Official Protocol Title:	A Phase I-II, Randomized, Double-Blind, Study to Evaluate the Safety, Tolerability, and Immunogenicity of Different Formulations of V114 in Healthy Adults and Infants
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TITLE:

A Phase I-II, Randomized, Double-Blind, Study to Evaluate the Safety, Tolerability, and Immunogenicity of Different Formulations of V114 in Healthy Adults and Infants

IND NUMBER: 14115
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
6.0 7.1.2.1	Trial Flow Chart Physical Examinations	For the Infant Cohort, a full physical examination will be performed at Visit 1 and a targeted physical examination will be performed at all subsequent vaccination visits (Visits 2, 3, and 5). Physical examinations at these time points in the infant cohort are no longer optional, per investigator's discretion.	Revision
2.1 4.3 5.6	Trial Design Benefit/Risk Rescue Medications & Supportive Care	Include an additional criterion for rescue dose: pneumococcal IgG antibody, as measured by Pn ECL assay, below 0.35 µg/mL for serotype 19A.	New Addition

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.1.3	Ongoing Clinical Trials	Added V114-006 as an ongoing clinical trial.	New Addition
5.1.2	Subject Inclusion Criteria	Infant Cohort, Inclusion Criterion #1: removed "if warranted" as physical examination is mandatory at Visit 1.	Clarification
8.6.1	Statistical Methods for Efficacy Analyses	Added a sentence clarifying that RCDCs will be included in the CSR.	Clarification
9.1	Investigational Product	Removed text related to clinical supplies for replacement subjects and other supplies.	Clarification
Overall	Overall	Minor editorial edits have been made in various sections throughout the protocol.	Revisions

1.0 TRIAL SUMMARY

Abbreviated Title	Safety/Immunogenicity of Different Formulations of V114
Sponsor Product Identifiers	V114
Trial Phase	I-II
Clinical Indication	Prevention of Pneumococcal Disease
Trial Type	Interventional
Type of control	Active Control
Route of administration	Intramuscular
Trial Blinding	Double-blind
Vaccination Groups	Vaccine groups for V114 recipients are represented as V114 medium or V114 high as they respectively refer to the concentration of polysaccharide for each of the vaccine serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) and Merck Aluminum Phosphate Adjuvant (MAPA). V114 medium contains capsular polysaccharides at 2µg/dose for all serotypes except 6B at 4µg/dose formulated with MAPA at 125µg/dose. In comparison, V114 high contains twice the amount of polysaccharide for each serotype (4µg/dose for all serotypes except 6B at 8µg/dose) and MAPA (250µg/dose). The investigational 15-valent pneumococcal conjugate vaccine containing all 15 serotypes conjugated to the same carrier protein (CRM_{197}) will be simply referred to as V114 while the investigational 15-valent pneumococcal conjugate vaccine containing at least one serotype conjugated to an alternative carrier protein and the remaining serotypes conjugated to CRM_{197} will be referred to as V114 with an alternative carrier protein. Stage 1 - Adult Cohort: Four (4) groups randomly assigned to receive a single dose of either V114 medium, V114 high, V114 medium with an alternative carrier protein, or V114 high with an alternative carrier protein. Stage 2 - Infant Cohort: Five (5) groups randomly assigned to receive either V114 medium, V114 high, V114 medium with an alternative carrier protein, V114 high with an alternative carrier protein, or Prevnar 13™ (control group). (See section 5.2 for a detailed description of the V114 formulation).
Number of trial subjects	Approximately 80 adult and 250 infant subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 21 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	*Stage 1 - Adult Cohort:* Each subject will participate in the trial for approximately 30 days from the time the subject signs the Informed Consent Form (ICF) through the final contact. Each subject will receive a single dose of the study vaccine on Day 1. After vaccination, each subject will be followed for 14 days for adverse experiences (AEs). Serious AEs (SAEs) will be collected from the time the consent is signed through completion of the subject's participation in the study (i.e., 30 days postvaccination). Blood samples will be collected prior to vaccination and 30 days postvaccination.

	Stage 2 - Infant Cohort: Each subject will participate in the trial for approximately 11 to 14 months from the time the parent/legal guardian signs the ICF through the final contact. Each subject will receive 4 doses of the study vaccine given at 2, 4, 6, and 12 to 15 months of age. After each vaccination, the study subject will be followed for 14 days for AEs. SAEs will be collected from the time the consent form is signed through 30 days postdose 4 (PD4) and/or completion of the subject's participation in the study. Blood samples will be collected 30 days following the 3rd dose, immediately prior to the 4th dose, and 30 days following the 4th dose.
Randomization Ratio	Stage 1 (adult cohort): 1:1:1:1 Stage 2 (infant cohort): 1:1:1:1:1

A list of abbreviations used in this document can be found in Section 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, randomized, double-blind (with in-house blinding procedures) study to evaluate the safety, tolerability, and immunogenicity of 4 different formulations of V114 in healthy adults and infants to be conducted in conformance with Good Clinical Practices (GCPs) at approximately 24 sites in the United States (US). Prevnar 13™ (pneumococcal 13-valent conjugate vaccine [diphtheria CRM_{197} protein], Wyeth Pharmaceuticals, Inc., Philadelphia, Pa) will serve as an active control in the infant stage of the study. This study will enroll approximately 80 healthy adults 18 to 49 years of age (Stage 1) and 250 healthy infants 6 to 12 weeks (≥42 to ≤90 days) of age (Stage 2). Prior to enrollment of infants, the safety and tolerability of a single-dose of the study vaccine must be demonstrated in healthy adults. Similarly, the safety and tolerability of the first dose of study vaccine must be demonstrated in a small cohort of infants prior to enrollment of the full infant cohort.

Stage 1 - Adult Cohort:

A total of 80 adult subjects will be randomly assigned to 1 of 4 formulations of V114:

(1) Merck investigational V114 medium (N=20)

(2) Merck investigational V114 high (N=20)

(3) Merck investigational V114 medium with an alternative carrier protein (N=20)

(4) Merck investigational V114 high with an alternative carrier protein (N=20)

The adult stage of this study is designed to evaluate the safety and tolerability of a single dose of 4 different formulations of V114 when administered intramuscularly to 80 healthy adults (20 per vaccination group).

Adverse events will be collected for 14 days following vaccination. After completion of a review of safety data from the adult cohort by an external Data Monitoring Committee (eDMC), Stage 2 of the study will begin.

Stage 2 - Infant Cohort:

Stage 2 will consist of 2 parts (Part I and Part II) during which a 0.5mL intramuscular dose of the study vaccine will be administered to healthy infants at 2, 4, 6, and 12 to 15 months of age. Each formulation of V114 will be first evaluated in a small number of infants (n=50) during Part I before initiating Part II which will enroll the remaining 200 infants. Prevnar 13™ will serve as control in both Part I and Part II.

Part I will involve 50 healthy infants (10 infants/group) who will be randomly assigned to receive 4 doses of 1 out of 4 different formulations of V114 or Prevnar 13™. Safety data following the first dose [Postdose 1; (PD1)] will be reviewed by the eDMC prior to initiation of Part II. In Part II, an additional 200 healthy infants (40 infants/group) will be enrolled into the trial.

In Part I and Part II, infants will be given either:

(1) V114 medium

(2) V114 high

(3) V114 medium with an alternative carrier protein

(4) V114 high with an alternative carrier protein

(5) Prevnar 13™

(See Section 5.2 for a detailed description of the V114 formulations).

The safety and tolerability profiles of the different formulations of V114 and procedures within the clinical trial will be carefully monitored throughout the study by the SPONSOR in accordance with standard procedures and also by the eDMC. For this Phase I/II study, a Merck Research Laboratories (MRL) statistician and a MRL statistical programmer assigned to the protocol will be unblinded throughout the duration of the study to allow for timely review of the interim safety data by the eDMC. All personnel directly involved with the conduct of this trial will remain blinded to the subject's treatment assignment until medical/scientific review of all safety and immunogenicity data has been performed, protocol deviations have been identified, and data have been declared final and complete. Any study subject from Stage 2 (infant cohort) with serotype-specific anti-pneumococcal IgG (as measured by pneumococcal electrochemiluminescence [Pn ECL] assay) below 0.35µg/mL for serotype 19A (individually) and/or 4 or more serotypes in common with Prevnar 13™ at 1 month Postdose 3 (PD3) will be offered an additional dose of licensed pneumococcal conjugate vaccine outside of this protocol. See Section 5.6 Rescue Medications & Supportive Care for additional details of the rescue plan.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1 and Figure 2

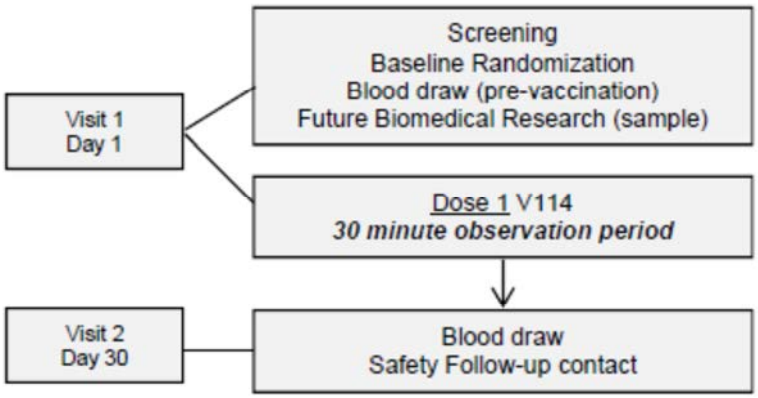

Figure 1 Trial Design of Stage 1 (Adults)

