Version 2.0

May 23, 2016

Safety and Immunogenicity of Anti-Pneumococcal Vaccines in HIV-Infected Pregnant Women: NICHD P1091

Sponsored by:
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For information on ordering study products, please refer to the NICHD P1091 Manual of Procedures (MOP). For randomization or enrollment questions, contact the Data Management Center (DMC) at 716-834-0900 or by email at rando.support@fstrf.org.

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List of Commonly Used Abbreviations

AE	Adverse Event
ANC	Absolute Neutrophil Count
ARV	Antiretroviral
BRI	Biomedical Research Institute
CAPiTA	Community-Acquired Pneumonia Immunization Trial in Adults
CBC	Complete Blood Count
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CDC	Centers for Disease Control and Prevention
CIN	Cervical Intraepithelial Neoplasia
CMC	Clinical Management Committee
CRF	Case Report Form
CSF	Cerebrospinal Fluid
DAIDS	Division of AIDS
DMC	Data Management Center
DNA	Deoxyribonucleic Acid
EAE	Expedited Adverse Event
EC	Ethics Committee
EIA	Enzyme Immunoassay
ELISA	Enzyme-Linked Immunosorbent Assay
FHR	Fetal Heart Rate
GMCSF	Granulocyte-Macrophage Colony-Stimulating Factor
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HMPV	Human Metapneumovirus
HUI	HIV-Uninfected Infants
IFN	Interferon
IgG	Immunoglobulin G
IL2	Interleukin-2
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IPD	Invasive Pneumococcal Disease
IRB	Institutional Review Board

List of Commonly Used Abbreviations (continued)

LAR	Legally Authorized Representative
LPC	Laboratory Processing Chart
LRTI	Lower Respiratory Tract Infection
MOP	Manual of Procedures
NaCl	Sodium Chloride
NICHD	*The Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NISDI	NICHD International Site Development Initiative
NP	Nasopharyngeal
NRTI	Nucleoside Reverse Transcriptase Inhibitors
OHRP	Office for Human Research Protections, DHHS
OP	Oropharyngeal
OPA	Opsonophagocytic Antibodies
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PCV-10	Pneumococcal Conjugate 10-Valent Vaccine
PPV-23	Pneumococcal Polysaccharide 23-Valent Vaccine
PID	Participant Identification Number
PMTCT	Prevention of Mother to Child Transmission
PNC	Pneumococcal
PPV	Pneumococcal Polysaccharides Vaccine
RA	Regulatory Affairs
RE	Regulatory Entity
RNA	Ribonucleic Acid
RSC	Regulatory Support Center
SAE	Serious Adverse Event/Serious Adverse Experience
SID	Study Identification Number
SMC	Safety Monitoring Committee
STGG	Skim Milk-Tryptone-Glucose-Glycerin
SUSAR	Suspected Unexpected Serious Adverse Reaction

List of Commonly Used Abbreviations (continued)

Tdap	Tetanus, Diphtheria, Pertussis
US	United States
WB	Western Blot
WHO	World Health Organization

Schema

Safety and Immunogenicity of Anti-Pneumococcal Vaccines in HIV-Infected Pregnant Women: NICHD P1091

Design:	Multi-center, Phase II, randomized, double-blinded, placebo-controlled.
Sample size:	Approximately 345 Human Immunodeficiency Virus (HIV)-infected pregnant women and their 345 infants (690 participants), equally distributed among three treatment arms to obtain ≥ 100 evaluable pairs/arm (300 total pairs, or 600 total participants).
Population:	HIV-infected pregnant women in their second or third trimester [≥ 14 weeks (14 weeks 0 days) to < 33 weeks (32 weeks 6 days)] on highly active antiretroviral (ARV) therapy (HAART) and their infants.
Regimen:	**Step 1.** Pregnant women will be randomized between ≥ 14 weeks (14 weeks 0 days) to < 33 weeks (32 weeks 6 days) of gestation to one of three blinded treatment arms (administered on Day 0): ■ Arm 1A: pneumococcal polysaccharide 23-valent vaccine (PPV-23); ■ Arm 1B: pneumococcal conjugate 10-valent vaccine (PCV-10); or ■ Arm 1C: placebo. **Step 2.** Women randomized to Arm 1C (placebo) who complete Step 1 will be screened for entry into Step 2 and will be randomized to receive PPV-23 (Arm 2A) or PCV-10 (Arm 2B) at 24 weeks after delivery. The women who received active vaccine during pregnancy (Arms 1A and 1B) will stop study at 24 weeks after delivery. **Step 3.** Women who were initially randomized to Arm 1C and meet an exclusion criterion for Step 2 due to new pregnancy will be enrolled in Step 3 and receive open label PCV-10 at the last study visit (which coincides with Step 1 24 weeks post-delivery). All infants will receive PCV-10 per local standard of care.
Treatment duration:	Participants will receive a single vaccination at entry and one vaccination postpartum, if in the placebo arm.
Study duration:	Up to 60 weeks for women (approximately 28 weeks pre-delivery; 32 weeks post-delivery) and up to 28 weeks for infants.
Objectives:	**<u>Primary</u>:** 1. To evaluate the safety of the PCV-10 and PPV-23 vaccines in HIV-infected pregnant women on HAART. 2. To compare the immunogenicity of PCV-10 with PPV-23 vaccines in HIV-infected pregnant women on HAART. 3. To compare the level of Pneumococcal (PNC) antibodies at 8 weeks of life in infants born to mothers who received PCV-10 or PPV-23 vaccines.

Secondary:

1. To compare the level of transplacentally transferred vaccine-serotype PNC antibodies in infants born to mothers who received PCV-10 or PPV-23 versus placebo.
2. To compare the immunogenicity of PCV-10 and PPV-23 vaccines with placebo in HIV-infected pregnant women on HAART.
3. To compare the persistence of vaccine-serotype PNC anti-capsular antibodies for up to 24 weeks after delivery in HIV-infected women vaccinated with PCV-10, PPV-23 or placebo.
4. To compare maternal antibody responses to PPV-23 or PCV-10 administered during pregnancy with responses to PPV-23 or PCV-10 administered 24 weeks postpartum.
5. To evaluate the effect of the following factors on the magnitude and persistence of the maternal antibody responses to PCV-10 and PPV-23: maternal age, ethnicity, cluster of differentiation 4 (CD4), cluster of differentiation 8 (CD8), plasma HIV RNA and gestational age at immunization.
6. To assess potential interference of maternal antibodies with infant vaccine-serotype PNC anti-capsular antibody responses after the first 2 doses of PCV-10 and determine if interference of maternal antibodies differs in PCV-10 from PPV-23 and from placebo recipients.

Tertiary:

1. To measure the incidence of pneumonia, meningitis, bacteremia and other manifestations of invasive pneumococcal disease (IPD) in mothers and infants up to 24 weeks postpartum.
2. To measure the incidence of congenital defects in infants born to vaccinated and unvaccinated mothers.
3. To assess the correlation of PNC antibodies measured by enzyme-linked immunosorbent assay (ELISA) and Opsonophagocytic Antibodies (OPA) after vaccine administration during pregnancy and of transplacentally transferred maternal antibodies.
4. To assess new PNC acquisition and pharyngeal carriage in HIV-infected pregnant women who received PCV-10, PPV-23 or placebo (See Appendix IV).
5. To assess PNC pharyngeal carriage in infants born to mothers who received PCV-10, PPV-23 or placebo during pregnancy.
6. To compare the maternal B- and T-cell responses to immunization with PCV-10 and PPV-23 during pregnancy versus placebo.
7. To investigate the association between B- and T-cell responses to PCV-10 and PPV-23 with antibody persistence.
8. To compare the maternal B- and T-cell responses to PCV-10 and PPV-23 immunization during pregnancy and postpartum.
9. To compare the B- and T-cell responses to childhood PCV-10 in infants born to mothers who received PCV-10, PPV-23 or placebo during pregnancy.

1.0 Introduction

1.1 Background

1.1.1 Burden of Pneumococcal Disease in Infants and in HIV-Infected Pregnant Women

Streptococcus pneumoniae is a leading cause of bacterial pneumonia, meningitis and sepsis in children with and without HIV infection. In developing countries, 50 percent of childhood pneumonias are caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* irrespective of HIV status.[1] Pneumococcus represents 42.5 percent of bacterial isolates from the cerebrospinal fluid (CSF) and 19.8 percent of isolates from the blood of young infants in developing countries.[2] A recent study of PNC disease in children 1 to 59 months of age estimated that PNC infections accounted for 11 percent of deaths in children of this age who were not infected with HIV.[3] In Chile, 48 percent of hospitalizations due to IPD in children 0 to 59 months of age occurred in children in the first 5 months of life.[4] Furthermore, in the Philippines, pneumococcus accounted for 6 percent and 31 percent of invasive bacterial infections in infants younger than 3 months and 6 months, respectively.[5] In Africa, up to 20 percent of the pediatric IPD occurs before completion of the primary immunization against pneumococcus.[6,7] Widespread use of the PCV in young children decreases the incidence of IPD in all segments of the population, including un-immunized infants < 6 months of age, probably by reducing PNC transmission through decreasing vaccine-serotype PNC pharyngeal carriage in vaccinated children. In areas where PCV is used sporadically or not used at all, the risk of IPD in infants younger than 6 months of age continues.

In HIV-infected children, pneumococcus is the most common bacterial infection. In HIV-uninfected infants (HUIs) born to HIV-infected mothers, the burden of IPD is not known. However, HUIs in developing countries have an increased incidence of lower respiratory tract infections (LRTIs) compared with children who are not exposed to HIV. The NICHD International Site Development Initiative (NISDI) perinatal study in Latin America showed that HUIs have a 21 percent incidence of LRTIs,[8] which is greater than that observed in a historical group of HIV-unexposed infants who had a 20 percent incidence of LRTIs and upper respiratory tract infections combined.[9] Many of the LRTIs documented in NISDI were severe and required hospitalization. It must be emphasized that 76 percent of the NISDI cohort was composed by Brazilian infants.[10]

High prevalence of LRTIs of 15 percent was also reported in HUIs younger than 12 months in Africa.[11] Viral infections, particularly respiratory syncytial virus, human metapneumovirus (HMPV), and other

respiratory viruses account for a majority of LRTIs in childhood. However, PNC superinfection plays an important role in the morbidity of viral LRTIs, as demonstrated by a 45 to 65 percent decrease in pediatric hospitalizations associated with influenza and HMPV in South Africa when PCV-9 was administered to these children.[12,13] Furthermore, a recent study in France showed that compared with HIV-unexposed children, HUIs had increased severe pneumonia and sepsis caused by encapsulated bacteria including PNC.[14] It is important to note that PCV has been in the childhood immunization schedule of France since 2003, but presumed herd immunity did not protect HUIs against PNC infection. A hypothesis that may explain the increased incidence of LRTIs in HUIs is that low maternal antibody transfer to the fetus, both antiviral and antibacterial, increases the susceptibility of HUIs to LRTIs during the first 6 months of life.

Pneumococcus is the leading cause of bacterial pneumonias in HIV-infected pregnant and non-pregnant adults.[15,16,17] Even with HAART, the incidence of IPD in HIV-infected individuals remains higher than that of same-age adults without HIV.[18,19] IPD is the single most morbid vaccine-preventable condition associated with HIV infection. Bacterial pneumonias are more common in HIV-infected pregnant women than in non-pregnant HIV-infected adults;[20] are associated with premature deliveries and infant low birth weight;[21] and account for a significant proportion of maternal deaths. The mortality rate of bacterial pneumonias in pregnancies complicated by HIV infection is even higher than in uncomplicated pregnancies.[22]

1.1.2 Pneumococcal Vaccines: Safety, Immunogenicity and Efficacy in HIV-Infected Individuals

IPD and other manifestations of PNC infection can be prevented to a great extent by the administration of a PNC vaccine. Two types of PNC vaccines are licensed in Brazil: a polysaccharide vaccine, PPV-23, directed against 23 serotypes and a conjugated vaccine, PCV-10, directed against 10 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, and 7F), which are also included in PPV-23.

PCV is the vaccine currently recommended for immunization of children against pneumococcus. In HIV-infected children, PCV-7 is safe and immunogenic.[23] A large efficacy trial conducted in South Africa showed a 65 percent efficacy of PCV-9 in HIV-infected children not receiving HAART and an 83 percent efficacy in uninfected children against serotypes contained in the vaccine. In HIV-infected and uninfected children there was a 50 percent and 42 percent efficacy, respectively, against all serotypes.[24]

Both PCV-13 and PPV-23 are currently recommended for immunization of adults against pneumococcus in the United States (US),[25] although data on the efficacy of PCV followed or preceded by PPV versus each of the individual vaccines are not available. Previous studies showed that antibody responses to PPV-23 are lower in HIV-infected participants with CD4 < 200 cells/µl.[26] Nevertheless, epidemiologic studies showed that participants with CD4 < 200 cells/µl at vaccination may benefit from the protective effect of PPV-23,[27] particularly if vaccination occurs after the initiation of HAART. Less information on efficacy of PPV-23 is available for higher CD4 thresholds. However, the existing information[28] suggests that antibody responses are similar in patients with CD4 ≥ or < 350 cells/µl who also have plasma viral load ≤ 10,000 HIV RNA copies/mL.

Vaccination of HIV-infected individuals on no ARVs or nucleoside reverse transcriptase inhibitors (NRTI) monotherapy, including PPV-23,[29] can generate transient increases in the HIV plasma viral load. Such increases do not have clinical consequences. Even more importantly, immunization of HIV-infected individuals on HAART with PCV-7 or PPV-23 was NOT accompanied by changes in HIV plasma viral load.[23,26,28,30] This is also true for other vaccines, both live-attenuated and inactivated, administered to HIV-infected individuals on HAART.[23,31,32]

The efficacy of PPV-23 for prevention of IPD and all cause pneumonias has been the subject of controversy. A recent Cochrane review concluded that it is efficacious in elderly individuals.[33] The single prospective efficacy study of PPV-23 in HIV-infected adults showed that HIV-infected Ugandans who received PPV-23 had a higher incidence of pneumonia compared with placebo recipients within the first 6 months following immunization,[34] but subsequent follow-up found a 16 percent reduction in all-cause mortality in PPV-23 recipients.[35] Other retrospective epidemiologic studies showed efficacy of PPV-23 against IPD and/or pneumonia in HIV-infected adults regardless of their CD4 counts,[27,36] with CD4 > 200 cells/µl,[37,38] ≥500 cell/µl,[39] or while receiving HAART.[19,37,40]

Another potential problem with PPV-23 is the generation of hyporesponsiveness to subsequent PPV-23. Hyporesponsiveness is a phenomenon common to polysaccharide vaccines and is also observed with meningococcal polysaccharide vaccine. Hyporesponsiveness after PPV-23 was demonstrated in children and adults without HIV infection. Hence, PPV-23 is generally administered at ≥ 5-year intervals. For HIV-infected adults who have not received any PNC vaccines, the Centers for Disease Control and Prevention (CDC) currently recommends administration of a single dose of PCV-13 followed by a first dose of PPV-23 ≥ 8 weeks later and a second dose of PPV-23 ≥ 5 years later. For

HIV-infected individuals who received PPV-23 in the past, the recommendation is to administer PCV-13 ≥ 1 year after the last dose of PPV-23. There are very few studies of immunogenicity of the proposed vaccination schedules and no studies of efficacy or effectiveness. There have not been any studies to determine the need/advantage of administering both PCV-13 and PPV-23, either.[41]

Studies comparing the immunogenicity of PPV-23 with PCV-7 generated heterogeneous results. In HIV-uninfected transplant recipients and cancer patients, antibody responses to PCV-7 and PPV-23 did not differ significantly.[42,43,44,45] In elderly HIV-uninfected adults, some studies showed higher antibody titers after PCV-7 and longer persistence of specific antibodies compared with PPV-23,[46,47] while other studies could not demonstrate significant differences.[48,49,50,51] The immunogenicity of PPV-23 is lower in HIV-infected than in uninfected adults even in the era of HAART[52,53] and higher antibody titers are generally demonstrated in response to PCV-7 compared with PPV-23.[30,54,55] PCV is not associated with hyporesponsiveness and it appears that even when administered to participants who received PPV-23 in the past, its immunogenicity is preserved.

