will receive a Vaccination Report Card at Entry to be maintained by the subject and/or caretaker. Symptoms and body temperature are to be recorded daily beginning the day of vaccination through Day 28 post-immunization. The symptoms to be recorded will include: cough, runny nose/nasal congestion, sore throat, irritability, headache, chills, vomiting, muscle aches, tiredness and if applicable, pain, redness and swelling at the vaccine injection site. This subject-recorded information for Arm B-IAIV, will be obtained by the site via phone contact on Days 3, 7, 14, and 21, and by personal contact during the clinic visit on Day 28. The same information for Arm A-FluMist™ will be obtained via personal contact during clinic visits on Days 3, 14, 28, and by phone contact on Days 7 and 21. Information regarding SAEs and significant new medical conditions (e.g., diabetes, autoimmune disease, chronic fatigue syndrome, etc.) will be obtained from all subjects via phone contact on Day 42. All subjects will return to clinic for the 6-month visit during which any significant new medical conditions will be recorded as well as any SAEs that may have occurred since the last phone contact (Day 42).

Alternate explanations for clinical and laboratory abnormalities must be sought prior to attribution to study vaccines. In the case of possible or probable viral infections being implicated in an adverse event, the results of appropriate viral cultures and/or rapid diagnostic methods can be used to determine etiology.

- Lower respiratory illnesses will be assessed for virologic etiology with culture and/or rapid diagnostic tests. Lower respiratory illness is defined as pneumonia, bronchitis, bronchiolitis, wheezing, or croup.
- Subjects and/or their caretakers will be instructed to call the study site immediately if anything occurs which is unusual or alarming. A clinic visit is required within 12 hours for all adverse reactions thought to be ≥ Grade 3 as defined by the standard Toxicity Table, Appendix II, and Appendix III.

All ACTG investigators will perform appropriate clinical management of adverse events according to the situation.

- The protocol chairs should be contacted (actg.teamp1057@fstrf.org) if the investigator has questions about adverse events potentially attributable to the vaccines.
- Abnormal clinical and laboratory findings should be followed. Repeat evaluations for toxicities ≥ Grade 3 within 72 hours.
- If toxicity is thought to be due to study vaccine, evaluations should be repeated every week or more frequently if medically indicated, until toxicity falls below Grade 2.

6.2 Study Management Plan
The trial has adopted specific stopping rules (see section 8.5). Once 10 subjects have been enrolled to Arm A and received FluMist™, the protocol team will evaluate these initial subjects’ safety data for vaccine-related Grade 3 and Grade 4 toxicities that occurred during the first 7 days post-vaccination. The vaccine will fail safety criteria and no further vaccine will be administered if:

1) any of these subjects have acute life-threatening toxicities (e.g., anaphylaxis) attributable to the vaccine, OR

2) 3 or more of these subjects have non-life-threatening Grade 3 or 4 toxicities attributable to vaccine.

While the protocol team is conducting this review of the safety data, sites may continue to screen potential subjects, but the randomization screens will be closed.

Thereafter, at two subsequent time points – when 75 subjects overall (Arm A and Arm B combined) and 150 subjects overall have enrolled into the trial – the statistician will determine if the cumulative incidence of Grade 3 or Grade 4 vaccine-related AEs in Arm A exceeds 20%, or any life-threatening toxicities (e.g., anaphylaxis) attributable to FluMist™ are observed. If this occurs at either time point, the study will be halted (randomization screens closed) pending a formal analysis and subsequent review by a Study Monitoring Committee.

6.3 Criteria for Study Discontinuation

6.31 The subject or legal guardian refuses treatment and/or follow-up evaluations.

6.32 The investigator determines that further participation would be detrimental to the subject's health or well-being.

6.33 The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.

6.34 Subject fails to meet vaccination eligibility criteria (see section 4.3).

6.4 Pregnancy

Pregnant women are not permitted to enroll to the study and all biologically capable women must be willing to continue an acceptable method of birth control for 3 months following vaccination. However, should a woman become pregnant while on study after being vaccinated, she will be followed per protocol for the duration of the trial (6 months) and pregnancy outcome will be noted. Given the short duration of the trial, it is most likely that outcome information will be
obtained after the study has ended. This will require a specific form to record delivery outcome.

There are no post-vaccination pregnancy tests required per the protocol. All females biologically capable of becoming pregnant will be asked pregnancy status at the following post-vaccination times: Day 28 clinic visit, Day 42 phone contact, and 6-month clinic visit.

An affirmative answer will trigger the use of a pregnancy/delivery outcome form to be completed via telephone contact with the woman at the expected time of her term delivery. It is the site’s responsibility to keep the form and follow up at the appropriate time. The data from the form will be keyed into the DMC database.

Enrollment in the Pregnancy Antiretroviral Registry is encouraged (http://www.apregistry.com).

7.0 SERIOUS ADVERSE EXPERIENCE REPORTING

This protocol follows intensive reporting requirements for the entire 6-month study period, which are defined in the current Division of AIDS Serious Adverse Experience (SAE) Reporting Manual (1 August 1998 version). Serious Adverse Experience (SAE) forms should be submitted to the DAIDS through the Regulatory Compliance Center (RCC) as described in the most recent SAE Reporting Manual.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

The primary objectives of this study are to evaluate the safety, immunogenicity, and shedding of vaccine virus in HIV-infected children immunized with FluMist™. Important secondary objectives are to examine how safety, immunogenicity, and viral shedding vary as a function of immune status at the time of vaccination and with prior immune suppression. The current standard of care is to immunize HIV-infected children with IAIV (Fluzone®). In order to examine whether the safety and/or immunogenicity of FluMist™ differs significantly from that of Fluzone® the study will contain two arms, with Arm A (n=150) receiving FluMist™ and Arm B (n=150) receiving Fluzone®.

Key statistical issues include the following:
1) The study will have limited statistical power for FluMist™ versus Fluzone® comparisons, given that they are expected to be similar with respect to overall safety and the rate of serious adverse events.

2) For FluMist™ versus Fluzone® comparisons, it is not expected that CAIV vs. IAIV effects will vary as a function of immdata; will be pooled across strata when there are no significant strata by vaccine effects. However, since there is a possibility that vaccine effects will vary across strata, calculations are presented below for within strata, as well as pooled analyses.

2)3) The confidence interval around the difference between the response rates of arms A and B will be estimated separately for toxicity and immunogenicity by exact methods (23, StatExact-5).

8.2 Outcome Measures

8.21 Primary Endpoints and Response Variables:

8.211 Grade ≥ 3 adverse events attributed to the vaccines.

8.212 Strain specific immune responses measured by HAI and Neutralization assays.

8.213 Shedding of vaccine strain influenza virus.

8.22 Secondary Endpoints and Response Variables:

8.221 To correlate immune responses and viral shedding with the immunologic Group of the vaccinee (i.e., defined as nadir and current CD4%).

8.222 Correlate vaccine responses and baseline antibody titer.

8.223 Determine responses in each Arm and Group after 6 months as a measure of persistence of antibody responses.

8.224 Correlate immune responses with CD4+ cell count, CD4%, and viral load at the time of immunization.

8.225 Determine the frequency, duration, and quantity of viral shedding in recipients of FluMist™ (Arm A) as a function of the Group of the vaccinee.

8.226 Determine the homotypic and heterotypic immune responses in each Arm and Group.
8.227 Correlate humoral and cellular immune responses.

8.228 Correlate viral shedding with humoral and mucosal immunity.

8.3 Randomization and Stratification

Subjects will be stratified on the basis of immunologic status into 3 strata, defined as follows:

Group 1: nadir CD4% of <15% and CD4% at screening ≥ 15%.

Group 2: nadir CD4% of ≥ 15% but < 25% and CD4% at screening ≥ 15%.

Group 3: nadir CD4% of ≥ 25% and CD4% at screening ≥ 25%.

Each Group will contain 100 subjects, randomized such that 50 receive FluMist™, while the other 50 receive Fluzone®.

8.4 Sample Size and Accrual

The study will accrue 300 subjects. All subjects (150 in each arm) need to be enrolled between the time the study opens to accrual at PACTG sites and the last date of vaccination (November 19, 2004) because of the changing nature of the influenza vaccines from year to year.

Section 8.6 presents 95% confidence intervals around potential differences between the FluMist™ and Fluzone® arms, with respect to rates of Grade ≥ 3 adverse events and immunologic response. These confidence intervals demonstrate the precision with which such differences can be estimated, given the limited sample size.

8.5 Monitoring

The safety and tolerability of the study medication will be monitored by means of adverse events reports (AER) and monthly toxicity reports presenting laboratory and clinical data. It is required that the data from these reports be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available. These reports and adverse events (whether determined to be vaccine-related or not), will be discussed by the protocol team on bimonthly conference calls during September and October (schedule dependent upon date of vaccine availability) and monthly conference calls thereafter. HIV RNA and CD4+ data will also be evaluated in an attempt to look for adverse vaccine effects which are reflected in lower CD4+ percentages or
increased plasma HIV RNA concentrations. The extent to which adverse events are over-represented in particular immunologic strata will also be monitored. If the protocol team observes any pattern which suggests that subject safety may be jeopardized, further accrual will be stopped pending a thorough investigation, and the study will not resume unless the team determines that it is safe to do so.