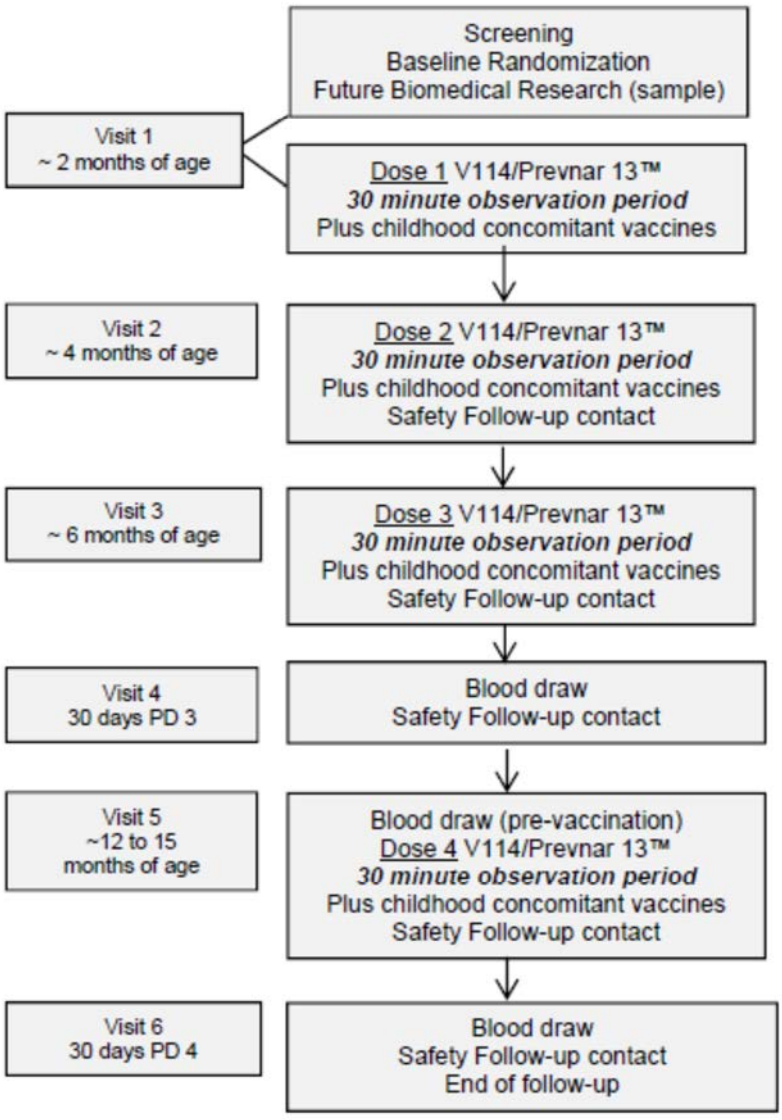

Figure 2 Trial Design of Stage 2 Parts I and II (Infants)

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

No hypothesis testing will be performed.

For Stage 2 (Infants ONLY), the primary and secondary objectives in Section 3.0 will address the safety and immunogenicity (as measured by IgG) of 2 different formulations of V114 (medium and high as related to their contents in polysaccharide and adjuvant) containing the same carrier protein for all 15 serotypes in the vaccine, and Prevnar 13. The

exploratory objectives will address the safety and immunogenicity (as measured by IgG) of 2 additional formulations of V114 (medium and high as related to their contents in polysaccharide and adjuvant) containing an alternative carrier protein for at least one of the 15 serotypes in the vaccine, as well as the opsonophagocytic activity (OPA) from all vaccination groups (4 different formulations of V114 and Prevnar 13), as measured by multiplexed OPA [MOPA-4] assay.

Stage 1 - *(Adults ONLY)*

1. To evaluate the safety profile of a single dose of V114 with or without an alternative carrier protein.

Stage 2 - *Parts I and II (Infants ONLY)*

1. To evaluate the safety and tolerability profiles following receipt of each dose and across all doses of V114 medium, V114 high, and Prevnar 13™ when administered as a 4-dose regimen to healthy infants at 2, 4, 6, and 12 to 15 months of age.

2. To evaluate the serotype-specific IgG geometric mean concentrations (GMCs) of V114 medium, V114 high, and Prevnar 13™, and the IgG GMC ratios between each of these V114 formulations and Prevnar 13™ for the 13 common serotypes at 1 month postdose 3.

3.2 Secondary Objective(s) & Hypothesis(es)

Stage 1 - *(Adults ONLY)*

1. To evaluate the serotype-specific IgG GMCs and fold-rises from baseline of V114 medium and V114 high at 1 month postvaccination.

Stage 2 - *Parts I and II (Infants ONLY)*

1. To evaluate the serotype-specific IgG response rates of V114 medium, V114 high, and Prevnar 13™, and the differences in IgG response rates between each of these V114 formulations and Prevnar 13™ for the 13 common serotypes at 1 month PD3, pre-dose 4, and 1 month PD4.

    - Serotype-specific IgG response rates will be based on the proportion of recipients of V114 and Prevnar 13™ achieving the World Health Organization (WHO)-accepted threshold value of 0.35µg/mL using the Pn ECL assay for each V114 formulation and Prevnar 13™.

2. To evaluate the serotype-specific IgG GMCs of V114 medium, V114 high, and Prevnar 13™, and the IgG GMC ratios between each of these V114 formulations and Prevnar 13™ for the 13 common serotypes at pre-dose 4 and 1 month PD4.

3.3 Other Objectives (Exploratory Objectives)

Stage 1 - *Adults Only*

1. To evaluate the serotype-specific IgG GMCs of V114 medium with an alternative carrier protein and V114 high with an alternative carrier protein at 1 month postvaccination.

Stage 2 – *Infants Only*

1. To evaluate the safety and tolerability profiles following receipt of each dose of V114 medium with an alternative carrier protein and V114 high with an alternative carrier protein when administered as a 4-dose regimen to healthy infants at 2, 4, 6, and 12 to 15 months of age.

2. To evaluate the serotype-specific IgG responses of V114 medium with an alternative carrier protein and V114 high with an alternative carrier protein, and the differences in IgG response rates/GMC ratios between each of these V114 formulations and Prevnar 13™ for the 13 common serotypes at 1 month PD3, pre-dose 4, and 1 month PD4.

    - Serotype-specific IgG responses will be based on the GMCs, the proportion of recipients of V114 with an alternative carrier protein achieving the WHO-accepted threshold value of 0.35µg/mL using the Pn ECL assay for each V114 formulation, and IgG GMC ratios between each V114 formulation with an alternative carrier protein and Prevnar 13.

3. To evaluate the effects of different pneumococcal polysaccharide/MAPA concentrations and use of an alternative carrier protein on serotype-specific GMCs measured at 1 month PD3 across the different formulations of V114.

4. To describe the proportions of subjects with OPA titer ≥8 and OPA geometric mean titers (GMTs) in all vaccination groups for the 13 common and 2 non-common serotypes between V114 and Prevnar 13™ at 1 month PD3, pre-dose 4, and 1 month PD4.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on V114.

4.1.1 Pharmaceutical and Therapeutic Background

The investigational Merck pneumococcal conjugate vaccine (hereafter referred to as V114) is a 15-valent vaccine that contains all of the pneumococcal polysaccharide conjugates in Prevnar 13™ (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F), plus 2 additional

serotypes (22F, 33F). The serotypes contained in V114 will provide broad coverage of the leading serotypes associated with pneumococcal disease worldwide. The vaccine is designed to meet continuing medical and public health needs for pneumococcal conjugate vaccines globally as well as to address the emergence of pneumococcal disease caused by serotypes not contained in Prevnar™ (pneumococcal 7-valent conjugate vaccine [diphtheria CRM_{197} protein], Wyeth Pharmaceuticals, Inc., Philadelphia, Pa) and Prevnar 13™ or other late-stage investigational pneumococcal conjugate vaccines. The serotype composition of V114 was based on the need to maintain coverage of the serotypes included in Prevnar 13™, and to add serotypes guided by current epidemiology data and emerging trends.

Streptococcus pneumoniae is a major cause of morbidity and mortality worldwide, and causes the deaths of 0.7 to 1 million children <5 years of age, mostly in developing countries [1]. Starting in 2000, Prevnar™ was introduced into national childhood vaccination schedules in the US, European Union (EU), and several other countries. According to the US pediatric vaccination schedule, the vaccine is administered to infants in a 3-dose infant series (2, 4, and 6 months of age), followed by a fourth dose at age 12 to 15 months. Widespread use of the vaccine has led to a significant reduction in invasive pneumococcal disease (IPD), pneumonia and otitis media caused by the 7 serotypes contained in the vaccine [1]. Use of the vaccine in children has also been shown to lower the prevalence of IPD caused by the vaccine serotypes in the non-vaccinated population via herd protection. Prevnar 13™ was approved in the EU in 2009, the US in 2010, and subsequently in other countries worldwide. The vaccine is licensed globally as Prevnar 13™ and Prevenar 13™, and in this protocol the vaccine will be referred to by the name Prevnar 13™. In 2009 a 10-valent pneumococcal conjugate vaccine, Synflorix™ (pneumococcal 10-valent conjugate vaccine [Non-Typeable *Haemophilus influenzae* (NTHi) protein D, diphtheria or tetanus toxoid conjugates], GlaxoSmithKline Biologicals s.a., Rixensart, Belgium) was licensed in Europe and other countries worldwide. Synflorix™ contains the serotypes contained in Prevnar™ conjugated to 3 different carrier proteins, plus 3 additional capsular polysaccharide conjugates (serotypes 1, 5, and 7F). This vaccine is not licensed in the US.

Despite these significant advances, serotype replacement remains a concern as new serotypes begin to fill the niche created by the suppression of nasopharyngeal colonization of vaccine serotypes. In particular, serotypes 22F and 33F, the 2 additional serotypes contained in V114 which are not contained in Prevnar 13™, contributed to approximately 1.3% of overall IPD in children under 5 years of age in the US in 1998 [2], but have now been estimated to represent 22.7% of IPD cases in this age group in 2011 (PPD US CDC, personal communication). This phenomenon of serotype replacement substantiates the need for the development of more broadly-based pneumococcal conjugate vaccines and the search for antigens, such as proteins, that are commonly shared among all pneumococcal serotypes.