Of utmost importance are the results of a recently published study from Malawi demonstrating the efficacy of PCV-7 in adults with previous histories of IPD, including a majority of HIV-infected individuals.[56] This is the only prospective randomized trial that showed efficacy of any PNC vaccine in high-risk groups of HIV-infected adults. In addition, the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) study showed 40 percent efficacy of PCV in elderly adults in the Netherlands.[57]

In summary, PCV-7 or 13 generates higher PNC antibody titers in HIV-infected adults compared with PPV-23. In contrast to PPV-23, the use of PCV products is not associated with hyporesponsiveness. Furthermore, PCV-9 and PCV-7 are highly efficacious in protecting HIV-infected adults and children, respectively, against PNC. The efficacy of PPV-23 in the HIV-infected adults is controversial, but PPV-23 can potentially confer protection against a larger number of PNC serotypes, including those that most commonly cause disease in adults.

1.1.3 Safety and Immunogenicity of Pneumococcal Vaccines Administered during Pregnancy

PPV-23 is safe and immunogenic when administered during pregnancy uncomplicated by HIV as demonstrated by studies conducted in various areas of the globe, including the US, Philippines, Papua New Guinea and Bangladesh (Table 1-1). Taken together, these studies report on over 1,000

women who received PPV-23 during pregnancy. Overall, the vaccine increased antibody titers in the mother. Antibodies against several capsular PNC antigens in the vaccine were detected in cord blood and persisted in the infants for up to 10 months of life. Only minor local and systemic maternal AEs were reported. There were no obstetric complications or infant morbidity ascribed to the vaccine. In the study by Zaman et al., PPV-23 and influenza inactivated vaccine administered during pregnancy had similar safety profiles.[6] In 44 HIV-infected pregnant women in Brazil,[40] PPV-23 had a good safety profile, but the average antibody rise was lower than previously reported in uninfected pregnant women. These women showed a decrease of the plasma HIV viral load after vaccination, which was most likely related to the recent introduction of ARV therapy for Prevention of Mother to Child Transmission (PMTCT). These data indicate that administration of PPV-23 does not induce HIV viral load increases in HIV-infected pregnant women on ARVs and are in accordance with our unpublished observations that administration of an inactivated pandemic H1N1 influenza vaccine to HIV-infected pregnant women who started HAART prior to or at the time of vaccination did not lead to any increases in the plasma HIV viral load.[58]

Table 1-1. Reports of PPV-23 safety and/or immunogenicity in pregnancy

Authors	N women received PPV-23	Study title	Ref ID	Reference
Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E et al.	168*	Effectiveness of maternal influenza immunization in mothers and infants	[6]	*N Engl J Med* 2008, 359: 1555-1564
Almeida VC, Mussi-Pinhata MM, De Souza CB, Kubo CA, Martinez EZ, Carneiro-Sampaio MM et al.	44	Immunogenicity of 23-valent pneumococcal polysaccharide vaccine in HIV-infected pregnant women and kinetics of passively acquired antibodies in young infants	[40]	*Vaccine* 2009, 27: 3856-3861
Vincent-Ballereau F, Fortier B, Armand J, Lafaix C	37	Pneumococcal vaccination of the pregnant woman in Africa and passive immunity of the child. Immunologic control by the ELISA method	[59]	Pathol Biol (Paris) 1985, 33: 764-767
Riley ID, Tarr PI, Andrews M, Pfeiffer M, Howard R, Challands P et al.	187	Immunisation with a polyvalent pneumococcal vaccine. Reduction of adult respiratory mortality in a New Guinea Highlands community	[60]	*Lancet* 1977, 1: 1338-1341
Shahid NS, Steinhoff MC, Hoque SS, Begum T, Thompson C, Siber GR	36	Serum, breast milk, and infant antibody after maternal immunisation with pneumococcal vaccine	[61]	*Lancet* 1995, 346: 1252-1257.

Table 1-1. Reports of PPV-23 safety and/or immunogenicity in pregnancy (continued)

Authors	N women received PPV-23	Study title	Ref ID	Reference
O'Dempsey TJ, McArdle T, Ceesay SJ, Banya WA, Demba E, Secka O et al.	75	Immunization with a pneumococcal capsular polysaccharide vaccine during pregnancy	[62]	*Vaccine* 1996, 14: 963-970
Munoz FM, Englund JA, Cheesman CC, Maccato ML, Pinell PM, Nahm MH et al.	20	Maternal immunization with pneumococcal polysaccharide vaccine in the third trimester of gestation	[63]	*Vaccine* 2001, 20: 826-837
Lehmann D, Pomat WS, Combs B, Dyke T, Alpers MP	235	Maternal immunization with pneumococcal polysaccharide vaccine in the highlands of Papua New Guinea	[64]	*Vaccine* 2002, 20: 1837-1845
Obaro SK, Deubzer HE, Newman VO, Adegbola RA, Greenwood BM, Henderson DC	56	Serotype-specific pneumococcal antibodies in breast milk of Gambian women immunized with a pneumococcal polysaccharide vaccine during pregnancy	[65]	*Pediatr Infect Dis J* 2004, 23: 1023-1029
Deubzer HE, Obaro SK, Newman VO, Adegbola RA, Greenwood BM, Henderson DC	57	Colostrum obtained from women vaccinated with pneumococcal vaccine during pregnancy inhibits epithelial adhesion of Streptococcus pneumoniae	[66]	*J Infect Dis* 2004, 190: 1758-1761
Quiambao BP, Nohynek HM, Kayhty H, Ollgren JP, Gozum LS, Gepanayao CP et al.	106	Immunogenicity and reactogenicity of 23-valent pneumococcal polysaccharide vaccine among pregnant Filipino women and placental transfer of antibodies	[67]	*Vaccine* 2007, 25: 4470-4477
Lopes CR, Berezin EN, Ching TH, Canuto JS, Costa VO, Klering EM	47	Ineffectiveness for infants of immunization of mothers with pneumococcal capsular polysaccharide vaccine during pregnancy	[68]	*Braz J Infect Dis* 2009, 13: 104-106
Almeida VD, Negrini BV, Cervi MC, Isaac MD, Mussi-Pinhata MM	45**	Pneumococcal nasopharyngeal carriage among infants born to human immunodeficiency virus-infected mothers immunized with pneumococcal polysaccharide vaccine during gestation	[69]	*Pediatr Infect Dis J* 2011, 30: 466-470
Holmlund E, Nohynek H, Quiambao B, Ollgren J, Kayhty H	106	Mother-infant vaccination with pneumococcal polysaccharide vaccine: persistence of maternal antibodies and responses of infants to vaccination	[70]	*Vaccine* 2011, 29: 4565-4575.

* Control group received PPV-23

**45 term HUIs born to HIV-infected mothers vaccinated with the PPV

Although PCV-10 has not been studied in pregnant women, PCV-9 was administered to 100 HIV-uninfected pregnant women in a recently published study.[71] The publication focused on infant outcomes and reported a lack of AEs, along with a small, but statistically significant, increased incidence of acute otitis media in the first 6 months of life in infants born to vaccine-recipients. In a personal communication, Dr. Patricia Ferrieri, the senior author of the recently published study, confirmed the absence of serious AEs in the vaccinated pregnant women.

Based on the evidence summarized above, that PCV preparations are more immunogenic than PPV-23 in HIV-infected adults, it is imperative to compare the safety and immunogenicity of PCV-10 with PPV-23 in HIV-infected pregnant women, because the conjugated vaccine preparation may confer better protection to the mother and ensure higher PNC antibody transfer to the infant. It is likely that PCV-10 will be more immunogenic in HIV-infected pregnant women than PPV-23. This, however, has to be balanced against the fact that PPV-23 contains more antigens.

1.1.4 PNC Vaccines in HIV-Infected and Uninfected Pregnant Women

The Brazilian guidelines consider PPV-23 vaccination of HIV-infected adults as an optional prophylactic measure, which relies on the health care provider's judgment, because it is considered controversial.[72] No specific recommendations are provided for HIV-infected Brazilian pregnant women.[73] However, considering the socio-epidemiological profile of most HIV-infected pregnant women, who are young, in a socioeconomic situation of vulnerability, with low schooling and multiparous, drug use and smoking habits,[74] it is anticipated that the risk of PNC infections either in the mother or in the infant is high,[75] and both mothers and infants would potentially benefit from maternal vaccination.

For over 20 years, administration of PPV-23 has been recommended in the US for HIV-infected adults (www.CDC.gov). Although this recommendation does not exclude HIV-infected pregnant women, the use of PPV-23 during pregnancies complicated by HIV has been exceedingly rare. A site survey conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) PMTCT Scientific Committee in 2009 found that only 1 of 65 US and international sites, including Brazil, Argentina, Malawi, South Africa, Zimbabwe, Uganda, Zambia, Tanzania, India, and Thailand, administered PPV-23 to HIV-infected pregnant women. There are several potential explanations of these surprising results:

1. There was no definitive recommendation for PNC vaccination in Brazil.

2. Health care providers were concerned about potential adverse effects on mother or fetus due to lack of safety data in HIV-infected pregnant women.

3. Health care providers assumed that antibody responses to PPV-23 might be better after pregnancy and postponed vaccination.

4. The absence of data showing the need for vaccination or proven potential benefits for mothers and/or infants.

Barriers to administration of vaccines during pregnancy are abundant. This was studied with respect to seasonal influenza vaccines, which are recommended for all pregnant women in the US and other resource-abundant countries.[76] In the US, before the H1N1 2009 pandemic, only 10 percent of pregnant women received seasonal influenza vaccines.[77] High levels of provider knowledge about maternal vaccination and positive attitudes towards influenza vaccination were identified as key elements favoring vaccination.[78] In contrast, the lack of information on effectiveness was a common deterrent for providers,[77] whereas concerns about safety were invoked both by mothers and providers.[79] After the 2009 H1N1 influenza pandemic, which underscored the severity of influenza in pregnant women, the administration of influenza vaccines during pregnancy increased to 40-60 percent in the US. In Brazil, a recently published study showed 96 percent vaccination in 300 highly educated pregnant women.[80]

As can be seen in Table 1-1, there are several reports showing safety and immunogenicity of the PPV-23 in pregnant non-HIV infected women. In a single study of HIV-infected pregnant women[40] performed at a clinical site in Ribeirão Preto, Sao Paulo, Principal Investigator Dr. Marisa Mussi-Pinhata demonstrated that the vaccine was safe. This clinical trial will enroll a larger number of HIV-infected pregnant women in each of the vaccine arms, thus providing extensive safety information that will be valuable in making the use of PNC vaccines during pregnancy acceptable to providers and mothers.

1.1.5 Transplacental Transfer of Maternal Antibodies and Protection of Infants against Infections

Maternal antibodies transferred to the infant through the placenta or breast milk protect infants against infections during the first few months of life. Administration of tetanus toxoid vaccine during pregnancy has been used for many decades to prevent neonatal tetanus. In recent years, maternal immunization against other infectious agents has been proposed with the objective of protecting both the mother and the infant. Zaman et al. showed that administration of influenza vaccines to pregnant women

prevented infections in mothers and infants up to 6 months after delivery.[6] Subsequently, it was shown that influenza immunization of HIV-infected compared with uninfected pregnant women had similar efficacy for the mothers and for their infants.[41] Most recently, tetanus, diphtheria, pertussis (Tdap) administration during pregnancy has been recommended and subsequently shown to be effective for protection of infants against whooping cough.[25]

A similar approach was proposed for prevention of PNC infections.[61,64] Several studies showed that PPV-23 administered during pregnancy increases the serum antibody concentrations in mother and infant.[61,63,67,81] Riley et al. showed in Papua New Guinea that administration of PPV-23 during pregnancy significantly decreased the incidence of LRTIs in infants born to vaccinated mothers compared with infants born to unvaccinated controls.[81] However, these results were not universally reproduced.[68] IPD has a relatively high incidence in HUIs < 6 months of age[80] and transplacental transfer of maternal PNC antibodies at levels associated with protection against IPD may particularly benefit HUIs.

The efficiency of transplacental transfer of maternal antibodies may be impaired in pregnancies complicated by HIV infection, such that vaccination of HIV-infected pregnant women may be even more relevant for protection of their infants when compared with HIV-uninfected women. Multiple mechanisms may contribute to the low transplacental transfer of specific antibodies in pregnancies complicated by untreated HIV infection, such as HIV-associated pathologic changes of the placenta, increased maternal levels of total Immunoglobulin G (IgG) and beta2-microgolobulin,[82] high HIV-specific antibody concentrations[83] and co-infections.[82,84,85] Hence, although HIV-infected women typically have higher levels of naturally-acquired antibodies against PNC capsular antigens compared with uninfected controls,[86] their transplacental transfer is low.[40] Furthermore, PNC antibodies of HIV-infected individuals with low CD4+ cell numbers and high plasma HIV viral loads have defective opsonic activity with lower serum bacterial killing and oxidative burst compared with antibodies of healthy participants.[87] It is likely that the use of HAART during pregnancy, which is currently recommended by the World Health Organization (WHO) and is already implemented in many countries for the PMTCT, will both enhance the quality of the PNC antibodies of HIV-infected individuals and will abrogate many of the conditions that hinder the transplacental transfer of maternal antibodies. This may translate into increased transplacental transfer of naturally acquired as well as vaccine-induced PNC antibodies. In this study, the team will examine whether maternal vaccination during pregnancy increases the transplacental transfer of PNC antibodies beyond natural infection coupled with the use of HAART and if the antibodies

transferred in vaccinated women have an improved functionality as compared with antibodies transferred after PNC infection.

