

**IMPAACT P1096
A Companion Protocol to CIR Protocol Number: CIR255**

Phase 1 Study to Determine the Safety, Infectivity, Immunogenicity and Tolerability of 2 Doses of Live Attenuated Recombinant Cold-passaged (cp) 45 Human Parainfluenza Type 3 Virus Vaccine, rHPIV3cp45, Lot PIV3#102A, Delivered as Nose Drops to HPIV3-Seronegative Infants and Children 6 to 36 Months of Age, at a 6 Month Interval

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

Sponsored by:

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National Institute of Allergy and Infectious Diseases (NIAID)
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IMPAACT P1096 PROTOCOL TEAM ROSTER

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1.0 PROTOCOL SUMMARY

P1096 (HPIV3): Phase 1 Study to Determine the Safety, Infectivity, Immunogenicity and Tolerability of 2 Doses of Live Attenuated Recombinant Cold-passaged (cp) 45 Human Parainfluenza Type 3 Virus Vaccine, rHPIV3cp45, Lot PIV3#102A, Delivered as Nose Drops to HPIV3-Seronegative Infants and Children 6 to 36 Months of Age, at a 6 Month Interval

- Volunteers: Healthy infants and children ages 6 months to 36 months (through 36 months, 30 days)
- Number of Subjects: A total of at least 30 evaluable subjects will be enrolled in the two companion protocols (combined) at IMPAACT and CIR sites. An evaluable subject is defined as a child who receives 2 immunizations and has a 1 month post dose 2 serology sample obtained. This IMPAACT protocol will enroll up to 30 subjects.
- Trial Design: A randomized, double-blind, placebo-controlled, outpatient trial evaluating the safety, infectivity, tolerability, and immunogenicity of rHPIV3cp45, Lot PIV3#102A human parainfluenza virus type 3 (HPIV3) vaccine, delivered as nose drops. The HPIV3-seronegative children will receive 2 doses of vaccine or placebo, delivered approximately 6 months apart.

Table 1: Immunization Schedule

Population	N	Treatment	Dose
Healthy HPIV3 Seronegative Children 6-36 months of age (through 36 months, 30 days)	20	Vaccine	10 ⁵ TCID ₅₀
	10	Placebo	0
Healthy 6-36 month old HPIV3 seronegative children will receive 2 doses of vaccine or placebo approximately 6 months apart.			

This protocol is a companion protocol to CIR 255; a study being conducted by the Center for Immunization Research (Johns Hopkins, Baltimore) and the Laboratory of Infectious Diseases (NIAID, Bethesda). The protocols have identical primary and secondary objectives; immunization schedule; evaluation assays and schedule; safety monitoring and reporting. The protocols will vary slightly in site selection, eligibility requirements, and procedures for randomization and site monitoring. These are all operational issues modified to account for the IMPAACT sites operations and infrastructure.

2.0 BACKGROUND

2.1 Background: Epidemiology and Immune Response to HPIV3

Human parainfluenza viruses are important causes of serious respiratory tract disease in infants and young children under 5 years of age⁽¹⁻³⁾. According to the Institute of Medicine, 25% of children under 5 years of age experience a clinically significant parainfluenza virus infection⁽³⁾. Four types of parainfluenza virus are

associated with respiratory disease in young infants and children: types 1 and 2 are the principal cause of croup; type 3 causes pneumonia, bronchiolitis, croup and bronchitis; and type 4 is usually associated with mild upper respiratory tract illness⁽¹⁻³⁾. Human parainfluenza virus type 3 (HPIV3) ranks second only to respiratory syncytial virus (RSV) as the most important cause of bronchiolitis and pneumonia in infants less than 6 months of age. The virus can cause severe disease throughout the first 2 years of life, and virtually all children have experienced primary HPIV3 infections by 3 to 4 years of age. In the U.S., HPIV3 is responsible for approximately 11% of hospitalizations for respiratory diseases in children⁽²⁾.

Immunity to the HPIVs is mediated largely by serum IgG and mucosal IgA neutralizing antibodies directed at the HN or F protein^(2;4). Cell-mediated immunity can also confer short-term protection against replication of challenge virus⁽⁵⁾. Since local IgA antibody and cell-mediated immunity contribute to resistance, immunization that optimally induces these adaptive immune responses is desired. A live attenuated intranasal virus vaccine for HPIV3 would be able to induce both protective immune responses. Previous efforts at paramyxovirus vaccine development have suggested that live-attenuated, intranasally-administered vaccine viruses represent the best strategy for the prevention of the severe lower respiratory tract disease that occurs in infants and children⁽⁶⁾. In addition to inducing the relevant protective immune responses, live attenuated viruses readily infect the upper respiratory tract of human infants despite the presence of maternally derived antibodies present in the serum of the infants, and thus they are able to induce protective immune responses in the presence of passively acquired antibodies⁽⁷⁾. Live-attenuated candidate vaccine viruses, including a cold-passaged (*cp*) human PIV3 (termed HPIV3*cp*45) and bovine PIV3 (BPIV3), have been developed and are under clinical evaluation⁽⁷⁻¹¹⁾.

Because HPIV3-associated lower respiratory illness (LRI) occurs in the first year of life, infants are the primary target population for HPIV3 vaccine development. Re-infections occur throughout life, but they are infrequently associated with LRI. Thus, in normal hosts, immunity conferred by initial infection with HPIV3 generally protects against LRI during subsequent infections. In recent years, attention has been directed toward the development of a live attenuated HPIV3 vaccine that is safe, genetically stable, and protective in young children against serious LRI. It is likely that an HPIV3 vaccine would be administered in combination with a live attenuated RSV vaccine during the first year of life to prevent the most common causes of virus-associated LRI in young children.

2.2 Experimental Vaccines against HPIV3

In recent years, efforts have focused largely on the development of live, attenuated HPIV3 vaccines for use in infants and children. Two types of vaccines have been evaluated in Phase I/II studies in these populations. BPIV3, a naturally occurring host range variant, has been shown to be highly attenuated in children and infants as young as one month of age^(8;9;12). However, the HN and F antibody titers to HPIV3 induced by this vaccine were of low titer, which was not

surprising based upon the limited antigenic relatedness of the human and bovine HN and F glycoproteins⁽⁹⁾. Reverse genetic techniques⁽¹³⁾ have been employed to develop chimeric viruses containing one or more internal genes from BPIV3 and HN and F genes from HPIV3⁽¹⁴⁾. Clinical evaluations of these experimental bovine/human chimeric vaccines are in progress.

The HPIV3 $cp45$ virus is a live attenuated HPIV3 vaccine that was initially developed by Dr. Robert Belshe. The HPIV3 $cp45$ mutant was selected during serial passage of the JS strain of wild type HPIV3 in monkey kidney cell culture at 20°C and 22°C⁽¹⁵⁾. This vaccine candidate has been evaluated in clinical trials during the past 15 years. The HPIV3 $cp45$ virus possesses the desirable properties of cold adaptation (*ca*), temperature sensitivity (*ts*), and attenuation (*att*) for rodents and nonhuman primates⁽¹⁵⁻¹⁹⁾. Studies using reverse genetics have demonstrated that HPIV3 $cp45$ contains at least 5 *ts* and non-*ts* mutations contributing to the *att* phenotype⁽²⁰⁾. It was therefore not surprising that HPIV3 $cp45$ was found to be highly stable following replication in experimental animals and humans^(7;10;18;19). Additional information regarding HPIV3 $cp45$ is contained in Section 2.5.

2.3 Vaccine Description

The experimental vaccine rHPIV3 $cp45$ (abbreviated as rcp45) is a live recombinant (r) attenuated HPIV3 virus that is genetically and phenotypically comparable to the extensively evaluated, biologically derived HPIV3 $cp45$ vaccine. The rHPIV3 $cp45$ was recovered from cDNA in qualified Vero cells using a set of 5 plasmids, 1 encoding a full-length antigenomic cDNA of HPIV3 $cp45$ under control of the T7 polymerase, the 3 support plasmids encoding the N, P, and L proteins, and a fifth plasmid expressing the T7 polymerase. Neither HEp-2 cells nor the MVA-T7 virus were used in the production of this recombinant virus. This Vero-recovered rHPIV3 $cp45$ virus is suitable for use in Phase I and Phase II studies in infants and children.

The seed virus for the production of this experimental vaccine was generated at the LID, NIAID, NIH, in Bethesda, MD. The recombinant HPIV3 $cp45$ vaccine virus was derived entirely from plasmid cDNA in qualified Vero cells at the NIH. Briefly, a full-length antigenomic sense HPIV3 cDNA containing all 15 coding and *cis*-acting element mutations identified in the biologically derived HPIV3 $cp45$ was transfected into qualified Vero cells along with support plasmids expressing the HPIV3 N, P, and L proteins, which are required for recovery of virus from plasmid DNA *in vitro*, and a fifth plasmid expressing the T7 polymerase protein, which drives expression of each of the 4 HPIV3 cDNA plasmids. Each of the 5 cDNA plasmids was grown in a plant-derived (animal product free) bacterial growth medium. The cDNAs were then transfected into Vero cells by electroporation. For electroporating plasmid DNA into Vero cells, Vero cells were grown for a single passage in medium containing fetal bovine serum (FBS). This was the only step during the entire manufacturing process for rHPIV3 $cp45$ Lot PIV3#102A that used FBS. For manufacture of the clinical lot virus in Vero cells, cell culture media without antibiotics or FBS was used. Virus

was recovered from the transfected Vero cells and was amplified once on Vero cell culture and then was purified by a total of 3 serial terminal dilutions on Vero cells. The biologically cloned recombinant virus preparation was then passaged twice on Vero cells to generate the seed virus preparation (rcp45 cl.# 2-A1). The seed virus was transferred to Charles River Laboratories (Malvern, PA) where it was tested for mycoplasma and bacterial contamination. Bacteria and mycoplasma were not detected in the seed virus preparation.

The clinical lot preparation of rHPIV3cp45 was generated by Charles River Laboratories using the seed virus provided by the NIH. Briefly, flasks of Vero cells were infected with the HPIV3cp45 seed virus, and supernatant was harvested after 6 days. Sucrose-phosphate-glutamate (SPG) buffer was added to a final concentration of 1X SPG (0.218M sucrose; 0.0038M KH₂PO₄; 0.0072M K₂HPO₄; 0.0054M glutamate) and the supernatant was clarified by centrifugation. Cryovials were filled with 0.6 mL of the clarified supernatant and were flash frozen at -70°C. The clinical lot preparation was then transferred to a freezer and stored at -70±10°C. Since manufacture of these vaccines, further evaluation of live attenuated paramyxoviridae vaccines (developed at the LID/NIH/NIAID) in both laboratory and clinical situations indicated that these viruses are stable and potent when stored at a temperature of -80°C ±15° C. The rHPIV3cp45 clinical lot (Lot PIV3#102A) was tested for sterility, infectivity, sequence identity, safety in animals, and the presence of adventitious agents in tissue culture. The clinical lot (Lot PIV3#102A) passed all of these tests. The final vial vaccine, designated Lot PIV3#102A, has a mean infectivity titer of 10^{7.1} tissue culture infectious doses (TCID₅₀) per mL. An enlarged example of a final vial label is shown below.

0904-0248 Lot PIV3#102A	Live Recombinant Parainfluenza Virus Type 3 rcp45 VERO Grown Virus Vaccine
	CAUTION:NEW DRUG LIMITED BY FEDERAL (USA) LAW TO INVESTIGATIONAL USE
	Store at -70°C or below Charles River Laboratories, Malvern PA

*NOTE: Since manufacture of the Final Drug Product, evaluation of live attenuated human parainfluenza virus vaccines (developed at the LID/NIH/NIAID) in both laboratory and clinical situations indicates that these viruses are stable and potent when stored at a temperature of -80°C ± 15°C. Therefore, -80°C ± 15°C is the recommended storage condition for the Final Drug Product.

2.4 Preclinical Studies

The preclinical information generated for this new clinical lot of rHPIV3cp45, Lot PIV3#102A, is limited in scope. However, the biologically derived HPIV3cp45 grown in either FRhL-2 or Vero cells has been extensively evaluated in humans. The complete nucleotide sequence of the new clinical lot of rHPIV3cp45 was compared to that of the biologically derived HPIV3cp45 viruses (see the

Investigator's Brochure for additional details). In addition, the new clinical lot of rHPIV3*cp45* was compared to that of the biologically derived HPIV3*cp45* for the presence of the *ts* and *ca* phenotypes in vitro and the *att* phenotype in vivo in hamsters. The new clinical lot of rHPIV3*cp45* possessed: (1) the 5 mutations known to independently contribute to the *att* phenotype, (2) the full set of 15 mutations that define the HPIV3*cp45*, (3) *ts*, *ca*, and *att* phenotypes like that of the biologically derived HPIV3*cp45* previously evaluated in humans. Thus, the preclinical information demonstrates the comparability of the new clinical lot of rHPIV3*cp45* to the biologically derived HPIV3*cp45* which was previously evaluated in adults, children, and infants.