Relationship of the Adverse Event to Study Vaccine:

Interpretation of the causal relationship of the vaccine to the AE in question will be based on the type of event, the relationship of the event to the time of vaccine administration, the known biology of the vaccine viruses, and the investigator’s medical judgment.

A vaccine-related AE refers to an AE for which there is a possibly related or definite relationship to the administration of the vaccine. The investigator determines the relationship to the vaccine by the following definitions:

1. **Unable to judge**
2. **Not Related**
3. **Possibly Related**
4. **Definitely Related**.

**Early Stopping Rule for Arm A:**

Once 10 subjects have been enrolled to Arm A and received FluMist™, the protocol team will evaluate these initial subjects’ safety data for vaccine-related Grade 3 and Grade 4 toxicities that occurred during the first 7 days post-vaccination.

The vaccine will fail safety criteria and no further vaccine will be administered if:

- any of these subjects have acute life-threatening toxicities (e.g., anaphylaxis) attributable to the vaccine, OR
- 3 or more of these subjects have non-life-threatening Grade 3 or 4 toxicities attributable to vaccine.

While the protocol team (including the statistician(s), Medical Officers and pharmaceutical company representatives) is conducting this review of the safety data, sites may continue to screen potential subjects, but the randomization screens will be closed. Once the evaluation of the 7-day post-vaccination data is completed and a decision has been made by the protocol team that it is safe to continue the trial, the randomization screens will be re-opened.
Given the small sample size, the information available for decisions concerning early stopping of the study will be imperfect. Two types of sampling errors are possible:

1) the sample data may pass the safety criteria, when the true toxicity in the population represented by the sample is unacceptably high.

2) the sample data may fail the safety criteria, when the true toxicity in the population represented by the sample is low enough to be considered safe.

The extent to which these safety criteria protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur, if the vaccine was used extensively among the subject population represented by the sample. The hypothetical situations presented below range from conditions under which the product would cause a high incidence of severe and life-threatening toxicities to conditions under which severe toxicities would be relatively rare and would not be life-threatening. For each of these hypothetical situations, we assume that an initial sample of 10 subjects in Arm A is drawn from the subject population and that the safety evaluation, summarized above, is followed.

The following table presents the probability that this evaluation would result in failing safety criteria and stopping the enrollment for further evaluation by the protocol team under each of the hypothetical rates of true toxicity.
Table 1: Probability of Failing Safety Criteria and Stopping the Enrollment for Further Evaluation by Protocol Team, Under Potential Rates of True Toxicity in the Population Represented by the Study Sample (10 subjects in Arm A)

<table>
<thead>
<tr>
<th>Grade ≥ 3 Toxicity Rates</th>
<th>Probability of Failing Safety Criteria</th>
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<tr>
<td>Non-Life-Threatening</td>
<td>Life-Threatening</td>
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This table shows that there is a 98% chance of failing the safety criteria under conditions in which the true rate of non-life-threatening grade 3 or 4 toxicity is 25% and the true rate of life-threatening toxicity is 25%. Failing the safety criteria is almost certainly desirable under these conditions; thus, the 2% chance of passing the criteria and continuing accrual to the study represents the chance of error. The table also shows that there is a 1-7% chance of failing the safety criteria, when the true rate of grade 3 or 4 toxicity is only 5-10% and the true rate of life-threatening toxicity is zero. Assuming that the potential benefits of the vaccine would outweigh the risks associated with this relatively low rate of toxicity, stopping the study under these conditions would be an error.

Stopping Rule for Arms A and B:

At two subsequent time points – when 75 subjects overall (inclusive of the initial 10 Arm A subjects noted above) and 150 subjects overall (inclusive of the initial 10 Arm A subjects noted above) have enrolled into the trial – the statistician will determine if the cumulative incidence of Grade ≥ 3 vaccine-related AEs in Arm A exceeds 20%, or any life-threatening toxicities (e.g., anaphylaxis) attributable to FluMist™ are observed. If this occurs at either time point, the study will be halted (randomization screens closed) pending review of the observed events. The protocol team will evaluate the evidence for designating an event as vaccine-related,
including utilization of available virological data and information on AEs occurring in Arm B (in this instance functioning as a control).

Due to the nature of this study and resulting short period for accrual, a greater burden has been placed on the protocol team with respect to trial monitoring. With such a timeframe it is not practical to suspend enrollment while convening an independent entity to review the safety data. However, if the criteria noted above (the cumulative incidence of Grade $\geq 3$ vaccine-related AEs in Arm A exceeds 20%, or any life-threatening toxicities (e.g., anaphylaxis) attributable to FluMist™ are observed) occurs at either or both time points (75 and/or 150 subjects enrolled), a formal analysis will be done by a Study Monitoring Committee (SMC) at the warranted time point(s).

These analyses will be reviewed by a SMC consisting of the Study Chair, Vice-Chairs, Medical Officers, Statisticians, Virologist, Data Manager, a MedImmune representative, one nominated member from the Complications Research Agenda Committee (RAC) who is not an investigator on the study and will serve as the chair of the SMC, and two members of the NIAID Therapeutics DSMB. The SMC will assess the results and make recommendations for continuation or suspension of vaccine administration, and study alterations to the Complications RAC.

If the events described above do occur, study enrollment will be halted pending a review. The FDA will be informed if such a halt is placed and will be informed of the decisions reached following the review.

After vaccination, adverse event information will be collected by the site via phone contact for Arm B-Fluzone® on Days 3, 7, 14, 21 and 42 and by personal contact during a clinic visit on Day 28. The same information will be collected via personal contact for Arm A-FluMist™ during clinic visits on Days 3, 14 and 28, and by phone on Days 7, 21 and 42. All subjects (both study arms) will return to clinic for the 6-month visit.

The contact via clinic visits for Arm A-FluMist™ at Days 3 and 14 is necessary for nasal swab collection. A history and physical exam will also be conducted at these two extra clinic visits in Arm A subjects. Therefore, it is possible that the information gathered on these extra visits for Arm A may result in a reporting bias, making it appear that Arm A has a greater incidence of adverse events than Arm B. However, in the judgment of the protocol team, it is unlikely that this will have an impact on the Grade $\geq 3$ adverse events, since the phone contact on Days 3 and 14 for Arm B should be sufficient to detect events of this level of severity. It should be noted that any bias which may occur will result in a conservative assessment of the safety of Arm A relative to Arm B.
8.6 Analysis

The primary analyses will consist of: 1) an estimate of the difference between Arms A and B, with respect to rates of Grade $\geq 3$ adverse events, bounded by a 95% confidence interval; 2) an estimate of the difference between the two Arms, with respect to rates of Grade $\geq 3$ adverse events judged to be vaccine-related, bounded by a 95% confidence interval and 3) an estimate of the difference in immunologic response rates between the two Arms, bounded by a 95% confidence interval.

Confidence intervals for GMTs will be constructed using a percentage-based bootstrap method. Logistic regression models will be used to test whether differences between Arms A and B vary significantly across immunologic strata with respect to rates of Grade $\geq 3$ events and/or immunologic response.

8.6.1 Safety

Tables 2A and 2B present exact 95% confidence intervals around potential differences between Arms A and B, with respect to rates of Grade $\geq 3$ adverse events, or the subset of such events that are judged to be vaccine related.

These calculations depend upon the following assumptions:

a) Sample size of 50 subjects in each of the 3 immunologic Groups, yielding a total of 150 subjects per Arm.

b) A 2% or 6% rate of Grade $\geq 3$ adverse events in Arm B, which represents the current standard of care.

c) Analysis to consist of an exact 95% confidence interval around the difference between the two Arms in the rate of Grade $\geq 3$ adverse events.

d) The vaccine effect may differ significantly across Groups; thus the calculations are done for within Group analyses, as well as the total sample.

If both the upper limit and lower limit of the 95% confidence interval around the difference in Grade $\geq 3$ adverse event rates (Arm A-Arm B) were below 0, this would provide 95% confidence that the true toxicity rate in the population represented by Arm A was less than that in the population represented by Arm B (superiority). Conversely, if both the upper limit and lower limit of this confidence interval were above 0, this would provide 95% confidence that the true toxicity rate in the population represented by Arm A was greater than that in the population represented by Arm B (inferiority).

As an example of how to read these tables: the second row of Table 2A shows that, if one Grade $\geq 3$ event is observed in Arm A while 3 occur in Arm B, the
The confidence interval around the difference in adverse events rate between Arms A and B has a lower limit of −0.051 and an upper limit of 0.019. Since zero is included in this 95% confidence interval, such a result would not provide 95% confidence that the population represented by Arm A differs significantly from that represented by Arm B.

Table 2A: 95% confidence intervals (exact) for difference of vaccine-related Grade ≥ 3 adverse event rates between two Arms (Groups pooled).