A maternal immunization program during pregnancy also has to take into consideration that high maternal antibody titers may interfere with infant responses to childhood vaccines. This is true for live attenuated vaccines, such as measles,[88] but was also demonstrated for inactivated vaccines, such as hepatitis A and diphtheria.[89,90] This observation did not alter the recommendation to administer tetanus vaccines to pregnant women when indicated. Conversely, there are studies suggesting that certain antigens, like hepatitis B, may be more immunogenic when complexed with antibodies.[91] There are no studies on the interaction of maternal immunization against pneumococcus and responses to PNC vaccines during infancy. A study presented in abstract form at the 7th International Symposium on Pneumococci and PNC Diseases[92] showed that infants born to immunized mothers had slightly lower antibody responses to PCV administered at 6, 10 and 14 weeks of age, but still over 0.35µg/mL, which is considered to be protective against IPD. OPA antibody responses to PCV were similar in babies born to mothers with or without PPV-23 during pregnancy.

1.1.6 Surrogate Markers of Protection against Pneumococcal Disease

Vaccine efficacy trials require large numbers of participants and intensive observations, characteristics that sometimes make efficacy studies prohibitively expensive. Surrogate markers of protection are frequently used to assess potential benefits conferred by vaccines. Protection against PNC infection was shown to correlate with robust OPA titers and with reduction of acquisition of vaccine-serotype PNC pharyngeal carriage. Serotype-specific IgG antibody concentrations of ≥ 0.35 µg/mL measured by ELISA have been adopted as putative measures of protection conferred by PCV-7 against IPD in children and will be used as infant immunologic endpoints in this study.

In addition, pharyngeal carriage with *Streptococcus pneumoniae* precedes PNC disease, including IPD, and is responsible for PNC transmission in the community. PCV immunization of children has been associated with reduced risk of pharyngeal acquisition of vaccine-serotypes commonly associated with asymptomatic carriage in children.[93] In contrast, PPV in adults has not been established to reduce pharyngeal carriage. Studies in mice showed that protection against pharyngeal carriage was conferred by PNC-specific Th17 cells[94] and evidence is accumulating that this may also be the case in humans.[95,96] Since the sample size of this study will not be sufficient to determine the efficacy of PCV on IPD, a conservative proxy of likely effect on PNC disease is to explore whether PCV reduces acquisition of vaccine-serotypes in the women as well as in their children.

This may help corroborate the clinical relevance of the immunogenicity data in mothers and their infants.

In areas of high PNC endemicity, 20-50 percent of adults and 50-70 percent of infants are colonized with PNC in their upper respiratory tract. In infants born to HIV-infected mothers who receive cotrimoxazole prophylaxis, PNC pharyngeal carriage is still around 30 percent.[69] it is anticipated that a moderate proportion of the mothers in this study will carry PNC at entry. In the maternal participants, a baseline NP and OP sample at the time of vaccination in Step 1 and a follow up NP and OP sample at delivery in order to describe the prevalence of vaccine-serotypes at these time points will be obtained. Using de novo acquisition of vaccine-serotypes in placebo recipients as the index measure, it will be determined whether PPV-23 or PCV-10 decreases acquisition of vaccine-serotypes in the mothers.

In the absence of PCV, infants progressively develop PNC pharyngeal carriage as they get older and become increasingly exposed to other children and adults. The epidemiology of PNC acquisition and invasive disease in developing countries differs from industrialized countries with earlier pharyngeal acquisition and peak incidence of disease. Studies of PCV-7 have clearly demonstrated an impact on the acquisition of vaccine serotypes and a reduction in overall IPD in infants beginning after the second dose of PCV. To investigate if maternal immunization will impact directly on PNC pharyngeal acquisition and serotype distribution, two NP and OP swabs, at 8±2 weeks of life, at the time infants receive the 1st dose of PCV and at 16±3 weeks, when they receive the 2nd dose of vaccine will be collected. The hypothesis is that prevalence of carriage of vaccine serotypes will be reduced in children born to mothers immunized with PCV at the 8-week time point and that acquisition of PNC pharyngeal will be decreased between the 8- and 16-week visit. Identification of PNC carriage at 2 and 4 months of age will provide an opportunity to evaluate if direct protection from PNC carriage in young infants can be achieved. This strategy will maximize PNC detection, because over a 2-month interval there may be PNC serotype substitutions, additions or spontaneous disappearance. Acquisition of PNC by infants born to mothers who received placebo, PPV-23 or PCV-10 in Step 1 of the protocol will be described and compared.

1.2 Significance

This study will considerably expand existing information on the safety and immunogenicity of PPV-23 in HIV-infected pregnant women and will determine for the first time the safety and immunogenicity of PCV-10 in this population. The study will increase the awareness of health care providers with respect to the safety and immunogenicity of PNC vaccines and the recommendation to vaccinate HIV-infected women during pregnancy. Health care providers and pregnant women may feel more comfortable with the administration of PNC vaccines as a result of the safety, immunogenicity and transplacental antibody transfer data that will be generated by this study. Demonstrating similar immunogenicity of the PNC vaccines during pregnancy and postpartum, and demonstrating potentially protective transplacental transfer of PNC antibodies to the infant, may increase the perceived benefit of PNC vaccination during pregnancy. It is anticipated that PCV-10 will be more immunogenic than PPV-23 in HIV-infected pregnant women, which may change the current recommendation from administration of PPV-23 to administration of PCV-10 during pregnancy complicated by HIV. Our results may also prompt countries with a high prevalence of IPD, where PNC vaccines are not currently recommended for HIV-infected adults, to consider immunization of HIV-infected pregnant women.

2.0 Study Objectives

2.1 Primary Objectives

2.1.1 To evaluate the safety of the PCV-10 and PPV-23 vaccines in HIV-infected pregnant women on HAART.

2.1.2 To compare the immunogenicity of PCV-10 with PPV-23 vaccines in HIV-infected pregnant women on HAART.

2.1.3 To compare the level of PNC antibodies at 8 weeks of life in infants born to mothers who received PCV-10 or PPV-23 vaccines.

2.2 Secondary Objectives

2.2.1 To compare the level of transplacentally transferred vaccine-serotype PNC antibodies in infants born to mothers who received PCV-10 or PPV-23 versus placebo.

2.2.2 To compare the immunogenicity of PCV-10 and PPV-23 vaccines with placebo in HIV-infected pregnant women on HAART.

2.2.3 To compare the persistence of vaccine-serotype PNC anti-capsular antibodies for up to 24 weeks after delivery in HIV-infected women vaccinated with PCV-10, PPV-23 or placebo.

2.2.4 To compare maternal antibody responses to PPV-23 or PCV-10 administered during pregnancy with responses to PPV-23 or PCV-10 administered 24 weeks postpartum.

2.2.5 To evaluate the effect of the following factors on the magnitude and persistence of the maternal antibody responses to PCV-10 and PPV-23: maternal age, ethnicity, CD4, CD8, plasma HIV RNA and gestational age at immunization.

2.2.6 To assess potential interference of maternal antibodies with infant vaccine-serotype PNC anti-capsular antibody responses after the first 2 doses of PCV-10 and determine if interference of maternal antibodies differs in PCV-10 from PPV-23 and from placebo recipients.

2.3 Tertiary Objectives

2.3.1 To measure the incidence of pneumonia, meningitis, bacteremia and other manifestations of IPD in mothers and infants up to 24 weeks postpartum.

2.3.2 To measure the incidence of congenital defects in infants born to vaccinated and unvaccinated mothers.

2.3.3 To assess the correlation of PNC antibodies measured by ELISA and OPA after vaccine administration during pregnancy and of transplacentally transferred maternal antibodies.

2.3.4 To assess new PNC acquisition and pharyngeal carriage in HIV-infected pregnant women who received PCV-10, PPV-23 or placebo (See Appendix IV).

2.3.5 To assess PNC pharyngeal carriage in infants born to mothers who received PCV-10, PPV-23 or placebo during pregnancy.

2.3.6 To compare the maternal B- and T-cell responses to immunization with PCV-10 and PPV-23 during pregnancy versus placebo.

2.3.7 To investigate the association between B- and T-cell responses to PCV-10 and PPV-23 with antibody persistence.

2.3.8 To compare the maternal B- and T-cell responses to PCV-10 and PPV-23 immunization during pregnancy and postpartum.

2.3.9 To compare the B- and T-cell responses to childhood PCV-10 in infants born to mothers who received PCV-10, PPV-23 or placebo during pregnancy.

3.0 Study Design

This is a multi-center, Phase II, randomized, double-blinded, placebo-controlled study of 345 HIV-infected pregnant women on HAART who are in the second or third trimester of pregnancy [≥ 14weeks (14 weeks 0 days) to < 33 weeks (32 weeks 6 days)], and their infants. This study is designed to investigate the safety, reactogenicity, immunogenicity, transplacental antibody transfer and interference with infant responses to childhood vaccination of maternal vaccination with PCV-10 or PPV-23 by comparison with placebo.

Step 1. At entry, mothers will be randomized to one of three arms: Arm 1A (PPV-23), Arm 1B (PCV-10), or Arm 1C (placebo) in a blinded fashion. They will receive one immunization on Day 0. They will be followed for safety, immunogenicity and vaccine-specific anti-capsular PNC antibody persistence until 24 weeks post-delivery. The women who received active vaccine during pregnancy (Arms 1A and 1B) will stop study at the 24 weeks post-delivery visit.

Step 2. Women randomized to Arm 1C (placebo) who complete Step 1 will be screened for entry into Step 2 and will be randomized to receive PPV-23 (Arm 2A) or PCV-10 (Arm 2B) at 24 weeks post-delivery. Enrollment into Step 2 may occur during the week 24 visit (at the time of randomization) or within 10 days of this visit (at Day 0, Step 2). The antibody responses to the vaccines administered 6 months postpartum will be measured 28 days after vaccination, i.e., approximately 7 months postpartum. The length of time between vaccine administration and immunogenicity testing is similar during pregnancy and postpartum.

Step 3. Women who were initially randomized to Arm 1C and meet an exclusion criterion for Step 2 due to ongoing new pregnancy will be enrolled in Step 3 and receive open label PCV-10 at the last study visit (which coincides with Step 1 24 weeks post-delivery). No data will be collected on these women and they will not be followed on study after the vaccine administration.

All infants will receive PCV-10 vaccinations per local standard of care.

4.0 Selection and Enrollment of Participants

4.1 Step 1 – Inclusion Criteria for Pregnant Women

4.1.1 Pregnant women ≥ 18 years old who provide written informed consent prior to study initiation.

4.1.2 Pregnant women < 18 years old with parent or legal guardian able and willing to provide signed informed consent, or who have the capacity to consent for themselves, as defined by the local Institutional Review Board (IRB), and who provide written informed consent prior to study initiation.

4.1.3 Gestational age [≥ 14 weeks (14 weeks 0 days) to < 33 weeks (32 weeks 6 days)] documented by the approximate date of the last menstrual period and corroborated by ultrasound if obtained as per local standard of care. Results of the ultrasound will be recorded on the Abdominal Ultrasound Form.

4.1.4 Documentation of HIV-1 infection defined as positive results from two samples collected at different time points as per standard of care. Results and source documentation may be obtained from the medical records.

The following diagnostic methods are acceptable, but testing must be done on two different specimens:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes.
- One rapid antibody test AND one [enzyme immunoassay (EIA) from a different manufacturer or using different epitopes than the rapid antibody test OR Western blot (WB) OR immunofluorescence OR chemiluminescence] .
- One EIA AND one [WB OR immunofluorescence OR chemiluminescence].
- One HIV combination antigen/antibody assay AND one [enzyme immunoassay (EIA) from a different manufacturer than the combo test OR Western blot (WB) OR immunofluorescence OR chemiluminescence OR rapid antibody test from a different manufacturer than the combo test].
- One HIV DNA polymerase chain reaction (PCR).
- One HIV RNA PCR.

- One HIV culture (prior to August 2009).
- One total HIV nucleic acid.

4.1.5 Receipt of HAART (a regimen of at least three ARV drugs) for ≥ 4 weeks prior to enrollment.

4.1.6 Documented platelet count of > 50,000/mm^3 and an absolute neutrophil count (ANC) of > 500/ mm^3 ≤ 28 days prior to study entry.

4.1.7 Women who are willing and able to comply with the study visits.

4.2 Step 1 – Exclusion Criteria for Pregnant Women

4.2.1 Receipt of any PCV or PPV-23 at any time prior to enrollment, documented by medical history or record.

4.2.2 Receipt of any live licensed vaccine ≤ 4 weeks or inactivated licensed vaccine ≤ 2 weeks prior to study entry.

4.2.3 Receipt of a non-licensed agent (vaccine, drug, biologic, device, blood product, or medication) ≤ 4 weeks prior to enrollment in this study, or expectations to receive another non-licensed agent before delivery unless approval from the protocol team is obtained.

4.2.4 Any significant (in the opinion of the site investigator) acute illness and/or oral temperature greater than or equal to 100.4°F ≤ 24 hours prior to study entry.

4.2.5 Women who plan to terminate their pregnancy.

4.2.6 Women who have a prior history of lupus or other autoimmune disorders.

4.2.7 Use of anti-cancer systemic chemotherapy or radiation therapy ≤ 48 weeks of study enrollment, or evidence of immunosuppression as a result of an underlying illness (other than HIV-1 infection) or treatment.

4.2.8 Ongoing neoplastic disease (excluding non-melanoma skin cancer, and human papilloma virus-related cervical dysplasia, cervical intraepithelial neoplasia (CIN) grades 1, 2 or 3).

4.2.9 Long term use of glucocorticoids, including oral or parenteral prednisone ≥ 20 mg/day or equivalent for more than 2 consecutive weeks (or 2 weeks total) within 12 weeks of study entry.

4.2.10 Women who received last dose of corticosteroids for preterm labor ≤ 1 week prior to study entry. Note: A woman can be enrolled if more than 1 week has elapsed from the last dose of corticosteroids, i.e., enrollment may be delayed to satisfy this criterion.

4.2.11 Receipt of immunoglobulin or other blood products (with exception of Rho D immune globulin) ≤ 12 weeks prior to enrollment in this study or is scheduled to receive immunoglobulin or other blood products (with the exception of Rho D immune globulin) during pregnancy or for the first 24 weeks after delivery.

4.2.12 Receipt of Interleukin-2 (IL2), interferon (IFN), granulocyte-macrophage colony-stimulating factor (GMCSF) or other immune mediators ≤ 12 weeks before enrollment.

4.2.13 History of a severe adverse reaction to inactivated polysaccharide or conjugated vaccines.

4.2.14 Any condition that would, in the opinion of the site investigator, place the participant at an unacceptable risk of injury or render the participant unable to meet the requirements of the protocol.

4.2.15 Pregnancy complications (in the current pregnancy) such as pre-term labor, and pre-eclampsia or any other pregnancy related complication, which in the opinion of the investigator might jeopardize the results of the study.

4.2.16 Chronic hepatitis B infection that may require administration of Hepatitis B Hyperimmune Globulin to neonates.

4.3 Step 2 – Inclusion Criteria for Women

4.3.1 24 weeks ± 4 weeks postpartum.