4.1.2 Pre-clinical and Completed Clinical Trials

Preclinical immunogenicity studies of V114 formulations have been conducted in 2 animal models (refer to the V114 IB).

A first-in-man Phase I study (V114-001) evaluated the safety and immunogenicity of a single dose of V114 in healthy adults and healthy toddlers who had completed a full 3-dose infant series of Prevnar™. A multicenter, randomized, double-blind Phase II trial (V114-003) was conducted to evaluate the safety, tolerability, and immunogenicity of V114 compared to Prevnar 13™ in approximately 1110 healthy infants. Study vaccines in V114-003 were administered concomitantly with other licensed pediatric vaccines routinely given at 2, 4, 6, and 12 to 15 months of age. Subjects were randomly assigned to 1 of 3 vaccination groups (1) V114, aluminum adjuvanted, (2) V114, non-adjuvanted, or (3) Prevnar 13™. Both formulations of V114 generated an immune response to all 15 serotypes contained within the vaccine and displayed an acceptable safety profile (see V114 IB).

4.1.3 Ongoing Clinical Trials

V114-004, a multicenter, randomized, double-blind dose ranging trial is currently being conducted to evaluate the safety and immunogenicity of various formulations of V114 containing different concentrations of polysaccharides and/or MAPA in healthy adults and infants. This study is ongoing and the data remain blinded.

V114-006, a randomized, multicenter, double-blind trial is currently being conducted to evaluate the safety, tolerability, and immunogenicity of a single dose of 2 different formulations of V114 in healthy, pneumococcal vaccine-naïve adults 50 years of age or older. The study is ongoing and the data remain blinded.

4.1.4 Information on Other Trial-Related Therapy

In Stage 2 (infants ONLY) of this study, Prevnar 13™ will be administered as one of the study vaccines, to serve as the active comparator. In addition to the administration of study vaccine (V114 or Prevnar 13™), other pediatric vaccines will be administered concomitantly according to the recommended schedule. These childhood vaccines will be representative of those recommended by the US Advisory Committee on Immunization Practices (ACIP) and are routinely administered at specified time points.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

This study is designed to support formulation optimization of the vaccine for those serotypes that yielded suboptimal antibody responses in a previous clinical trial and to evaluate the clinical performance of a V114 formulation consisting of at least one serotype conjugated to an alternative carrier protein. The vaccine formulations for this study also include a new excipient, Polysorbate 20 (PS20) instead of Poloxamer 188 used in V114-004. PS20 is an acceptable excipient with a good safety profile and will help ensure necessary product stability as well as the manufacturing robustness of the vaccine. Preclinical studies have demonstrated that the use of PS20 results in a vaccine product that is more resistant to the routinely occurring physical stresses of processing, manufacturing, and shipping and does not negatively impact chemical stability or potency of the PCV15 antigen. Also included in this

study is a limited evaluation of dose range with respect to polysaccharide conjugates and MAPA.

This study will aid in the clinical assessment of the impact of conjugated polysaccharide and adjuvant concentration on the safety and immunogenicity of V114. Because of limitations in preclinical models and the uniqueness of the immature immune system of infants, this assessment can only be done adequately by conducting clinical studies in the relevant population, to further inform on the development of the vaccine.

Healthy adults (18 to 49 years of age) will be included in Stage 1, which will assess the safety of a single-dose of 4 different formulations of V114 with or without an alternative carrier protein. Stage 2 will enroll healthy infants at approximately 2 months of age, which is consistent with current recommendation of routine vaccination with pneumococcal conjugate vaccine in early childhood.

4.2.2 Rationale for Dose Selection/Regimen

Polysaccharide Conjugate Concentration:

This study is designed to evaluate the safety and immunogenicity of formulations containing conjugates produced using a modified conjugation process aimed at increasing the number of conjugate bonds. The proposed dose levels of polysaccharide conjugate to be evaluated in the study will be 2µg/dose for each serotype with the exception of serotype 6B (4µg/dose) or 4µg/dose for each serotype with the exception of 6B (8µg/dose). These 2 concentrations of polysaccharides are also being evaluated in the currently ongoing V114-004 trial.

For 2 formulations of V114, all serotypes will be conjugated to CRM_{197}; the remaining 2 other formulations of V114 will consist of up to 14 serotypes conjugated to CRM_{197} and at least one serotype conjugated to an alternative carrier protein. This study will compare the clinical performance of V114 containing 2 different carrier proteins for at least one serotype.

Dose of Aluminum Phosphate Adjuvant:

Two (2) different concentrations of MAPA (125µg/dose and 250µg/dose) will be evaluated in this trial. The lowest concentration was already evaluated in V114-003 and study results showed that V114 formulated with 125µg of MAPA was associated with a small improvement in the magnitude of vaccine-induced antibody responses in comparison to the non-adjuvanted formulation of V114. Importantly, a higher amount of MAPA (250µg/dose) appears to be helpful with stability of the V114 formulation containing higher amounts of polysaccharide. It is anticipated that the doubling of the amount of MAPA in V114 may provide higher levels of serotype-specific antibodies than that induced by V114 containing a lower amount of MAPA. These MAPA concentrations are also being evaluated in the currently ongoing V114-004 trial.

Dosing Regimen:

The dosing regimen is consistent with current recommendations for the administration of licensed pneumococcal conjugate vaccines in infants in many countries worldwide, including the US. A 0.5-mL dose of study vaccine will be administered intramuscularly to healthy adults (single dose) or as a 4-dose series to healthy infants at 2, 4, 6, and 12 to 15 months of age. Pneumococcal vaccine is not currently recommended for routine immunization of healthy adults 18 to 49 years of age.

Rationale for the use of Polysorbate 20:

Polysorbates are non-ionic surfactants and are acceptable excipients used in cosmetics and in parenteral administration of biologics and vaccines. A surfactant is needed in order to reduce potential risk of agitation-induced aggregation associated with physical stresses of processing, manufacturing, and shipping of the vaccine. Both Polysorbate 80 (PS80) and Polysorbate 20 (PS20) have been used in many pediatric and adult vaccines including Prevnar 13™, Infanrix™, Pentacel™, Havrix™, Twinrix™, Fluarix™, and Flubok™. Polysorbate 20 was selected in the formulation of V114 as it was shown to provide satisfactory results and did not negatively impact the chemical stability of the vaccine antigen. A concentration up to 0.2% (w/v) per dose will be used to accommodate the different concentrations of polysaccharide and adjuvant to be evaluated in the study.

Among PS20-containing products administered in infants, an intravenously infused multivitamin (M.V.I. Pediatric®, Hospira, Lake Forest, IL) containing 0.8 mg of PS20 per 5 mL/dose is indicated as daily multivitamin maintenance dosage for infants and children receiving parenteral nutrition weighing as low as less than 1kg. Infants weighing 3kg or more are to receive the full dose of 5 mL which is equivalent to a total dose of up to 0.3 mg/kg of PS20. The administration of such amount of PS20 has been shown to be safe and well-tolerated. This dose is higher than the highest dose of PS20 projected to be used in V114 as 0.2% is equal to an administered dose of 0.2 mg/kg for an infant weighing 5 kg, the mean weight of a 6-8 weeks old infant.

Rationale for the use of an alternative protein carrier:

Previous studies have indicated that levels of serotype-specific antibodies required for protection against IPD vary between serotypes. The induction of a satisfactory response for serotypes requiring high antibody concentrations has been a challenge for many pediatric pneumococcal conjugate vaccines. The use of a different carrier protein with higher content in T helper epitopes than carrier proteins used in licensed PCVs could provide better antibody responses to those measured with currently licensed vaccines (See V114 IB).

4.2.2.1 Rationale for The Use of Comparator

Prevnar 13™ will be used as the comparator for this trial. Prevnar 13™ is currently the recommended vaccine for the prevention of invasive pneumococcal disease in infants.

4.2.3 Rationale for Endpoints

4.2.3.1 Immunogenicity Endpoints

Adult Cohort (Stage 1)

For the adult cohort, serum will be collected at 2 pre-specified time points during the trial:

1) Prevaccination

2) Approximately 30 days postvaccination

Sera will be used for the following measurements in adults:

1. The measurement of serotype-specific IgG using Pn ECL assay.
2. Immunogenicity measurements for the development and validation of future pneumococcal assays.
3. If there are remaining sera after IgG testing, and development of future pneumococcal assays, the leftover sera may be used for Future Biomedical Research (FBR), (Section 4.2.3.3) providing the FBR Informed Consent Form (ICF) has been signed.

In this study, immunogenicity objectives for the adult cohort are not tested as primary objectives; they are evaluated as secondary and exploratory objectives.

Infant Cohort (Stage 2 - Parts I and II)

For the infant cohorts, serum will be collected at 3 pre-specified time points during the trial:

1) Approximately 30 days PD3

2) Pre-dose 4

3) Approximately 30 days PD4

Sera will be used for the following measurements:

1. IgG responses measured using the Pn ECL assay for the study objectives.
2. Functional antibody activity, OPA, will be measured using the MOPA-4 assay in the first 50% of infant subjects who have sufficient serum volume at PD3 to perform both the PnECL and MOPA-4 assays.
3. Immunogenicity measurements for the development and validation of future pneumococcal assays.

4. If there are remaining sera after IgG testing, OPA testing, and development of future pneumococcal assays, the leftover sera may be used for Future Biomedical Research (FBR), (Section 4.2.3.3) providing the FBR Informed Consent Form (ICF) has been signed.