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Arm A Observed adverse events rate (FluMist™)</th>
<th>Arm B Observed adverse events rate (Control)</th>
<th>A-B Difference of adverse events rate</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>0.00 (00/150)</td>
<td>0.02 (03/150)</td>
<td>-0.020</td>
<td>-0.057</td>
<td>0.005</td>
</tr>
<tr>
<td>150</td>
<td>0.01 (01/150)</td>
<td>0.02 (03/150)</td>
<td>-0.013</td>
<td>-0.051</td>
<td>0.019</td>
</tr>
<tr>
<td>150</td>
<td>0.01 (02/150)</td>
<td>0.02 (03/150)</td>
<td>-0.007</td>
<td>-0.045</td>
<td>0.030</td>
</tr>
<tr>
<td>150</td>
<td>0.02 (03/150)</td>
<td>0.02 (03/150)</td>
<td>0.000</td>
<td>-0.040</td>
<td>0.040</td>
</tr>
<tr>
<td>150</td>
<td>0.03 (04/150)</td>
<td>0.02 (03/150)</td>
<td>0.007</td>
<td>-0.034</td>
<td>0.049</td>
</tr>
<tr>
<td>150</td>
<td>0.04 (06/150)</td>
<td>0.02 (03/150)</td>
<td>0.020</td>
<td>-0.022</td>
<td>0.067</td>
</tr>
<tr>
<td>150</td>
<td>0.06 (09/150)</td>
<td>0.02 (03/150)</td>
<td>0.040</td>
<td>-0.005</td>
<td>0.092</td>
</tr>
<tr>
<td>150</td>
<td>0.07 (10/150)</td>
<td>0.02 (03/150)</td>
<td>0.047</td>
<td>0.003</td>
<td>0.101</td>
</tr>
<tr>
<td>150</td>
<td>0.00 (00/150)</td>
<td>0.06 (09/150)</td>
<td>-0.060</td>
<td>-0.111</td>
<td>-0.027</td>
</tr>
<tr>
<td>150</td>
<td>0.01 (02/150)</td>
<td>0.06 (09/150)</td>
<td>-0.047</td>
<td>-0.098</td>
<td>-0.004</td>
</tr>
<tr>
<td>150</td>
<td>0.02 (03/150)</td>
<td>0.06 (09/150)</td>
<td>-0.040</td>
<td>-0.092</td>
<td>0.005</td>
</tr>
<tr>
<td>150</td>
<td>0.04 (06/150)</td>
<td>0.06 (09/150)</td>
<td>-0.020</td>
<td>-0.075</td>
<td>0.033</td>
</tr>
<tr>
<td>150</td>
<td>0.06 (09/150)</td>
<td>0.06 (09/150)</td>
<td>0.000</td>
<td>-0.058</td>
<td>0.058</td>
</tr>
<tr>
<td>150</td>
<td>0.08 (12/150)</td>
<td>0.06 (09/150)</td>
<td>0.020</td>
<td>-0.040</td>
<td>0.082</td>
</tr>
<tr>
<td>150</td>
<td>0.10 (15/150)</td>
<td>0.06 (09/150)</td>
<td>0.040</td>
<td>-0.023</td>
<td>0.106</td>
</tr>
<tr>
<td>150</td>
<td>0.12 (18/150)</td>
<td>0.06 (09/150)</td>
<td>0.060</td>
<td>-0.005</td>
<td>0.129</td>
</tr>
<tr>
<td>150</td>
<td>0.13 (19/150)</td>
<td>0.06 (09/150)</td>
<td>0.067</td>
<td>0.001</td>
<td>0.137</td>
</tr>
</tbody>
</table>
Table 2B: 95% confidence intervals (exact) for difference of vaccine-related Grade ≥ 3 adverse event rates between two Arms (per Group).

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Arm A Observed adverse events rate (FluMist&lt;sup&gt;TM&lt;/sup&gt;)</th>
<th>Arm B Observed adverse events rate (Control)</th>
<th>A-B Difference of adverse events rate</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.00 (00/50)</td>
<td>0.02 (01/50)</td>
<td>-0.02</td>
<td>-0.107 - 0.054</td>
</tr>
<tr>
<td>50</td>
<td>0.02 (01/50)</td>
<td>0.02 (01/50)</td>
<td>0.00</td>
<td>-0.088 - 0.088</td>
</tr>
<tr>
<td>50</td>
<td>0.04 (02/50)</td>
<td>0.02 (01/50)</td>
<td>0.02</td>
<td>-0.071 - 0.119</td>
</tr>
<tr>
<td>50</td>
<td>0.08 (04/50)</td>
<td>0.02 (01/50)</td>
<td>0.06</td>
<td>-0.037 - 0.175</td>
</tr>
<tr>
<td>50</td>
<td>0.12 (06/50)</td>
<td>0.02 (01/50)</td>
<td>0.10</td>
<td>-0.005 - 0.223</td>
</tr>
<tr>
<td>50</td>
<td>0.14 (07/50)</td>
<td>0.02 (01/50)</td>
<td>0.12</td>
<td>0.011 - 0.248</td>
</tr>
<tr>
<td>50</td>
<td>0.00 (00/50)</td>
<td>0.06 (03/50)</td>
<td>-0.06</td>
<td>-0.166 - 0.014</td>
</tr>
<tr>
<td>50</td>
<td>0.02 (01/50)</td>
<td>0.06 (03/50)</td>
<td>-0.04</td>
<td>-0.146 - 0.052</td>
</tr>
<tr>
<td>50</td>
<td>0.06 (03/50)</td>
<td>0.06 (03/50)</td>
<td>0.00</td>
<td>-0.112 - 0.113</td>
</tr>
<tr>
<td>50</td>
<td>0.12 (06/50)</td>
<td>0.06 (03/50)</td>
<td>0.06</td>
<td>-0.059 - 0.190</td>
</tr>
<tr>
<td>50</td>
<td>0.18 (09/50)</td>
<td>0.06 (03/50)</td>
<td>0.12</td>
<td>-0.012 - 0.261</td>
</tr>
<tr>
<td>50</td>
<td>0.20 (10/50)</td>
<td>0.06 (03/50)</td>
<td>0.14</td>
<td>0.006 - 0.283</td>
</tr>
</tbody>
</table>

8.62 Immunogenicity

The strain specific immune responses among all subjects and baseline seronegative subjects will be evaluated by:

**Serum HAI:**
- Number and percent of subjects with ≥ 4-fold rises GMT;
- Number and percent of subjects with titers ≥ 1:32 (or ≥ 1:40).

**Serum Neutralization:**
- Number and percent of subjects with ≥ 4-fold rises GMT.

Key immunogenicity analyses will consist of exact 95% confidence intervals around differences between Arms A and B, with respect to rates of immunologic response. Tables 3A, 3B, and 3C present confidence intervals around potential differences that might be observed. These calculations depend upon the following assumptions:
a) Sample size of 50 subjects in each of the 3 immunologic Groups, yielding a total of 150 subjects per Arm.

b) A 50% rate of immunologic response to IAIV (Arm B), which represents current standard of care.

c) Analysis to consist of an exact 95% confidence interval around the difference in immunologic response rates (Arm A - Arm B).

d) The vaccine effect may differ significantly across Groups; thus the calculations are done for within Group analyses, as well as the total sample.

e) The HAI seronegativity rate at baseline: seronegative is defined as HAI ≤ 1:4 in children 5-8 years of age and as HAI ≤ 1:8 in children 9-17 years of age.

If both the lower limit and upper limits of the 95% confidence interval around the difference in immunologic response rates (Arm A - Arm B) were above 0, this would provide 95% confidence that the true response rate in the population represented by Arm A was greater than that in the population represented by Arm B (superiority). Conversely, if both the lower and upper limit of this confidence interval were below 0, this would provide 95% confidence that the true response rate in the population represented by Arm A was lower than that in the population represented by Arm B (inferiority).

To guard against the loss of statistical power, due to suboptimal response definitions, further group comparisons on the immunologic data will be performed using parametric or rank order methods, depending upon the distributions of these data.

f) Exploratory analyses of safety in the 28 day post-vaccination period by immunologic response for both treatment arms may be conducted.
### Table 3A: 95% confidence intervals (exact) for difference of immunologic response rates between two Arms (Groups pooled).

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Arm A Observed response rate (FluMist™)</th>
<th>Arm B Observed response rate (Control)</th>
<th>A-B Difference of response rate</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>0.80 (120/150)</td>
<td>0.50 (75/150)</td>
<td>0.300</td>
<td>0.193 - 0.402</td>
</tr>
<tr>
<td>150</td>
<td>0.70 (105/150)</td>
<td>0.50 (75/150)</td>
<td>0.200</td>
<td>0.089 - 0.308</td>
</tr>
<tr>
<td>150</td>
<td>0.62 (93/150)</td>
<td>0.50 (75/150)</td>
<td>0.120</td>
<td>0.006 - 0.232</td>
</tr>
<tr>
<td>150</td>
<td>0.61 (92/150)</td>
<td>0.50 (75/150)</td>
<td>0.113</td>
<td>0.000 - 0.225</td>
</tr>
<tr>
<td>150</td>
<td>0.56 (84/150)</td>
<td>0.50 (75/150)</td>
<td>0.060</td>
<td>-0.055 - 0.174</td>
</tr>
<tr>
<td>150</td>
<td>0.50 (75/150)</td>
<td>0.50 (75/150)</td>
<td>0.000</td>
<td>-0.116 - 0.116</td>
</tr>
<tr>
<td>150</td>
<td>0.44 (66/150)</td>
<td>0.50 (75/150)</td>
<td>-0.060</td>
<td>-0.174 - 0.055</td>
</tr>
<tr>
<td>150</td>
<td>0.40 (60/150)</td>
<td>0.50 (75/150)</td>
<td>-0.100</td>
<td>-0.212 - 0.014</td>
</tr>
<tr>
<td>150</td>
<td>0.39 (58/150)</td>
<td>0.50 (75/150)</td>
<td>-0.113</td>
<td>-0.225 - 0.001</td>
</tr>
<tr>
<td>150</td>
<td>0.38 (57/150)</td>
<td>0.50 (75/150)</td>
<td>-0.120</td>
<td>-0.232 - 0.006</td>
</tr>
</tbody>
</table>

### Table 3B: 95% confidence intervals (exact) for difference of immunologic response rates between two Arms (Groups pooled) in baseline HAI seronegative participants (assuming 50% seronegativity rate).