4.3.2 Completion of Step 1.

4.3.3 Receipt of placebo on Step 1.

4.4 Step 2 – Exclusion Criteria for Women

4.4.1 Pregnancy.

4.4.2 Receipt of any live licensed vaccine ≤ 4 weeks or inactivated licensed vaccine ≤ 2 weeks prior to Step 2 entry*.

4.4.3 Receipt of a non-licensed agent (vaccine, drug, biologic, device, blood product, or medication) ≤ 4 weeks prior to vaccination, or expects to receive another non-licensed agent within 28 days after vaccination*.

4.4.4 Any significant (in the opinion of the site investigator) acute illness and/or oral temperature greater than or equal to 100.4°F within 24 hours of entry except when, in the opinion of the physician, withholding the agent entails even greater risk*.

4.4.5 Use of anti-cancer systemic chemotherapy or radiation therapy or has developed immunosuppression as a result of an underlying illness (other than HIV-1 infection) or treatment.

4.4.6 Use of glucocorticoids, including oral or parenteral prednisone ≥ 20 mg/day or equivalent for more than 2 consecutive weeks (or 2 weeks total) within 2 weeks of entry in Step 2*.

4.4.7 Receipt of immunoglobulin or other blood products (with exception of Rho D immune globulin) within 12 weeks prior to entry in Step 2 or is scheduled to receive immunoglobulin or other blood products (with the exception of Rho D immune globulin) during the 28 days following vaccination*.

4.4.8 Receipt of IL2, IFN, GMCSF or other immune mediators ≤ 12 weeks before entry in Step 2*.

*__NOTE:__ Entry in Step 2 may be deferred for up to 4 weeks to allow for resolution of a condition/ event in exclusion criteria 4.4.2, 4.4.3 or 4.4.4, 4.4.6, 4.4.7, and 4.4.8. The clinical site coordinator needs to obtain approval from the protocol team to defer participant entry in Step 2 beyond the window allowed by the Schedule of Evaluations.

4.5 Step 3 – Inclusion Criteria for Women

4.3.1 24 weeks ± 4 weeks postpartum.

4.3.2 Completion of Step 1.

4.3.3 Receipt of placebo on Step 1.

4.3.4 Met Step 2 exclusion criterion 4.4.1.

4.6 Step 3 – Exclusion Criteria for Women

None.

4.7 Concomitant Medication Guidelines

Administration of any medication, therapies and vaccines will be documented in the study case report forms (CRFs). Concomitant medications will include all medications and vaccines 12 weeks prior to enrollment through end of study or early termination, whichever occurs first.

4.7.1 Vaccines

Receipt of any maternal and infant vaccines besides the study product and that do not meet exclusion criteria will be collected throughout the study from enrollment to the off study visit. The administration of inactivated licensed vaccines to the mother should be at least 2 weeks prior to the administration of the study vaccine or delayed until 2 weeks after the study vaccine has been administered.

The administration of live vaccines is contra-indicated during pregnancy. After delivery, live vaccines are permitted but should not be administered ≤ 4 weeks prior to study vaccine administration in Step 2 or should be delayed until 2 weeks after the study vaccine has been administered.

Administration of any anti-PNC vaccines to the mothers, other than the study product, is not permitted while on study.

4.7.2 Disallowed/Precautionary Medications

The following medications should be avoided, if possible, and alternative treatments sought. Medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary. Medications in this category include, but are not limited to:

- Glucocorticoids, i.e., oral, parenteral and high-dose inhaled steroids.
- Immunosuppressive or cytotoxic drugs.
- Intravenous immunoglobulin or other IgG preparations other than Rhogam.
- Anti-PNC vaccines other than the study products.

4.8 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol document and the protocol consent form(s) approved, as appropriate, by their local IRB/Ethics Committee (EC) and any other applicable regulatory entity (RE).

4.8.1 Enrollment to Step 1

Participants meeting the study eligibility criteria will be enrolled through the DMC registration screens. Written informed consent for study participation must be obtained before any study-related procedures are performed. Participants registered to Step 1 will be randomly assigned to receive PPV-23, PCV-10 or placebo in a blinded fashion.

4.8.2 Enrollment to Step 2

Participants from Arm 1C will be enrolled into Step 2 at the week 24 postpartum visit (or within 10 days after the week 24 visit). At this time, the enrollment system will randomize mothers to receive the PPV-23 or PCV-10 vaccine, with additional study visits to follow. Participants from Arms 1A and 1B will be taken off study.

4.8.3 Enrollment to Step 3

Participants from Arm 1C who were not enrolled into Step 2 at the week 24 postpartum visit (or within 10 days after the week 24 visit) will be enrolled in Step 3. At this time, they will receive open label PCV-10 vaccine, after which they will be taken off study, with no additional study visits to follow.

4.9 Co-enrollment Procedures

Co-enrollment in other studies is allowed, except for protocols that would violate the exclusion criteria. The protocol team has to be consulted before co-enrollments.

4.10 PPV-23 and PCV-10 Availability at Participating Sites

Both PPV-23 and PCV-10 are licensed and available in Brazil. These vaccines will be provided to women through the study for protocol-defined vaccine doses. Infants will receive PCV-10 through local standard clinical care.

5.0 Study Treatment

In Step 1, women will be randomized initially to one of three blinded treatment arms: Arm 1A (PPV-23), Arm 1B (PCV-10) or Arm 1C (placebo).

In Step 2, women who were randomized to Arm 1C (placebo arm) will be randomized again at 24 weeks postpartum to one of two blinded treatment arms: PPV-23 (Arm 2A) or PCV-10 (Arm 2B). Women who were initially randomized to Arm 1C and meet an exclusion criterion for Step 2 due to new pregnancy will be enrolled in Step 3 and will receive open label PCV-10 at the last study visit (Step 1 24 weeks post-delivery).

All infants will receive PCV-10 per local standard of care.

5.1 Drug Regimens, Administration and Duration

Step 1

- **Entry.** At entry into Step 1, women will be randomized to one of the following three blinded treatment arms:
  - **Arm 1A (PPV-23).** Women in Arm 1A will be administered a 0.5 mL dose of PPV-23 intramuscularly once.
  - **Arm 1B (PCV-10).** Women in Arm 1B will be administered a 0.5 mL dose of PCV-10 intramuscularly once.
  - **Arm 1C (placebo).** Women in Arm 1C will be administered a 0.5 mL dose of 0.9 percent Sodium Chloride (NaCl) intramuscularly once.

Step 2

- **24 weeks Postpartum.** Upon entry into Step 2 at 24 weeks postpartum, women who were randomized to Arm 1C (placebo arm) will be randomized again to one of two blinded treatment arms:
  - **Arm 2A (PPV-23).** Women in Arm 2A will be administered a 0.5 mL dose of PPV-23 intramuscularly once.
  - **Arm 2B (PCV-10).** Women in Arm 2B will be administered a 0.5 mL dose of PCV-10 intramuscularly once**.**
  - A new prescription must be written with a new Study Identification number (SID) when registering participants to Step 2.

Step 3

- **24 weeks Postpartum.** The women who were randomized to Arm 1C (placebo arm) and who failed the entry into Step 2 at 24 weeks postpartum due to ongoing new pregnancy, will be administered a 0.5 mL dose of PCV-10 intramuscularly once.

A new prescription must be written with a new Study Identification number (SID) when registering participants to Step 3.

5.2 Study Product Formulation

PPV-23 (Pneumovax 23®) is a clear liquid injectable vaccine supplied as 0.5 mL dose per single dose vial. PPV-23 is manufactured by Merck & Co., Inc. Store PPV-23 single dose vial refrigerated at **2°C to 8°C**. Do not freeze.

PCV-10 is a suspension injectable vaccine supplied as 0.5 mL per single dose vial (preferred) and 1 mL per multi dose vial. PCV-10 is manufactured by Glaxo-SmithKline, Inc. Store PCV-10 vials refrigerated at **2°C to 8°C**. Do not freeze.

NaCl for injection 0.9 percent non-bacteriostatic, single dose vials must be purchased by the site locally. For the purpose of this study and to maintain blinding of the study product, store NaCl for injection 0.9 percent non-bacteriostatic, single dose vial refrigerated at **2°C to 8°C** if it is in accordance with the manufacturer's storage recommendation.

5.3 Pharmacy Procedures

- Study Product Acquisition
  - NaCl will be purchased locally. PPV-23 and PCV-10 will be provided through the coordinating pharmacy at site 5074, University of Sao Paulo Brazil Ribeirão Preto Medical School. Please refer to the most current version of the MOP and the Drug Distribution Plan, available on the NICHD website for further details on study product acquisition.
- Study Product Accountability, Preparation, Distribution, and Destruction
  - The Pharmacy general procedures to be followed by the research site pharmacist are provided in the most current version of the Pharmacy Guidelines and Instructions for Division of AIDS (DAIDS) Clinical Trials Networks, available on the NICHD website. The ordering, preparation, dispensing, use, and disposition of study products for the

P1091 protocol is detailed in the MOP and in the Drug Distribution Plan available on the NICHD website.

- Each research site pharmacist is required to maintain complete records of all study products received from the study coordination center or locally procured and subsequently dispensed including the 0.9 percent NaCl. Disposal of and/or destruction of used/empty vials handled by the study pharmacist during the dose preparation, used study product syringes, vials and needles, or other materials used in preparation must be in accordance with site/institutional/local guidelines. Disposal/destruction of unused (returned, expired, remaining) study products should be documented in the Returns Log, available on the NICHD website, and kept in quarantine for monitoring review.

- Please refer to the most current version of the MOP available on the NICHD website for further details on the accountability, preparation, distribution, and destruction of study products.

6.0 Participant Management and Adverse Event Reporting

6.1 Definitions

Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), for example, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious Adverse Event (SAE):

An SAE (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Expedited Adverse Event (EAE) Form:

A paper form used to document AEs that meet the seriousness criteria (SAEs) and need to be reported to NICHD in an expedited manner. **Suspected Unexpected Serious Adverse Reaction (SUSAR):**

- A SUSAR is an event that is:
  - Serious (See SAE definition above).
  - Related (i.e., there is a reasonable possibility that the AE may be related to the study product).
  - Unexpected (see definition below).

Unexpected Adverse Event:

An AE, the nature or severity (intensity) of which is not consistent with the applicable agent information (Investigator's Brochure, package insert, or summary of agent characteristics).

6.2 Toxicity Management

6.2.1 Women

It is anticipated that vaccine-associated AEs will occur frequently, but that these will be minor local reactions and side effects. The site investigators will perform appropriate clinical management of AEs according to the situation.

- Toxicities will be classified by the most current version of the DAIDS Table for Grading the Severity of Adult and Pediatric AEs (http://rsc.tech-res.com/safetyandpharmacovigilance).
  - A clinic visit is required within 72 hours from initiation of symptoms for maternal vaccine-related (in the opinion of the investigator) AEs Grade ≥ 3. Other vaccine-unrelated Grade ≥ 3 events will be managed as per local standard of care. Vaccine-related AEs Grade ≥ 3 need to be followed up until they reach Grade ≤ 2. The follow up will be recorded on the appropriate CRF.

    Examples of AEs of Grade ≥ 3 that may be related to the vaccines in the absence of an alternative explanation:

    1. Abnormal laboratory values, signs and symptoms or diagnoses.
    2. Local AEs, including pain, tenderness, redness, and swelling post vaccination.
    3. Systemic AEs, including feverishness, malaise, body aches (exclusive of the injection site), nausea, and headache post vaccination.
    4. Adverse pregnancy outcomes, including maternal, fetal and infant complications.
  - Study participants will be asked to keep a record of any AEs that occur within 28 days of vaccination (see Appendices V and VI) and report these events to the clinical personnel. ALL Grade ≥ 3 maternal AEs regardless of association to vaccine should be recorded on the appropriate CRF. The Protocol Chairs and NICHD should be contacted [nichd.teamp1091@fstrf.org] if the investigator is unsure of the relationship of the toxicities to the study vaccine, or feels that abnormal values or events may be due to intercurrent infection or another drug.

6.2.2 Infants

Infant death, congenital anomalies, prematurity, low birth weight, neonatal infections/sepsis, Neonatal Intensive Care Unit (NICU) admission, HIV transmission to infant, functional defects (hearing impairment, growth impairment, developmental delay) and Grade ≥ 3 AEs will be recorded on the appropriate CRF and, if applicable, on the EAE Report Form.

- Grade 1 and 2 infant AEs are not recorded.
- Grade ≥ 3 infant AEs are recorded on the appropriate CRF.
- In addition to being recorded on the appropriate CRF, all infant AEs that meet the criteria for expedited reporting are also recorded on the EAE Report Form.

Management of the infant will be as per local standard of care. [Note: Low grade AEs (i.e., all the Grade 1 and 2 AEs) are not collected, because PCV-10 is licensed for use during childhood, and there are numerous and extensive studies of safety and reactogenicity of PCV-10 in HIV-infected and uninfected children around the world.]

6.3 Participant Management

6.3.1 Screening and study entry may occur on the same day; however, entry may be delayed up to 28 days after screening, if needed.

6.3.2 Maternal history at screening/entry should include all history of cancer and allergies, history of all immunizations received within the past 12 weeks, status of current pregnancy and history of previous pregnancy complications, CDC classification for HIV status, and all medications taken within the past 12 weeks. Adherence to ARVs will be assessed at entry and at each subsequent visit using the adherence questionnaire. After entry, cancer, allergies, all pregnancy-related diagnoses, and current medications, as well as possible PNC illnesses (pneumonia, meningitis, sepsis, otitis media, or other lower respiratory infection) should be reported. All diagnoses of congenital anomalies should be reported for the infant.

6.3.3 Physical exam at screening/entry should include vital signs (temperature, blood pressure, heart rate, and respiratory rate) and complete physical exam as per local standards. After entry, physical exam should include vital signs and targeted exam based on current signs and symptoms.

6.3.4 Women will remain in the clinic for at least 30-60 minutes after vaccination in Step 1 or Step 2, so that clinic personnel can observe for

any potential adverse reactions to the vaccine. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected AE.

6.3.5 Maternal temperature and fetal heart rate (FHR) will be measured within 60 minutes prior to maternal vaccination and FHR will be documented 30-60 minutes after vaccination in Step 1.

6.3.6 Vaccine-related local (redness, swelling, tenderness, itching) and systemic (fever, malaise, myalgia, nausea, headache, rash, uterine cramps, contractions, changes in fetal movement, vaginal bleeding or discharge) AEs will be collected up to 28 days after immunization in Step 1 using the study-specific home record/diary card and/or participant interview. SAEs will be reported as described under Section 7.1.

6.3.7 Antipyretics should not be routinely given in anticipation of AEs after vaccination, but should not be withheld if symptoms occur. Antipyretics should be recorded on the home record/diary card and reported to the site staff.