A primary immunogenicity objective is to summarize the antibody response induced by V114 medium, V114 high, and Prevnar 13™, based on the serotype-specific IgG GMCs measured by Pn ECL assay at 1 month following receipt of the third dose of the study vaccine.

A secondary immunogenicity objective of the study is to summarize the proportion of subjects meeting the serotype-specific threshold value of ≥0.35 μg/mL by Pn ECL assay at 1 month following receipt of the third dose of the study vaccine.

The threshold value of ≥0.35 μg/mL measured in the Pn ECL assay corresponds to the IgG level of ≥0.35 μg/mL in the WHO reference ELISA for the 7 serotypes in Prevnar™ (4, 6B, 9V, 14, 18C, 19F, and 23F), based on the results of an analytical bridging study comparing the 2 assays. The use of the ≥0.35 μg/mL threshold value as measured by the WHO reference ELISA has been recommended by a WHO expert panel as an acceptable threshold value for evaluating the clinical performance of pneumococcal conjugate vaccines[3],[4].

Another secondary immunogenicity objective is to summarize the serotype-specific responses for V114 medium, V114 high, and Prevnar 13™, based on IgG GMCs and the proportion of subjects meeting the serotype-specific threshold value of ≥0.35μg/mL by Pn ECL assay immediately prior (pre-dose 4) and 1 month following receipt of the fourth dose of the study vaccine.

Functional antibody activity, OPA, will also be evaluated in approximately 50% of infants with sufficient serum available at PD3 to perform both the Pn ECL assay and the OPA testing on all 15 serotypes in V114. Pre-dose 4 and PD4 OPA measurements will be conducted for all of the subjects who had PD3 OPAs performed and for which there is sufficient serum. The proportion of subjects meeting OPA titer ≥8 and the OPA GMTs at PD3 and separately at pre-dose 4 and PD4 will be summarized for each serotype.

4.2.3.2 Safety Endpoints

Adult Cohort (Stage 1)

Adverse experiences (AEs) will be documented on a validated vaccination report card (VRC). The VRC was developed to be administered electronically via a hand-held device. All AEs will be graded for severity.

1. Subjects will be observed for 30 minutes postvaccination for any immediate AEs.

2. Solicited injection-site AEs (redness, swelling, and pain/tenderness) will be collected Day 1 to Day 5 after vaccination.

3. Solicited systemic AEs (muscle pain, joint pain, headache, and tiredness) will be collected Day 1 to Day 14 after vaccination.

4. Any other unsolicited systemic or injection-site AEs will be collected Day 1 to Day 14 after vaccination.

5. Serious AEs will be collected from the time the consent form is signed through completion of the subject's participation in the study (approximately 30 days postvaccination).

6. Body temperature will be measured during Day 1 to Day 5 after vaccination.

7. Severity of AEs will be assessed according to a toxicity grading scale as mild (Grade 1), moderate (Grade 2), severe (Grade 3), and potentially life-threatening and death (Grade 4) for both serious and non-serious adverse experiences, in this study. During the safety follow-up period, clinical adverse experiences will be recorded on the VRC by the subject at the time of occurrence. The investigator will use the information provided by the subject both on the VRC, and verbally at the time of VRC review, to apply the appropriate toxicity grade (1 through 4). The grade assigned by the investigator will be recorded in the electronic database on the corresponding eCRF. Death is not mentioned in the Toxicity Grade Guidance for Industry. For this protocol, a death will be assessed as toxicity Grade 4. This study uses an alpha scale for injection-site toxicity grading (A through E). For this protocol, use the Injection-Site AE Toxicity Grading Scale that follows the Industry Guidance in Appendix 12.6. All other toxicity evaluations must be performed per the applicable industry guidance. Refer to the Investigator File Trial Binder for guidance. The scale provided in the appendices is to be used for the measurement of the injection site AEs of redness, swelling, and pain/tenderness.

This adverse experience toxicity grading is in addition to the grading of adverse experiences by maximum intensity (mild, moderate, or severe).

The 14-day safety follow-up period for AEs occurring following receipt of each dose of the study vaccine is consistent with our Phase II study in healthy adults (V114-002), the ongoing clinical trial in healthy adults (V114-006), and other clinical trials evaluating the safety of licensed pneumococcal conjugate vaccines in healthy adults.

Infant Cohort (Stage 2 - Parts I and II)

Adverse experiences (AEs) will be documented on a validated vaccination report card (VRC). The VRC was developed to be administered electronically via a hand-held device. All AEs will be graded for severity.

1. Study subjects will be observed for 30 minutes postvaccination for any immediate AEs.

2. Solicited injection-site AEs (redness, swelling, hard lump, and pain/tenderness) and solicited systemic AEs (irritability, drowsiness, hives/welts, and appetite lost) will be collected Day 1 to Day 14 after each vaccination.

3. Any other unsolicited systemic or injection-site AEs will be collected Day 1 to Day 14 after each vaccination.

4. Serious AEs will be collected from the time the consent form is signed through 30 days PD4 and/or completion of the subject's participation in the study.

5. Body temperature will be measured during Day 1 to Day 7 after each vaccination. If fever is suspected, temperature will also be measured during Day 8 to Day 14 postvaccination.

The 14-day safety follow-up period for AEs occurring following receipt of each dose of the study vaccine is consistent with our Phase II study in healthy infants (V114-003), the ongoing clinical trial (V114-004), and other clinical trials evaluating the safety of licensed pneumococcal conjugate vaccines in healthy infants.

Safety Monitoring

Safety and tolerability profiles will be carefully monitored throughout the study by the SPONSOR in accordance with standard procedures and also by an external Data Monitoring Committee (eDMC). The eDMC consists of experienced physicians and scientists in the field of infectious diseases and/or vaccines who are not employees of the SPONSOR. An eDMC charter of operations will be written and approved by the eDMC before the eDMC reviews any clinical data. The eDMC will have the responsibility of study surveillance to monitor safety outcome events and identify safety issues in order to make recommendations (including the potential to terminate the study due to a safety concern) to the Merck clinical director. The Merck clinical director will then forward the recommendations to the Executive Oversight Committee (EOC) who will decide the path forward for the trial based on the recommendations made by the eDMC. The eDMC will meet at pre-specified time points, defined in the eDMC charter, to review safety data, and a set of safety criteria proposed as stopping rules will be used by the eDMC in their evaluation of the safety data during the conduct of the study (see section 7.3.2 Data Monitoring Committee). The eDMC will review the safety data from the adult cohort (Stage 1) prior to the initiation of the small infant cohort (Stage 2 – Part I).

In order to evaluate the safety profile of V114 in infants, VRC-prompted injection-site adverse experiences (redness, swelling, hard lump [rated by size] and pain/tenderness) and VRC-prompted systemic adverse experiences (irritability, drowsiness, appetite lost, hives/ welts) will be recorded for 14 days. If a hard lump at the injection site is present for 72 hours, the subject's parent/legal guardian should immediately contact the site to schedule an appointment with the study site for an evaluation within 48 hours, where the study doctor will diagnose the injection-site reaction (e.g., induration or nodule). If hives/welts (urticaria) occur, the subject's parent/legal guardian should immediately contact the site to schedule an

appointment with the study site for an evaluation within 48 hours, where the study doctor will determine whether the hives/welts represent an urticarial-like eruption. Unsolicited systemic or injection-site adverse experiences or serious adverse experiences will be collected from Day 1 through Day 14 after each vaccination. All serious adverse experiences (regardless of the investigator's assessment of causality) from the time the consent form is signed through completion of the subject's participation in the study at 30 days after the last dose of study vaccine will be collected. Any immediate adverse experiences occurring in the 30 minutes postvaccination observation period will be recorded. Information about any medications, including any analgesic/antipyretic use on the day of vaccination that the subject receives, should be documented throughout the study on the VRC for the 14-day safety follow-up period following each vaccination.

4.2.3.3 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

A subset of subjects will receive Prevnar 13™ which is the standard of care and is serving as the active comparator in this study. V114 is aimed at providing comparable immune responses to Prevnar 13™ for the shared serotypes while providing additional coverage for the 2 serotypes (22F and 33F) unique to V114. It is unknown if the investigational V114 will have the same benefit as Prevnar 13™. As a possible rescue medication in this study, subjects who fail to achieve adequate immune responses to serotype 19A (individually) and/or to 4 or more serotypes in common between Prevnar 13™ and V114 following the

third dose of study vaccine will be offered an additional dose of licensed pneumococcal conjugate vaccine between 9 and 12 months of age. (See section 5.6 Rescue Medications & Supportive Care for additional details).

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Healthy male and female subjects between the ages of 18 and 49 years of age for the adult cohort AND between 42 and 90 days (approximately 2 months of age) for the infant cohort (inclusive) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

Adult Cohort (Stage 1):

1. Be an adult, age 18 to 49 years and in good health. Any underlying chronic illness must be documented to be in stable condition.

2. Is able to read, understand, and complete the study questionnaires (i.e., the VRC).

3. Be able to attend all scheduled visits and to comply with the study procedures.

4. Meet one of the following categories:

   a) The subject is a male.

   b) The subject is a female who is not of reproductive potential, defined as a female who either: (1) is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age); (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.

   c) The subject is a female who is of reproductive potential and agrees to avoid becoming pregnant while receiving study vaccine and for 6 weeks after the last dose of study vaccine by complying with one of the following: (1) practice abstinence[†] from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

[‡]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

5. Understand the study procedures, alternate treatments available and risks involved with the study, and voluntarily agree to participate by giving written informed consent. The subject may also provide consent for FBR. However, the subject may participate in the main trial without participating in the FBR.

Infant Cohort (Stage 2 - Parts I and II):

1. Be healthy (based on medical history and physical examination) male or female infant approximately 2 months of age (42 days to 90 days), inclusive.
2. Have a parent/legal guardian who understands the study procedures, alternate treatments available, and risks involved with the study.