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Arm A Observed response rate (FluMist™)</th>
<th>Arm B Observed response rate (Control)</th>
<th>A-B Difference of response rate</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>0.80 (56/70)</td>
<td>0.50 (35/70)</td>
<td>0.300</td>
<td>0.137 - 0.447</td>
</tr>
<tr>
<td>70</td>
<td>0.70 (49/70)</td>
<td>0.50 (35/70)</td>
<td>0.200</td>
<td>0.035 - 0.357</td>
</tr>
<tr>
<td>70</td>
<td>0.67 (47/70)</td>
<td>0.50 (35/70)</td>
<td>0.171</td>
<td>0.006 - 0.331</td>
</tr>
<tr>
<td>70</td>
<td>0.66 (46/70)</td>
<td>0.50 (35/70)</td>
<td>0.157</td>
<td>-0.009 - 0.317</td>
</tr>
<tr>
<td>70</td>
<td>0.57 (40/70)</td>
<td>0.50 (35/70)</td>
<td>0.071</td>
<td>-0.098 - 0.238</td>
</tr>
<tr>
<td>70</td>
<td>0.50 (35/70)</td>
<td>0.50 (35/70)</td>
<td>0.000</td>
<td>-0.171 - 0.171</td>
</tr>
<tr>
<td>70</td>
<td>0.43 (30/70)</td>
<td>0.50 (35/70)</td>
<td>-0.071</td>
<td>-0.238 - 0.098</td>
</tr>
<tr>
<td>70</td>
<td>0.34 (24/70)</td>
<td>0.50 (35/70)</td>
<td>-0.157</td>
<td>-0.317 - 0.009</td>
</tr>
<tr>
<td>70</td>
<td>0.33 (23/70)</td>
<td>0.50 (35/70)</td>
<td>-0.171</td>
<td>-0.331 - 0.006</td>
</tr>
</tbody>
</table>
Table 3C: 95% confidence intervals (exact) for difference of immunologic response rates between two Arms (per Group or assuming 30% baseline seronegative rate for pooled Groups).

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Arm A Observed response rate (FluMist™)</th>
<th>Arm B Observed response rate (Control)</th>
<th>A-B Difference of response rate</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.90 (45/50)</td>
<td>0.50 (25/50)</td>
<td>0.40</td>
<td>0.212 - 0.558</td>
</tr>
<tr>
<td>50</td>
<td>0.80 (40/50)</td>
<td>0.50 (25/50)</td>
<td>0.30</td>
<td>0.098 - 0.473</td>
</tr>
<tr>
<td>50</td>
<td>0.70 (35/50)</td>
<td>0.50 (25/50)</td>
<td>0.20</td>
<td>-0.017 - 0.367</td>
</tr>
<tr>
<td>50</td>
<td>0.68 (34/50)</td>
<td>0.50 (25/50)</td>
<td>0.18</td>
<td>-0.100 - 0.294</td>
</tr>
<tr>
<td>50</td>
<td>0.60 (30/50)</td>
<td>0.50 (25/50)</td>
<td>0.10</td>
<td>-0.100 - 0.294</td>
</tr>
<tr>
<td>50</td>
<td>0.50 (25/50)</td>
<td>0.50 (25/50)</td>
<td>0.00</td>
<td>-0.203 - 0.203</td>
</tr>
<tr>
<td>50</td>
<td>0.40 (20/50)</td>
<td>0.50 (25/50)</td>
<td>-0.10</td>
<td>-0.294 - 0.100</td>
</tr>
<tr>
<td>50</td>
<td>0.32 (16/50)</td>
<td>0.50 (25/50)</td>
<td>-0.18</td>
<td>-0.367 - 0.017</td>
</tr>
<tr>
<td>50</td>
<td>0.30 (15/50)</td>
<td>0.50 (25/50)</td>
<td>-0.20</td>
<td>-0.385 - -0.005</td>
</tr>
</tbody>
</table>

8.63 Virus Shedding

Virus shedding will be evaluated for all three strains combined and by strain for FluMist™ recipients and among the subset of participants seronegative at baseline as measured by HAI. Seronegative is defined as HAI titer ≤ 4 in 5-8 year olds and as HAI titer ≤ 8 in 9-17 year olds. The proportion of FluMist™ recipients shedding at any timepoint and at each timepoint will be summarized along with corresponding two-sided exact 95% confidence interval.

9.0 HUMAN SUBJECTS

The Division of AIDS has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in clinical trials and should NOT be considered by local IRBs for the recruitment of prisoners.

9.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent document (Appendix VIII), and any subsequent modifications must be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot
consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or parent or legal guardian).

9.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA, the pharmaceutical sponsor, the NIAID, IRB, the Office for Human Research Protection (OHRP), or sponsor’s designee.

9.3 Study Discontinuation

The study may be discontinued at any time by the NIAID, the pharmaceutical sponsor, the FDA, IRB or other government agencies as part of their duties to ensure that research subjects are protected.

10.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by PACTG policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

11.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other bloodborne 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.

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing
Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions.
REFERENCES


## APPENDIX I
### SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>EVALUATIONS</th>
<th>Screen¹</th>
<th>Entry¹</th>
<th>Day 0¹</th>
<th>3 days</th>
<th>7 days</th>
<th>14 days</th>
<th>21 days</th>
<th>28 days</th>
<th>42 days</th>
<th>6 months</th>
<th>Early D/C⁹</th>
<th>Expected Term-Delivery</th>
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<tbody>
<tr>
<td>Signed Informed Consent</td>
<td>X</td>
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<tr>
<td>History &amp; Physical exam²</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X⁴⁰</td>
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<td>Documentation of HIV-1 Infection⁶</td>
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</tr>
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<td>Pregnancy Status (verbal)³</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Pregnancy Test (urine)⁴</td>
<td></td>
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<tr>
<td>Pregnancy/Delivery Outcome⁵</td>
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<tr>
<td>Vaccination w/ FluMist or Fluzone</td>
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<tr>
<td>Post-immunization monitoring in clinic (15 minutes)</td>
<td></td>
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<tr>
<td>Vaccination Report Card⁴</td>
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</tr>
<tr>
<td>Site Initiated Telephone Contact⁵</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HIV-1 RNA</td>
<td>(2 mL)⁶</td>
<td>2 mL</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal Swab (vaccine strain influenza)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm A - FluMist ONLY⁷</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
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<td></td>
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<tr>
<td>Special Immunology</td>
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<tr>
<td>Saliva (IgG and IgA anti-influenza AB)</td>
<td>X</td>
<td>X</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Serum (neutralizing and HAI anti-influenza AB)</td>
<td>2 mL</td>
<td>2 mL</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ELISPOT²⁷ (anti-influenza CMI)</td>
<td>9 to 13.5 mL</td>
<td>9 to 13.5 mL</td>
<td>9 to 13.5 mL</td>
<td>9 to 13.5 mL</td>
<td>9 to 13.5 mL</td>
<td>9 to 13.5 mL</td>
<td>9 to 13.5 mL</td>
<td>9 to 13.5 mL</td>
<td>9 to 13.5 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME (mL)</td>
<td>12-18.5</td>
<td>14-18.5</td>
<td></td>
<td>14-18.5</td>
<td>14-18.5</td>
<td>14-18.5</td>
<td>14-18.5</td>
<td>14-18.5</td>
<td>14-18.5</td>
<td>14-18.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX I (cont.)

*** WINDOWS:

- Post-Vaccination Clinic Visits: 3 days ± 1 day; 14 days ± 3 days, 28 days ± 5 days, 6 months ± 4 weeks
- Site Initiated Calls to subject or caretaker: Day 7 is absolute; Day 21± 3 days; 42 days ± 7 days

CLINIC VISITS BY ARM:

- Arm A (FluMist™) subjects will be seen in clinic – Screening, Entry/Day 0, Days 3, 14, 28, and 6 months.
- Arm B (Fluzone®) subjects will be seen in clinic – Screening, Entry/Day 0, Day 28 and 6 months.

SITE INITIATED PHONE CONTACT BY ARM:

- Arm A (FluMist™) subjects will be called on Days 7, 21, and 42.
- Arm B (Fluzone®) subjects will be called on Days 3, 7, 14, 21, and 42.

1. Screening evaluations should be completed within 14 days prior to study Entry (randomization). The day of vaccination is designated Day 0. If vaccination does not occur the same day as the subject is randomized (Entry), then vaccination should occur within 72 hours following study Entry (exception to this as stated in section 4.32). If vaccination and randomization occur on the same day, then the evaluations designated in the Schedule for Entry and for Day 0, should all be done on the same day.