2.5 Previous Clinical Experience

HPIV3*cp45* has been extensively evaluated in Phase I and II clinical trials in children and infants as young as one month of age (Table 2)^(7;10;21). The earliest clinical trials with this vaccine candidate used vaccine grown in FRhL-2 cells and administered at a dose of $10^{5.0}$ TCID₅₀. For subsequent studies, vaccine was grown in Vero cells because of the greater yield of vaccine virus in this cell line, and was administered at doses of $10^{5.0}$ TCID₅₀ to infants and children over 6 months of age and at doses of $10^{4.0}$ TCID₅₀ to infants less than 6 months of age. The rHPIV3 *cp45* vaccine has also been evaluated in a Phase I trial in 6-12 month old infants. Both vaccine preparations were found to be highly infectious, satisfactorily attenuated, immunogenic, and genetically stable following replication in seronegative infants and young children^(7;10;21).

Table 2: Clinical trials evaluating biologically derived HPIV3-cp45 vaccine in seronegative infants and children

Publication	Study Type	N evaluated seronegative only (vaccine vs placebo)	Age (range in months)	Safety Outcomes
Karron et al., 2003 PMID: 12792378	Phase 1 Age de-escalation single dose 10e5 pfu	21 / 4	6-36	Safe and immunogenic. No significant difference in the frequency of fever, URI, congestion, LRI or cough. 4/21 vaccinees vs. 0/4 placebo recipients developed otitis media. Duration of shedding of vaccine virus 12±3 days.
Karron et al., 2003 PMID: 12792378	Phase 1 Age de-escalation 2-dose 10e4 pfu	33 / 16	1-2 (4-12 weeks)	Safe and immunogenic. No LRI or otitis media in any vaccinee. Duration of shedding of vaccine virus 18±5 days.
Belshe et al., 2004 PMID: 14745704	Phase 2 single dose 10e5 pfu	114 / 112	6-18	No significant difference in the occurrence of adverse events (i.e., runny nose, cough, or temperature ≥38°C) during the first two weeks after vaccination. No difference in frequency of otitis media. Safe & immunogenic.
Belshe et al., 2004 PMID: 15551207	Phase 1 cp45 given alone or concurrent with live-att. RSV vaccine 10e5 pfu	33 / 9	6-18	Similar frequencies of solicited AEs. Otitis media was more frequent in vaccinees but study not powered to detect differences. Mean duration of shedding 16 days. Safe and immunogenic.
Madhi et al., 2006 PMID: 16406170	Transmission Study single dose 10e5 pfu	24 / 26	4-25	No definite vaccine virus transmission detected. Probability of definite vaccine virus transmission between 0.003 (95% CI 0.0–0.0009, Reed-Frost model) and 0.04 (95% CI 0.01–0.19, Greenwood model). Probability of definite vaccine virus transmission between 0.018 (95% CI 0.007–0.03, Reed-Frost model) and 0.19 (95% CI 0.09–0.38, Greenwood model).

The HPIV3cp45 virus has also been administered in combination with a live attenuated RSV vaccine candidate, RSV *cpts*248/404, to 6-18 month old children who were seronegative for both RSV and HPIV-3⁽²²⁾. In this trial, the mean subject age was 10 months; RSV *cpts*-248/404 and HPIV3cp45 vaccines were combined in a dose of 10⁵ plaque-forming units of each vaccine and compared to monovalent vaccines or placebo. When the group that received the monovalent RSV *cpts*-248/404 vaccine was compared with the group that received the combination vaccine, no differences in the viral shedding pattern of RSV were observed. A modest reduction in the shedding of HPIV3cp45 vaccine virus was found in recipients of the combined vaccine relative to recipients of the monovalent HPIV3 vaccine; 16 of 21 (76%) of the group given combination vaccine shed HPIV3cp45 versus 11 of 12 (92%) in the monovalent HPIV3 vaccine group. The combined vaccine was safe in the pediatric subjects. Both vaccines were immunogenic, and antibody responses were not significantly different in the monovalent groups versus the combination group. These

observations indicate that a bivalent RSV/HPIV3 vaccine is feasible to develop as a combination vaccine. Future studies will require the identification of optimal vaccine strains and dosages for each of the 2 viruses.

The live attenuated recombinant parainfluenza virus type 3 vaccine rHPIV3 cp45 produced by the National Institutes of Health was evaluated at the Center for Immunization Research (CIR) in a 2-dose double-blind, placebo-controlled trial in 6-12 month old unselected infants. To date, 24 infants have been enrolled: 16 received 10^5 TCID₅₀ of vaccine and 8 received placebo. One child who received vaccine was withdrawn by his parent on Study Day 15 following the first planned dose of vaccine. The remainder of the children have received 2 doses of vaccine or placebo and completed the acute phase of their safety evaluations.

The rcp45 vaccine was well-tolerated: lower respiratory tract illness and otitis media were not observed in any participant and other reactogenicity events (low grade fever and/or upper respiratory tract illness) occurred in 38% of vaccinees and 38% of placebo recipients following dose 1, and 13% of vaccinees and 63% of placebo recipients following dose 2. Evaluation of serum specimens revealed that 10 of the 16 infants who received vaccine were HPIV3 seronegative (hemagglutination inhibition [HAI] titers $\leq 1:8$) prior to vaccination. The 10 seronegative vaccinees shed rcp45 with mean peak titers of $10^{3.5}$ TCID₅₀/mL of nasal wash fluid, which is comparable to titers of virus recovered from seronegative recipients of the biologically derived cp45 ($10^{3.3}$ TCID₅₀/mL⁽¹⁰⁾).

Following the second dose of vaccine, only 1 of 15 children shed vaccine virus, with a peak titer of $10^{2.5}$ TCID₅₀/mL. None of the vaccinees or placebo recipients had a 4-fold rise in serum HAI following the second dose of vaccine.

The patterns of viral shedding and of antibody responses following the first dose of vaccine were comparable to what has previously been observed with the biologically-derived cp45 vaccine. The lack of response to the second dose of vaccine was most likely the result of administration within a relatively short interval following the first dose of vaccine (mean, 5.8 weeks, range 4 to 8 weeks). For this reason, it would be useful to determine whether a longer interval between doses would be associated with higher rates of infection with vaccine virus and a 'booster' antibody response following the second dose of vaccine. Although this study will evaluate the safety, infectivity, and immunogenicity of 2 doses of rcp45 given separately from routine immunizations, 6 month was chosen as the interval for initial evaluation since immunity induced by the first dose would likely have waned by that time and the interval would fit well into recommended schedules for well child visits (Appendix 5).

2.6 Diluent/Placebo

Leibovitz L-15 cell culture medium is used as vaccine diluent (and as placebo) because L-15 is a phosphate buffered solution that maintains an approximate pH of 7.4 at ambient temperature without the need for carbon dioxide supplementation. Parainfluenza viruses are very sensitive to acidic pH because

viral glycoproteins undergo dramatic structural rearrangements at low pH that can result in loss of infectivity.

LID/NIAID has many years of experience with L-15 in human subject trials, indicating that L-15 is safe and not reactogenic following intranasal administration. L-15 is free of animal-derived raw materials, and its composition does not differ substantially from the medium used to grow LID vaccine viruses.

1x L-15 is prepared from a designated safety-tested lot of 2X-L-15 media by 1:1 dilution with sterile water for injection. LID/NIAID has filed a Master File with the FDA for a safety and identity-tested lot of 2XL-15 (BB-MF#12959). Prior to release, each new lot of L-15 is tested for sterility, general safety, bacteriostasis / fungistasis, identity (amino acid composition) and pH.

2.7 Clinical Development Plan

The rHPIV3cp45 candidate vaccine will be evaluated in 6-36 month-old seronegative infants. The major purpose of this study is to confirm the safety and immunogenicity of this new preparation of vaccine for infants in this age group, in preparation for 2 additional studies to be conducted under separate protocols: a) evaluation of the safety, infectivity, and immunogenicity of this dose of vaccine in infants 1 to 2 months of age b) preliminary proof-of-principle evaluation of the efficacy of this vaccine in a Phase IIB study. The virus will be administered intranasally at a dose of 10^5 TCID₅₀/ 0.5 mL to approximately 30 seronegative infants 6 to 36 months of age (at a 2:1 ratio of vaccinees to placebo recipients) in a placebo-controlled, double-blind outpatient trial. A second dose of 10^5 TCID₅₀/ 0.5 mL or placebo will be administered approximately 6 months later.

The safety of the vaccine and the serum antibody response will be assessed in all of the infants. If the outcome of these studies indicates the rHPIV3cp45 vaccine candidate is safe, infectious, and immunogenic, then additional clinical protocols will be generated so that the additional Phase I and Phase IIB studies described above can be conducted.

2.8 Participation of Children

The vaccine being tested in this protocol has been designed to be given to infants and children. Previous studies have demonstrated the safety of HPIV3cp45 in children and infants as young as 1 month of age. These studies have been summarized in Section 2.5 (Table 1). The rHPIV3cp45 virus is genetically and phenotypically comparable to HPIV3cp45, and was shown to be comparably attenuated in preclinical studies and in a previous Phase I trial in infants and children.

2.9 Statement of Compliance

This trial will be conducted in compliance with Good Clinical Practice guidelines and FDA Regulations.

3.0 OBJECTIVES

3.1 Primary Objectives

To determine the safety and immunogenicity of 2 doses of rHPIV3cp45, Lot PIV3#102A in 6-36 month old (through 36 months, 30 days) seronegative infants by:

- Determining the frequency of vaccine-related reactogenicity events (REs) and other adverse events (AEs)
- Determining the amount of serum antibody induced by the vaccine in each recipient

3.2 Secondary Objectives

- To quantify the amount of vaccine virus shed by each recipient.
- To assess the immunogenicity of a second dose of vaccine and the protection of the first dose against re-infection with the second dose of vaccine.
- To determine the number of vaccinated infants infected with rHPIV3cp45 after receipt of vaccine. NOTE: Infection is defined as recovery of vaccine virus from nasal wash and/or a ≥ 4 -fold rise in HAI antibodies.
- To determine the number of vaccinated subjects infected with a second dose of rHPIV3cp45 vaccine.
- To determine the phenotypic stability of vaccine virus shed.

4.0 STUDY DESIGN

4.1 Summary

This is a randomized, double-blind, placebo-controlled outpatient trial in which subjects seronegative for HPIV3 will be randomized in a 2:1 ratio to receive 2 doses of vaccine or placebo, respectively. A second dose of vaccine or placebo will be administered approximately 6 months after the first dose. Placebo recipients are needed in pediatric studies because of the frequent occurrence of mild respiratory and febrile illnesses in young infants and children. For the purpose of this study, 'seronegative' status will be defined as having an HPIV3 HAI antibody titer of $< 1:8$.

The study will be conducted at select domestic IMPAACT Network clinical research sites. Subjects will be healthy infants who are eligible to participate and

whose parents or guardians are willing to enroll their infants and have signed the informed consent form.

Blood counts and chemistries will not be performed at screening; instead, blood will be drawn for HPIV3 antibody tests. Tests such as blood counts and chemistries are not routinely performed as part of well-child care, since the risk of undiagnosed liver and renal diseases is much lower in children than in adults⁽²³⁾. This approach has recently been used in Phase I studies of other live respiratory virus vaccines. A study physician, nurse, or nurse practitioner will inform parents of any significant abnormal physical findings and, after obtaining parental release of information, will make appropriate referrals back to the child’s primary care giver if necessary.

Approximately forty 6-36 month-old (through 36 months, 30 days) children will be enrolled to reach a minimum of 30 evaluable subjects. Infants will be randomized to receive 2 doses of 10⁵ TCID₅₀ of vaccine virus or placebo (1x-L-15, made from a designated safety-tested lot of 2x L-15 media (BB-MF#12959) diluted 1:1 with sterile water for injection), approximately 6 months apart (Table 3). All subjects will be monitored for acute REs for 18 days following each inoculation. The infectivity and phenotypic stability of the vaccine virus will be assessed by obtaining nasal washes for viral culture and quantitation during each study visit. The duration of participation for each subject will be up to 32 weeks (~4 weeks post Dose #2).