3. Have a parent/legal guardian who is able to read, understand, and complete the VRC and voluntarily agree to participate by giving written informed consent.

4. Be able to attend all scheduled visits and to comply with the study procedures.

5. Have a parent/legal guardian that has access to a telephone.

6. The subjects' parent/legal guardian may also provide written informed consent for FBR. However, the subject may participate in the main trial without participating in FBR.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

For items with an asterisk (*), if the subject meets these exclusion criteria, the Day 1 Visit may be rescheduled for a time when these criteria are not met.

Adult Cohort (Stage 1):

1. Has had prior administration of any pneumococcal vaccine.

2. Has a history of invasive pneumococcal disease (positive blood culture, positive cerebrospinal fluid culture, or other sterile site) or known history of other culture-positive pneumococcal disease.

3. Has known hypersensitivity to any component of the pneumococcal conjugate vaccine, or any diphtheria toxoid-containing vaccine.

4. Has known or suspected impairment of immunological function, history of congenital or acquired immunodeficiency (e.g. splenomegaly), documented HIV infection, functional or anatomic asplenia, history of autoimmune disease including multiple sclerosis (MS), MS-like disease, systemic lupus erythematosus, polymyositis, inclusion body myositis, dermatomyositis, Hashimoto's thyroiditis, Sjogren's syndrome, rheumatoid arthritis, or other autoimmune disorders.

5. Has a coagulation disorder contraindicating intramuscular vaccinations.

6. *Has received systemic corticosteroids (equivalent of ≥ 2 mg/kg total daily dose of prednisone or ≥ 20 mg/d for persons weighing > 10 kg) for ≥ 14 consecutive days and has not completed treatment at least 30 days prior to study entry. Has received systemic corticosteroids exceeding physiologic replacement doses (~5 mg/d prednisone equivalent) within 14 days prior to the first vaccination.

7. *Has received other licensed non-live vaccines within the 14 days before receipt of study vaccine. (Exception: Inactivated influenza vaccine may be administered

during the study but must be given at least 2 weeks prior to receipt of the study vaccine or at least 4 weeks after receipt of the study vaccine).

8. *Has received a licensed live virus vaccine within 30 days prior of receipt of study vaccine.

9. *Had a recent febrile illness (≥100.4°F [38.0°C] oral or equivalent) or received antibiotic therapy for any acute illness occurring within 72 hours before receipt of study vaccine.

10. Has received a blood transfusion or blood products, including immunoglobulins within the 6 months before receipt of study vaccine or is scheduled to receive a blood transfusion or blood product within 30 days of receipt of study vaccine. Autologous blood transfusions are not considered an exclusion criterion.

11. Has participated in another clinical study of an investigational product within 2 months before the beginning of or any time during the duration of the current clinical study. Subjects enrolled in observational studies may be included; these will be reviewed on a case-by-case basis for approval by the SPONSOR.

12. Is breast-feeding.

13. Cannot be adequately followed for safety according to the protocol.

14. Is unlikely to adhere to study procedures, keep appointments, or is planning to relocate during the study.

15. Has any other reason that, in the opinion of the investigator, may interfere with the evaluation required by the study.

16. Is or has an immediate family member (e.g. spouse, parent/legal guardian, sibling, or child) who is investigational site or sponsor staff directly involved with this trial.

For items with an asterisk (*), if the subject meets these exclusion criteria, the Day 1 Visit may be rescheduled for a time when these criteria are not met.

Infant Cohort (Stage 2 - Parts I and II):

1. Had prior administration of any pneumococcal vaccine.

2. Has a known hypersensitivity to any component of the pneumococcal conjugate vaccine, or any diphtheria toxoid-containing vaccine.

3. *Had a recent febrile illness (rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) occurring within 72 hours of receipt of study vaccine.

4. Has a known or suspected impairment of immunological function.

5. Has a history of congenital or acquired immunodeficiency (e.g. splenomegaly).

6. Has or his/her mother has a documented Human immunodeficiency virus (HIV) infection.

7. Has or his/her mother has a documented hepatitis B surface antigen - positive.

8. Has functional or anatomic asplenia.

9. Has a history of failure to thrive.

10. Has a coagulation disorder contraindicating intramuscular vaccination.

11. Has a history of autoimmune disease including systemic lupus erythematosus, anti-phospholipid syndrome, Behcet's disease, autoimmune thyroid disease, polymyositis and dermatomyositis, scleroderma, type I diabetes mellitus, and other autoimmune disorders.

12. Has a known neurologic or cognitive behavioral disorder, including encephalitis/myelitis, acute disseminating encephalomyelitis, pervasive development disorder, and related disorders.

13. Has received systemic corticosteroids (equivalent of ≥ 2 mg/kg total daily dose of prednisone or ≥ 20 mg/d for persons weighing > 10 kg) for ≥ 14 consecutive days and has not completed treatment at least 30 days prior to study entry. Has received systemic corticosteroids within 14 days prior to the first vaccination or is expected to require systemic corticosteroids within 30 days after each vaccination during conduct of the study.

14. Has received other licensed non-live vaccines within the 14 days before receipt of study vaccine.

15. Has received a licensed live virus vaccine within the 30 days prior of receipt of study vaccine.

16. Had prior receipt of a blood transfusion or blood products, including immunoglobulins.

17. Has participated in another clinical study of an investigational product before the beginning or anytime during the duration of the current clinical study. Subjects enrolled in observational studies may be included; these will be reviewed on a case-by-case basis for approval by the SPONSOR.

18. Has a history of invasive pneumococcal disease (positive blood culture, positive cerebrospinal fluid culture, or other sterile site) or known history of other culture positive pneumococcal disease.

19. Cannot be adequately followed for safety according to the protocol plan.

20. Has a parent/legal guardian who is unlikely to adhere to study procedures, keep appointments, or is planning to relocate during the study.

21. Has any other reason that in the opinion of the investigator may interfere with the evaluation required by the study.

22. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

5.2 Trial Vaccination(s)

The vaccines to be used in this trial are outlined below in Table 1 and Table 2.

Table 1 Trial Vaccination – Adult Cohort

Vaccination at Visit 1 (18 to 49 years of age) with 0.5mL given IM			
Vaccine	Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14 18C, 19F, 19A, 22F, 23F and 33F	MAPA	Use in Study
V114 medium	2 µg; except 6B (4 µg)	125 µg	Investigational
V114 high	4 µg; except 6B (8 µg)	250 µg	Investigational
V114 medium with an alternative carrier protein	2 µg; except 6B (4 µg)	125 µg	Investigational
V114 high with an alternative carrier protein	4 µg; except 6B (8 µg)	250 µg	Investigational

Table 2 Trial Vaccination – Infant Cohort

Vaccination at Visit 1 (~2 months of age), Visit 2 (~4 months of age), Visit 3 (~6 months of age) and Visit 5 (~12 to 15 months of age) with 0.5-mL given IM			
Vaccine	Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14 18C, 19F, 19A, 22F, 23F and 33F	MAPA	Use in Study
V114 medium	2 µg; except 6B (4 µg)	125 µg	Investigational
V114 high	4 µg; except 6B (8 µg)	250 µg	Investigational
V114 medium with an alternative carrier protein	2 µg; except 6B (4 µg)	125 µg	Investigational
V114 high with an alternative carrier protein	4 µg; except 6B (8 µg)	250 µg	Investigational
Prevnar 13™	Prevnar 13™		Active comparator

Trial vaccination is given on the day of randomization or as close as possible to the date on which the subject is allocated/assigned.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.2 Timing of Dose Administration

For adult cohort (Stage 1), V114 will be administered as a 0.5-mL intramuscular injection at Visit 1.

For the infant cohorts (Stage 2, Parts I and II), V114 or Prevnar 13™ will be administered as a 0.5-mL intramuscular injection at Visit 1 (approximately 2 months of age [≥42 or ≤90 days of age]), Visit 2 (4 months of age to 1 day prior to 5 months of age), Visit 3 (6 months of age to 1 day prior to 7 months of age) and Visit 5 (12 months of age to 1 day prior to 16 months of age). Other pediatric vaccines will be administered concomitantly on the same day as study vaccine according to the recommended schedule. Concomitant oral vaccines may be

administered prior to the study vaccine and other injectable concomitant vaccines. Precautions must be taken to prevent choking during the administration of oral vaccines. Concomitant injectable vaccines should be administered on the same day as study vaccine and after the study vaccine has been administered. To avoid any confounding results, non-study injectable vaccines should not be administered in the same limb as study vaccine.

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. V114 will be dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the vaccine administration or clinical evaluation of the subjects are unaware of the group assignments.

In-house blinding procedures will be used. Note: Because the study vaccine and Prevnar 13™ have a different appearance, a member of the study site staff will be unblinded for the purpose of receiving, maintaining, and preparing/administering the study vaccine. In order to avoid bias, the unblinded study personnel will have no further contact with study subjects for any study-related procedures/assessments after administration of study vaccines, which includes all safety follow up procedures. Contact between subjects and unblinded study personnel after vaccination administration is strictly prohibited.

For this Phase I-II study, MRL statisticians and an MRL statistical programmer assigned to the protocol will be unblinded throughout the duration of the study to facilitate reviews of the safety data by the eDMC, and the performing of the 2 planned interim analyses of the immunogenicity and safety data. All other MRL employees directly involved with the conduct of this trial will remain blinded to the subject level treatment assignment, and will receive only group level summaries of immunogenicity and safety data from the analyses.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Vaccine Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 4 V114 adult vaccination arms. Subjects will be assigned randomly in a 1:1:1:1 ratio to each of the 4 V114 vaccination groups in Stage 1, for the adult cohort. The infant cohort (Stage 2) will have 5 vaccination arms during which subjects will be randomly assigned in a 1:1:1:1:1 ratio to each of the 4 V114 vaccination groups or control (Prevnar 13™), respectively. Each formulation of V114 will be first evaluated in a small number of infants (10/arm) during Part I before initiating Part II, which will enroll the remainder of the infant cohort.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Any concurrent medication or medical treatment must be recorded on the appropriate electronic case report form (eCRF). During the influenza season, it is anticipated that study subjects 6 months of age and older may be given an influenza vaccine. Influenza vaccine should be administered either 2 weeks prior to or 4 weeks after the administration of the study vaccine.