2. Height, weight, vital signs, symptoms, (including assessment of HIV-related symptoms), chest auscultation for evidence of bronchospasm. Subjects must be carefully evaluated at baseline (Screening, Entry/Day 0) for bronchospasm/wheezing to be sure that what is recorded post-vaccination represents an actual change. All baseline diagnoses and medications should be recorded at the Screening visit; all new diagnoses, changes in medications, and symptoms present since preceding study visit are to be recorded at subsequent visits through Day 28 or during the site-initiated telephone contact through Day 28. All new diagnoses will continue to be recorded during the Day 42 phone contact and 6-month clinic visit.

   - Schedule for clinic visits by ARM as noted at top of this page.

3. At screening, females who are biologically capable of becoming pregnant (menses within the last year) should be asked whether they are pregnant and response documented. On the day of vaccination (Day 0), all menstruating females must have a urine pregnancy test. The study staff must check that the pregnancy test result is negative prior to administering vaccine. Pregnancy status will be asked again and the response documented at the following post-vaccination times: Day 28 clinic visit, Day 42 phone contact, and the 6-month clinic visit. If the response is affirmative, please refer to section 6.4 for the required pregnancy/delivery outcome follow-up.
4. **Vaccination Report Card** – following vaccination on Day 0, the subject or their caretaker will be given the daily assessment worksheet with instructions. Thermometers will be provided at this time to the subjects or caretakers through the study by MedImmune. Safety assessments (vaccine reactions, AEs, temperature, and concomitant medications) will be recorded by the subject or their caretaker every day from Day 0 (evening of the day they were vaccinated) through Day 28. The Report Card is to be used solely as a memory aid for the participant and will NOT be utilized as a source document. Therefore, it will NOT be collected by the site at the end of the 28-day period.

5. **Phone contact** with caretakers or subjects to review and record what they have written on the Vaccination Report Card and to remind them to maintain the Card for 28 days post-vaccination. During this contact, sites will also inquire about adverse events and any unplanned health care provider visits. All information will be recorded on the appropriate CRF.

Day 42 phone contact will collect any significant new medical conditions (e.g., diabetes, auto-immune disease, chronic fatigue syndrome etc.) and SAEs that have occurred since the Day 28 clinic visit.

- Schedule for phone contact by ARM as noted at top of this page.

6. **At screening visit**, the only subjects to have blood drawn for HIV-1 RNA testing would be those individuals with inadequate documentation (as defined in 4.16) of HIV status and/or no plasma HIV-1 RNA results within 60 days prior to screening. **All** subjects will have blood drawn for HIV-1 RNA determinations at remaining visits.

7. **For subjects in Arm A-FluMist™ ONLY** (see Appendix VI).

    For any Day 28 culture which is positive, the University of Colorado lab will notify the respective site. The site is to request that the subject return to clinic within 7 days of site notification for a repeat nasal swab for attempted isolation of vaccine strain influenza.

8. **Limited to the first 25 subjects in each Group in each Arm** (total of 150 overall with 75 per arm). Blood volume required for ELISPOT is 9 mL (2 green top tubes) for children < 6 years of age and 13.5 mL (3 green top tubes) for children ≥ 6 years of age.

    **NOTE:** (see Appendix VII - ELISPOT). Samples must be shipped Monday, Tuesday, Wednesday ONLY, same day as blood draw. This means that the clinic visits at which the sample is to be collected MUST be scheduled for a Monday, Tuesday or Wednesday ONLY.

9. **Early D/C Visit** – if this occurs ≥ 2 months post-vaccination, do all the same evaluations as requested at the 6 month visit. If this occurs < 2 months post-vaccination, then do the evaluations required for what would have been the next scheduled clinic visit.

10. Safety will also be evaluated at a clinic visit 6 months after vaccination to collect any significant new medical conditions (e.g., diabetes, auto-immune disease, chronic fatigue syndrome etc.) and SAEs that have occurred since the Day 42 phone contact.
APPENDIX I (cont.)

For insufficient blood draws, priorities are as follows:
1. Immunology
2. Virology
If there is any uncertainty, please contact the protocol team at actg.teamp1057@fstrf.org.
## APPENDIX II

**SUPPLEMENTAL TOXICITY TABLE FOR PULMONARY/RESPIRATORY SYMPTOMS**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchospasm, wheezing</td>
<td>Bronchospasm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 1: Minimally troublesome, i.e. not sufficient to interfere with normal daily activity or sleep.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 2: Sufficiently troublesome to interfere with normal daily activity or sleep.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 3: So severe as to prevent normal activity and/or sleep.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 4: Life-threatening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 5: Death</td>
</tr>
</tbody>
</table>

Source: Selected adverse event terms from the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (available at [http://ctep.cancer.gov/reporting/ctc.html](http://ctep.cancer.gov/reporting/ctc.html)). For Bronchospasm, wheezing the definitions for Grade 1, 2 and 3 were modified by the PACTG P1057 Protocol Team by adapting the terminology from prior pediatric asthma trials, the CAMP (Childhood Asthma Management Program) and SOCS (Salmeterol or Corticosteroids Study).
### APPENDIX III

**SUPPLEMENTAL TOXICITY TABLE FOR VACCINE-RELATED TOXICITIES OCCURRING WITHIN 28 DAYS OF VACCINATION**

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3*</th>
<th>GRADE 4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema: diameter (mm) of skin redness at the site of injection</td>
<td>Present but &lt; 10 mm³</td>
<td>≥10 mm³ but &lt; 50% of the extremity</td>
<td>≥50% of the extremity</td>
<td></td>
</tr>
<tr>
<td>Induration: diameter (mm) of palpable hardness of the skin at the site of injection</td>
<td>Present but &lt; 10 mm³</td>
<td>≥10 mm³ but &lt; 50% of the extremity</td>
<td>≥50% of the extremity</td>
<td></td>
</tr>
<tr>
<td>Pain: at site of injection</td>
<td>Crying or protest to touch</td>
<td>Crying on movement of site - not touching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever: rectal temperature</td>
<td>≥100.4°F but &lt; 103°F</td>
<td>≥103°F but ≤105°F</td>
<td>&gt;105°F</td>
<td></td>
</tr>
<tr>
<td>Fatigue/weakness/malaise/myalgia</td>
<td>Transient, no limit on ADL, no therapy needed</td>
<td>Mild to moderate impact on ADL; &lt;48 hours (no intervention needed)</td>
<td>&gt;48 hours; marked impact on ADL requiring medical intervention</td>
<td>Completely disabling requiring hospitalization</td>
</tr>
<tr>
<td>Irritableness: subjective parent report</td>
<td>Irritable or fussy, but otherwise normal routine</td>
<td>Mild to moderate impact on ADL; &lt;48 hours (no intervention needed)</td>
<td>&gt;48 hours: marked impact on ADL requiring medical intervention</td>
<td>Completely disabling requiring hospitalization</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Mild lethargy, irritability, headache (no treatment)</td>
<td>Mild to moderate impact on ADL; &lt;48 hours (no intervention needed)</td>
<td>&gt;48 hours: marked impact on ADL requiring medical intervention</td>
<td>Completely disabling requiring hospitalization</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>Transient rash</td>
<td>Persistent, diffuse rash</td>
<td>Mild urticaria,</td>
<td>Severe urticaria, anaphylaxis, angioedema within 48 hours of vaccination. Exfoliative dermatitis, Stevens-Johnson syndrome or erythema multiforme, moist desquamation.</td>
</tr>
</tbody>
</table>

- ≥ Grade 3 adverse reactions require a clinic visit within 12 hours of the event.
- ADL = activities of daily living.
## APPENDIX IV

### HIV - VIROLOGY COLLECTION AND SHIPPING INSTRUCTIONS

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| HIV-1 RNA PCR (plasma)     | 2 mL blood collected by venipuncture | Tripotassium EDTA Vacutainer™ tube (lavender top) | • Gently invert tubes several times to mix. Do not shake.  
• Specimen should be kept at room temperature (18-24 °C) and processed within 4 to 6 hours of collection.  
• Specimen should be logged into LDMS, identified as to patient ID#, study ID#, visit ID#, date and time of collection, primary, derivative, additive and sub/additive derivative codes. |
| (Roche Amplicor HIV-1 Monitor™, version 1.5) |                                  |                                        |                                                                        |

**SPECIMEN PROCESSING:**

- Centrifuge blood at 800 x g for 10 minutes at 18°-24°C.
- Transfer plasma to a centrifuge tube; centrifuge at 800 x g for 10 minutes to completely remove platelets and cell debris.
- If plasma not to be tested within 30 minutes of separation, aliquot plasma (0.6 mL/tube) into sterile, labeled cryovials (label with same information as blood tubes) and store at -60° to -80°C or below for batch testing.
- Log into LDMS as BLD/EDT/PL2.

**DESIGNATED LABORATORY/CONTACT PERSON:**

HIV-1 RNA assays will ONLY be run at CLIA (Clinical Lab Improvement Act, 1988) or equivalent (e.g., CAP, NY State) + DAIDS VQA-approved laboratories. Each site MUST use the same CLIA (or equivalent)/ DAIDS VQA-approved laboratory for the duration of the study to prevent inter-lab variability.