Table 3: Immunization Schedule

N	Treatment	Dose
20	Vaccine	10 ⁵ TCID ₅₀
10	Placebo	0

4.2 Study Procedures

4.2.1 Recruitment of Study Subjects

This is a multi-site study. Subjects will be recruited from outpatient clinical sites at IMPAACT sites. Each site will determine site specific appropriate recruitment sites and recruitment materials, to be reviewed and approved by site IRBs and by the protocol team through approval of a site implementation plan.

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

4.2.2 Screening Procedures, Informed Consent, and Pre-inoculation Blood Draw

Procedures for the enrollment visit can be found in Section 8.2 and in the Manual of Procedures.

4.2.3 Randomization, Stratification, Blinding, and Unblinding

Subjects meeting all the study inclusion criteria and none of the exclusion criteria can be enrolled in IMPAACT P1096 by utilizing the Subject Enrollment System (SES) located on the IMPAACT DMC website at www.fstrf.org. Subjects will be randomized in a 2:1 ratio to rHPIV3cp45 vs. placebo, using a dynamic permuted blocks method with block size of 3. This will yield approximately 20 vaccinees and 10 placebo recipients. Randomization will be balanced within site. There will be no stratification.

Routine unblinding may be performed by the site once the subject completes their final study visit post Dose #2. Randomization numbers will be assigned by the unblinded pharmacist when the vaccine is prepared. Vaccine syringes will be labeled with the subject randomization number, the study number, the date and time of preparation. Vaccine and placebo are both clear liquids, thus syringe contents need not be concealed. The pharmacist will add time of administration and subject initials to the label after vaccination, and return the syringe and label to the pharmacy, along with a copy of the vaccine administration sheet.

A copy of the randomization codes will be retained by the pharmacist where the vaccine is prepared, and will not be released until the 18 day acute observation period following the second dose is complete for that subject. A copy of the randomization codes will also be provided to the Data and Safety Monitoring Board (DSMB) Executive Secretary (See Section 9.3.3).

In the event of a serious illness (such as high fever or lower respiratory tract illness), the need may arise to unblind a specific subject's assignment prior to completion of the acute observation phase. Requests for unblinding should be sent to the protocol team including reason for unblinding. Unblinding will be performed in the event of a lower respiratory tract illness associated with rHPIV3cp45, since the Stopping Rules specify that additional vaccinations will be suspended if one or more subjects develop LRI associated with rHPIV3cp45 vaccine infection (See Section 9.3.4). In the event that early unblinding is required, only that specific subject's assignment will be unblinded. Whenever possible, the study Principal Investigator and protocol team will make a decision regarding early unblinding in collaboration with the Sponsor's Medical Monitor. The Sponsor and the DSMB Executive Secretary and Drs. Karron and Englund will also be notified of the event in real time.

4.2.4 Vaccine Administration

On the day of inoculation, a physical examination or assessment will be performed, and, if the subject is healthy, he/she will receive a single dose of vaccine or placebo.

Detailed directions for diluting, labeling and transporting study vaccine are provided in the P1096 study MOP. Briefly, 0.5 mL of vaccine or placebo in a 1 mL syringe that is labeled with subject number, the date, and time of preparation will be administered intranasally (0.25 mL per nostril) within 4 hours from the time of removal from the freezer using a needleless tuberculin syringe while the subject is supine. There is no nasal preparation prior to administration and subjects will remain supine for approximately 60 seconds following dosing. All subjects will receive either 10^5 TCID₅₀ of vaccine virus or placebo.

To maintain blinding, the pharmacist preparing the vaccine will not be involved in assessing study outcomes. This designated individual will be unblinded and will prepare vaccine to the indicated dose according to the instructions detailed in the P1096 MOP. The pharmacist will be instructed not to reveal the identity of the vaccine to the subject or their parent/guardian, nor to personnel (e.g., investigator, study nurse, study monitor) involved in the conduct or monitoring of the trial until the subject completes their final study visit. Additional information regarding randomization and blinding can be found in Section 4.2.3 above and in the P1096 MOP.

4.2.5 Supplies

Vaccine virus for this protocol will be stored at an approved NIH repository until the site has identified the first eligible subject. Thereafter, the site can request shipment of vaccine/placebo for the anticipated number of enrollees.

Vaccine will be stored at the site in a locked -80°C ($\pm 15^{\circ}\text{C}$) freezer until time of use. If the freezer is not in the pharmacy, there must be restricted access to the freezer and the vaccine must be physically separated from other items in the freezer (e.g. separate shelf). The vaccine is supplied as a concentrate that must be diluted to the proper dose prior to administration. Prior to vaccination, a study investigator will supply to the pharmacist a vaccine request form which will include the protocol number, the vaccine virus name, the vaccine titer (concentration), the Investigational New Drug (IND) number, for each subject to be vaccinated. The designated pharmacist will prepare the correct dose of vaccine for each volunteer using sterile technique. Vaccine will be diluted with a designated safety-tested lot of L-15 media (BB-MF#12959). The L-15 media will also be used as placebo. The diluted vaccine (or placebo) will be drawn up in a syringe and labeled with the subject PID. The vaccine and vaccine administration sheet from the pharmacy will be transported to the appropriate vaccination site in a cooler on wet ice. Vaccine must be used within 4 hours of being removed from the freezer. Used syringes, a copy of vaccine administration sheet, and any unused vaccine are returned to the pharmacy for disposition after the vaccination visit.

4.2.6 Vaccine Storage

The rHPIV3cp45 vaccine should remain frozen at -80°C ($\pm 15^{\circ}\text{C}$) until just prior to use. Vaccine should never be refrozen for reuse. Diluent and placebo components are stored at $2-8^{\circ}\text{C}$ in accordance with the manufacturer's recommendation. Vaccine and diluent components should be opened from new containers for each use. No component should be reused for vaccine or placebo preparation.

4.2.7 Vaccine Accountability

The study pharmacist is responsible for maintaining an accurate inventory and accountability record of vaccine supplies for this study. Partially used vials of vaccine components may not be administered to other subjects.

4.2.8 Disposition of Used / Unused Supplies

After the study pharmacist has diluted the vaccine and drawn up the syringes for administration, they will remove the label from the vaccine vial and place it in the accountability log. In this manner, monitoring personnel will be able to verify the accountability of all vaccine vials used for the study. One 150 microliter aliquot of undiluted leftover vaccine (if available) and 3 x 150 microliter aliquots of diluted leftover vaccine (labeled with diluted/undiluted, date aliquoted and frozen, and PID number) will be frozen and stored at -80°C ($\pm 15^{\circ}\text{C}$), separate from the study vaccine product in the Investigational Pharmacy. The aliquots of previously used vaccine (undiluted and diluted) will be batch shipped to Johns Hopkins Bloomberg School of Public Health (see MOP for shipping address) for re-titration at a later time. If there is any vaccine left after the syringes have been drawn up and aliquots removed for titering, it will be destroyed at the clinical site by autoclaving.

4.2.9 Immunization Procedure

All study subjects will receive 2 doses of vaccine or placebo 6 months (26 weeks) apart. The window for Dose #2 is between 24 and 30 weeks after vaccine Dose #1. Vaccine will be kept frozen at -80°C ($\pm 15^{\circ}\text{C}$) until just before use, whereupon it will be thawed and diluted. Vaccine will be kept on wet ice from the time it is diluted until it is delivered to clinical staff for administration. A volume of 0.5 mL will be delivered as nose drops (0.25 mL per nostril) using a needle-less syringe while the subject is supine. There is no nasal preparation prior to administration and subjects will remain supine for approximately 60 seconds following dosing.

4.2.10 Sample Size

Approximately 30 evaluable infants will be enrolled and randomized to receive 10^5 TCID₅₀ of vaccine (N=20) or placebo (N=10). Duration of participation is up to 30 weeks (~4 weeks after the second dose). Enrollment will be concurrent at each site. Distribution of enrollment will be dependent on availability of subjects.

The total enrollment for each of the two companion studies combined will be at least 30 evaluable subjects with evaluable defined as receipt of 2 doses of study vaccine/placebo and collection of post dose 2 serology. It is anticipated that the two studies combined will enroll at least 40 subjects to assure a minimum of 30 evaluable subjects, however accrual to both studies as well as rate of loss to follow up will be monitored and adjustments to total enrollment may be made. NOTE: IMPAACT study sites will not enroll more than 30 total subjects.

4.3 Monitoring Methods

Parents or guardians will report temperatures and symptoms, which will be recorded by study personnel based on information obtained from daily interviews with parents during study visits or by telephone. For temperature measurements, parents or guardians will be instructed to use the Phillips Sensor Touch[®] thermometer or similar temporal artery thermometer to screen for elevated temperatures. Temporal artery thermometers will be provided to the parents or guardians for use during the study. These devices are used to minimize the number of rectal temperature measurements, and have been shown to be an effective screening tool for rectal fever⁽²⁴⁾.

Following manufacturers' directions, the parent or guardian will measure temporal artery temperatures 3 consecutive times. The temperature is displayed digitally on the apparatus. The highest of the 3 readings will be recorded. Any temporal artery temperature of 100°F or above will be verified with a rectal temperature within 20 minutes⁽²⁴⁾. Standard digital rectal thermometers will be provided for use during the study. A child will be considered febrile if he/she has a rectal temperature of 100.7°F or above. Temporal artery temperatures $\geq 100.0^\circ\text{F}$ that are not confirmed by the parent with a rectal temperature will be considered to be reactivity events for the purposes of this study.

Parents or guardians will be provided with written instructions on the use of both temporal artery and rectal thermometers.

4.3.1 Duration and Frequency of Clinical Assessment

The duration and frequency of assessment was based upon previous experience with the biologically derived HPIV3cp45 vaccine^(7;10;21;22).

Reactogenicity will be monitored by recording temperature and signs of illness daily for 18 days after each dose of vaccine or placebo, and a clinical assessment will be performed on Days 0; 3 (or 4), 6 (or 7 or 8), and 12 (or 13, or 14) after each dose of vaccine or placebo. There will also be approximately 15 phone reports to qualified study personnel after each dose. Infants with reported illness may have additional visits to assess the etiology and severity of the illness and treatment will be provided if necessary. From Day 18 after dose 1 until receipt of the second dose and on Days 18-28 (+ 7 days) after the second dose, only data on serious adverse events (SAEs) will be recorded. At those times, physical examinations will be performed and nasal washes obtained only in the event of lower respiratory tract illness.

Follow-up visits will occur 49-63 days after dose 1 and 28-35 days after dose 2. There is a longer interval after dose 1 because this time may be required to develop a primary antibody response. A shorter interval is indicated after dose 2 because an anamnestic antibody response is likely. Individuals performing the clinical evaluations will not have access to the laboratory data (below) until completion of the acute phase of observation for each randomization group.

4.3.2 Laboratory Evaluation: Viral Detection

Nasal washes will be obtained on Days 0; 3, 6, and 12 following each dose of vaccine or placebo. Nasal wash specimens will be tested for vaccine virus by quantitative viral culture, and also for adventitious respiratory viruses on Day 0. Whenever possible, nasal wash specimens will also be obtained from any subject with a respiratory or febrile illness and will be cultured for adventitious respiratory viruses.

4.3.3 Laboratory Evaluation: Immunologic Assays

Serum specimens will be obtained up to 30 days prior to the initial vaccination, at Days 49-63 following the first dose of vaccine, up to 7 days prior to the second vaccination and at Days 28-35 after the second vaccination for measurement of serum antibodies to HPIV3. With parental permission, sera collected during this study will be banked for future use in establishing antibody assays for pediatric respiratory viruses.

4.3.4 Research Laboratory Testing

All samples for laboratory assays for all sites will be shipped to the CIR laboratories (see shipping info in MOP). Quantitation of shedding of the vaccine virus and HPIV3 antibody assays will be performed at CIR. Assessment of nasal washes for adventitious viral agents may be performed at CIR and/or LID, NIAID.

4.3.5 Plan for Use and Storage of Biological Samples

The child's parent/guardian will be asked if the child's unused blood specimens can be stored at the CIR specimen repository once the study is completed. These unused blood samples may be used for future research to learn more about parainfluenza and other related respiratory viruses and respiratory virus vaccines. These blood samples will only be used for research and will not be sold or used directly for the production of commercial products. There will be no human genetic tests performed on the unused blood samples. These specimens will be coded with a unique number and not by patient name.