If a medical condition requires the use of immunoglobulin, blood, or blood products during a subject's participation in this study, one of the individuals listed on the SPONSOR Contact Information page must be notified immediately and any such use must be documented on the appropriate eCRF.

Adults:

Subjects should not receive systemic corticosteroids during the study, unless medically required and with a goal of down-titrating/discontinuing as soon as medically feasible. Short-term (< 14 days) or alternate day administration at low to moderate doses (equivalent of < 2 mg/kg total daily dose of prednisone or < 20 mg/d for persons weighing > 10 kg) are approaches to mitigate potential risks associated with immunosuppression.

Subject should not receive systemic corticosteroids (equivalent of > 2 mg/kg total daily dose of prednisone or > 20 mg/d for persons weighing > 10 kg for > 14 consecutive days) following vaccine administration through the VRC specified follow-up period.

Intra-articular or soft-tissue (e.g., bursa, tendon) injections of steroids are permitted. Topical, ophthalmic and inhaled steroids are also permitted.

For the adult cohort (Stage 1), V114 will be administered at Visit 1. No other investigational compound or device or prohibited concomitant vaccines (see Section 5.1.3 Subject Exclusion Criteria) may be administered at any time during this study without prior approval by the SPONSOR.

Infants:

For the infant cohort (Stage 2, Parts I and II) the study vaccines (V114 and Prevnar 13™) will be administered at 2, 4, 6, and 12 to 15 months of age. On the day of vaccination, it is

important to record the use of any analgesic or antipyretic use on the VRC and appropriate eCRF.

Subjects should not receive systemic corticosteroids (equivalent of ≥2 mg/kg total daily dose of prednisone or ≥20 mg/d for persons weighing >10 kg for ≥14 consecutive days) starting from 30 days prior to vaccination through 30 days after each vaccination. Topical, ophthalmic and inhaled steroids are permitted.

Other pediatric vaccines will be administered concomitantly according to the recommended schedule. These concomitant non-study vaccinations will be recorded on the appropriate eCRF.

Concomitant vaccines (oral or injectable) should be administered on the same day as study vaccine. Concomitant oral vaccines may be administered prior to the study vaccine and other injectable concomitant vaccines. Precautions must be taken to prevent choking during the administration of oral vaccines. Other pediatric injectable vaccines administered concomitantly should be given after the study vaccine. To avoid any confounding results, non-study injectable vaccines should not be administered in the same limb as study vaccine. Documentation of which limb was used for the administration of study vaccine should be recorded on the appropriate eCRF. As the study is reporting injection-site AEs from the study vaccine (and not from the concomitant vaccines), this information should also be recorded on the VRC to inform the parent/legal guardian of the appropriate limb to monitor for AEs ONLY related to the study vaccine.

No other investigational compound or device may be administered at any time during this study without prior approval by the SPONSOR.

5.6 Rescue Medications & Supportive Care

Infant subjects who fail to achieve adequate serologic responses following the third dose of study vaccine will be offered an additional dose of licensed pneumococcal conjugate vaccine outside of this protocol. Any study subject with serotype-specific pneumococcal IgG (as measured by Pn ECL assay) below 0.35 µg/mL for serotype 19A (individually) and/or 4 or more serotypes in common between V114 and Prevnar 13™ at 1 month PD3, will be given one dose of licensed pneumococcal conjugate vaccine as soon as possible after serological results are available. All subjects who meet the rescue criterion must be discontinued from the study prior to administering the additional dose of licensed pneumococcal conjugate vaccine. The discontinuation date should be the date the parent/legal guardian was notified of the child's meeting the rescue criterion. Adverse events or changes to medical history occurring after the 14 days of safety follow up for Dose 3 and the discontinuation should be reported in the database; no additional immunogenicity blood sample should be drawn. If an SAE occurs between the 14 days of safety follow up for Dose 3 and the discontinuation, that event must be reported. The serologic threshold value of 0.35 µg/mL was recommended by a WHO expert panel as an acceptable threshold value for evaluating the clinical performance of pneumococcal conjugate vaccines in infants [3],[4]. Adequate treatment provisions,

including epinephrine, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

5.7 Diet/Activity/Other Considerations

No special dietary restrictions apply to this study.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

In this trial, a subject may discontinue from vaccination but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Discontinuation from vaccination is permanent. Once a subject has discontinued vaccination, even though he/she continues to be monitored in the trial, he/she shall not be allowed to begin vaccination again.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or SPONSOR, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.
- In stage 2 (Parts I and II), any infant subject that fails to achieve adequate serologic responses, as described in Section 5.6, will be discontinued from the study.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

The eDMC will be provided with the following stopping rules as guidance for temporarily halting or terminating the study:

If any of the following events occurs, administration of study vaccine will be temporarily discontinued until a thorough review of accumulated safety data is undertaken by the eDMC, the investigator, and /or the SPONSOR's representative.

- Death in any subject, unless the cause of death is due to obvious alternative etiology;
- Unexpected life-threatening event in any subject, unless due to obvious alternative etiology. Event should not have been previously observed with similar pneumococcal vaccines, or vaccines administered concomitantly in this study;
- Any serious adverse event, unless due to obvious etiology, with the exception of those already reported for pneumococcal conjugate vaccines or for other concomitantly administered vaccines and deemed related to those vaccines;
- Event which in the opinion of the investigator and/or safety monitoring committee contraindicates further dosing of additional subjects.

Conclusions about the overall safety of the investigational product will otherwise be determined from any SAE and solicited systemic AEs with a severe intensity rating, regardless of relationship to vaccination. The relationship to study vaccine is determined by the study investigator.

The study site and SPONSOR's personnel involved in the conduct of the study (excluding the MRL statistician and statistical programmer) will remain blinded as to the treatment allocation of the study subject.

6.0 TRIAL FLOW CHART

Adult Cohort		
Visit Number:	1	2
Visit Timing:	Day 1 **DOSE 1**	30 days after Visit 1
Visit Window:		+ 14 days
Administrative Procedures		
Informed Consent[a]	X	
Informed Consent for Future Biomedical Research (FBR)[b]	X	
Inclusion/Exclusion Criteria	X	
Subject Identification Card	X	
Urine Pregnancy Test[c]	X	
Medical History	X	
Concomitant Medication Review	X	X
Vaccination Allocation/Randomization	X	
Study Vaccine Administration[d]	X	
Provide Electronic Vaccination Report Card (VRC)	X	
Review VRC data		X
Clinical Procedures/Assessments		
Targeted Physical Examination (optional, per investigator's discretion; perform if needed to assess inclusion/exclusion criteria)	X	
Obtain Oral Temperature	X	
30 Minutes Postvaccination Observation Period	X	
Adverse Experience Monitoring[e]	X	X
Assess for Serious Adverse Experiences[e]	X	X
Laboratory Procedures/Assessments		
Collect blood samples for immunogenicity assays (40 mL)[f,g]	X	X
Collect Buccal Swabs for Future Biomedical Research [b]	X	

Adult Cohort		
Visit Number:	1	2
Visit Timing:	Day 1 **DOSE 1**	30 days after Visit 1
Visit Window:		+ 14 days

a. Consent must be obtained prior to any study procedures.
b. Informed consent for future biomedical research samples must be obtained before the collection of the buccal swab DNA samples. Buccal swab DNA samples for analysis should be obtained prior to the vaccination, on Day 1, on randomized subjects only, or at a later date as soon as the informed consent is obtained.
c. Urine pregnancy test (sensitive to 25 IU β-hCG) must be done prior to vaccination in women of reproductive potential
d. In order to avoid bias, the unblinded study personnel will have no further contact with study subjects for any study-related procedures/assessments following administration of the study vaccines. This includes all safety follow-up procedures. Contact between subjects and unblinded study personnel after vaccination administration is strictly prohibited.
e. Adverse experiences (serious and non-serious) are to be reported from Day 1 to 14 days following the vaccination. Serious Adverse Experiences are to be reported throughout the subject's study participation.
f. Leftover serum samples collected from the main study will be stored for future use if the FBR consent is signed.
g. Collect blood prior to vaccination.