6.3.8 Laboratory confirmed IPD in mothers and infants will be investigated and treated as per standard of care. IPD diagnoses can include, but are not limited to pneumonia, meningitis, sepsis, endocarditis, peritonitis, and arthritis, and should be confirmed by bacterial culture of blood, CSF or other appropriate specimen. If IPD is diagnosed, the following will apply:

- Study visit (to occur as soon as possible after the IPD diagnosis and preferably within 3 weeks) for history and physical exam.
- If possible, obtain an aliquot of the IPD diagnostic culture. Aliquots will be stored on site, and batch shipped to a central study laboratory for PNC serotyping (for details, see Laboratory Processing Chart (LPC)).

6.3.9 Blood for Peripheral Blood Mononuclear Cells (PBMC) will be collected only from the first 150 women enrolled in Step 1 and all women who are vaccinated in Step 2. The DMC will monitor the collection of PBMCs and notify the sites to stop collecting these specimens once the target enrollment of 150 participants with available specimens has been reached.

6.3.10 Infants will receive PCV-10 per standard of care. See Infant Schedule of Evaluations (Appendix II). Infant AEs are managed as per local standard of care.

6.4 Criteria for Treatment Discontinuation

- Women who receive treatment with disallowed medications, listed in Section 4.4.3, at enrollment into Step 2 except for cases in which enrollment can be delayed to avoid exclusion.

6.5 Criteria for Study Discontinuation

- The participant or legal guardian refuses further treatment and/or follow-up evaluations.
- The investigator determines that further participation would be detrimental to the participant's health or well-being.
- The participant fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.

6.6 Study Results

- The results of the ELISA antibody tests will be made available to study participants as soon as final results are available at the completion of the study.

7.0 Expedited Adverse Event Reporting

7.1 Reporting Requirements

To ensure compliance with the safety reporting requirements of the US regulations at 45 Code of Federal Regulations (CFR) part 46 and per the ICH-E6 and E2A guidelines, site investigators must report immediately all AEs that meet the criteria for expedited reporting (SAEs), regardless of presumed relationship to the study product, to the Sponsor, NICHD, via the Westat Regulatory Affairs (RA). The Sponsor will carefully review the safety information to monitor the study product's toxicity profile and patient safety. The site investigators will promptly notify the IRBs of any unanticipated problems involving risks to subjects or to others following the institutional policies for reporting such information.

- The study products for which expedited reporting are required are the following:
  - Maternal PPV-23, PCV-10 and placebo during pregnancy.
  - Maternal PPV-23 and PCV-10 after delivery.
- AEs will be reported without knowledge of treatment arm. At the end of the study, when the treatment groups will be known to the protocol team, the SAE will be attributed to one of the active products or to placebo.

The site investigator will report on an expedited basis any SAE following exposure to the study product that results in the following conditions, regardless of relatedness:

1. Results in death;
2. Is life-threatening; (*the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*
3. Requires inpatient hospitalization or prolongation of existing hospitalization; (*per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event.)*
4. Results in persistent or significant disability/incapacity;
5. Is a congenital anomaly/birth defect; or
6. Is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Examples include the following: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; etc.

7.2 Recording of Adverse Events requiring Expedited Reporting

Each AE that requires expedited reporting should be recorded in standard medical terminology on the EAE Report Form. Whenever possible, the event should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. For example, cough, runny nose, sneezing, sore throat, and head congestion should be reported as 'upper respiratory infection'. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.

The EAE Report Form will be submitted by email or fax to the Westat RA within 24 hours after the research staff becomes aware of the event.

The investigator will evaluate all SAEs with regard to grading and relationship to study products.

7.3 Grading Severity of Adverse Events

The most current version of the DAIDS Table for Grading the Severity of Adult and Pediatric AEs is used and is available on the Regulatory Support Center (RSC) web site (http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf).

7.4 Relationship to Study Products

The site investigator is responsible for assessing whether there is a reasonable possibility that the study product caused or contributed to the AE. The relationship between the AE and the study product falls under two categories:

- Related- there is a reasonable possibility that the AE may be related to the study product.
- Not Related- there is no reasonable possibility that the AE may be related to the study product. An alternative etiology or explanation for the AE should be provided. If new information becomes available, the relationship assessment of any AE will be reviewed again and updated, as required.

7.5 Expedited Adverse Event Reporting Category

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for reporting AEs in an expedited manner to NICHD, via the Westat RA.

7.6 Adverse Event Reporting Period

The reporting period for this protocol continues from study enrollment of an individual participant until study completion or discontinuation of the participant from study participation for any reason.

After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs will be reported to the Westat RA if the study staff become aware of the events on a passive basis (from publicly available information).

7.7 Follow-up Expedited Adverse Event Report

Sites must follow each SAE until stable or resolved.

The investigator should report promptly to the Westat RA any change in the initial EAE Report Form information or additional information that becomes available after the date of the initial EAE Report Form submission.

8.0 Statistical Considerations

8.1 General Design Issues

The primary objectives of this study are to assess the safety and immunogenicity of PPV-23 and PCV-10 multivalent vaccines in pregnant women and their infants. Comparisons will be made between participants receiving either of the two vaccine products and between those receiving vaccines versus those receiving placebo. With respect to immunogenicity, the study will be powered for the primary comparisons on which the smallest group differences are expected. This will provide more than sufficient power for other immunologic comparisons for which larger differences are expected. With respect to safety, few SAEs are expected; thus, the analyses will be descriptive and the study will not be powered for these analyses. However, the precision with which rates of AEs can be estimated, as well as the size of effects which can be detected with 80 percent power, given the sample size, will be presented below. The study will not be powered for the considerable number of potential secondary comparisons.

A review of the literature showed that HIV-infected pregnant women, like other adults, have PNC antibodies before receiving PNC vaccines. However, these antibodies seem to be insufficient to protect them against IPD. Although maternal antibodies cross the placenta and are transferred to the infants, they rapidly wane and become undetectable by 2 months of age. Widely accepted correlates of protection against IPD in infants immunized with PCV-10 are ELISA-measured antibody titers ≥ 0.35 μg/mL, but these parameters do not correlate with protection in adults. In adults, there is no threshold antibody level associated with protection against IPD. In the absence of a threshold antibody value that correlates with protection against IPD, response to vaccination is measured by a two-fold increase over baseline in ELISA-measured antibody concentrations. For infants, ELISA-measured antibody titers ≥ 0.35 μg/mL at 2 months as primary outcome measures will be used. The 2-month time point was chosen because the highest level of vulnerability of infants to IPD is in the first few months of life, before the second dose of infant PCV-10 vaccine confers sufficient specific antibodies to protect them against IPD. Furthermore, the literature suggests that, in the absence of vaccination, maternal antibodies would usually wane to unprotective levels by the age of 8 weeks.

8.2 Outcome Measures

8.2.1 For Primary Objectives

8.2.1.1 Safety

- Grade ≥ 3 AEs in mothers or in neonates; and

- Grade ≥ 3 AEs judged to be at least possibly related to the study treatment.

8.2.1.2 Maternal Immunogenicity

- The serotypes measured by ELISA are: 1, 4, 5, 6B, 7F, 14, 23F and 33F. For each serotype, a two-fold increase in ELISA-measured IgG PNC antibody concentrations from baseline to 28 days after immunization in Step 1 defines a response to the vaccine. The primary endpoint is a response to ≥ 5 serotypes.

8.2.1.3 Infant Immunogenicity

- ELISA-measured IgG PNC antibody levels ≥ 0.35ug/mL at 8 weeks of age is the primary endpoint for antibody persistence in the infant. Reaching this level of antibodies for ≥ 5 serotypes listed in Section 8.2.1.2 defines success.

8.2.2 For Secondary Objectives

- The ratios of infant/mother PNC antibody levels to serotypes listed in Section 8.2.1.2, measured at birth/delivery; and
- The maternal and infant immunogenicity that are described in the primary objective outcomes (but at different time points and from different groups).

8.2.3 For Tertiary Objectives

- Episodes of maternal illness possibly or probably caused by PNC;
- Episodes of pneumonia, IPD, meningitis, acute otitis media and any other diseases caused by PNC in infants;
- Changes in HIV viral load and in CD4/CD8 counts in pregnant women;
- Infant congenital defects;
- Mother to child HIV transmission;
- OPA-measured antibodies to 4 PNC serotypes (4, 6B, 14 and 23F) in 20 women who received PCV-10 and 20 women who received PPV-23;
- Density of PNC in NP and OP swabs at Day 0 and at delivery in women;

- Density of PNC in NP and OP swabs at weeks 8 and 16 in infants;
- B- and T-cell responses at day 28 after vaccination and at week 24 after delivery in mothers and at birth and 24 weeks of life in infants; and
- B- and T-cell responses to childhood PCV-10 in infants born to mothers who received PCV-10, PPV-23 or placebo during pregnancy.

8.3 Randomization and Stratification

At the Step 1 study entry, pregnant women will be randomized using a dynamic permuted block system to 3 groups at ratio 1:1:1, receiving PPV-23, PCV-10 or placebo, with approximately 115 pregnant women in each group. Women who received placebo in Step 1 will enter Step 2 at 24 weeks postpartum and will be randomized at Step 2 entry using a dynamic permuted block system to 2 groups at ratio 1:1 to receive PPV-23 (Arm 2A) or PCV-10 (Arm 2B). The women who received active vaccine during pregnancy (Arms 1A and 1B) will stop study at the week 24 visit. Women who were initially randomized to Arm 1C and meet an exclusion criterion for Step 2 due to ongoing new pregnancy will be enrolled in Step 3 and receive open label PCV-10 at the 24 weeks postpartum visit. No data will be collected on these women and they will not be followed on study after the vaccine administration.

The participants will be unblinded following the NICHD P1091 unblinding plan at the end of Step 1 to unblind the participants in the placebo arm (Arm 1C) so they may be randomized into Step 2. All the women will be unblinded after the last woman has completed Step 2.

8.4 Sample Size and Accrual

8.4.1 Sample Size Calculation

8.4.1.1 To Compare Maternal Vaccine Response

- The proportion of mothers meeting the primary response criterion at 28 days after immunization will be compared between the groups receiving PPV-23 versus PCV-10.
- Table 8-1, below, shows that samples of approximately 100 evaluable participants per group will yield 80 percent statistical power to detect differences in response rate of 20 percent between these two groups.

Table 8-1. Maternal response: sample sizes needed to provide 80 percent statistical power to detect differences in response rate as a function of PPV-23 versus PCV-10.

	Lower response rate			
	.30	**.40**	**.50**	**.60**
.40	376			
.50	103	408		
.60	48	107	408	
.70	29	48	103	376
.80	18	27	44	90

Higher response rate

8.4.1.2 To Compare Infant Vaccine Response

The proportion of infants meeting the primary maternal antibody persistence criterion at 8 weeks of age will be compared between the groups whose mothers have received PPV-23 versus PCV-10. Table 8-2 shows that samples of approximately 100 evaluable participants per group will yield 80 percent statistical power to detect differences in response rate of 20 percent between these two groups.

Table 8-2. Infant rate of protective antibody titers: sample sizes needed to provide 80 percent statistical power to detect differences in protective rate as a function of PPV-23 versus PCV-10

	Lower rate of protective antibody titers			
	.30	**.40**	**.50**	**.60**
.40	376			
.50	103	408		
.60	48	107	408	
.70	29	48	103	376
.80	18	27	44	90

Higher rate of protective antibody titers

8.4.1.3 Targeted Total Sample Size for Accrual

To allow for a 10-15 percent rate of loss-to-followup, the study will enroll 345 mother/infant pairs (115 per group), with the aim of having at least 100 evaluable mother/infant pairs per study arm in Step 1.

It is anticipated that all participants will be enrolled within 2 years after version 1.0 becomes available.

8.5 Monitoring

Safety and tolerability of the study vaccine will be monitored by means of AEs and toxicity reports presenting laboratory and clinical data. The data to be reviewed by the Clinical Management Committee (CMC) will be pooled across treatment arms. It is required that these data be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available. The accrual and toxicity reports will be discussed by the CMC (comprised of the Protocol Chairs, Medical Officers, statisticians, data managers, and protocol specialist) on monthly conference calls.

The attribution of relationship of AEs to study vaccine will be discussed on the CMC calls and the relationship will be determined by the CMC, taking into account the site and the Medical Officer's assessment of the event. Interpretation of vaccine-relationship to AEs will be based on the type of event, the relationship of the event to the time of immunization, the known biology of the vaccine and the investigators' medical judgment. Gradation of relationship will use the following terminology: "not related" or "related".

In addition to monthly toxicity reviews by the CMC, the study will be monitored by a Safety Monitoring Committee (SMC) who will meet yearly/ad hoc. SMC members will be independent of the study (except for the statistician) and have no financial or perceived conflict of interest. The committee will meet via conference call to review relevant data as described in Section 8.5.1. The Chair of the SMC or designee will be responsible for reporting the SMC's comments to the protocol team.

The Medical Officer may request for the SMC to review any safety data and for the SMC to be unblinded (with treatment arms labeled) or review the entire safety report by treatment arms, and request an immediate SMC review/meeting when necessary.

8.5.1 Early Stopping Rules for Safety

The following stopping rules will be applied in order to protect the study participants from unnecessary exposure to the vaccine, should the safety profile prove unacceptable in this population.

- For all deaths and Grade 4 life-threatening events, excluding neutropenia, that are assessed by the site investigators as related to study treatment, vaccination will be paused until the SMC reviews the event and related data and determines that it is safe to resume vaccination.

- For all deaths and grade 4 life-threatening events, excluding neutropenia, that are assessed by the site investigators as not related, vaccination will continue.

8.5.2 Early Safety Assessment by the Protocol Team

After 20 mothers have been enrolled in each of the 3 arms, all infants have reached 1 month of age, and the CMC has reviewed all the blinded safety data, the study statistician will summarize the decisions made by the CMC.

If 7 or more mothers or 7 or more infants have met a safety endpoint judged to be related to study treatment, then the study statistician will unblind the treatment assignments and summarize toxicities occurring in the participants receiving placebo and those receiving the PPV-23 or PCV-10 vaccines. In collaboration with one or more SMC member(s), the statistician will inform the CMC whether ≥ 30 percent of the mothers or infants belonging to either of the maternal vaccine groups met safety endpoints that are vaccine-related. If this has occurred, the CMC will request an independent review of the data by the SMC. Otherwise, enrollment will continue.

8.6 Analyses

- Safety

For each group of mothers, the proportion of participants who experience grade ≥ 3 AEs up to 4 weeks after vaccination in Step 1 or Step 2 and grade 4 AEs or death up to 24 weeks postpartum will be presented and bounded by 90 percent confidence intervals.

For each group of infants, the proportion of participants with congenital defects, in-utero or perinatal HIV infection, pneumonia or IPD will also be presented and bounded by 90 percent confidence intervals.

The confidence intervals will provide 95 percent confidence that the true population proportion is no higher than the upper limit of the interval. The proportion of mothers or infants experiencing grade ≥ 3 AEs judged to be treatment-related will also be shown.