4.4 Enrollment Procedures

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

Site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO. Sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

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

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

Subjects meeting the study eligibility criteria will be enrolled through the Data Management Center (DMC) registration screens. Written informed consent for

study participation must be obtained before any study related procedures are performed.

5.0 SELECTION AND ENROLLMENT OF STUDY SUBJECTS

5.1 Screening Visit (Up to 30 Days before Enrollment)

During this initial screening visit, detailed study information will be presented and informed consent for screening and study participation will be obtained. Procedures for the screening visit can be found in Section 8.1 and in the MOP.

5.2 Enrollment Visit

Once it is determined that a child is eligible, the study personnel will notify the parent/guardian and arrange an enrollment visit. Dose #1 of the study vaccine will be administered at the enrollment visit. Procedures for the enrollment visit can be found in Sections 8.2 and 8.3 and in the MOP.

5.3 Inclusion and Exclusion Criteria

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

5.3.1 Inclusion Criteria

- Healthy 6 to 36 month old infants and children (up to 36 months plus 30 days of age) whose parent/guardian(s) can demonstrate their understanding of the study (by taking a multiple choice questionnaire) and sign the informed consent and who agree to vaccine administration following detailed explanation of the study.
- Seronegative for HPIV3 as defined by serum antibody titer HAI \leq 1:8 as determined within 30 days prior to inoculation.
- Subject's history has been reviewed and subject has undergone a physical examination indicating that he/she is in good health.
- In the view of the site investigator, subject has received routine immunizations appropriate for age, administered at least 2 weeks prior to study entry (inactivated and subunit vaccines and rotavirus vaccine) or at least 4 weeks prior to study entry (live vaccines except rotavirus vaccine) (see also exclusion criteria).
- Subject is expected to be available for the entire study period and parent/guardian can be reached by telephone for post-inoculation contacts.
- For children born to HIV-infected women, the child can be considered HIV negative if he/she has either two negative PCR tests with one

collected when >1 month of age and one collected when >4 months old; or two negative antibody tests.

- If there is a child in the household who is <5 years of age, their last CD4 must be >15%.

5.3.2 Exclusion Criteria

- Known or suspected impairment of immunological functions, HIV infection, or currently (within the last 30 days) receiving immunosuppressive therapy including systemic corticosteroids.

NOTE: Topical steroids, topical antibiotic and topical antifungal medications are acceptable

- Bone marrow/solid organ transplant recipients
- Major congenital malformations, including congenital cleft palate, cytogenetic abnormalities, or serious chronic disorders
- Previous immunization with HPIV3 vaccine
- Previous serious vaccine-associated adverse event or anaphylactic reaction
- Known hypersensitivity to any vaccine component
- Lung or heart disease, including reactive airway disease. Subjects with clinically insignificant cardiac abnormalities requiring no treatment may be enrolled. Subjects who wheezed once or received bronchodilator therapy once in the first year of life but who have not had any additional wheezing episodes or bronchodilator therapy for at least 12 months may also be enrolled.
- Premature infants (born before 37 weeks gestation) if less than 12 months of age
- Members of a household which contains immunocompromised individuals (including, but not limited to, those with HIV related immunodeficiency, defined as CD4<300 within the previous 6 months. or any household members who have received chemotherapy within the last 12 months).

NOTE: Sites should ask the parent/caregiver what the child's recent CD4 count was; this can be accepted verbally if the parent/caregiver seems sure. If the parent/caregiver is unsure of the child's CD4 count, the site will need to verify this value from clinic records.

- Members of a household which contains infants less than 6 months of age
- Attends day care with infants less than 6 months of age and whose parent/guardian is unable or unwilling to suspend daycare for 14 days

following immunization. (Facilities that separate children by age and minimize opportunities for transmission of virus through direct physical or aerosol contact are acceptable)

- Participation in another investigational vaccine or drug trial within 30 days of receiving the investigational vaccine or until the final follow up blood draw

5.3.3 Temporary Exclusion Criteria

The following exclusion criteria are temporary or self-limiting conditions, and once resolved (after 24 hours and 3 normal measurements for fever) the subject may be enrolled, if otherwise eligible.

- Fever (rectal temperature of $\geq 100.7^{\circ}\text{F}$), or acute upper respiratory illness (including nasal congestion significant enough to interfere with successful vaccination), or acute otitis media.
- Subject has received any killed or subunit vaccine or rotavirus vaccine within the last 2 weeks, any live vaccine, except rotavirus, within the last 4 weeks, or gamma globulin (or other antibody products) within the past 3 months (see Appendix IV).
- Subject has received short-term systemic antibiotics or systemic steroid therapy for an acute illness within the previous 5 days prior to vaccination; or is currently receiving long-term prophylactic antibiotics (NOTE: Topical steroids, topical antibiotics or topical antifungal preparations are permitted).
- Subject has received aspirin or aspirin-containing products within the past month. The subject should not have received aspirin or aspirin-containing products for 30 days.
- Infants born at <37 weeks gestation will be deferred from participation until they are ≥ 12 months of age.

5.4 Access to Medical Records

The medical history of a pediatric subject will be obtained directly from the subject's parent or guardian. Medical records will be reviewed for all subjects after the parent/guardian signs a medical release. Only those portions of the medical record that are pertinent to the study will be maintained in the study chart. Medical records will be reviewed for the following reasons:

- to clarify whether subject meets eligibility criteria
- to confirm immunization status
- to clarify or confirm any Adverse Events (AEs) or Reactogenicity Events (REs) that occur during the study

No medical record will be requested without the informed written consent of the parent or guardian.

5.5 Treatments that Could Potentially Interfere with Vaccine-Induced Immunity and Require Treatment Discontinuation if Identified Prior to Dose 2 of Vaccine

The following criteria should be checked prior to each inoculation and at the follow up visit after each inoculation. If any become applicable during the study, the subject should not receive additional study agent. Additionally, the participant will not be included in the immunogenicity evaluations after the time of exclusion. The parent/guardian of the participant will, however, be encouraged to have the participant remain in the safety evaluation for the duration of the study.

- Use of any investigational drug or investigational vaccine other than the study article during the study period (Days -30 through the final follow up blood draw)
- Chronic (defined as more than 14 days) administration of immunosuppressant's or other immune-modifying drugs during the study period (Days -30 through the final follow up blood draw)
- Receipt of a licensed killed vaccine or live attenuated rotavirus vaccine from Day -14 through and including Day 13 for each dose
- Receipt of immunoglobulin's and/or any blood products during the entire study (Days -30 through the final follow up blood draw)
- Receipt of a licensed live virus vaccine, except rotavirus vaccine, from Day -28 through and including Day 27 for each dose

5.6 Subject Withdrawal/Termination Criteria

A pediatric subject will not be considered to be evaluable if any of the following conditions apply. However, the parent or guardian of any pediatric subject who has received vaccine or placebo will be encouraged to remain in the safety evaluation for the duration of the study.

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

- *The study is stopped or cancelled* – applies to the situation where the entire study is stopped or cancelled for any reason prior to the last study visit.
- *Withdrawal of consent* – applies to a pediatric subject whose parent or guardian withdraws consent to participate in the study for any reason.
- *Noncompliant with protocol* – applies to a pediatric subject whose parent or guardian does not comply with protocol-specific visits or evaluations, on a consistent basis, such that adequate follow-up is not possible and the subject's safety would be compromised by continuing in the trial. Additionally, this

applies to a pediatric subject who is lost to follow-up and whose parent or guardian is not reachable by telephone or other means of communication, and therefore not able to be located.

- *Subject withdrawal* may occur if the investigator believes that it is in the best interest of the pediatric subject to withdraw the subject.
- *Other* – is a category used when previous categories do not apply and requires an explanation.

6.0 REPLACEMENT OF STUDY SUBJECTS

The intention is to enroll 30 evaluable subjects which may require enrolling up to 40 total subjects to assure that at least 30 receive both immunizations and complete the final study visit. The team will not replace specific patients but rather will enroll up to 40 to assure a total of 30 with complete data. Those who receive a first dose but do not complete the study will be included in all analysis up to the point when they are discontinued from study.

Analysis of seroconversion rates for subjects who have received the first dose will include only those subjects for whom the dose 1 follow up blood sample was obtained. Analysis of seroconversion rates for study dose 2 will include only those subjects for whom follow up dose 2 blood sample was obtained.

7.0 ENROLLMENT AND INOCULATION (STUDY DAY 0)

For the purposes of this protocol, enrollment will correspond to inoculation with investigational product.

8.0 CLINICAL MONITORING AND EVALUATION

8.1 Screening

During this initial screening visit, detailed study information will be presented. Informed consent for screening and study participation should also be obtained. Screening must occur ≤ 30 days prior to enrollment.

The child's parent/guardian will be encouraged to ask questions, and then take a multiple-choice questionnaire to evaluate consent comprehension. Study staff will use incorrect answers from the questionnaire to identify those areas of the informed consent form that need further review with the parent/guardian. This will help ensure that the parent/guardian has sufficient understanding before signing the consent form. If the parent/guardian needs additional time to consider the screening process, another visit will be scheduled and no procedures will be done. If used, information regarding topical anesthetic medication will be presented and consent will be obtained before anesthetic is applied to several potential sites for the blood draw.

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

- Explain the study and screening process to the parent/guardian and answer any questions.
- Administer the study comprehension exam and ensure that the parent/guardian understands the study. Parent/guardians should be able to correctly answer any questions that were initially answered incorrectly. (See MOP for further information on this quiz.)
- Obtain informed consent from the parent or guardian and ensure the parent/guardian has signed the consent.
 - Ensure parent/guardian has authorized or denied authorization for use of samples for future studies.
 - Ensure parent/guardian has authorized or denied authorization for use of topical anesthetic (if used) for blood draw.
 - The parent/guardian should also receive a copy of the signed informed consent that they can take home with them.
 - Obtain parent/guardian authorization to obtain subject's medical record from private health care provider (if applicable)
- Ensure parent/guardian has signed medical release to obtain records of any AEs that might occur which necessitate medical record clarification or confirmation. Only those portions of the medical record that are pertinent to the study will be maintained in the study chart.
- Obtain medical history and perform complete physical examination.
- If parent/guardian has agreed, apply topical anesthetic cream to several potential venipuncture sites, cover with occlusive dressing, and allow it to penetrate skin for the appropriate duration of time. This is optional.
- Remove dressings and obtain approximately 5 mL of blood to:
 - Test for serum antibodies to parainfluenza 3 (HPIV3)
 - Act as a pre-vaccination blood specimen
- Remove anesthetic cream from unused sites, if used
- Schedule a return visit, if needed

Serum from screening visit will be shipped weekly to JHU from each clinical site. Serologic testing will be performed weekly and results will be sent via email to the site.

8.2 Study Day 0 (Dose 1 – Entry)

- Interim history and focused physical assessment, including check of ears, nose, throat, regional lymph nodes, chest, and heart, concentrating on any acute complaint areas
- Review Inclusion and Exclusion criteria including treatments that could potentially interfere with vaccine-induced immunity.
- Prior to dose of vaccine or placebo:
 - Obtain nasal wash for viral culture, and adventitious agent testing
Record temporal and/or rectal temperature, heart rate, and respiratory rate.
- Administer vaccine.
- Observe for approximately 30 minutes after vaccination to evaluate for immediate adverse reactions.
- Record any positive findings on adverse event page of CRF.
- Provide parent/guardian with temporal artery thermometer and digital, rectal thermometer, and instruct in use.
- Provide and explain the memory aid, thermometer, illness criteria, and study personnel contact information.

NOTE: The memory aid should not be collected by the clinic and may not be used as a source document.

- Schedule Days 1 and 2 telephone contact and Day 3 visit.

8.3 Study Day 0 (Dose 2)

NOTE: Dose #2 should be between 26 and 30 weeks after Dose #1. Sites should contact the team for instructions if there is a delay beyond 30 weeks.

- Obtain detailed interim history and focused physical assessment, including check of ears, nose, throat, regional lymph nodes, chest and heart, concentrating on any acute complaint areas.
- If parent/guardian has agreed, apply topical anesthetic cream to several potential venipuncture sites, cover with occlusive dressing, and allow it to penetrate skin for the appropriate duration of time. This is optional.
- Obtain approximately 5mL of blood for immunologic assays.
- Review Inclusion and Exclusion criteria including treatments that could potentially interfere with vaccine-induced immunity (Section 5.5). Infants will not receive a second dose of vaccine or placebo if they have experienced any lower respiratory tract illness (i.e. wheezing, rales, rhonchi, croup, and pneumonia) during the study.
- Prior to dose of vaccine or placebo:
 - Obtain nasal wash for viral culture, and adventitious agent testing

- Record temporal and/or rectal temperature, heart rate, and respiratory rate.
- Administer vaccine.
- Observe for approximately 30 minutes after vaccination to evaluate for immediate adverse reactions.
- Record any positive findings on adverse event page of CRF.
- Remind parent/guardian directions for use of temporal artery thermometer and digital, rectal thermometer.
- Provide and explain the memory aid, thermometer, illness criteria, and study personnel contact information.