Infant Cohort						
Visit Number:	1[a]	2[a]	3	4	5	6
Visit Timing:	Age:~2 months **DOSE 1**	Age:~ 4 months **DOSE 2**	Age:~6 months **DOSE 3**	30 days after Visit 3	Age:~12 to 15 months **DOSE 4**	30 days after Visit 5
Visit Window:	≥42 days of age to ≤90 days of age	4 months of age to 1 day prior to 5 months of age	6 months of age to 1 day prior to 7 months of age	28 to 42 days PD3	12 months of age to 1 day prior to 16 months of age	28 to 42 days PD4
Administrative Procedures						
Informed Consent[b]	X					
Informed Consent for Future Biomedical Research (FBR)[c]	X					
Inclusion/Exclusion Criteria	X					
Subject Identification Card	X					
Medical History	X					
Update Medical History (New condition not already recorded as medical history or adverse experiences)		X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X
Vaccination Allocation/Randomization	X					
Study Vaccine Administration[d]	X	X	X		X	
Childhood Vaccines[e]	X	X	X		X	
Provide Electronic Vaccination Report Card (VRC)	X					
Review VRC data[f]		X	X	X		X
Clinical Procedures/Assessments						
Full Physical Examination	X					
Targeted Physical Examination		X	X		X	
Obtain Rectal Temperature[g]	X	X	X		X	
30 Minutes Postvaccination Observation Period	X	X	X		X	
Adverse Experience Monitoring[f]	X	X	X	X	X	X
Assess for Serious Adverse Experiences[f]	X	X	X	X	X	X
Laboratory Procedures/Assessments						
Collect blood samples for immunogenicity assays (4-5 mL)[h, i]				X	X	X
Collect Buccal Swabs for Future Biomedical Research[c]	X					

Infant Cohort						
Visit Number:	1[a]	2[a]	3	4	5	6
Visit Timing:	Age:~2 months **DOSE 1**	Age:~ 4 months **DOSE 2**	Age:~6 months **DOSE 3**	30 days after Visit 3	Age:~12 to 15 months **DOSE 4**	30 days after Visit 5
Visit Window:	≥42 days of age to ≤90 days of age	4 months of age to 1 day prior to 5 months of age	6 months of age to 1 day prior to 7 months of age	28 to 42 days PD3	12 months of age to 1 day prior to 16 months of age	28 to 42 days PD4

a. For Visits 1 and 2, study coordinator should review the electronic Vaccination Report Card (VRC) in the vendors database at 14 days postvaccination (0 to plus 5 day window) and call the parent/legal guardian if there is a need to address questions (document phone call in study chart). The site will review VRC with parent/legal guardian at next visit.
b. Consent must be obtained prior to any study procedures.
c. Informed consent for future biomedical research samples must be obtained before the collection of the buccal swab DNA samples. Buccal swab DNA samples for analysis should be obtained prior to the vaccination, on Day 1, on randomized subjects only, or at a later date as soon as the informed consent is obtained.
d. In order to avoid bias, the unblinded study personnel will have no further contact with study subjects for any study-related procedures/assessments following administration of the study vaccines. This includes all safety follow-up procedures. Contact between subjects and unblinded study personnel after vaccination administration is strictly prohibited.
e. Concomitant (or routine pediatric) vaccines are to be given according to recommended schedule. Any injectable concomitant vaccines provided at the visit must be given after the study vaccine and in a separate limb, may be given during the 30-minute observation period, and do not require additional observation time
f. Adverse experiences (serious and non-serious) are to be reported from Day 1 to 14 days following each vaccination. Serious Adverse Experiences are to be reported throughout the subject's study participation.
g. Pre-vaccination temperatures taken by study staff at Visits 1, 2, 3 and 5. Parent/legal guardian to measure and record rectal temperature per VRC instructions.
h. Leftover serum samples collected from the main study will be stored for future use if the FBR consent is signed.
i. Collect blood prior to vaccination.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. A urine pregnancy test will be obtained for all female subjects of child bearing potential. Medical history for the adult subjects should be reported for the previous 5 years.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject before starting the trial. Prior medications should only be reported for a 30 day period prior to the first study vaccination.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

Any concurrent medication or medical treatment must be recorded on the appropriate electronic case report form (eCRF). On the day of vaccination, it is important to record the use of any analgesic or antipyretic use on the VRC and appropriate eCRF.

If a medical condition required the use of immunoglobulins, blood, or blood products during a subject's participation in this study, one of the individuals listed on the SPONSOR Contact Information page must be notified immediately and any such use must be documented on the appropriate eCRF.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 randomization number.

After the consent form has been signed and dated, the subject's medical history has been reviewed and all eligibility criteria have been met, and after a screening number is assigned, the subject will be assigned an allocation/randomization number using IVRS. It is the responsibility of the unblinded person(s) to allocate subjects using the IVRS.

7.1.1.8 Trial Compliance

7.1.1.8.1 Study Vaccination

All subjects will be given a card, at the time of screening, identifying them as participants in a research study. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

Unblinded study personnel not otherwise involved in the conduct of the study will prepare and administer the study vaccine. Unblinded study personnel should not have contact with subjects for any study-related procedures/assessments after administration of study vaccines, which includes all safety follow up procedures.

Prior to administration of Prevnar 13™ or V114, shake vigorously to obtain a homogenous white suspension. Do not use the vaccine if it cannot be resuspended. Visual inspection of study vaccine for particulate matter and discoloration prior to administration should be completed. The study vaccine should not be used if particulate matter or discoloration is found. If appearance is otherwise, do not administer. Partial or empty vaccine syringes should be properly discarded as biohazardous waste. US sites should follow instructions for the Clinical Supplies Return Form and contact your SPONSOR representative for review of shipment and form before shipping.

All safety and immunogenicity assessments will be conducted by blinded personnel, and the subject or subjects' parents/guardians will be blinded to the study vaccine received by the study subject. Vaccination information, such as Component Identification Number and time of vaccination, must be recorded on the appropriate eCRF as per the Data Entry Guideline (DEG) instructions.

Stage 1: Adult Cohort

Subjects will be randomly assigned to 1 of 4 vaccination arms:

(1) V114 medium

(2) V114 high

(3) V114 medium with an alternative carrier protein

(4) V114 high with an alternative carrier protein

Stage 1 of the study will enroll approximately 80 adult subjects (20 subjects per arm). A 0.5-mL intramuscular dose of study vaccine will be administered to healthy adults on Day 1. The vaccines should be administered at a 90° angle in the deltoid muscle using the provided syringe with a 22- to 25-gauge needle of the following length specifications:

- Men and women weighing < 130 lbs (60 kg), use a 5/8- to 1-inch needle
- Women weighing 130 to 200 lbs (60 to 90 kg) or men weighing 130 to 260 lbs (60 to 118 kg), use a 1- to 11/2-inch needle
- Women weighing > 200 lbs (90 kg) or men weighing > 260 lbs (118 kg), use a 11/2-inch needle
- Refer to the CDC Pink Book, Appendix D for additional details

Stage 2: Infant Cohort

Subjects will be randomly assigned to 1 of 5 vaccination arms:

(1) V114 medium

(2) V114 high

(3) V114 medium with an alternative carrier protein

(4) V114 high with an alternative carrier protein

(5) Prevnar 13™

Stage 2 of the study will enroll approximately 250 subjects (50 subjects per arm). A 0.5-mL intramuscular dose of study vaccine will be administered to healthy infants at 2, 4, 6, and 12 to 15 months of age.

The vaccines should be administered at a 90° angle in the anterolateral thigh muscle using the provided syringes with the following needle length and gauge specifications[1] : 1 inch needle, 22 to 25 gauge for infants (2-6 months) and 1 to 1¼ inch needle, 22 to 25 gauge for toddlers (12 to 15 months). (See CDC Pink Book, Appendix D for additional details).

To ensure that parents do not become confused regarding the location of the study vaccine injection-site, Doses 1, 2, and 3 of the study vaccine are to be administered in the same limb (e.g. if the study vaccine is provided in the right thigh for dose 1, subsequent doses should also be provided in the right thigh). Dose 4 may be administered in the deltoid region instead of the thigh, at the discretion of the investigator[2]. If an abnormality (i.e., rash) is observed at the site where the previous dose of the study vaccine was administered, it is permissible to use the anterolateral muscle of the other limb to administer the following dose of the study vaccine. (See attachment, CDC Pink Book, Appendix D for additional details).

7.1.1.8.2 Concomitant Vaccinations

No other investigational compound or device may be administered at any time during this study without prior approval by the SPONSOR.

Stage 2: Infant Cohort

The study vaccines will be administered at 2, 4, 6, and 12 to 15 months of age. Other pediatric vaccines will be administered concomitantly according to the mandated schedule at sites in the United States. These concomitant non-study vaccinations will be recorded on the appropriate eCRF. Combination MMRV vaccines should not be given in this study; however, MMR and Varicella vaccines are permitted if administered concomitantly in 2 separate limbs.

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[1] Needles provided in Prevnar 13™ blister packages may also be used.

[2] Per investigator discretion, dose 4 can be administered in the deltoid muscle instead of the anterolateral thigh muscle; if given in the deltoid muscle, the needle length should be 5/8 to 1 inch (a 5/8 inch needle may be used only if the skin is stretched tight, subcutaneous tissue is not bunched, and injection is made at a 90-degree angle).

Concomitant vaccines (oral or injectable) should be administered on the same day as study vaccine. Concomitant oral vaccines may be administered prior to the study vaccine and other injectable concomitant vaccines. Precautions must be taken to prevent choking during the administration of oral vaccines. Concomitant injectable vaccines should be administered after the study vaccine. To avoid any confounding results, non-study injectable vaccines should not be administered in the same limb as study vaccine. Documentation of which limb was used for the administration of study vaccine should be recorded on the appropriate eCRF. As we are requesting the reporting of injection-site adverse experiences from the study vaccine (and not from the concomitant vaccines), this information should also be recorded on the VRC to inform the parent/legal guardian of the appropriate limb to monitor for adverse experiences ONLY related to the study vaccine.

7.1.1.9 Dispense Electronic Vaccination Report Cards

The vaccination report card was developed to be administered electronically via a hand-held device. This item was structured as recommended in the final FDA Patient Reported Outcome (PRO) Guidance. The investigator or delegate will train the subject or parent/legal guardian in the use of the electronic vaccination report card prior to dispensing it at Visit 1. Body temperatures, injection-site AEs, VRC-prompted systemic complaints, other complaints or illnesses, and medications will be recorded on the VRC throughout the study. The investigator or delegate will review the data captured on the VRC with the adult subject at Visit 2 and with the parent/legal guardian for the infant stage at Visit 2 through Visit 6.

Interruptions from the protocol specified vaccination require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examinations

For adult subjects, a targeted physical examination may be performed to assess inclusion/exclusion criteria.

For infant subjects a full physical examination will be performed at Visit 1. Any clinically significant abnormality will be recorded as part of the medical history on the appropriate eCRF. A targeted physical examination will be performed at subsequent vaccination visits (Visits 2, 3, and 5). Any clinically significant abnormality will be recorded as part of the updated medical history on the appropriate eCRF.