Since relatively few events of this severity are expected both in vaccine- and placebo-recipients, these analyses will be descriptive. However, should an unexpected epidemic of respiratory, central nervous system, or other febrile illness occur during the study, there will be more AEs and a more formal analysis will be performed. In this case, the inclusion of the placebo group will allow us to examine whether the symptoms associated with these AEs are

significantly more prevalent among vaccines than among placebo recipients and should be attributed to the vaccination (Step 1 data only).

Table 8-3 presents 90 percent confidence intervals around a range of potential rates of primary endpoints in a sample of 115 participants representing populations exposed to PPV-23, PCV-10 or placebo. These confidence intervals would apply to all of the endpoints defined in Section 8.2.1 for either the mothers or the infants.

Table 8-3. 90 percent confidence intervals around potential rates of grade ≥ 3 AEs within any of the treatment groups (N = 115)

Point estimate	Lower limit	Upper limit
.02	.00	.04
.04	.01	.07
.06	.02	.10
.08	.04	.12
.10	.05	.15
.12	.07	.17
.14	.09	.19
.16	.10	.22
.18	.12	.24

Because few SAEs are anticipated, there may be limited statistical power for formal comparisons between groups on the basis of the proportions of participants meeting safety endpoints. However, the following table shows that, if the absolute rate of true AEs associated with one of the vaccine products were 8-10 percent higher than that of placebo, the sample size would provide reasonable power to detect such a difference.

Table 8-4. Statistical power for pairwise comparisons between either of the vaccine groups and the placebo group with respect to the proportions of participants with grade ≥ 3 AEs. (1-tailed Fisher's exact tests of vaccine > placebo, alpha=.05)

	Placebo group (N2)=115			
		.02	**.04**	**.06**
Vaccine group (N1)=115	.04	.10	NA	NA
	.06	.31	.10	NA
	.08	.56	.25	.09
	.10	.77	.46	.23
	.12	.89	.66	.40
	.14	.96	.81	.59
	.16	.99	.91	.74
	.18	.996	.96	.86

- Immunology

  - Maternal:

    1. Primary Analysis

       To compare the maternal response rates at 28 days after immunization, between the groups receiving PPV-23 versus PCV-10, the Chi-square test will be used. Logistic regression analysis may also be performed, should the need arise to control for certain covariates (Step 1 data only).

    2. Secondary Analyses

       Similar analyses to the primary analysis discussed above, comparing responses between placebo and each vaccination group at 28 days, will have 80 percent power to detect ≥ 20 percent difference in proportion of responders between each group of vaccines and the placebo recipients. Since placebo recipients are not expected to meet response criteria and response rates in HIV-infected pregnant women immunized with PPV-23 and PCV-10 have been reported to be at least 20 percent, and often much greater, it is anticipated that the sample size will be sufficient to detect an effect of each vaccine compared with placebo (Step 1 data only).

       Similar analyses to the primary analysis comparing all groups with respect to immunologic response at other time points will be performed. Responses to the vaccine during pregnancy with responses after delivery (pregnancy placebo recipients vaccinated at 24 weeks after delivery) will also be compared. Differences in immunogenicity of either vaccine administered during pregnancy versus postpartum is not anticipated, and the study is not powered for such a comparison (both Step 1 and Step 2 data).

       In addition to the aggregate response, the level of PNC antibodies within each serotype measured will be compared at 28 days after immunization and at 24 weeks after delivery, among the treatment groups, using the baseline level as a covariate. Parametric methods will be used if the log-transformed titers are normally distributed, otherwise nonparametric analysis will be performed. Since most of the serotypes tested are in both vaccines, and 33F is present only in the PPV-23 vaccine, it is expected that women who received the PCV-10 vaccine will have lower levels of 33F antibodies.

       For the analysis of transplacental transfer of maternal antibodies, the ratios of infant/mother anti-capsular antibodies for the serotypes listed in Section 8.2.1.2, measured at delivery/birth will be calculated. For

each serotype, the ratios across all three treatment groups using a Kruskal-Wallis test will be compared. For the serotypes for which this analysis is statistically significant, pairwise comparisons to see which groups differ from each other will be performed.

3. Tertiary Analyses

The incidence of pneumonia, meningitis, bacteremia and other manifestations of IPD between vaccine and placebo groups, during pregnancy and postpartum will be compared. The PNC serotypes associated with maternal IPD according to their presence in PCV-10 and PPV-23, or in PPV-23 only will be grouped. Since relatively few cases are expected, the analysis will be descriptive (both Step 1 and Step 2 data).

At the completion of the study, 60 women-infant pairs will be randomly selected from those who have complete antibody data (20 women who received PCV-10, 20 who received PPV-23 and 20 who received placebo during pregnancy). OPA will be performed for 4 PNC serotypes (4, 6B, 14 and 23F) at 24 days after maternal vaccination during pregnancy and at birth in infants. A correlation analysis of OPA and ELISA measured antibody levels will be performed in these 60 women and their infants. These will consist of Pearson correlations, if the data are normally distributed or Spearman correlations if normality assumptions are not met.

Descriptive analyses of changes from entry in HIV viral load and in CD4/CD8 counts in pregnant women will be presented.

Descriptive analyses of the density of PNC in NP and OP swabs will be presented. In addition, an exploratory comparison of the number of pharyngeal new vaccine serotype acquired after maternal vaccination in each group will be performed.

PNC-specific and nonspecific B- and T-cell maternal and infant responses will be compared among treatment groups. Correlation analyses of PNC-specific B- and T-cell responses with antibody titers and PNC pharyngeal carriage, respectively, will also be performed.

– Infant:

1. Primary Analysis

Chi-squared tests will be used to compare the proportion of infants meeting the primary criterion for the persistence of maternal antibody at 8 weeks of age between the groups whose mothers have received PPV-23 versus PCV-10. Logistic regression analysis may also be

performed, should the need arise to control for certain covariates (Step 1 data only).

2. Secondary Analyses

   Similar analyses to the primary analysis discussed above, comparing responses between placebo and each vaccination group at 8 weeks, will be performed. These analyses will indicate whether maternal vaccination provides additional infant protection, over and above that which would be present in the absence of vaccination. Power for these analyses will be similar to that described in Table 8-4, such that power will be at least 80 percent to detect true differences of 20 percent or greater (Step 1 data only).

   Similar analyses will also compare all groups with respect to persistence of protective antibodies at other time points. Moreover, antibody responses to PNC 33F, which is part of PPV-23 but not of PCV-10, in infants born to mothers who received PCV-10 with infants born to mothers who received PPV-23 and those of infants whose mothers received placebo (both Step 1 and Step 2 data) will be compared.

3. Tertiary Analyses

   The incidence of pneumonia, meningitis and other manifestations of IPD and of acute otitis media will be compared between vaccine and placebo groups. PNC serotypes associated with maternal IPD according to their presence in PCV-10 and PPV-23, or in PPV-23 will be grouped. Since relatively few cases are expected, the analysis will be descriptive (Step 1 only).

   The number of cases of mother-to-child HIV transmission will be summarized descriptively.

9.0 Human Subjects

This study will be conducted in compliance with the protocol, Good Clinical Practice Guidelines and 45 CFR Part 46.

9.1 Institutional Review Board and Informed Consent

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

Each site that receives US Department of Health and Human Services funding and follows the US CFR Title 45-Public Welfare, Part 46-Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric participants and determines when a study participant must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. LAR means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participants involvement in the research. The plan will include how the site determines when an LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all IRB/EC, local, state, national and/or host country guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

9.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain participant confidentiality. All records will be kept in a secured area with limited access. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the Office for Human Research Protections (OHRP), the local IRB or EC, local or national regulatory agencies, NICHD, study staff, study monitors, and other sponsors, as applicable.

The Protocol Chairs and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any

data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from NICHD must be obtained for the disclosure of any said confidential information to other parties.

9.3 Study Discontinuation

The study may be discontinued at any time by the NICHD, OHRP, the IRB or EC, other governmental agencies, or local or national regulatory agencies as part of their duties to ensure that research participants are protected.

10.0 Publication of Research Findings

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

11.0 Biohazard Containment

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

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 Guidelines for Shipment and Receipt of Category B Biological Substance Shipment and Instruction for Overnight Shipments documents at https://www.hanc.info/labs/labresources/procedures/Pages/actgImpaactLabManual.aspx.

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Appendix I
Maternal Schedule of Evaluations

Event	Screening[1]	Step 1					Step 2 (For women from Arm1C only)		Un-scheduled Visit[13]	Invasive Pneumococcal Disease (IPD)[14]	Early Discont.
		WK 0 Day 0 (Entry)	WK 1	WK 4	Labor and Delivery	24 Weeks Post-Delivery[10]	Day 0 (Step 2 Entry)[11]	WK 4 after Step 2 Entry			
Visit Windows			+ 3 days	+ 7 days	+ 7 days	± 28 days	+ 10 days	+ 7 days			
Clinical Evaluations											
Informed Consent	✓										
History[2]	✓	✓	✓		✓	✓		✓	✓	✓	✓
Physical Exam[3]	✓	✓	✓				✓		✓	✓	
Documentation of Ultrasound Result[4]	✓	✓[4]									
Documentation of HIV Status[5]	✓										
Fetal Heart Rate (FHR)[6, 7]		✓									
Vaccination		✓[7]					✓				
Reactogenicity Assessment[8]		✓	✓	✓							✓
Laboratory Evaluations											
Hematology[9]	1 mL			1 mL							
Pregnancy Test[12]							✓				
Virology											
HIV-1 RNA PCR		3 mL		3 mL			3 mL				
Immunology											
Immunophenotyping (CD4/CD8)		2 mL		2 ml			2 mL				
Serum for PNC Antibodies		2 mL		2 mL	2 mL	2 mL		2 mL			
Blood for Plasma and Cryopreserved PBMC[15]		20 mL[15]		20 mL[16]			20 mL	20 mL			
Bacteriology											
PNC Culture/Specimen Storage for PNC Serotyping										✓	
NP and OP Swabs for PNC Serotyping by PCR		✓			✓						
Total Blood Volumes	**1 mL**	**27 mL**	**0 mL**	**28 mL**	**2 mL**	**2 mL**	**25 mL**	**22 mL**	**0 mL**	**0 mL**	**0 mL**

Footnotes

1. Screening and study entry may occur on the same day; however, entry may be delayed up to 28 days after screening, if needed.
2. A targeted medical history is required at screening and entry, as well as subsequent clinic visits, and should include information on (see Section 6.3.2):
   - Life-long history of cancer and allergies at the screening/entry visit.
   - Information regarding current status of the participant's pregnancy; history of previous pregnancy complications will be recorded at the screening/entry visit.
   - List of medications taken currently as well as within the 12 weeks prior to enrollment, and immunizations within the past 12 weeks.
   - CDC classification for HIV status at screening/entry and 6 months post-delivery/early discontinuation.
   - Pregnancy-related diagnoses and diagnoses of possible PNC infection (pneumonia, meningitis, sepsis, otitis media and other lower respiratory infections) during study participation.
   - Adherence questionnaires.
3. At screening/entry, physical exam should include vital signs (temperature, blood pressure, heart rate, and respiratory rate) and complete physical exam according to local standards. After entry, physical exam should include vital signs, and a targeted exam based on current signs and symptoms.
4. Ultrasound is performed as per standard of care. Results are abstracted from the medical records.
5. HIV diagnosis requires testing two different specimens. If the first test was performed at an outside facility, a copy of the laboratory result is required.
6. FHR will be measured within 60 minutes prior to maternal vaccination and 30-60 minutes after vaccination in Step 1. For participants that are < 20 weeks gestational age, monitoring of fetal heart rate is optional. Site standard of care should be implemented for these participants.
7. Following administration of vaccine, observe participant in clinic for 30-60 minutes. Additionally, FHR at appropriate gestational age should be recorded at 30-60 minutes post vaccination.
8. Reactogenicity assessments will include review of participant's home record/diary card and provision of an assessment of AEs, which includes review for any of the following symptoms: erythema, induration, pain and tenderness at the injection site, fever, fatigue, myalgia (exclusive of the injection site), headache, nausea and rash.
9. Hematology must include complete blood count (CBC) with differential and platelet count. **Platelet count (> 50,000 mm^3) and ANC (> 500 mm^3) results obtained within 28 days of enrollment can be used. All the results will be recorded on the appropriate CRF.**
10. This will be the off study visit for the women who received active vaccine during pregnancy (Arms 1A and 1B). Women from Arm 1C will be screened for entry into Step 2. Women enrolled in Arm 1C who do not meet an eligibility criterion to enter Step 2 due to new pregnancy, will be enrolled into Step 3 and receive open label PCV-10 at this visit, which will also be their last study visit. There will be no follow-up afterwards for these participants and they will be immediately taken off study.
11. ONLY women who received placebo during pregnancy (Arm 1C) will be randomized to Step 2 to receive a PPV-23 (Arm 2A) or PCV-10 (Arm 2B) vaccination. This visit can be completed on the same day or within 10 days of the 24 week post-delivery visit.
12. A urine or serum pregnancy test should be completed, and be confirmed as negative, within 24 hours prior to Step 2 immunization.
13. Unscheduled visits are required within 72 hours for vaccine-related (in the opinion of the investigator) adverse reactions Grade ≥ 3. Laboratory evaluations may be conducted at this visit, if needed, in the opinion of the site investigator.
14. This visit will only occur if the participant develops laboratory-confirmed PNC disease during the study. The visit should be scheduled as soon as possible after the diagnosis of IPD, and preferably within 3 weeks. If possible, obtain an aliquot of the IPD diagnostic culture. Aliquot will be stored on site, and batch shipped to the testing laboratory at the end of the study or earlier if requested by the protocol team for PNC serotyping. See LPC for additional collection, processing, and shipping information.
15. Blood for PBMC will be collected from the first 150 women enrolled in Step 1 and all women who are vaccinated in Step 2.
16. Collect blood for PBMC only from women who had the collection done at Day 0.