NOTE: The memory aid should not be collected by the clinic and may not be used as a source document.

- Schedule Days 1 and 2 telephone contact and Day 3 visit.

8.4 Study Days with Clinic Visits (Doses 1 & Dose 2)

After each delivery of vaccine, clinic visits are scheduled to take place on Day 3 (window of +1 day), Day 6 (window of +2 days) and Day 12 (window of +2 days).

- Obtain and record interim history and temperatures since last contact.
- Perform focused physical assessment, including check of ears, nose, throat, regional lymph nodes, chest and heart, emphasizing assessment for any acute complaints.
- Record temperature (temporal and/or rectal), pulse and respirations.
- Obtain nasal wash for culture of vaccine virus. Specimens will be tested for adventitious agents from any subject with a febrile or respiratory illness.
- Schedule next visit.
- Day 12, Day 13 or Day 14 clinic visit only- instruct parent to notify study nurse immediately of any interim illness that requires medical care, any hospitalization, or any lower respiratory tract illness, including croup, pneumonia, or wheezing.

8.5 Telephone Contacts

NOTE: Telephone contact should be made with the subject on all non-clinic visit days, post Dose #1 and post Dose #2.

- Obtain interim history and temperature from parent/guardian via phone contact.
- Clarify any positive findings.

- Schedule illness visit if child meets criteria for illness and does not have a routine clinic/home visit within the next 72 hours (See Section 8.7 for procedures for a sick visit).
- Confirm next clinic/home visit.

8.6 Follow-Up Clinic/Home Visits

Follow-up clinic/home visits will be scheduled for Day 56 (± 7) after the first dose of vaccine and on Day 31 (± 4) after the second dose of vaccine.

- Obtain interim history, including treatments that could potentially interfere with vaccine-induced immunity and including any unscheduled medical visits, hospitalizations, or immunizations, or lower respiratory tract illness (croup, pneumonia, wheezing, and bronchiolitis).
- If parent/guardian has agreed, apply topical anesthetic cream to several potential venipuncture sites, cover with occlusive dressing, and allow it to penetrate skin for the appropriate duration of time. This is optional.
- Obtain approximately 5 mL of blood for immunologic assays.
- Provide parent with compensation (gift cards and/or checks) for participation as determined by local sites (estimate \$25 per scheduled visit and \$5 for each scheduled telephone contact and \$25 study completion bonus). Compensation may be provided in increments during the study for those families that request it. Parents will be compensated for only that portion of the study which is completed.
- At study completion, thank parent for participation and inform them of child's randomization status if unblinding has occurred. Parents will be notified by telephone or letter of the child's vaccination status once the code has been broken. The child's primary care giver will be informed of the child's participation and vaccination status with written parent/guardian permission, after the code is broken.
- Refer to Appendix IA and IB for schedule of evaluations of study procedures as well as the P1096 MOP.

8.7 Sick Visits

If the subject reports any parainfluenza-like symptoms as listed in Appendix II, the subject will be asked to come in for a sick visit, if a routine clinic visit is not already scheduled for within the next 72 hours. Appendix IA and IB describe the required evaluations for sick visits.

Reactogenicity events, such as those in Appendix II, will be recorded on the CRFs as usual. Any symptoms of lower respiratory tract illness within 28 days following Dose #1 and Dose #2 are required to be reported as SAEs for this study (see Section 9.1.3).

9.0 ADVERSE EVENT MONITORING

9.1 Definitions

9.1.1 Adverse Event (AE)

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

All AEs must be graded for severity as described in Section 9.2.8 and assessed for relationship to the investigational vaccine as described in Section 9.2.4 of this protocol. The following common childhood events will not be recorded on CRF's as AEs unless concomitant medications are given: non-infectious diaper rashes, teething pain, and spitting up (NOTE: Treatment with topical agents is considered concomitant medication).

The study agents in this study are Human Parainfluenza Type 3 Virus vaccine (rHPIV3cp45, Lot PIV3#102A) and Placebo.

9.1.2 Reactogenicity Events (REs)

Reactogenicity events (REs) are predefined AEs that can occur after vaccine administration. Reactogenicity will be assessed during the acute phase of this study (Days 0-18 after each dose).

For the subjects enrolled in this study, reactogenicity events include:

- Fever
- Upper Respiratory Tract Illness
 - Rhinorrhea
 - Pharyngitis
 - Cough without Lower Respiratory Tract Illness
 - Hoarseness
- Otitis media
- Change in feeding sufficient to warrant contact with health care provider
- Lower respiratory tract illness
 - Wheezing
 - Pneumonia
 - Laryngotracheobronchitis (croup)
 - Rhonchi
 - Rales

Definitions of these illnesses are listed in Appendix II.

9.1.3 Serious Adverse Event (SAE)

A serious adverse event (SAE) is an AE, whether considered related to the investigational vaccine or not, that meets any of the following outcomes:

- Death.
- Life threatening: defined as an event that places a subject at immediate risk of death at the time of the event and does not refer to an event that hypothetically might have caused death were it more severe.
- Hospitalization (or prolongation of existing hospitalization) defined as at least an overnight stay in the hospital or emergency ward for treatment that would have been inappropriate if administered in the outpatient setting.
- Results in a congenital anomaly or birth defect.
- Results in a persistent or significant disability or incapacity: defined as a substantial disruption of the study participant's ability to carry out normal life functions.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
- For the purpose of this study, any lower respiratory tract illness (see Appendix II) occurring during the first 28 days post each dose will be reported as an SAE.

9.1.4 Study Reporting Period for Adverse Events and Reactogenicity Events

The reporting period for REs is the period immediately following the administration of study dose through the acute monitoring phase (Days 0-18) after each dose.

Details of all Adverse Events will be properly recorded in the case report form and source documents.

All SAEs during study participation (regardless of when they occur during the trial) will be recorded, assessed for relationship to the study vaccine, and assigned a severity grade for the duration of the study. All SAEs will be reported following the instructions in the MOP and Section 9.2.9 of the protocol. Study participation will be considered complete at the time of the Day 31 follow up visit following the second dose.

9.2 Assessment of Safety

9.2.1 Assessment of Reactogenicity Events

The primary REs to be measured are described in Section 9.1.2, with the full definition provided in Appendix II. All REs will be analyzed for each individual subject taking the pattern of viral shedding into account. Key parameters (e.g. numbers of subjects with fever, cough, URI, LRI, otitis media) will be summarized for REs following Dose #1 and Dose #2.

9.2.2 Reactogenicity Events Elicited by History

Reactogenicity events elicited by parental history that are not confirmed by physical assessment will be reported on the CRFs. However, they will not be counted as a true reactogenicity event unless they meet the definition of illness (Appendix II. For example, rhinorrhea, cough, and pharyngitis must each occur on 2 consecutive days to meet the definition of illness).

9.2.3 Identification of Adverse Events

Assessment of safety will include clinical observations and monitoring of subjects. Subjects will be closely monitored from the time of vaccine administration until the end of the acute monitoring phase (Day 18) after each dose of vaccine). During this time, all AEs will be recorded on the AE CRF and the relationship to study product will be assessed. A study clinician will perform assessments on Study Day 0 (Entry), Day 3, Day 6 and Day 12 after each dose. A study clinician will also be available by telephone 24 hours a day during the study evaluation period (on Days 0-18 after each dose) and during working hours for the entire study.

Transient mild symptoms such as rhinorrhea, pharyngitis or cough that do not meet the RE study definitions (see Appendix II) will not be classified as AEs; however this information will be captured and recorded on source documents.

9.2.4 Association with Receipt of Study Agent

All AEs and REs will have their relationship to study agent assessed using the following terms:

- Definitely related: Clear-cut temporal association, and no other possible cause.
- Probably related: Clear-cut temporal association and a potential alternative etiology is not apparent.
Possibly related: Less clear temporal association; other etiologies also possible.
- Unlikely related: Temporal association between the AE and the vaccine or the nature of the event is such that the vaccine is not likely to have had any

reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible).

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

9.2.5 Adverse Event Reporting

Adverse events may be observed by the Investigator, elicited from the parent/guardian or subject, reported on subject temperature cards, or volunteered by the parent/guardian or subject.

9.2.6 Medical Follow-up

Medical follow up (such as history, physical examination, and laboratory testing and/or treatment) may be necessary if a subject experiences an Adverse Event.

9.2.7 Details of Adverse Events

Details of all AEs will be properly documented in the source documents, recorded on the AE CRF, and reported to the study team and sponsor's medical monitor in monthly reports. All AEs will also be reported annually to all applicable IRBs.

9.2.8 Determination of Severity

All AEs and REs, other than feeding, will be assessed by the investigator using the following protocol-defined system:

Table 4: Adverse Event Grading

Severity	Defined
Grade (0)	None
Grade (1) - Mild	No intervention required; may include use of over-the-counter medications managed by the subject or caregiver
Grade (2) - Moderate	Outpatient medical intervention by a health care provider required; may include use of over-the-counter and/or prescription medications.
Grade (3) - Severe	Prolonged medical intervention and/or hospitalization required
Grade (4) - Immediately Life-Threatening	Life-threatening illness requiring hospitalization with intensive care

Table 5: Fever Grading: Rectal Temperature Measurement for Infants and Children

Grade (0)	<100.7°F	(<38.2°C)
Grade (1)	≥100.7°F but ≤101.4°F	(≥38.2°C but ≤38.6°C)
Grade (2)	≥101.5°F but ≤102.4°F	(≥38.7°C but ≤39.1°C)
Grade (3)	≥102.5°F but ≤104.8°F	(≥39.2°C but ≤40.5°C)
Grade (4)	≥104.9°F	(≥40.6°C)

9.2.9 Reporting Serious Adverse Events to the IND Sponsor

SAEs will be documented on the RCHSPB/IND Sponsor SAE Report Form and

sent to the IND Sponsor Clinical Safety Office (CSO). Deaths and immediately life threatening SAEs must be reported within 1 business day after the clinical site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness. SAE Report Forms will be sent by e-mail attachment or fax to the CSO at:

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

9.2.9.1 Sponsor's Reporting Responsibilities

SAEs that are considered unexpected (as determined by the Sponsor) and related (possibly, probably, and definitely) to the study agent will be reported by the Sponsor as expedited IND Safety Reports to the FDA and to all participating investigators per 21 Code of Federal Regulations (CFR) 312.32.

9.2.9.2 Reporting Serious Adverse Events to the IRB

All IMPAACT sites will report SAEs to their local IRB following the institution/IRB's standard operating practices.

9.3 Adverse Event Monitoring

9.3.1 Sponsor's Medical Monitor

The Sponsor has appointed a Medical Monitor, Dr. Barry A. Eigel, for oversight of safety in this clinical trial. In this capacity, the Sponsor's Medical Monitor will:

- 1) Review all AEs at least monthly throughout the trial,
- 2) Review all SAEs;
- 3) Be available to advise the investigators on trial-related medical questions or problems; and
- 4) Evaluate cumulative subject safety data and make recommendations regarding the safe continuation of the study.

The Protocol Chairs are responsible for ensuring that the Medical Monitor is aware of all new safety information during the course of the clinical trial.

9.3.2 Serious Adverse Event Review

The Sponsor's Medical Monitor will review all SAEs determined to be possibly, probably, or definitely related to the study agent. Any such SAE will be reported to the DSMB Executive Secretary for distribution to the DSMB for their review. The Sponsor's Medical Monitor may also halt vaccination of subjects until the SAE has been reviewed by the DSMB, and the DSMB agrees with resuming

vaccination. The DSMB Executive Secretary will provide the Sponsor's Medical Monitor and the Protocol Chairs with the DSMB's recommendations as soon as possible.