**SHIPPING:** Real-Time

**OTHER INSTRUCTIONS:**
APPENDIX V

HIV - IMMUNOLOGY COLLECTION AND SHIPPING INSTRUCTIONS

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte Subsets</td>
<td>1 mL blood collected by venipuncture</td>
<td>Tripotassium EDTA Vacutainer® tubes (lavender top)</td>
<td>• Gently invert tubes several times to mix. Do not shake.</td>
</tr>
<tr>
<td>(CD3/CD4, CD3/CD8, CD19)</td>
<td></td>
<td></td>
<td>• Specimen should be identified as to subject ID#, study ID#, site ID#, visit ID#, date and time of collection, and specimen type.</td>
</tr>
</tbody>
</table>

PROCESSING INSTRUCTIONS: Ship ambient overnight to your local CLIA/IQA certified laboratory.

DESIGNATED LABORATORY/CONTACT PERSON:
Subsets will ONLY be run at CLIA (Clinical Lab Improvement Act, 1988) or equivalent (e.g., CAP, NY State) + DAIDS IQA-approved laboratories. Each site MUST use the same CLIA (or equivalent)/ DAIDS IQA-approved laboratory for the duration of the study to prevent inter-lab variability.

SHIPPING: All specimens are to be shipped ambient temperature to local CLIA/IQA certified laboratory.

OTHER INSTRUCTIONS:
APPENDIX VI

INFLUENZA - VIROLOGY COLLECTION AND SHIPPING INSTRUCTIONS

PROCEDURE FOR THE COLLECTION AND PROCESSING OF NASAL SWAB SPECIMENS

- Label the Transport Medium tube with the PID, SID, collection date, and visit designation.
- Position the participant in sitting position.
- Open the Dacron Swab package at handle end so that sterile tip remains inside wrapper until just before use.
- Remove the cap from the medium tube.
- Remove the Dacron Swab from the package, keep tip sterile and gently insert into inner anterior nostril (insert just until tip disappears). Using small circular motion ensure that the tip comes into contact with inner nostril at top, sides and bottom. Swab one nostril.
- Exit nostril and immediately place swab tip in medium. Swirl the swab in the liquid and then press swab tip against side of container to express liquid as swab is REMOVED.
- Repeat this procedure on the second nostril using another Dacron Swab and place the swab in the same tube of medium.
- Recap the medium tube and store refrigerated at 2-8 °C until shipped (on cold packs at 2-8 °C) to the University of Colorado clinical virology laboratory, within 24 hours of collection.
## APPENDIX VI (cont.)

### INFLUENZA - VIROLOGY COLLECTION AND SHIPPING INSTRUCTIONS

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza vaccine strain cultures</td>
<td>NASAL SWAB</td>
<td>M4 Viral Transport Medium</td>
<td>• Use Dacron nasal swab to swab inside nostril. Place swab tip in M4 transport medium, then press swab tip against side of container to express liquid as swab is removed.</td>
</tr>
<tr>
<td>FluMist™ Arm ONLY</td>
<td></td>
<td>These tubes will be supplied to the sites by the study.</td>
<td>• Specimen should be identified as to subject ID#, study ID#, site ID#, visit ID#, date and time of collection, and specimen type.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Store specimen at 2º to 8º C (refrigerator) until shipped.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Ship specimen the same day for overnight delivery on cold packs at 2-8°C to Virology lab at University of Colorado Hospital for culture.</td>
</tr>
</tbody>
</table>

**SPECIMEN PROCESSING:** None; ship labeled at 2 – 8 ºC

**DESIGNATED LABORATORY/CONTACT PERSON:**
Dorothea Longfellow  
Virology Lab Desk, University of Colorado Hospital, Clinical Virology Lab, 4200 E. Ninth Ave. CC029, Denver, Colorado 80262. Phone: (303) 372-8182; FAX: (303) 372-8590

**SHIPPING:** Ship (on cold packs at 2-8°C) same day of collection by FED EX or overnight courier to UCH virology lab.

**OTHER INSTRUCTIONS:**
APPENDIX VII

INFLUENZA - IMMUNOLOGY COLLECTION AND SHIPPING INSTRUCTIONS

**Saliva Collection**

1. Remove the cap from the sealed plastic container that has the cotton ball on a plastic handle.

2. Take out the cotton applicator and rub it on the side of the teeth next to the inside of the cheek for 30 seconds. Then wedge the cotton between the cheek and the teeth and leave in place for 2 minutes. This 2-minute period will require site staff monitoring and in the case of young children, may require the staff to distract the child (play with the child, read to the child, etc.).

3. Remove the cap from the tube containing a liquid.

4. After removing the cotton (with its handle) from the mouth, plunge it into this tube containing a liquid.

5. Snap off the plastic handle.

6. Place the cap securely on the tube containing the cotton ball.

7. Label this tube with subject ID#, study ID#, site ID#, visit ID#, date and time of collection, and specimen type.
### APPENDIX VII (cont.)

**INFLUENZA - IMMUNOLOGY COLLECTION AND SHIPPING INSTRUCTIONS**

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALIVA (IgG and IgA anti-influenza AB)</td>
<td>Saliva</td>
<td>OraSure® specimen collection device</td>
<td>• Follow collection instructions page 1 of this Appendix.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>These collection devices will be supplied to the sites by the study.</td>
<td>• After the 2 min collection period insert the pad to the bottom of the vial. Bend the pad handle and snap off end of handle. Cap vial completely.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Specimen should be identified as to subject ID#, study ID#, site ID#, visit ID#, date and time of collection, and specimen type.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Send to processing lab.</td>
</tr>
</tbody>
</table>

**PROCESSING INSTRUCTIONS:** Snap off end of vial to produce a hole in bottom of vial. Place a 15 mL centrifuge tube over the bottom of the vial with pad and invert. Spin both tubes at 1200 x g at 4°C for 15 min in a swinging bucket centrifuge. Collect supernatant in a cryovial which is labeled as to subject ID#, study ID#, site ID#, visit ID#, date and time of collection, and specimen type. Store supernatant at -20°C to -70°C. Log into LDMS as SAL/ORA/SAL.

**DESIGNATED LABORATORY/CONTACT PERSON:**
Patricia Defechereux, PhD; UCSF Medical Center, Pediatric Immunology Lab, Rm.1441 HSE, (LDMS Lab 134)
505 Parnassus Avenue, San Francisco, CA 94143
Phone: (415) 467-3993; Fax: (415) 476-5795

**SHIPPING:** batch ship (on DRY ICE); sites will be notified by the protocol team.

**OTHER INSTRUCTIONS:**
**APPENDIX VII (cont.)**

### INFLUENZA - IMMUNOLOGY COLLECTION AND SHIPPING INSTRUCTIONS

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| SERUM (neutralizing and HAI anti-influenza AB) | 2 mL blood collected by venipuncture | Red-top tube (no additive) | • Specimen should be identified as to subject ID#, study ID#, site ID#, visit ID#, date and time of collection, and specimen type.  
• Allow blood to clot up to 30 min at room temperature. |

**PROCESSING INSTRUCTIONS:** Centrifuge at 1200 x g for 10 min. Place serum in a vial labeled as to subject ID#, visit ID#, date and time of collection, primary, derivative, additive and sub/additive derivative codes. Log into LDMS BLD/NON/SER. The samples should be stored at 

-20°C.

**DESIGNATED LABORATORY/CONTACT PERSON:**  
Julie Patterson, UCHSC  
PEDIATRIC INFECTIOUS DISEASES, 4200 EAST 9TH AVE, SOM ROOM 1534 (LDMS Lab 174), Denver, CO 80262  
Phone: (303) 315-3772; Fax: (303) 315-1019.

**SHIPPING:** The site will be notified by the protocol team when specimens should be batch-shipped (cold pack at 2°-8° C).

**OTHER INSTRUCTIONS:**
### APPENDIX VII (cont.)

**INFLUENZA - IMMUNOLOGY COLLECTION AND SHIPPING INSTRUCTIONS**

<table>
<thead>
<tr>
<th><strong>ASSAY</strong></th>
<th><strong>SPECIMEN</strong></th>
<th><strong>COLLECTION CONTAINER</strong></th>
<th><strong>IMMEDIATE SPECIMEN HANDLING</strong></th>
</tr>
</thead>
</table>
| ELISPOT        | 3 x 4.5 mL blood for children ≥6 years.                                     | Green-top tube (sodium heparin) | • Fill tube completely.  
• Invert 10-15 times gently.  
• Specimen should be identified as to subject ID#, study ID#, site ID#, visit ID#, date and time of collection, and specimen type.  
• Ship to University of Colorado PICL at ambient temperature same day as draw. |
|                | 2 x 4.5 mL blood for children < 6 years.                                    |                          |                                                  |
|                | All collected by venipuncture.                                               |                          |                                                  |

**PROCESSING INSTRUCTIONS:** None

**DESIGNATED LABORATORY/CONTACT PERSON:** Julie Patterson, UCHSC. PEDIATRIC INFECTIOUS DISEASES, 4200 EAST 9TH AVE, SOM ROOM 1534 (LDMS Lab 174), Denver, CO 80262  
Phone: (303) 315-3772; Fax: (303) 315-1019

**SHIPPING:** Ship ambient temperature same day as draw to UCHSC on Mon, Tues, Wed ONLY. Fax shipment notification before shipping.