For insufficient blood draws, priorities are as follows:

1. Serum for PNC antibodies.
2. Immunophenotyping.
3. Plasma HIV RNA.

Appendix II
Infant Schedule of Evaluations

Event	WK 0 Birth[1]	WK 8 (≤ 7 days before the 1st dose of PCV-10)[5]	WK 16 (≤ 7 days before the 2nd dose of PCV-10)[5]	WK 24 (≥28 Days after the 2nd dose of PCV-10)[6]	Invasive Pneumococcal Disease (IPD)[7]	Early Discont.
Visit Windows	+7 days	± 14 days	± 28 days	28 days		
Clinical Evaluations						
Interval History[2]	✓	✓	✓	✓	✓	✓
Physical Exam[3]	✓				✓	
Immunology and Microbiology						
Serum for PNC Antibodies	2 mL	2 mL	2 mL	2 mL		
Blood for Plasma and Cryopreserved PBMC	3 mL			5 mL		
PNC Culture/Specimen Storage for PNC Serotyping					✓	
NP and OP Swabs for PNC Serotyping by PCR[4]		✓	✓			
Total Blood Volumes	**5 mL**	**2 mL**	**2 mL**	**7 mL**	**0 mL**	**0 mL**

Footnotes:

1. Neonates will receive their own PID at the time of maternal study enrollment.
2. Interval history will include reporting of infant death, congenital anomalies, prematurity, low birth weight, neonatal infections/sepsis, NICU admission, HIV transmission to infant, functional defects (hearing impairment, growth impairment, and developmental delay), breastfeeding and Grade ≥ 3 AEs**, as outlined in Section 6.2.2**. Abstract from the history pneumococcal vaccination since last visit. Infant data will be abstracted from the maternal and/or infant charts as needed. HIV test results should be collected and recorded through the interval history.
3. Physical exam will include: height, weight, head circumference and Apgar scores (at birth).
4. If the infant is breastfed, the collection of the NP and OP swabs should occur at least 1 hour after the last feeding.
5. PCV-10 will be administered as per standard of care. The vaccine may be administered at an outside facility. Administration of each dose of PCV-10 will be documented as indicated in footnote 2. WK 8 and 16 study visits have to occur ≤ 1 week before the 1st and 2nd dose of infant PCV-10, respectively, are administered. Blood draw and vaccination can occur on same day as long as blood draw precedes vaccination.
6. If possible, please schedule the maternal and infant visits at the same time; however please ensure that at least 28 days have passed since the infant's second PCV-10 immunization.
7. This visit will only occur if the participant develops laboratory-confirmed PNC disease during the study. The visit should be scheduled as soon as possible after the diagnosis of IPD, and preferably within 3 weeks. If possible, obtain an aliquot of the IPD diagnostic culture. Aliquots will be stored on site, and batch shipped to the testing laboratory at the end of the study or earlier if requested by the protocol team for PNC serotyping. See LPC for additional collection, processing, and shipping information.

For insufficient blood draws, priority is as follows:

1. Serum for PNC antibodies.

Appendix III
P1091 Protocol Testing Laboratories

Oropharyngeal and nasopharyngeal swabs for PNC serotyping by PCR:*
Stephen Ira Pelton, M.D.
Boston University School of Medicine
Boston Medical Center
774 Albany Street, Room 512
Boston, MA 02118
Phone: (617) 414-7407
FAX: (617) 414-5806
Email: spelton@bu.edu

* **NOTE:** All other samples (serum and plasma) are to be shipped to the Central Repository (Biomedical Research Institute (BRI)) for redistribution to the testing laboratories. See LPC for specific collection, processing, and shipping information.

Serum for PNC antibodies by ELISA and OPA:
David Goldblatt, MB.Ch., Ph.D., F.R.C.P., F.R.C.P.C.H.
Great Ormond Street Hospital (GOSH)
Immunobiology
Institute of Child Health, University College London (UCL)
30 Guilford Street
London WC1N 1EH
Phone: 020-7905-2215
Email: d.goldblatt@ucl.ac.uk

Plasma and PBMC for PNC B and T cell-mediated immunity:
Adriana Weinberg, M.D.
University of Colorado Denver
Mail Stop 8604
12700 E. 19th Avenue, Room 11126
Aurora, CO 80045
Phone: 303-724-4480
Email: adriana.weinberg@ucdenver.edu

Serum for PNC antibodies by ELISA:
Marisa Mussi, M.D.
Ribeirão Preto School of Medicine University of São Paulo
Av. Bandeirantes 3900
Ribeirão Preto
Sao Paulo
CEP 14049-900
Brazil
Phone: +55 16 3602 2807
Email: mmmpinha@fmrp.usp.br

Appendix IV
Instructions for Nasopharyngeal (NP) and Oropharyngeal (OP) Sample Collection

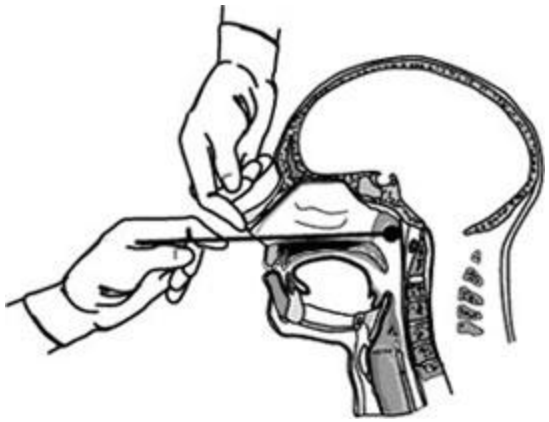
I. Materials

Dacron or Rayon swabs with plastic shaft
2.0 mL sterile cryovials (product code: 02-681-374; Fisher Scientific)
Skim milk-tryptone-glucose-glycerin (STGG) medium

II. Technique

1. NP samples are collected by inserting the swab through the nose until encountering the resistance of the pharyngeal wall (see illustration below). Swabs are swirled and rapidly withdrawn from the nose and inserted in the STGG medium-containing tube.

Figure 1. Proper technique for obtaining a NP specimen



2. OP samples are collected by inserting the swab through the mouth, swirling it against the pharynx and tonsils, but avoiding the tongue. The individual collecting the sample visually follows the tip of the swab during the procedure to make sure that the correct sites are being sampled.

3. The swab is inserted in the STGG tube. The shaft of the swab is broken or cut leaving the tip in the STGG-containing cryovial.

4. The vial is capped and transported to the lab where the cryovials are stored at ≤ -20ºC until shipment.

5. Refer to the SOE and LPC for final procedures and shipping instructions.

Appendix V
Study Participant Information Sheet

After you receive the study vaccine, and during the remainder of the study, we would like you to look for side effects from the vaccine, and other illnesses you may have, and report them to your study nurse.

During the first 28 days after receiving the vaccine:

Please report to your study nurse any of the following:

- Fever
- Rash
- Changes in skin appearance or sensation at the site of the shot
- Changes in behavior
- Changes in appetite
- Any pain or other problems that appeared after the shot and bothered you
- Nausea
- Headache
- Any cramps in your uterus
- Any contractions
- Any vaginal bleeding
- Any vaginal discharge
- Any changes in fetal movements

We would like for you to keep track of these on the home record/diary card.

During the study:

- We would like you to report any illnesses that you have between study visits.
- If you become so ill that you need to stay overnight in the hospital, please contact your study nurse as soon as possible.
- If you are prescribed antibiotics for any illness, even if you do not have to stay in the hospital, please contact your study nurse as soon as possible.

Contact information:

Appendix VI
Home Record/Diary Card for P1091

NOTE for the sites: This should be formatted for your site. Please add pictures, etc.

Please review the patient information sheet. Please keep track of any signs and symptoms you have for the first 28 days after receiving the immunization. These include:

- Fever
- Rash
- Changes in skin appearance or sensation at the site of the shot
- Changes in behavior
- Changes in appetite
- Any pain or other problems that appeared after the shot and bothered you
- Nausea
- Headache
- Any cramps in your uterus
- Any contractions
- Any vaginal bleeding
- Any vaginal discharge
- Any changes in fetal movements

Please write down when it started and stopped and how severe it was.

- 1=not severe, no changes in my routine.
- 2=mild, I took medicine to relieve it, it changed my routine a little.
- 3=more severe, I needed to go to the clinic.
- 4=very severe, I needed to stay in the hospital.

If you took medication for it, please write that down.

What happened?	When did it start?	When did it stop?	How bad was it?	What medicine did you take?

Appendix VII
Sample Informed Consent

Safety and Immunogenicity of Anti-Pneumococcal Vaccines in HIV-Infected Pregnant Women: NICHD P1091

INTRODUCTION

You are being asked to take part in this study because you have the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS); are pregnant; and are on Highly Active Antiretroviral Therapy (HAART). The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports this study. The doctor in charge of this study at this site is: (insert name of Principal Investigator). We want you to know more about the study before you decide if you want to be a part of it.

This consent form will help you learn about this study. You are free to ask the study staff questions about this study at any time. If you agree to be in this study and let your baby take part in this study, you will be asked to sign this consent form. You will get to keep a copy for your records.

Before you decide if you want to be in this study, you should know that:

- You decide to be part of this study.
- Your baby will be part of this study once you deliver.
- You can stop being in this study **at any time** and this will not affect your or your baby's health care at the clinic (or any other benefits she/he might have).

WHY IS THIS STUDY BEING DONE?

You are being asked to take part in this study about vaccines that may keep you safe from a bad infection known as pneumococcal disease. The disease is caused by a germ (bacterium) and can affect your lungs (causing pneumonia) and brain (causing meningitis). The disease can be very bad and cause people to die. Babies and children can get this disease, too. You can help keep yourself safe from pneumococcal disease with the use of vaccines.

This study will compare two kinds of pneumococcal vaccines with a harmless saltwater shot that looks the same as the vaccine but does not do anything to fight any germs (placebo). These vaccines have been safely used in Brazil. The names of the vaccines are PPV-23 and PCV-10. We are looking at whether there are more side effects by getting the vaccine when you are pregnant. We are also looking at whether the levels of antibodies (your blood's ability to fight germs) in response to the vaccine are as high if you get the vaccine in pregnancy compared to several months after delivery. Getting the vaccine during pregnancy may also increase the antibodies passed to the baby and help protect the baby from pneumococcal infections before they can get the shots themselves. Researchers need to learn more about this.

This study could help doctors make better decisions about giving pneumococcal vaccines to HIV-infected women when they are pregnant.

Doctors will take care of you and your baby to make sure that you do not get sick from the pneumococcal germs during this study. If you do get sick from any germs, you will be given medicine.

LEARNING HOW THESE VACCINES MAY HELP WOMEN SUCH AS YOURSELF

Researchers have learned about PPV-23 and PCV-10 in a lot of people, including pregnant women, people with HIV and people who do not have HIV. This is the first study that looks at PPV-23 and PCV-10 in pregnant women with HIV. Also, this is the first time that PCV-10 will be given to pregnant women with HIV, although a similar vaccine, PCV-9, has been given to pregnant women with HIV. The researchers want to study PCV-10 in pregnant women with HIV because it may work better than PPV-23.

The United States Food and Drug Administration (FDA) and the United States Centers for Disease Control and Prevention (CDC) said that adults and pregnant women with HIV should get the PPV-23 vaccine. Early PPV-23 research shows that it helps these people from getting sick.

The other vaccine, PCV-10, is considered safe to use in children who have and do not have HIV. Different groups including the FDA, CDC, the World Health Organization (WHO), and the Brazilian Ministry of Health agree on the vaccine's safety.

At the end of the study, the researchers will let you know the level of antibodies that you had before and after vaccination and if the vaccine increased your antibodies. They will also let you know the level of antibodies in your baby.

KEEP TAKING YOUR HAART MEDICATIONS DURING THE STUDY

You will need to take your medicine to fight your HIV, and you need to take all your medicine so your HIV does not get worse when you get the PCV-23 or PCV-10 vaccine; if your HIV virus gets worse, you may give your baby HIV.

You will be randomly given either PPV-23, or PCV-10, or a harmless salt water shot (placebo) that looks the same as the vaccine but does not do anything to fight any germs. After you have your baby, if you received the saltwater shot during pregnancy, you will get PPV-23 or PCV-10. By the end of the study, all women will get PPV-23 or PCV-10, but you will not know which one you got until the end of the study. All babies will get PCV-10.

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

If you agree to be in this study, you will be asked some questions. By being in this study, you are also telling us that your baby can be in this study.

FOR YOU:

Screening Visit (while you are pregnant):

After you read and sign this consent form, you will have the following done at the screening visit to see if you can be in the study:

- You will be asked questions about your medical history and how often you take your anti-HIV medications.
- You will be asked if the research team can look at your medical records.
- You will have a physical exam that will look at your height, weight, blood pressure and heart rate. Your doctor may decide that you need more exams.
- You will have 1 mL (about ¼ teaspoon) of blood taken:
  - For regular blood tests.
- This visit will take about 30 minutes.

Week 0 (Entry - Day 0, day of vaccine or placebo application) (while you are pregnant):

Note: This visit may occur on the same day as the screening visit.

Once it is known that you can be in this study, you will have an entry visit. You will be assigned by chance, as if by the toss of a coin, to receive either PPV-23, or PCV-10, or a harmless saltwater shot (placebo). You have a 1 in 3 chance of receiving the placebo. Neither you nor your doctor will know whether you are receiving PPV-23, PCV-10, or the placebo.

At this visit:

- You will be asked questions about your medical history and how often you take your anti-HIV medications.
- You will have a physical exam (like the one you had during the screening visit).
- We will check your baby's heart rate before and about 30-60 minutes after you receive the vaccination.
- You will be given one dose of the vaccine with a needle in your upper arm.
- You will remain in the clinic for about 30-60 minutes after receiving the vaccine to make sure that you are safe after getting the vaccine and to check your baby's heart rate.
- We will quickly put a swab into your nose, and will take a second swab from across the back of your throat to get samples. We will test these samples to see if you have the pneumococcus germ.
- You will be given a piece of paper (called a home record/diary card) that tells you what could happen. You will be asked to write down anything strange that you feel on this home record/diary card.
- You will have7 mL (about 1.5 teaspoons) of blood taken:
  - To measure how much HIV is in your blood.
  - To measure how your body is responding to HIV.

  - You may be asked to have about 20 mL (about 4 teaspoons) of blood taken for special blood tests to see if your body can protect yourself from the pneumococcus germ. You may decide not to have this additional blood drawn. If you decide that this additional blood may be drawn, but you are not one of the first 150 people enrolled, no additional blood will need to be taken. If you decide not to have this blood drawn, this will not affect your clinical care and study participation.
- This visit will take about 2 hours.

Week 1 - Study Day 7 to 10 (while you are pregnant):

At this visit:

- You will be asked questions about your medical history and how often you take your anti-HIV medications.
- You will have a physical exam to see if your body has reacted to the vaccine.
- You will review your home record/diary card with the study staff.
- This visit will take about 30 minutes.

Week 4 - Study Day 28 to 35 (while you are pregnant):

At this visit:

- You will review your home record/diary card with the study staff.
- You will have 28 mL (about 5-6 teaspoons) of blood taken:
  - For routine blood tests.
  - To measure how much HIV is in your blood.
  - To measure how your body is responding to HIV.
  - For special blood tests to see if your body can protect yourself from the pneumococcus germ.
- This visit will take about 30 minutes.

Labor/Delivery Visit (while you are pregnant):

This study visit will be when you come to the hospital to have your baby.

At this visit:

- You will be asked questions about your medical history and how often you take your anti-HIV medications.
- Like before, we will use swabs to collect samples from your nose and throat. We will test these samples to see if you have the pneumococcus germ.
- You will have 2 mL (about ½ teaspoon) of blood taken:
  - For special blood tests to see if your body can protect yourself from the pneumococcus germ.

24-Week Post-Delivery Visit (for you):

At 24 weeks (about 6 months after you have your baby), you will be asked to come back to the clinic.