9.3.3 Data and Safety Monitoring Board

The NIAID Intramural Data and Safety Monitoring Board (DSMB) consists of experts in infectious diseases, biostatistics, and clinical trials and is responsible for reviewing the safety data of NIAID clinical studies that require DSMB oversight. The DSMB will review the protocol prior to opening the study to enrollment. The Principal Investigator will submit the Sponsor's Medical Monitor's written recommendations and cumulative safety data, grouped according to treatment cohorts, to the DSMB Executive Secretary for semi-annual DSMB review. The DSMB will then meet to review the completeness of the study data collected, the adherence to the protocol, and the Sponsor's Medical Monitor's review summaries. The DSMB Executive Secretary will provide the Principal Investigator with DSMB recommendations as soon as possible, and the official DSMB Report will then be provided through the office of the NIAID Clinical Director. The Protocol Chairs will submit the written DSMB recommendations to the IRBs upon receipt.

9.3.4 Stopping Rules

If any of the following occur, additional vaccinations will be suspended until reviewed with the DSMB and the study sponsor (RCHSPB):

- One or more subjects experience a SAE (as defined in Section 9.1.3 in this protocol) that is determined to be possibly, probably, or definitely related to the vaccine OR
- One or more subjects experiences a grade 4 fever or any grade 3 or grade 4 reactogenicity event other than fever OR
- One or more subjects develops LRI associated with shedding of the rHPIV3cp45 vaccine

10.0 DATA COLLECTION AND MONITORING

10.1 Source Documentation

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

10.2 Study Documentation

Study-related documentation will be completed as required by the IRBs, the Sponsor, and regulatory authorities. Continuing review documentation will be submitted by the Investigator to the IRBs on the anniversary date of initial review as specified by each IRB. An annual report will be submitted by the Sponsor to the FDA on the anniversary date that the IND for the HPIV3 cp45 recombinant vaccine went into effect. These reports will provide a brief description of the progress of the investigation as outlined in 21 CFR 312.33, and will include any revisions of the protocol.

The Investigator will maintain adequate records of the disposition of the investigational product, including dates of receipt and disposition, quantity, and use by subjects. If the study is terminated, suspended, or completed, the Investigator will return all unused supplies of the investigational product to vaccine repository.

10.3 Retention of Records

The site principal investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. Trial-related documents will be maintained by the Investigator for a period of 2 years after final marketing approval of the vaccine, or if 2 years have elapsed since the formal discontinuation of clinical development of the product. These records are also to be maintained in compliance with IRB/EC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law. It is the investigator's responsibility to retain copies of source documents until receipt of written notification to the contrary from the Regulatory Compliance and Human Subjects Protection Branch (RCHSPB) of the National Institute of Allergy and Infectious Diseases (NIAID). No study documents should be destroyed without prior written agreement between RCHSPB/NIAID and the principal investigator. Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator must provide written notification of such intent to RCHSPB/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. NIAID must be notified in writing and written NIAID permission must be received by the site prior to destruction or relocation of research records.

10.4 Protocol Revisions

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

The DSMB will be made aware of all protocol revisions (other than administrative) and will review and recommend approval of any changes to the

protocol that involve changes to the data and safety monitoring plan of the study. The DSMB will be notified along with the Sponsor in the event of a medical emergency that did not allow for pre-review.

10.5 Clinical Investigator's Brochure

Investigators will receive the current version of the Clinical Investigator's Brochure which comprehensively describes all the available preclinical experience with the experimental vaccine. If relevant new information becomes available during the course of the trial, the Investigators will receive a revised Investigator's Brochure or an amendment to the current version.

10.6 Study Monitoring

The trial will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP), and any applicable regulatory requirement(s). The study site monitoring will be conducted according to the NIAID/DAIDS and NICHD Clinical Research Site Monitoring Guidelines.

11.0 STATISTICAL CONSIDERATIONS

11.1 General Design

The goal of the Phase I vaccine trial is to demonstrate the safety, infectivity, and immunogenicity of the rHPIV3cp45 vaccine candidate in human volunteers. The data from the two comparison studies will be combined for final analysis.

11.2 Description of the Statistical Methods to be Employed

This study, like other Phase I studies, is basically exploratory rather than confirmatory; its purpose is to estimate event rates and patterns of immune responses rather than to test formal statistical hypotheses. Descriptive approaches will be used to meet the protocol objectives as stated in Section 3.0 of this protocol, as well as formal statistical tests as outlined below. Results will be presented in tabular format, as well as graphically where appropriate.

11.3 Sample Size

Given the small sample size, the study will have limitations with respect to detecting adverse events (AE) and reactogenicity (RE) and in estimating the rates of such events in the population represented by the study sample. The following tables demonstrate these limitations.

Table 6 presents the probabilities of seeing up to 7 AEs or REs within the sample of 20 vaccinees, under a range of assumptions concerning the true rate of such events in the patient population represented by this sample. Note that, if true event rates

are as high as 5% there is a good probability of observing at least one event in a sample of 20 subjects; conversely, with true event rates as low as 1%, there is a relatively low probability of seeing at least 1 event in a sample of this size.

TABLE 6.

For N=20, probability of observing:	True underlying rate of AE or RE			
	1%	5%	10%	20%
1 or more AE's or RE's	0.18	0.64	0.88	0.99
2 or more AE's or RE's	0.02	0.26	0.61	0.93
3 or more AE's or RE's	0.001	0.08	0.32	0.79
4 or more AE's or RE's	<0.001	0.02	0.13	0.59
5 or more AE's or RE's	<0.001	0.003	0.04	0.37
6 or more AE's or RE's	<0.001	<0.001	0.01	0.20
7 or more AE's or RE's	<0.001	<0.001	0.002	0.09

Table 7 presents 95% confidence intervals (CI) around potential rates of AEs or REs that might be observed in the sample of 20 vaccinees. The CIs around similar rates in a sample of 10 placebo recipients are also presented. Note that if no AEs are detected among the 20 vaccinees, there is a 95% probability that the true rate of AEs is no greater than 17%.

TABLE 7: Percent of Subjects Experiencing AEs or REs with Exact 95% Confidence Intervals

N	% AEs or REs	95% C.I.
10	0%	0% -- 31%
20	0%	0% -- 17%
10	10%	0.3% -- 45%
20	10%	1% -- 32%
10	20%	3% -- 56%
20	20%	6% -- 44%
10	30%	7% -- 65%
20	30%	12% -- 54%

11.4 Analyses

11.4.1 Primary Objective 1

To determine the frequency of vaccine-related REs and other AEs for the rHPIV3cp45 vaccine.

- Summarize the frequency of REs and other AEs.
- Line listing of individual clinical REs and other AEs. These will be displayed in tabular format and stratified by dose cohort.

- Where appropriate, Chi-square or Fisher's exact test will be used to determine significant differences between groups.

11.4.2 Primary Objectives 2 and 3

To determine the immunogenicity and infectivity of the rHPIV3_{cp45} vaccine candidate.

- Line listing of peak titer of virus shed by individual. These will be displayed in tabular format.
- Line listing of HPIV3 antibody responses by individual. These will be displayed in tabular format.
- Where appropriate, the Mann-Whitney U test or Tukey Kramer multiple comparison post test will be used to determine significant differences between groups.

11.5 Outcome Measures

11.5.1 Safety

The primary safety endpoint is the frequency of vaccine-related REs that occur during the acute monitoring phase of the study (Days 0-18 for each dose).

11.5.2 Immunogenicity

The primary immunogenicity endpoint is the proportion of subjects that develop 4-fold or greater rises in HAI antibody titer following 2 doses of vaccine.

12.0 PROTECTION OF HUMAN SUBJECTS

12.1 Institutional Review Board

The Investigator at each site will be responsible for obtaining IRB approvals for the study. Before the start of the study, the appropriate documents (including the Protocol, Investigator's Brochure, Informed Consent Form, information sheets, and advertisements) will be submitted to, and approved by, each site's local IRB/EC. A copy of the study approvals (including approval of the informed consent form) is to be maintained in the Investigator's study document binder. During the study, the Investigator is responsible for providing the IRBs with all documents subject to review (i.e., Protocol Amendments, informed consent form updates, advertisements, and any written information that may be provided to the subject). Annual reports on the progress of the study will be made to the IRBs by the site Investigator in accordance with IRB guidelines and government regulations.

12.2 Informed Consent

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

12.3 Risks

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

12.3.1 Venipuncture

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

12.3.2 Nasal Wash

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

12.3.3 Immunization

If the rHPIV3cp45 vaccine is insufficiently attenuated, subjects could also experience fever, rhinorrhea, cough, or lower respiratory tract illness. Immediate hypersensitivity reactions including urticaria, anaphylaxis, or other IgE mediated responses are possible as with any vaccine. As with any investigational vaccine, there is a theoretical possibility of risks about which we have no present knowledge. Parents/guardians will be informed of any such risks should further data become available.

12.4 Benefits

Volunteers may not receive any direct benefit from participation in this study. It is possible that some infants who receive vaccine may be protected against infections with one type of parainfluenza virus that circulates in the community. It is hoped that information gained in this study will contribute to the development of a safe and effective vaccine for the prevention of illness associated with infection by one type of parainfluenza virus.

12.5 Compensation

The parent/guardian of pediatric subjects will receive compensation as determined by each research site for participation (approximately at the rate of \$25 per scheduled study visit, \$5 per scheduled telephone contact and a \$25 bonus for study completion). The parent/guardian will be compensated only for those portions of the study that are completed. Pediatric subjects may also receive age appropriate books or small toys.

12.6 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 Office for Human Research Protections (OHRP), the NIAID, the local IRB or Ethics Committee and by the study staff, and study monitors.

13.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention.

All infectious specimens will be transported in compliance with Federal Regulations and 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 and to the ACTN Guidelines for Shipment and Receipt of Category B Biological Substance Shipment and ACTN Instruction for Overnight Shipments documents at

<http://www.hanc.info/labs/labresources/procedures/Pages/actgImpaactLabManual.aspx>

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APPENDIX IA: rHPIV3cp45 Vaccine: Schedule of Evaluations – Dose #1

	Screening ¹	Entry (Day 0)	Day 1	Day 2	Day 3 ⁴	Day 4 ⁴	Day 5	Day 6 ⁵	Day 7 ⁵	Day 8 ⁵	Day 9	Day 10	Day 11	Day 12 ⁶	Day 13 ⁶	Day 14 ⁶	Day 15	Day 16	Day 17	Day 18	Day 56	Day 84	Day 112	Day 140	Sick / AE Visits	Early D/C	
Study visit windows (days)	30 days																				± 7	± 7	± 7	± 7			
Clinical Evaluations																											
Informed consent	X																										
Complete history & physical exam	X																										
Interim history & targeted physical exam ³		X			X			X						X							X				X	X	
Vaccine administration (Dose #1)		X																									
Temperature card		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Telephone call report			X	X		X	X		X	X	X	X	X		X	X	X	X	X	X		X	X	X			
Laboratory Evaluations																											
Serum HPIV3 for screening and antibody	5mL																				5mL						5mL
Nasal wash for viral culture & quantitation ²		X			X			X						X											X	X	
Total Blood Volume	5mL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5mL	0	0	0	0	0	5mL

Footnotes:

1. Window for screening is up to 30 days prior to entry.
2. Other adventitious respiratory agent testing (PCR) will be performed if illness occurs on any of these visits.
3. Physical exam for this vaccine visit should include a focused physical assessment, including check of ears, nose, throat, regional lymph nodes, chest, and heart, concentrating on any acute complaint areas.
4. If the subject comes into clinic for a visit on Day 3, staff should make phone contact with the subject on Day 4 (phone report); likewise, if the subject comes in on Day 4, phone contact should be made with the subject on Day 3 (phone report) to ensure all reactogenicity or adverse events are collected.
5. If the subject comes into clinic for a visit on Day 6, staff should make phone contact with the subject on Days 7 and 8 (phone report); likewise if the subject comes in on Day 7 or 8, staff should make phone contact with the subject on the days the child is not seen to ensure all reactogenicity or adverse events are collected.
6. If the subject has a for a visit on Day 12, staff should make phone contact with the subject on Days 13 and 14 (phone report); likewise if the subject is seen on Day 13 or 14, staff should make phone contact with the subject on the days not seen to ensure all reactogenicity or adverse events are collected.