**OTHER INSTRUCTIONS:**
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DIVISION OF AIDS
PEDIATRIC AIDS CLINICAL TRIALS GROUP (PACTG)
SAMPLE INFORMED CONSENT
For protocol:  PACTG P1057

“A PHASE I/II RANDOMIZED TRIAL OF THE SAFETY AND IMMUNOGENICITY OF COLD ADAPTED INFLUENZA VACCINE (FLUMIST™) IN HIV-INFECTED CHILDREN AND ADOLESCENTS”, Version 1.0 dated August 09, 2004

SHORT TITLE FOR PACTG P1057: “SAFETY AND IMMUNOGENICITY OF COLD ADAPTED INFLUENZA VACCINE (FLUMIST™)”, Version 1.0 dated August 09, 2004

INTRODUCTION

You are/your child is being asked to take part in this research study comparing two influenza (flu) vaccines because you are/your child is infected with HIV and have/has received a flu vaccine in at least one of the prior two years.

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 to be/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 study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree/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?

This study will compare the safety of two influenza (flu) vaccines in HIV-infected children and adolescents. One is a cold-adapted live attenuated influenza vaccine known as FluMist™, which is FDA-approved for use only in healthy individuals 5-49 years of age. The other is an inactivated influenza vaccine known as IAIV or Fluzone®. The study will also look at how well each of the vaccines stimulates the immune system, including the development of antibodies which are proteins that fight disease. In this case the antibodies produced may fight and prevent flu infection.

The FluMist™ vaccine uses a weakened form of the influenza virus to stimulate a protective immune response in the body. Although the vaccination does not cause someone to develop the flu, there is “shedding” of flu virus which in rare situations, may result in spread to another person. Although such spread has not produced illness (just as the vaccine does not cause illness when given on purpose to a patient), people who have received the vaccine have been told to
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avoid close contact (living in the same house, for example) for 21 days with an individual whose immune system is very compromised (someone who is receiving chemotherapy or with advanced HIV disease). This study will look at how common this “shedding” of flu virus is and how long it lasts after vaccination.

Fluzone® is currently approved by the FDA to be used in the children the same ages as those participating in this study (5 to 17 year olds) and is approved to be used in HIV-infected children. FluMist™, although approved for this study age-group, is not approved by the FDA for use in HIV-infected individuals.

Presently, vaccines like Fluzone® are given by doctors to HIV-infected individuals during the flu season. However, there is limited information regarding the benefits of flu vaccination with Fluzone® in HIV-infected individuals.

FluMist™ is being given in an investigational manner because the study is not following the FDA-approved way of giving two doses of FluMist™ to young children (ages 5 to 8) the first time they receive FluMist™. One of the requirements to participate in this study is that you have/ your child has received an inactivated flu virus vaccine in at least one of the prior two years. Both vaccines, FluMist™ and Fluzone®, are believed to work best when there has been a prior vaccination in children between 5 to 8 years of age who had not previously been vaccinated. However, a government advisory committee has since indicated that any type of prior flu vaccine is acceptable. It is this committee’s guidelines that the P1057 trial is following.

The FluMist™ vaccine has been given to 24 HIV-infected children (1 to 7.9 years of age) who were not seriously ill due to HIV. The symptoms and reactions experienced by the HIV-infected children due to the vaccine were similar to those of the uninfected children after one or more doses of the vaccine. It is not known if other HIV-infected children will respond differently to FluMist™, depending on how well their immune system is functioning. One of the questions being asked in this study is whether the HIV-infected children with the lower CD4+ cell counts will respond as well to the FluMist™ (or Fluzone®) vaccine as those children with the higher CD4+ counts. To answer this question, you/your child will be in one of 6 Groups on the study. Which Group you/your child belongs to will be determined by the vaccine received and how well your/your child’s immune system is doing as measured by how many CD4+ cells are present in the blood.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Screening
If you decide or allow your child to join this study, and you sign this consent form, the following procedures will be done to see if you are/your child can participate in this study:

• Study staff will review your/your child’s medical history and a physical exam will be done.
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- Girls/women who have had their first menstrual period will be asked if they are pregnant.
- Because there is a chance that a vaccinated individual may unintentionally infect others with the flu virus, you/your child will not be able to participate if there are other members of your household who have advanced HIV or other diseases which affect their immune systems, are receiving chemotherapy or have undergone organ transplantation. Therefore, you will be asked questions regarding these situations.
- In addition the study staff may need access to your/your child’s medical records, either current medical chart or records from the past, to get information that may be relevant to any health problems which may occur while you are/your child is participating in P1057.

HIV-1 RNA

If you do not have sufficient past test results that determined you are/your child is HIV infected and/or you/your child has not had this test performed within 60 days prior to the screening visit, some blood (less than ½ teaspoon) will be drawn to check the amount of HIV that is in your/your child’s blood.

Lymphocyte Subsets

An additional small amount of blood (less than ½ teaspoon) will be drawn to determine how your/your child’s immune system is responding to the HIV infection by looking at the number of special white blood cells (T cells) that are affected by the HIV virus.

These two tests which provide information about your/your child’s HIV disease will be performed at several clinic visits during the study. The results of these two tests, whenever they are done during the study, will be provided to you once they are available.

If it is determined that you are/your child is not eligible to participate in the study, any remaining blood collected for the purposes of these two assays will be discarded.

The following three special immunology tests -

1. Saliva (IgG and IgA anti-influenza AB)

A sample of saliva will be collected to test for antibodies against the influenza (flu) viruses. Antibodies are small proteins that protect us against infection. Finding antibodies against influenza in the saliva indicates that the vaccine might prevent the flu virus from invading the body.

In order to collect the saliva, the study nurse will use a cotton swab and rub it on the side of the teeth next to the inside of the cheek for 30 seconds. Then the swab will be placed between the cheek and the teeth for 2 minutes. You/your child will probably be asked to remain seated during this time and relatively still.
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2. Serum (neutralizing and HAI anti-influenza AB)
Less than 1 teaspoon of blood will be collected to test for antibodies and other cells of the immune system that can fight the flu viruses should they enter the body.

3. Elispot (anti-influenza CMI)
If you are/your child is among the first 25 subjects to join the study within your Group (this represents 50% or half of the subjects), this test will be performed. If your child is under 6 years of age, about 2 teaspoons of blood will be drawn and if your child is older than 6, or you are the study participant, about 3 teaspoons of blood will be drawn for this test.

This test looks at how much of a substance (cytokines) is secreted or released by cells of the immune system (T cells) when trying to fight the flu virus. This substance is not an antibody but is released by T cells when the immune system is stimulated (as happens when your body fights the flu virus).

These special immunology tests will not be completed while the study is ongoing, but performed after the study is completed. Individual results will not be provided at any time.

If it is determined that you are/your child is not eligible to participate in the study, the samples collected at the screening visit for these three special immunology tests will be discarded.

During Study
Subjects on Arm A (FluMist™), will be seen in clinic – Entry/Day 0, Days 3, 14, 28, and 6 months. Subjects on Arm B (Fluzone®) will be seen in clinic less frequently - Entry/Day 0, Day 28 and 6 months. These clinic visits are not expected to take very long, approximately 1 hour.

Study staff will be calling you at home several times during the study. Subjects on Arm A (FluMist™) will be called on Days 7, 21, and 42. Subjects on Arm B (Fluzone®) will be called on Days 3, 7, 14, 21, and 42.

At Entry/ Day 0
If the tests show that you are/your child is eligible to take part in the study and that it is safe for you/your child to do so, you/your child will be assigned to receive one of two flu vaccines. You/your child cannot choose which vaccine you will receive. You will be assigned by chance, like flipping a coin with an equal (50:50) chance of receiving either vaccine. You and the doctors will know which vaccine you or your child receive(s).

Girls/women who have had their first menstrual period will have a pregnancy test done before receiving any vaccination. A small amount of urine will be used for this test. You/your child will be informed of the test result as soon as it is available. If you are/your child is pregnant before being vaccinated, you/your child cannot be in this study.
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If you are in Arm A, you/your child will receive FluMist™. The dose you will receive is administered into the nostrils (intranasally), with half the dose being sprayed into each nostril. The study nurse will do this for you/your child; you/your child will be asked to be seated and tilt your head back. If you/your child are in Arm B you will receive the IAIV/ Fluzone® vaccine. This vaccine will be given as a single injection into the muscle of the upper arm. All subjects will be required to remain in the clinic for approximately 15 minutes to be observed after receiving either vaccine.

In addition to being vaccinated you/your child will also have a physical exam and a medical history reviewed. Blood will also be drawn for the following tests:

**HIV-1 RNA**

You may have had this test done at your first clinic visit (screening) or this may be the first time for this study. Some blood (less than ½ teaspoon) will be drawn to check the amount of HIV that is in your/your child’s blood. This test will be repeated at 28 days, and 6 months post-vaccination.

**Lymphocyte Subsets**

This test, which you/your child had done during the screening visit, will be repeated at Entry and again at 28 days, and at 6 months post-vaccination.

**Saliva (IgG and IgA anti-influenza AB); Serum (IgG anti-influenza AB); Elispot (anti-influenza CMI)**

The three special immunology tests that you/ your child had done at the earlier screening visit, will be repeated at Entry and again at 28 days, and 6 months post-vaccination.

**Vaccination Report Card and Site-Initiated Phone Contact**

You will be given a Vaccination Report Card by the study nurse on the day you are/your child is vaccinated. This is to be used to record any symptoms that you/your child may have, for example, cough, runny nose/nasal congestion, sore throat, irritability, headache, chills, vomiting, muscle aches, tiredness. If you/your child received the vaccine by injection, you will also need to note any pain, redness and swelling at the injection site. You must also record your/your child’s body temperature every day; a thermometer will be given to you for this purpose. You will need to record the information on this Report Card each and every day for 28 days following vaccination beginning the evening of the day of vaccination.