At this visit:

- You will be told if you got the vaccine or the harmless salt water shot (placebo) during pregnancy.
- You will be asked questions about your medical history and how often you take your anti-HIV medications.
- You will have 2 mL (about ½ teaspoon) of blood taken:
  - For special blood tests to see if your body can protect yourself from the pneumococcus germ.
- This visit will take about 30 minutes.

If you received a real vaccine during pregnancy, this **will be your last visit.**

If you received the harmless salt water shot (placebo) during pregnancy, you will be offered enrollment into step 2 of the study.

Step 2 - Entry (Day 0, day of vaccine application for women who received placebo) on the same day or within 10 days of the 24-Week Post-Delivery Visit:

Note: This visit may happen on the same day of the 24-week post-delivery visit.

At this visit:

- You will have a physical exam and you will be asked a few questions. A pregnancy test will be performed.
- If you are NOT pregnant and are not taking any medication that may interact with the study vaccine:
  - You will be assigned by chance, as if by the toss of a coin, to receive PCV-10 or PPV-23. The vaccine will be injected into your arm. Neither you nor your doctor will know which vaccine you will receive.
  - You will have 25 mL (about 5 teaspoons) of blood taken:
    - To measure how much HIV is in your blood.
    - To measure how your body is responding to the HIV virus.
    - For special blood tests to see if your body can protect yourself from the pneumococcus germ.
- If you are pregnant, and are not receiving any medication that may interact with the study vaccine:
  - You will receive PCV-10 so you can be protected by the vaccine.
  - This will be your last study visit.

- You will remain in the clinic for at least 30 minutes after the shot to make sure you are safe from the vaccine.
- This visit will take about 1 hour.

Step 2 - Week 4 (28 days after Day 0, day of vaccine application for women who received placebo):

At this visit:

- You will be asked questions about your medical history and how often you take your anti-HIV medications.
- You will have 22 mL (about 4-5 teaspoons) of blood taken:
  - For special blood tests to see if your body can protect yourself from the pneumococcus germ.
- This visit will take about 30 minutes.

Unscheduled Visit:

At the beginning of the study, you will be asked to write down anything strange that happens to your body on a home record/diary card. At any time during the study, if you feel like something strange is happening to your body, you will be asked to come in to the clinic within 72 hours.

At this visit:

- You will be asked questions about your medical history and how often you take your anti-HIV medications.
- You will have a physical exam.
- You will be taken care of by your doctor/ physician (care provider).

Invasive Pneumococcal Disease (IPD) Visit:

If, during the study, you or your baby gets sick and has to stay in the hospital, you will be asked to tell your study nurse as soon as possible. If the reason for your or your baby's hospitalization was a bad infection with the pneumococcus germ, you will be asked to come to the clinic as soon as possible. We can do this visit while you are at the hospital.

At this visit:

- You will be asked questions about your or your baby's medical history.
- You or your baby will have a physical exam.
- You or your baby will get care from your or your baby's doctor based on your or your baby's needs and local standards.

- If possible, we will get a sample from the hospital that was used to tell if you have a bad infection with the pneumococcus germ. This sample will be used for study-related tests. We will not repeat any tests, and it will not cause more discomfort for you or your baby.

Early Study Discontinuation Visit:

If you no longer want to be in this study, or no longer can be in this study, you will be asked to come to the clinic one last time. If this visit occurs after your baby was born, we will ask you to bring your baby to the visit.

At this visit:

- You will be asked questions about your medical history and how often you take your anti-HIV medications.
- You will review your home record/diary card with the study staff.
- This visit will take about 1 hour.

FOR YOUR BABY: If you agree to take part in this study, your baby will be in this study.

Week 0 (Day 0 - in the first hours after birth, before your baby receives hospital discharge, or within 7 days of birth):

At this visit:

- Your baby will have a physical exam including height, weight, head size, test to see if your baby needs any emergency care (Apgar score), and vital signs.
- Your baby will have 5 mL (about 1 teaspoon) of blood taken:
  - To check if your baby's blood is protected from the vaccines you received.
- This visit will take about 1 hour.

Week 8 (When your baby is 2 months of age and before he/she receives the first dose of PVC-10):

This visit will happen within 7 days before your baby receives the first dose of PCV-10. At this visit:

- All babies will receive PCV-10 per local standard of care.
- We will collect swab samples from your baby's nose and throat. We will test these samples to see if your baby has the pneumococcus germ.
- Your baby will have 2 mL (about ½ teaspoon) of blood taken:
  - To check if your baby's blood is protected from the vaccines you received.
- This visit will take about 1 hour.

Week 16 (When your baby is 4 months of age and before he/she receives the second dose of PVC-10):

This visit will happen within 7 days before your baby receives the second dose of PCV-10. At this visit:

- As done before, we will collect swab samples from your baby's nose and throat. We will test these samples to find out if your baby has the pneumococcus germ.
- Your baby will have 2 mL (about ½ teaspoon) of blood taken:
  - To check if your baby's blood is protected from the vaccine they received at 2 months.
- This visit will take about 1 hour.

Week 24 (When your baby is 6 months of age and at least 28 days after your baby receives the 2nd dose of PCV-10):

This visit will happen 28 days or longer after your baby receives the second dose of PCV-10. At this visit:

- Your baby will have 7 mL (about 1 teaspoon) of blood taken:
  - To check if your baby's blood is protected from the vaccine they received at 4 months.
- This visit will take about 1 hour.

TESTING AND STORAGE OF BLOOD SAMPLES

Some of your and your child's blood samples will be shipped to specialized laboratories in Brazil and outside of Brazil for testing.

About 20 mL (about 4 teaspoons) of blood will be taken from the first 150 women enrolled in Step 1 for special blood tests to see if your body can protect yourself from the pneumococcus germ.

Also, some of your and your baby's blood that is left over after the study will be stored in a special laboratory in the United States (Fisher Bioservices Laboratory) for possible future use in HIV-related research. Researchers will not collect any extra samples for future research. They will only use what they already have. These samples sent to the United States will not have your or your baby's name. The samples will have a special code, the same as the code that you and your baby received for the study, called a Participant Identification (PID) number. The documents that permit researchers to link this code to your and your baby's information will be kept in a safe place in the research center, away from your and your baby's medical charts. By doing this, you and your baby will be protected.

The only people who will see your and your baby's stored samples are researchers and people who work at the facility and keep track of the samples. None of them will have information that tells them it is you and your baby. Your and your baby's samples will not be sold or used to make commercial products.

If a researcher wants to do a new study with your and your baby's samples, they will ask for permission from NICHD. They will make sure you and your baby will be kept safe and will also need permission from the sites' Institutional Review Board (IRB), the Ethics Committee of XXXX. Also, the Brazilian National IRB Comissão Nacional de Ética em Pesquisa (CONEP) will review this study to make sure that the study remains safe. An IRB is a committee that watches over the safety and rights of research subjects.

According to the rules, your and your baby's samples will be kept for up to 5 years. If the study wants to keep your samples for more time, the researchers must be asked and provide a report that tells about what has been done with the samples.

Your and your baby's samples will be used only when a researcher has a new study. We do not know when this will be, but you have the right to know what has been done with your and your baby's samples and the results of testing when there is important information to share about your and your baby's health and medical care. Your local IRB will decide if you need to know the results of testing or the new study findings. To get this information, you must tell the study staff of any changes in your address or phone number.

There is a small risk that someone may use your or your baby's samples or information wrongly. For example, someone could find out which test results are yours and use this information to harm you and this could cause problems for you. For this to happen, the person would have to get into a database that has results with your name. To prevent this from happening, researchers protect this by limiting access to databases, not linking names to results, and not placing results in medical records.

There will be no direct benefit to you or your baby from future research using your or your baby's stored samples and information. However, the information learned may help others. It may take the researchers many years to have any results. In most cases, you will not receive future research results from the researchers.

There is no cost to you or your baby for allowing researchers to use your samples and information for future research.

You and your baby will not receive any money to let researchers use your or your baby's samples and information for future research. However, some research may lead to new things, such as new medicines or tests. You and your baby will not receive any money from these new medicines or tests.

You may decide that you do not want your and your baby's samples to be stored for future research studies. You and your baby can still participate in this study even if you make this decision.

You may decide that you do not want to let your and your baby's samples be used anymore. If you decide you do not want these to be used anymore, the samples will be destroyed.

Please read the following statement carefully and then mark your initials in the appropriate space provided.

I agree to allow my blood samples and my baby's blood samples to be stored for use in future NICHD-approved, HIV-related research studies and by the Brazilian agencies of Administrative and Ethics regulation.

_____ Yes _____ No ___/___/_____ Date

OTHER INFORMATION

When the study is over and all the information has been looked at, you will be told by your study staff what vaccine you got and how well this vaccine did. You will be given the results of your tests. The results of special laboratory tests (to test your immune response to the vaccine) might be provided to you or your doctor, if requested by your doctor. Some of your blood and nose and throat samples will be sent to the United States for testing.

The information from this study may be used for other HIV research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 345 women and their babies will take part in this study.

HOW LONG WILL I/MY BABY BE IN THIS STUDY?

You will be in this study for up to 60 weeks (about 28 weeks before you have your baby and 32 weeks after you have your baby), and your baby will be in this study for up to 28 weeks.

WHY WOULD THE DOCTOR TAKE ME/MY BABY OFF THIS STUDY EARLY?

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

- The study is stopped by the United States NICHD, the Office for Human Research Protections (OHRP), the site's IRB, CEP-XXXXXX, or the Brazilian National IRB CONEP.
- A Safety Monitoring Committee (SMC) recommends that the study be stopped early. An SMC is group of people that makes sure the study is safe.
- You and your baby are not able to come to the study visits.

The study doctor may also need to take you and your baby off the study product(s) without your permission if:

- Continuing the study vaccine may be harmful to you or your baby.
- You and your baby need a treatment that you and your baby may not take while on the study.
- You and your baby are not able to take the vaccines as required by the study.

During the study:

If your baby needs to stop taking the PCV-10 before the study is over, the study staff will talk about other choices for you and your baby. The study doctor may ask you to let your baby be part of the study and come back for some study visits and tests.

WHAT ARE THE RISKS OF THE STUDY?

This study may involve risks to you or your baby which are not known. You or your baby may feel faint or may feel some pain while having blood taken. There may be some tenderness, swelling, bleeding, or bruising where the needle goes into the skin, or a small blot clot may develop. There is a small risk of getting an infection where the needle goes into the skin to take blood.

Risks Related to the Vaccines (PPV-23 or PCV-10):

A vaccine, like any medicine, could cause a serious reaction. But the risk of a vaccine causing serious harm, or death, is extremely small. If reactions do occur, it will be within a few minutes to a few hours after the vaccination. Please also reference the participant information sheet you will receive from the study staff about the vaccines.

PPV-23:

About half of the people who get PPV-23 have mild side effects, such as redness or pain where the shot is given. Less than 1% of people develop a fever, muscle aches, or more severe problems.

People who receive a 2nd dose of PPV-23 less than 5 years after the 1st dose may have less protection from the 2nd dose of vaccine.

PCV-10:

Some adults who receive PCV-10 may develop pain in the arm, fever, or malaise. No serious problems have happened from this shot.

Placebo:

Women who get the vaccine during pregnancy may prevent infection caused by the pneumococcus germ or lessen their symptoms if they get infected, but if they get a placebo (harmless saltwater shot) this may not happen until later.

ARE THERE RECOMMENDATIONS RELATED TO THE STUDY?

The Brazilian rules say that it is HIV-infected adults' choice to decide whether or not to get the PPV-23 vaccine to prevent infections caused by the pneumococcus germ. They rely on their doctors to help them decide. There are no specific recommendations for HIV-infected Brazilian pregnant women.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you and your baby take part in this study, there may be a benefit to you and your baby, but no promise can be made. You may prevent infection caused by the pneumococcus germ or lessen your symptoms if you get infected.

You and your baby may receive no benefit from being in this study. It not known whether these vaccines will increase or decrease your baby's risk of HIV infection, even if you and your baby are on medications to prevent HIV. This study may help others who have HIV.

WHAT OTHER CHOICES DO I/DOES MY BABY HAVE BESIDES THIS STUDY?

Instead of being in this study, you may choose to receive PPV-23 outside of the study. PPV-23 is available from the Ministry of Health. If you choose to receive PPV-23 outside of this study, your doctor will give you the vaccine if it is available in his/her office or will give you a prescription for this vaccine and inform you how to fill it.

Please talk to your doctor about these and other choices available to you and your baby. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

The doctors and research staff will work to keep your and your baby's information confidential/private. Your and your baby's information will be replaced by a random number called a code. Anything written/published about this study will not use your or your baby's name.

Your and your baby's information may be looked at (without disclosing your or your baby's name) by groups in the United States such as the OHRP and the NICHD, the site IRB (HCFMRP-USP), study staff, study monitors, and drug companies working on the study, when agreed on by the doctors and site staff, and in compliance with the Code of Ethics of the Federal Counsel of Medicine and Brazilian laws that protect study participants.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME/MY BABY? WILL I/MY BABY RECEIVE ANY PAYMENT?

There are no costs to you and your baby for the study vaccine, study visits, or study procedures. You and your baby will not receive any form of payment to take part in this study. You and your baby will receive a ticket for travel and a meal ticket for coming to the study visits at no cost to you.

WHAT HAPPENS IF I AM/MY BABY IS INJURED?

If you or your baby are hurt from this study or due to the study vaccines, you or your baby will be taken care of with no costs to you. This care is promised by the Principal Investigator (PI) at the HCFMRP-USP. You will not be paid any money through the National Institute of Health (NIH), which is the main sponsor of this study. If necessary you will receive help for your baby's health if he or she is injured during the study, for how long it is needed, as well as payment for these problems. The research site has insurance to cover costs. You will not be giving up any of your or your baby's legal rights by signing this consent form.

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH SUBJECT?

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

We will tell you about new information from this or other studies that may affect your and your baby's health or your choice to stay in this study. Your decision will not affect whether or not you can be in other studies by the NICHD and will not take any of your benefits away. If you want the results of this study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

For questions about your and your baby's rights as a research subject, contact:

SIGNATURE PAGE – NICHD P1091
AUTHORIZATION FOR ACCESSING DATA FROM RESEARCH PARTICIPANT MEDICAL CHART.

During your AND your baby's participation in the study, the responsible researcher will need to have access to your medical data recorded in the charts. For this, we require that you also allow the researcher to access these data; marking the box below if this is your decision.

I authorize the study investigator to have access to my and my baby's medical data contained in the medical charts.
( ) **Yes** ( ) **No**

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

Participant's Name (print)	Participant's Name (signature)	Date
Participant's Mother or guardian (print)	Mother or guardian (signature)	Date
Father's Name (print) (If father's consent is required)	Father's Name (signature) (If father's consent is required)	Date
Participant's Legal Guardian (print)	Legal Guardian's (signature)	Date
Study Staff Conducting (print)	Study Staff (signature)	Date
Consent Discussion (print)	Consent Discussion (signature)	Date
Witness's Name (print)	Witness's Name (signature)	Date