APPENDIX IB: rHPIV3cp45 Vaccine: Schedule of Evaluations – Dose #2

	Day 0 ¹	Day 1	Day 2	Day 3 ⁵	Day 4 ⁵	Day 5	Day 6 ⁶	Day 7 ⁶	Day 8 ⁶	Day 9	Day 10	Day 11	Day 12 ⁷	Day 13 ⁷	Day 14 ⁷	Day 15	Day 16	Day 17	Day 18	Day 31	Sick / AE Visits	Early Study D/C
Study visit windows (days)	-7																				±4	
Clinical Evaluations																						
Informed consent																						
Complete history & physical exam	X																					
Interim history & targeted physical exam ³				X			X						X							X	X	X
Vaccine administration (Dose #2) ²	X																					
Temperature card	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Telephone call report		X	X		X	X		X	X	X	X			X	X	X	X	X	X			
Laboratory Evaluations																						
Serum HPIV3 for screening and antibody	5mL																			5mL		5mL
Nasal wash for viral culture & quantitation ⁴	X			X			X						X								X	X
Total Blood Volume	5mL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5mL	0	5mL

Footnotes:

1. Window for interim history / physical exam and blood draw for serum HPIV3 is within 7 days prior to the administration of Dose #2 vaccine.
2. Vaccine Dose #2 should be administered between 26 and 30 weeks following vaccine Dose #1.
3. Physical exam for this vaccine visit should include a focused physical assessment, including check of ears, nose, throat, regional lymph nodes, chest, and heart, concentrating on any acute complaint areas.
4. Other adventitious respiratory agent testing (PCR) will be performed if illness occurs on these visits.
5. If the subject comes into clinic for a visit on Day 3, staff should make phone contact with the subject on Day 4 (phone report); likewise, if the subject comes in on Day 4, phone contact should be made with the subject on Day 3 (phone report) to ensure all reactogenicity or adverse events are collected.
6. If the subject comes into clinic for a visit on Day 6, staff should make phone contact with the subject on Days 7 and 8 (phone report); likewise if the subject comes in on Day 7 or 8, staff should make phone contact with the subject on the days the child is not seen to ensure all reactogenicity or adverse events are collected.
7. If the subject has a for a visit on Day 12, staff should make phone contact with the subject on Days 13 and 14 (phone report); likewise if the subject is seen on Day 13 or 14, staff should make phone contact with the subject on the days not seen to ensure all reactogenicity or adverse events are collected.

APPENDIX II:
Definitions of Parainfluenza-Like Symptoms and/or Illness (Reactogenicity Events)

Fever	Rectal temperature of $\geq 100.7^{\circ}\text{F}$ confirmed by retake within 20 minutes.
Cough without Lower Respiratory Tract Illness	2 or more consecutive days of 3 or more episodes of cough during a 15 minute timed observation period, in the absence of signs or symptoms suggestive of lower respiratory infection. Not associated with eating or drinking.
Rhinorrhea	2 or more consecutive days of clear or purulent discharge from the nares not associated with crying, change of room temperature, or eating and drinking.
Pharyngitis	2 or more consecutive days of pharyngeal erythema accompanied by exudate, and/or enlarged tender lymph nodes. May be associated with sore throat, painful or difficult swallowing.
Hoarseness	A harsh, raspy, or strained voice or a change in the pitch or quality of the voice.
Upper Respiratory Tract Illness	2 or more days of rhinorrhea, pharyngitis and/or cough
Acute Otitis Media#	Loss of tympanic membrane landmarks, accompanied by erythema and loss of mobility. May or may not be associated with fever or other respiratory symptoms. Confirmed with tympanometry if possible.
Wheezing*+	Sustained, high pitched, musical breath sounds, especially during the expiratory phase, which do not clear with cough.
Pneumonia*+	Rales and crackles, originating in the lower respiratory tract, usually accompanied by tachypnea, which do not clear with cough. May be confirmed by x-ray showing areas of consolidation.
Laryngotracheobronchitis (croup)*+	Barking cough, hoarseness and inspiratory stridor
Rhonchi*+	Coarse breath sounds which are not transmitted noises from the upper airway and do not clear with cough.
Rales*+	Abnormal lung sound heard through a stethoscope. Rales may be sibilant (whistling), dry (crackling) or wet (more sloshy) depending on the amount and density of fluid refluxing back and forth in the air passages.
Lower Respiratory Tract Illness*+	Any professionally confirmed wheezing, rales, pneumonia, croup and /or rhonchi, or radiographic evidence of pneumonia.
Feeding difficulty	Change in feeding practice sufficient to warrant contact with health care provider
<p>Note: *Must be sustained over 20 minutes # Diagnosis must be made by a medical professional +Diagnosis must be made by a medical professional and confirmed by a second medical professional if possible.</p>	

APPENDIX III: Standard Abbreviations

AAP	American Academy of Pediatrics
AE	Adverse event
AGM	African Green monkey
cDNA	Complementary deoxyribonucleic acid
CIR	Center for Immunization Research
CMV	Cytomegalovirus
CRF	Case report form
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HI	Hemagglutination-inhibiting antibody titer
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPIV3	Human parainfluenza virus type 3
ICH	International Conference on Harmonization
IgA, IgG, IgE	Immunoglobulin A, G, E
IND	Investigational New Drug Application
IRB	Institutional Review Board
LID	Laboratory of Infectious Diseases
LRI	Lower respiratory illness
LRT	Lower respiratory tract
NIAID	National Institute of Allergy and Infectious Diseases
OHRP	Office for Human Research Protections
ORF	Open reading frame
PFU	Plaque forming unit
PI	Principal Investigator
RCHSPB	Regulatory Compliance and Human Subjects Protection Branch
RE	Reactogenicity event
RSV	Respiratory syncytial virus
SAE	Serious adverse event
SPG	Sucrose-phosphate-glutamate buffer
TCID ₅₀	50% Tissue culture infectious dose
URI	Upper respiratory illness
URT	Upper respiratory tract

APPENDIX IV: Recommendations for Preventive Pediatric Health Care (RE9535) Committee on Practice and Ambulatory Medicine

Each child and family is unique; therefore, these **Recommendations for Preventive Pediatric Health Care** are designed for the care of children who are receiving competent parenting, have no manifestations of any important health problems, and are growing and developing in satisfactory fashion. **Additional visits may become necessary** if circumstances suggest variations from normal.

These guidelines represent a consensus by the Committee on Practice and Ambulatory Medicine in consultation with national committees and sections of the American Academy of Pediatrics. The Committee emphasizes the great importance of **continuity of care** in comprehensive health supervision and the need to avoid **fragmentation of care**.

AGE ¹	INFANCY*								EARLY CHILDHOOD*					MIDDLE CHILDHOOD*				ADOLESCENCE*											
	PRENATAL ¹	NEWBORN ²	2-4d ³	By 1mo	2mo	4mo	6mo	9mo	12mo	15mo	18mo	24mo	3y	4y	5y	6y	8y	10y	11y	12y	13y	14y	15y	16y	17y	18y	19y	20y	21y
HISTORY Initial/Interval	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
MEASUREMENTS Height and Weight Head Circumference Blood Pressure		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
SENSORY SCREENING Vision Hearing		S O ⁷	S S	S S	S S	S S	S S	S S	S S	S S	S S	S S	O ⁴ O	O	O	O	O	O	S S	O O	S S	S S	O O	S S	S S	O O	S S	S S	
DEVELOPMENTAL/ BEHAVIORAL ASSESSMENT*		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
PHYSICAL EXAMINATION*		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
PROCEDURES-GENERAL ¹⁰ Hereditary/Metabolic Screening ¹¹ Immunization ¹² Hematocrit or Hemoglobin ¹³ Urinalysis		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
PROCEDURES-PATIENTS AT RISK Lead Screening ¹⁴ Tuberculin Test ¹⁷ Cholesterol Screening ¹⁸ STD Screening ¹⁶ Pelvic Exam ²⁰									•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
ANTICIPATORY GUIDANCE ²¹ Injury Prevention ²² Violence Prevention ²³ Sleep Positioning Counseling ²⁴ Nutrition Counseling ²⁵	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
DENTAL REFERRAL ²⁶									•																				

- A prenatal visit is recommended for parents who are at high risk, for first-time parents, and for those who request a conference. The prenatal visit should include anticipatory guidance, pertinent medical history, and a discussion of benefits of breastfeeding and planned method of feeding per AAP statement "The Prenatal Visit" (1996).
- Every infant should have a newborn evaluation after birth. Breastfeeding should be encouraged and instruction and support offered. Every breastfeeding infant should have an evaluation 48-72 hours after discharge from the hospital to include weight, formal breastfeeding evaluation, encouragement, and instruction as recommended in the AAP statement "Breastfeeding and the Use of Human Milk" (1997).
- For newborns discharged in less than 48 hours after delivery per AAP statement "Hospital Stay for Healthy Term Newborns" (1995).
- Developmental, psychosocial, and chronic disease issues for children and adolescents may require frequent counseling and treatment visits separate from preventive care visits.
- If a child comes under care for the first time at any point on the schedule, or if any items are not accomplished at the suggested age, the schedule should be brought up to date at the earliest possible time.
- If the patient is uncooperative, rescreen within 6 months.
- All newborns should be screened per the AAP Task Force on Newborn and Infant Hearing statement, "Newborn and Infant Hearing Loss: Detection and Intervention" (1999).
- By history and appropriate physical examination; if suspicious, by specific objective developmental testing. Parenting skills should be fostered at every visit.

- At each visit, a complete physical examination is essential, with infant totally unclothed, older child undressed and suitably draped.
- These may be modified, depending upon entry point into schedule and individual need.
- Metabolic screening (eg, thyroid, hemoglobinopathies, PKU, galactosemia) should be done according to state law.
- Schedule(s) per the Committee on Infectious Diseases, published annually in the January edition of Pediatrics. Every visit should be an opportunity to update and complete a child's immunizations.
- See AAP Pediatric Nutrition Handbook (1998) for a discussion of universal and selective screening options. Consider earlier screening for high-risk infants (eg, premature infants and low birth weight infants). See also "Recommendations to Prevent and Control Iron Deficiency in the United States. MMWR. 1998;47 (RR-3):1-29.
- All menstruating adolescents should be screened annually.
- Conduct dipstick urinalysis for leukocytes annually for sexually active male and female adolescents.
- For children at risk of lead exposure consult the AAP statement "Screening for Elevated Blood Levels" (1998). Additionally, screening should be done in accordance with state law where applicable.
- TB testing per recommendations of the Committee on Infectious Diseases, published in the current edition of Red Book: Report of the Committee on Infectious Diseases. Testing should be done upon recognition of high-risk factors.

- Cholesterol screening for high-risk patients per AAP statement "Cholesterol in Childhood" (1998). If family history cannot be ascertained and other risk factors are present, screening should be at the discretion of the physician.
- All sexually active females should have a pelvic examination. A pelvic examination and routine pap smear should be offered as part of preventive health maintenance between the ages of 18 and 21 years.
- Age-appropriate discussion and counseling should be an integral part of each visit for care per the AAP Guidelines for Health Supervision III (1998).
- From birth to age 12, refer to the AAP injury prevention program (TIIPP) as described in A Guide to Safety Counseling in Office Practice (1994).
- Violence prevention and management for all patients per AAP Statement "The Role of the Pediatrician in Youth Violence Prevention in Clinical Practice and at the Community Level" (1999).
- Parents and caregivers should be advised to place healthy infants on their backs when putting them to sleep. Side positioning is a reasonable alternative but carries a slightly higher risk of SIDS. Consult the AAP statement "Positioning and Sudden Infant Death Syndrome (SIDS): Update" (1996).
- Age-appropriate nutrition counseling should be an integral part of each visit per the AAP Handbook of Nutrition (1998).
- Earlier initial dental examinations may be appropriate for some children. Subsequent examinations as prescribed by dentist.

Key:
• = to be performed
S = subjective, by history
◀ → = the range during which a service may be provided, with the dot indicating the preferred age.
•* = to be performed for patients at risk
O = objective, by a standard testing method

NB: Special chemical, immunologic, and endocrine testing is usually carried out upon specific indications. Testing other than newborn (eg, inborn errors of metabolism, sickle disease, etc) is discretionary with the physician.

The recommendations in this statement do not indicate an exclusive course of treatment or standard of medical care. Variations, taking into account individual circumstances, may be appropriate. Copyright ©1999 by the American Academy of Pediatrics. No part of this statement may be reproduced in any form or by any means without prior written permission from the American Academy of Pediatrics except for one copy for personal use.



APPENDIX V: Informed Consent

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

Informed Consent Template

For Protocol IMPAACT P1096

**Phase 1 Study to Determine the Safety, Infectivity, Immunogenicity and Tolerability
of 2 Doses of Live Attenuated Recombinant Cold-passaged (cp) 45 Human
Parainfluenza Type 3 Virus Vaccine, rHPIV3cp45, Lot PIV3#102A, Delivered as
Nose Drops to HPIV3-Seronegative Infants and Children 6 to 36 Months of Age,
at a 6 Month Interval
Version 1.0, dated October 17, 2010**

SHORT TITLE FOR IMPAACT P1096: Safety, Infectivity, Immunogenicity and
Tolerability of 2 Doses of rHPIV3cp45 Vaccine

INTRODUCTION

You are being asked to allow your child to take part in this research study to test a vaccine to prevent parainfluenza type 3 (paraflu 3) illness in infants and children. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be 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 to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to look at the safety (side effects) and antibody (germ fighters) response of infants and children to 2 doses of an investigational paraflu 3 vaccine. An investigational vaccine is one that is not licensed by the U.S. Food and Drug Administration (FDA).