The study nurse will call you to review what you have written on this Report Card on Days 7, and 21 post-vaccination if you received FluMist™ (Arm A); and on Days 3, 7, 14, and 21 post-vaccination if you received Fluzone® (Arm B). The symptoms you report will be recorded by the nurse in your/your child’s chart.
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Regardless of which vaccine you received, the study nurse will also call you on Day 42 after vaccination to ask you questions regarding your/your child’s health including if any new medical conditions have occurred since your/your child’s last visit.

*Nasal Swabs (vaccine strain influenza)*

For those subjects in Arm A who receive the FluMist™ vaccine, this test will be done to detect if types (strains) of flu virus from the vaccine are found in the nasal passages and how much is present.

A wipe of your/your child’s nasal passages with a cotton swab will be done 3, 14, and 28 days post-vaccination.

This test will not be completed while the study is ongoing, but performed after the study is completed. Individual results will not be provided at any time.

*6-Month Visit*

Your/your child’s last study visit will be at 6 months after vaccination. About 3 to 4 teaspoons of blood will be drawn for some of the same tests done at earlier clinic visits. You/your child will be asked questions regarding your/their health and if any new medical conditions have occurred since your/your child’s last visit.

*Post-vaccination Pregnancy Status*

Anyone who had a pregnancy test done prior to vaccination and was eligible for the study (negative test result), will be asked their pregnancy status at the following times: during the Day 28 clinic visit, the Day 42 phone contact, and the 6-month visit.

If you/your child become(s) pregnant after being vaccinated, you/your child may continue to participate in the study. You/your child will be asked questions about the pregnancy at clinic visits and during phone contact during the 6 months this study is to last. All pregnant girls and women will be contacted by site staff via telephone at the time of expected full-term delivery to find out the outcome of the pregnancy and delivery.

*Early Discontinuation Visit*

Should you decide at any time that you no longer want to participate in this study, you/your child will be asked to return for a final visit. If this visit occurs 2 months or later after vaccination, the tests performed will be the same as those described for the 6-month visit. If this visit occurs within 2 months of being vaccinated, the tests done will be those that would have been completed at your next scheduled visit.
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Storage of Blood Samples

Once the tests which have been specifically described above have been completed, no leftover blood obtained during the course of this study will be stored for future PACTG-approved, HIV-related research.

Other Information

The information collected in this study may be used for other PACTG-approved HIV-related research.

To fully answer questions about your/your child’s medical history, it may be necessary for the study staff to review medical charts or records from health care providers not involved in this trial. You may be asked to sign a consent form to allow this information to be shared.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 300 children and adolescents will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You/your child will be in this study for about 6 months.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you/your child off the study early without your permission if:

- the study is cancelled by the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the drug company supporting this study, or the site’s Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.)
- the study may also be cancelled by the Safety Monitoring Committee which will include some of the research investigators involved in the trial as well as a few independent reviewers from National Institute of Allergy and Infectious Disease (NIAID) which is part of NIH;
- you are/your child is not able to attend the study visits as required by the study;
- you or your child fail to follow the study requirements so as to cause harm to yourself/him/herself or seriously interfere with the accuracy of the study results;
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- you/your child need(s) a treatment or medication that may not be taken while on the study;
- withdrawal of parent/legal guardian permission (if applicable).

WHAT ARE THE RISKS OF THE STUDY?

Side effects or risks not related to either vaccine:

Risk of blood draw – You may faint or feel some discomfort when blood is drawn for this study. Other risks include bleeding or bruising where the needle enters the body and lightheadedness. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of minor infection at the blood draw site.

Risk of nasal swab – if you/your child receive(s) the FluMist™ vaccine, you will have nasal swabs taken at 3 visits after being vaccinated. There may be some irritation at the site swabbed. You could have a nose bleed.

Risk of saliva collection – None.

If you/your child experience(s) the side effects listed below or any other symptoms, you should contact your/your child’s physician as soon as possible. Expected side effects include but are not limited to:

Side effects and risks that may occur with the FluMist™ vaccine:

- runny nose/nasal congestion
- cough
- irritability
- headache
- decreased activity
- sore throat
- muscle aches
- low grade fever (> 100°F oral)
- chills
- vomiting

There is a possibility of passing the flu virus to others. If you/your child were/was in Arm A of the study and received the FluMist™ vaccine, for at least 21 days after the vaccination, you/your child should avoid close contact (e.g., within the same household) with people who have very weakened immune systems (including some HIV-infected individuals).
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You may not take/give your child aspirin or aspirin-containing products for 42 days (6 weeks) after receiving FluMist™. This is to prevent the possibility of Reye’s syndrome (a rare form of brain toxicity which has occurred in children with the flu who take aspirin). Your/your child’s doctor can recommend aspirin substitutes if necessary during this time.

*Side effects and risks that may occur with the Fluzone® vaccine:*

- soreness, redness or swelling at the injection site
- fever
- malaise (tiredness)
- muscle aches and pains

*Side effects or risks that may occur with either vaccine:*

- Guillain-Barré Syndrome (paralysis).
- Serious, though rare, side effects that can occur with the vaccines in this study include severe allergic reactions that include skin rash, hives, itching, difficulty breathing, hoarseness or wheezing, fast heart beat and shock.

**ARE THERE RISKS RELATED TO PREGNANCY?**

Because the safety of receiving either vaccine during pregnancy is not known, pregnant females may not join this study. If you/your child are/is capable of becoming pregnant, you/she must have a urine pregnancy test before being vaccinated. The test must show that you are *not* pregnant.

Effects of either vaccine on the unborn baby are unknown, and the effects of transmission through breast milk (vaccine virus present in breast milk) are unknown. You/your child should *not* become pregnant while participating in this study. Pregnancy and breast-feeding should be avoided for 3 months following vaccination.

If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a female pregnant. If you are a sexually active male, you must use condoms.

All female participants of childbearing potential must use a medically accepted form of birth control as defined below for 3 months post-vaccination:

- Male or female condoms with or without a cream or gel that kills sperm,
- Diaphragm or cervical cap with a cream or gel that kills sperm,
- Intrauterine device (IUD),
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- Hormonal birth control drugs that are taken as pills, given as shots, or placed under or on the skin,
- or abstain from sexual intercourse.

For those women taking a protease inhibitor (PI) as part of their HAART regimen:
Some of the anti-HIV medicines that you may be taking (protease inhibitors) make some birth control drugs less effective. This type of birth control is given by pills, shots, or placed under or on the skin. This means you cannot depend on this method of birth control alone. You must use a different method or an additional method of birth control which may be:
- Male or female condoms with or without a cream or gel that kills sperm
- Diaphragm or cervical cap with a cream or gel that kills sperm
- Intrauterine device (IUD).

You and your partner must use reliable birth control that you discuss with the study staff.

For those subjects who are taking efavirenz (Sustiva®, EFV) as part of their HAART regimen:
It is not known if efavirenz causes harm to unborn babies; tests in pregnant animals do show some risk. The risks to unborn babies due to efavirenz are listed in the manufacturer’s package insert.

Because of the risk involved, you and your partner must use two barrier methods of birth control that you discuss with the study staff. You may choose two of the birth control methods listed below:
- Male or female condoms with or without a cream or gel that kills sperm
- Diaphragm or cervical cap with a cream or gel that kills sperm.

If you/your child become(s) pregnant during the study, you should tell your/her study doctor or nurse right away. You/your child will be allowed to continue on the study for the entire 6 month duration.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you/your child take(s) part in this study, there may be a direct benefit to you/your child, but no guarantee can be made. It is also possible that you/your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV.
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WHAT OTHER CHOICES DO I/DOES MY CHILD HAVE BESIDES THIS STUDY?

Alternatives to your/your child’s participation in this study include receiving from your clinician a flu vaccine which is already approved by the FDA for use in HIV-infected individuals.
Please talk to your doctor about these and other choices available to you/your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

People who may review your records include: the U.S. Food and Drug Administration (FDA), the site IRB (insert name of site IRB), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

[The researchers should include language such as the following if they intend to make voluntary disclosure about things such as child abuse]

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances. [ The researchers should state here the conditions under which voluntary disclosure will be made]

WHAT ARE THE COSTS TO ME?
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Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you/your child is/are taking part in a research study.

This study requires that you/your child be taking antiretroviral (ARV) medicines for treatment of HIV infection. These ARVs will not be provided by the study and the cost of these medications will be your responsibility or covered by your/your child’s insurance.

WHAT HAPPENS IF I AM INJURED?

If you/your child is/are injured as a result of being in this study, you/your child will be given immediate treatment for your injuries. 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). You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take your child out of the study at any time. You/your child will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your/your child’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

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

For questions about your/your child’s rights as a research subject, contact:
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- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above
SIGNATURE PAGE

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.

_____________________                              __________________________________________
Participant’s Name (print)   Participant’s Signature and Date

____________________________                __________________________________________
Participant’s Legal Guardian (print)  Legal Guardian’s Signature and Date
(As appropriate)

________________________                        _________________________________________
Study Staff Conducting   Study Staff Signature and Date
Consent Discussion (print)

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