Paraflu 3 is a virus (a germ) that can make children sick. Mild illness is common and may include:

- Fever
- Runny nose
- Sore throat
- Cough that lasts for a few days

- Croup (barky cough with hoarseness)

Some children become very ill from the paraflu virus and develop illnesses such as pneumonia (infection of the lungs), severe croup or wheezing. At this time, there is no licensed vaccine to prevent paraflu 3 illness.

Doctors who develop vaccines at the NIH have made a vaccine that may help prevent paraflu 3 illness in babies and children. This investigational paraflu vaccine contains a live, weakened form of the virus, and is given as nose drops. A paraflu vaccine that was similar to this one was tested in over 150 infants and young children and caused no serious side effects. This study vaccine has been given to 16 infants less than 1 year of age in a previous study.

We are asking if we may give your child this investigational vaccine. If you agree, we will give your child either 2 doses of study vaccine or 2 doses of placebo. (Both are administered like nose drops but the placebo does not contain any vaccine). Approximately 40 children will be in this part of the study. Your child was chosen to be in this part of the study because your child is between 6 and 36 months of age. We will test your child's blood to determine if your child has already been infected with paraflu 3. Your child will be able to participate in the study if your child has never previously been infected with paraflu 3.

WHAT DOES MY CHILD HAVE TO DO IF HE/SHE IS IN THIS STUDY?

Your child will receive nose drops. Approximately 2 of each 3 enrolled children will receive the experimental vaccine and approximately 1 of the 3 enrolled children will receive nose drops without vaccine (placebo). Your child will be randomized (assigned like a flip of a coin) either to receive this vaccine or the placebo. The vaccine/placebo will be given to your child by squirting it up their nose like nose drops. The amount is very small, less than 0.5ml. Your child will need to lie down on his/her back for one minute after receiving the vaccine/placebo. Neither you or the study doctors or study nurses will know whether your child got the study vaccine or placebo until the study ends. However, this information is available to the study doctor if needed.

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

Your child cannot take part in this study if he or she lives in a house with, or is in the same room at a daycare with babies less than 6 months of age. Additionally, your child cannot take part in this study if any household members have an immune abnormalities (CD4 counts <300) or have received chemotherapy within the past 12 months. You must allow 2 to 4 weeks between the time your child receives the investigational vaccine and he or she receives other routine vaccines, depending on which routine vaccines are scheduled.

The study will require at least 11 visits and 33 telephone calls. Study visits will last about 30 minutes, except on the day when your child is screened and on the days your child is given the study vaccine. Those visits may take 1-1½ hours each. Some visits will occur in the clinic and some may occur at your home.

Screening Visit

This visit is to find out if your child is eligible to join in this study. It will take about 1½ hours and will include:

- Completing a quiz to see if you understand the study
- Reviewing and signing the study consent form
- Obtaining your child's medical history
- Obtaining permission to review your child's immunization record and review his or her medical record
- Collecting a small amount of blood (about 1 teaspoon) to test for antibodies (germ fighters) against paraflu 3 virus to determine if your child can be enrolled into the study. Your child can only be enrolled in the study if this test shows that he/she has never previously been infected with paraflu 3.

Vaccination Visits

Your child will have 2 vaccination visits about 6 months apart. At these visits, your child will either receive a dose of study vaccine or placebo and will have the following procedures completed. This visit may take up to 1 hour.

- Review your child's medical history
- Complete a physical examination on your child
- Check your child's temperature, pulse and breathing rate
- Clean your child's nose (a nasal wash) using a bulb syringe and salt water (less than 2 tablespoons) to check for study vaccine and other viruses.
- During the 2nd vaccination visit, we will take a small amount of blood (about 1 teaspoon) from your child's vein before the nose drops are given
- Give your child a dose of study vaccine or placebo given as nose drops using a small syringe without a needle
- Your child will be lying on his or her back while we give the nose drops and for about 1 minute afterwards
- After the nose drops are given, we will watch your child in the clinic for 30 minutes.
- You will be given 2 thermometers and a card to record your child's temperature daily, for the first 18 days after each dose, and at any other time you are concerned about fever. You will be asked to take your child's temperature using a special thermometer at your child's temple and if your child's temperature is elevated, you will be asked to check the temperature rectally (*Sites may use whatever local word may be better understood*) as well.

Other Study Visits

After screening and entry visits (Vaccine Dose #1), your child will also have a visit on Day 3, Day 6, Day 12 and Day 56. After Vaccine Dose #2, your child will also have a visit on Day 3, Day 6, Day 12 and Day 31. For the first 18 days following each vaccination, if your child does not have a visit scheduled, the study nurse will call you by phone to check your child's temperature. We will give you a card listing dates of the visits and phone calls. Each visit will take about 30 minutes and during the visit we will:

- Check your child's temperature, pulse, and breathing rate
- Perform a brief physical assessment
- Ask about your child's health since the last visit
- At clinic visits we will take a specimen from your child's nose using a bulb syringe and salt water (less than 2 tablespoons) at three more visits after each vaccine.
- Your child will have the last follow-up visit about 4 weeks after the second study nose drops were given.
- For the first 18 days after each dose, you will receive a call from the study nurse or you will be asked to contact the study nurse daily to report temperatures and any illness your child has during the study.
- On study days when there is a regular visit, you can report your child's health status and temperature at the visit, rather than by telephone.
- At 2 of the visits, 4-8 weeks after each vaccination we will take a small amount of blood (about 1 teaspoon) from your child's vein to measure antibodies in the blood
- We also ask you to call us right away to report respiratory illness that your child has from the day he or she receives the first dose of nose drops up to the final follow-up visit (4 weeks after the second dose).
- A study nurse or study doctor will be available by telephone to answer your questions 24 hours a day during the first 18 days after each dose, then available during working hours from Day 18 the final follow-up visit (4 weeks after the second dose).
- If your child becomes ill, we may ask you to bring him or her to the clinic for an examination. We may do a nasal wash at that time to look for the paraflu 3 vaccine virus or any other virus which may be in the mucus in your child's nose.

HOW MANY CHILDREN WILL TAKE PART IN THIS STUDY?

There will be approximately 30 children taking part in the entire study; however we may need to enroll up to 40 children.

HOW LONG WILL MY CHILD BE IN THIS STUDY?

Your child will be in the study for about 8 months.

TOPICAL ANESTHETIC PERMISSION

Before we take your child's blood, we can put anesthetic skin cream (numbing medicine) in several places on your child's arm to help decrease the pain. The numbing medicine

takes at least 30 minutes to work. If you wish, we can obtain the blood sample without using the numbing medicine. Your choice will not have any effect on your child's taking part in this study.

Please let us know if you give permission for the use of numbing medicine on my child to help decrease the pain from drawing blood. (Please check one and initial below)

Yes: Initials _____ Date _____

No: Initials _____ Date _____

WHAT ARE THE RISKS OF THE STUDY?

This experimental vaccine has been tested in adults and children as young as 6 months of age.

Risks of the Study Vaccine

- If the study vaccine is not weakened enough, it may cause a runny nose, ear infection, fever, cough, or other signs of a cold.
- The vaccine could cause more serious illness, such as wheezing or pneumonia. This has not been seen when this vaccine or a closely related paraflu vaccine was tested in over 150 infants and young children.
- There is no specific medicine to treat paraflu illness. If any symptoms occur, your child will receive prompt medical care.
- This is an investigational live virus vaccine that may include material that has not been identified.
- There may be other side effects of the study vaccine that are not yet known. If new information about possible side effects of this study vaccine becomes available, we will let you know.
- It is possible, but not likely, that the study vaccine virus could be spread from your child to other people in the home or daycare and make them sick. We have not seen this type of spread when vaccines like this one were studied.
- A vaccine, like any food or medicine, could cause a severe allergic reaction. A severe reaction can cause hives, throat swelling, rapid heart rate, weakness, difficulty breathing, and death if untreated. Such reactions are rare with any vaccine.
- Participation in this study will not prevent illnesses caused by other germs that your child might get during or after the study.

Risks of Nasal Washes

Nasal washes may cause brief discomfort like the feeling of getting salt water in the nose and may rarely cause a nosebleed. Nasal washes are not standard care in adults and healthy children and are not usually performed on ill children, although many parents are advised to use saline nose drops and nasal bulb suction (the two components of our nasal wash procedure) to clear a young child's congested nostrils during a cold.

Risks of Having Blood Drawn

Your child may feel faint or may feel some discomfort while having blood taken. There may be some swelling, bleeding, or bruising where the needle goes into the skin, or a small blood clot may develop. There is a small risk of infection forming where the needle goes into the skin to take blood.

Risks of the Numbing Medicine (Anesthetic)

Possible side effects of the numbing medicine include skin rash, temporary change in skin color (pale) on the places where the numbing cream is placed, hives (an itchy rash), and rarely, feeling dizzy or sleepy.

WHY WOULD THE DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?

The study doctors or the sponsor have the right to end your child's participation in the study at any time without your consent for any of the following reasons:

- It would be dangerous for your child to continue.
- You do not follow study procedures as directed by the study doctors.
- New information becomes available regarding the safety of the study vaccine.
- The study is stopped or cancelled.
- A Data Safety Monitoring Board (DSMB) recommends that the study be stopped early. This committee is an outside group of experts that monitors the study.
- If it is in your child's best interest.
- You do not later consent to any future changes that may be made in the study plan.
- Or for any other reason

WHAT HAPPENS IF MY CHILD IS INJURED?

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

WILL MY CHILD RECEIVE ANY COMPENSATION?

You will be paid for your child's participation in this study at the following rate: \$25 per visit and \$5 per scheduled telephone call. This is a total of \$225 for each dose of the vaccine and follow-up visits completed (6 visits per dose = \$150; 15 calls per dose = \$75). There will also be a \$25 bonus for those who complete the study without missing any visits or telephone calls. Payments will be made at the follow-up visit approximately one month after each dose of vaccine. Total payment will be [(\$225 per dose X 2 doses) plus \$25 bonus] \$475 if your child completes the entire study. If you withdraw your

child before completing the study, you will only be paid for the days of the study your child completed.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

- If your child receives the live virus study vaccine, he or she may be protected against illness from one type of parafly germ that occurs in the community, but this cannot be guaranteed.
- Because your child may not receive study vaccine, he or she may receive no benefit.
- Your child's involvement in the study may help find a vaccine that works well to prevent serious parafly illness.
- Such a vaccine may be of future benefit to babies and children in this country and in the rest of the world.

WHAT OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?

There are no licensed vaccines to protect against parafly 3 illness at this time. There is no other similar study or licensed vaccine that we can offer your child. You may choose to not allow your child to take part in this study.

WHAT ABOUT CONFIDENTIALITY?

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

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

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

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

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

WHAT ARE THE COSTS TO ME / MY CHILD?

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

WHAT ARE MY CHILD'S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to have your child take part in this study or leave this study at any time. Your decision will not have any impact on your child's participation in other studies and will not result in any penalty or loss of benefits to which you or your child are otherwise entitled.

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

- If you decide to withdraw your child from the study early, we ask that you notify the study nurse or study doctor.
- Any child who has received the study vaccine will be encouraged to remain in the safety evaluation for the duration of the study.
- It is important that you do not enroll your child in other studies where your child receives vaccines or medications while in this study.
- At the end of the study, you will be told in writing whether your child was given the vaccine or the placebo

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 rights or your child's rights as a research subject, contact:

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

STORAGE OF SPECIMENS for both NIAID and NICHD Sites

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

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

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

SPECIMEN STORAGE PERMISSION

Your choice will not have any effect on your child's taking part in this study. I will allow the use of my child's identifiable unused blood samples to be stored indefinitely and to be used in future laboratory studies for the purposes described above. (Please check one and initial below)

Yes: Initials _____ Date _____

No: Initials _____ Date _____

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

SIGNATURE PAGE

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

Participant's Name (print)

Participant's Legal Guardian (print)

Legal Guardian's Signature and Date

Second Legal Guardian (print)
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness's Name (print)
(As appropriate)

Witness's Signature and Date