The full and targeted physical examination procedures both include obtaining vital signs (heart rate, respiratory rate, and oral temperature), auscultation of the heart and lung, and examination of the abdomen. In addition, a full physical examination will include an assessment of the head, eyes, ears, nose and throat (HEENT), skin, lymph nodes, neurological system, and musculoskeletal system.

Findings related to the physical examinations should be documented in the subject chart/source documentation.

7.1.2.2 Temperature Methods

Stage 1: Adult Cohort

Subjects will be instructed to record their oral temperature on the VRC from Day 1 through Day 5 postvaccination. Measurements of body temperature should be taken at approximately the same time each day. In addition, subjects will be instructed to record any concomitant medications and/or vaccinations on the VRC.

Stage 2: Infant Cohort

The subject's parent/legal guardian will be asked to record a rectal temperature reading on the VRC from Day 1 through Day 7 following each vaccination. Temperature measurement must be recorded in the VRC if fever is suspected during Day 8 through Day 14. Although underarm (axillary) temperature measurement is acceptable, rectal temperature is the preferred method for fever evaluation. If an axillary temperature is performed and is reported to be ≥37.8°C (≥100.0°F), it must be confirmed with a rectal temperature. In this case, both axillary and rectal temperatures must be recorded on the VRC. Temperature readings should be taken at approximately the same time each day.

7.1.2.3 Assess Adverse Experiences

Stage 1: Adult Cohort

Study subjects will be observed for 30 minutes postvaccination for any immediate AEs. The time at which the event occurred within the 30 minute timeframe, as well as the event itself and resolution of the event must be recorded on the appropriate eCRF. Instructions on completing the VRC will be reviewed with each study subject. Solicited injection-site AEs (swelling, redness, and pain/tenderness) occurring Day 1 through Day 5 postvaccination and systemic AEs (muscle pain, joint pain, headache, and tiredness) occurring Day 1 through Day 14 following vaccination will be recorded by the subject on the electronic VRC. See Section 7.2 for detailed information concerning the assessment and recording of AEs.

Stage 2: Infant Cohort

Study subjects will be observed for 30 minutes postvaccination for any immediate AEs. The time at which the event occurred within the 30 minute timeframe, as well as the event itself and resolution of the event must be recorded on the appropriate eCRF. Instructions on completing the VRC will be reviewed with each study subject's parent/legal guardian. Injection-site and systemic AEs occurring Day 1 through Day 14 following each vaccination will be recorded by the subject's parent/legal guardian on the electronic VRC; this includes VRC-prompted injection-site AEs (redness, swelling, hard lump, and pain/tenderness) and VRC-prompted systemic AEs (irritability, drowsiness, appetite lost, hives or welts). See Section 7.2 for detailed information concerning the assessment and recording of AEs.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be drawn over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.4.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

There are no laboratory safety evaluations required by the protocol.

Pneumococcal Electrochemiluminescence (Pn ECL) Assay

The purpose of the Pn ECL assay is to detect serum IgG antibody to the pneumococcal polysaccharides (PnPs) serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 22F, 23F, and 33F before and after vaccination with PnPs containing vaccine(s). The serotypes are assayed in a group of 7 (types 1, 5, 6A, 7F, 19A, 22F, 33F) and a group of 8 (types 3, 4, 6B, 9V, 14, 18C, 19F, 23F). Antibodies to these serotypes are measured in mass units (µg/mL) read from a standard curve prepared from a pool of adult serum, collected postvaccination with a PPV23 and referred to as 007sp.

The assay is based on the MSD™ technology which employs multi-spot microtiter plates fitted with a series of electrodes associated with the bottom of the well. Serotype-specific PnPs are spotted to the MSD™ plates and used as the solid phase antigen. Experimental, control, and standard curve sera are pre-adsorbed with pneumococcal cell wall polysaccharide (CPs) and non-vaccine heterologous serotype PnPs (types 25 and 72) to reduce the nonspecific antibody response in the assay, and subsequently incubated in the PnPs antigen-coated wells. Anti-PnPs, which bind to the solid phase PnPs, are subsequently detected with a ruthenium-labeled anti-human IgG conjugate. Plates are read by measure of the chemiluminescent signal emitted from the ruthenium tag upon electrochemical stimulation initiated at the electrode surfaces of the microplates. The intensity of the luminescence is directly proportional to the amount of anti-PnPs in the sample.

Standard curves are prepared from the human Pneumococcal Standard Reference Serum, 007sp (Center for Biologics Evaluation and Research, U.S. FDA). The following standard and controls are run in each assay: (a) a 12-point standard curve which includes a serum diluent blank and an 11-point, 2.5-fold dilution series of 007sp that begins with an initial dilution of 1:400; (b) two different dilutions (1:1000 and 1:10,000) of Giebink serum 16 (G16) and one dilution (1:1000) of Giebink serum 5 (G5), both individual human immune sera obtained after vaccination with PPV23 by [redacted]PPD
(c) a serum sample from a previous Merck clinical trial tested at 1:10,000 dilution.

Clinical testing on the Pn ECL assay will be performed at Merck Research Laboratories (MRL) or its designated partners that are qualified to perform the assay.

Multiplex Opsonophagocytic Assay (MOPA-4)

The 4-Fold Multiplexed Opsonophagocytic Killing Assay for antibodies against *Streptococcus pneumoniae* (MOPA-4) is used to measure sera of patients vaccinated with multivalent pneumococcal vaccines for antibody titers (opsonic activity/killing) against the capsular polysaccharides for specific *S. pneumoniae* serotypes. The method is multiplexed permitting testing of 4 serotypes per run, eliminating excessive use of infant sera. The assay utilizes complement (baby rabbit source), a critical component, which requires qualification prior to use in the MOPA-4. The opsonophagocytic killing assay (OPA) also utilizes HL-60 human Promyelocytic Leukemia cells which are transformed into phagocytes for this assay. Complement is added in addition to bacterial strains (pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 18C, 19F, 22F, 23F, and 33F; strains tested in groups of 4) and patient sera. The ability of antibodies in patient sera, at a series of dilutions, to initiate the killing of the pneumococcal bacteria is the basis for assignment of antibody titer of the sample. The opsonization titers (OT) are defined as the serum dilution that kills 50% of bacteria and are determined using a linear interpolation algorithm. The results are reported as the reciprocal of the dilution. The MOPA-4 was developed and published by Professor Moon Nahm (Director of the US WHO and NIH pneumococcal serology reference laboratory) [5].

Merck has been involved in the development and implementation of the MOPA-4 in collaboration with PPD (University of Alabama [UAB], Birmingham) and with PPD (Institute of Child Health [ICH], London England). Both labs are qualified to generate clinical results and one of them will support MOPA-4 testing for this study.

Both the UAB and ICH MOPA-4 produced results comparable to other OPAs, including those used by industry, in a WHO-sponsored inter-laboratory comparison study [6]. The assay has been subject to a number of iterative development and optimization cycles, especially at the ICH.

Stage 1: Adult Cohort

Serum samples (approximately 40 mL) collected on Day 1 prior to vaccination and on Day 30 postvaccination will be used to measure vaccine-induced immune responses (IgG) to the 15 serotypes contained in V114. These serum samples will be assayed using the Meso-Scale Discovery MSD Pn ECL assay, which was developed by Merck & Co., Inc. for the measurement of pneumococcal capsular polysaccharide IgG antibodies. After completion of protocol-specified immunogenicity assays, leftover sera may be used for the development of future pneumococcal assays. Any remaining sample will then be retained for future biomedical research providing the future biomedical research (FBR) consent has been signed.

Stage 2: Infant Cohort

Subjects will have blood drawn (approximately 4-5 mL) at 3 time points: (1) Day 30 following the third study vaccination (PD3), (2) immediately prior to administration of the fourth study vaccination, and (3) Day 30 following the fourth study vaccination (PD4). Sera

will be used to measure vaccine-induced immune responses (IgG and opsonophagocytic killing activity [OPA]) to all 15 vaccine serotypes included in V114. These serum samples will be assayed using the Meso-Scale Discovery MSD Pn ECL assay, which was developed by Merck & Co., Inc. for the measurement of pneumococcal capsular polysaccharide IgG antibodies. Serum samples will also be assayed using a 4-Fold Multiplex Opsonophagocytic Assay which Merck has developed and implemented in collaboration with PPD from the University of Alabama. If a serum sample does not have enough volume for both the IgG and OPA testing, the IgG testing will take priority. OPA will be evaluated in approximately 50% of subjects with sufficient PD3 sera available to perform both the PnECL and the OPA testing on all 15 serotypes in V114. PD4 OPAs will be conducted for all of the subjects who had PD3 OPAs performed and for which there is sufficient serum. Leftover sera may also be used for the development of future pneumococcal assays. Any remaining sera will be retained for future biomedical research providing the future biomedical research (FBR) consent has been signed.

7.1.3.2 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Buccal swabs for genomics use
- Leftover serum samples collected in the main study, which would routinely be discarded after the main study is over

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from vaccination prior to completion of the vaccination regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox PPD and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the

responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the intensity/toxicity grade of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

At the end of the trial, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

7.1.4.3 Domiciling

Adult subjects will report to the clinical research unit (CRU) on the day of trial vaccination administration (Day 1) and remain in the CRU for 30 minutes following vaccination. Subjects will return 30 days later for Visit 2.

Infant subjects will report to the CRU on the day of the administration of study vaccine (Visit 1, 2, 3, and 5) and remain in the unit for 30 minutes postvaccination. At the discretion of the investigator, subjects may be requested to remain in the CRU longer. Infants will return to the CRU at Visits 4 and 6 for blood draws.

7.1.4.4 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Refrigerators
- -20° freezers
- Centrifuges

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Screening procedures will be performed at Visit 1. A separate screening visit is not required.

7.1.5.2 Treatment Period/Vaccination Visit

Adult subjects will be required to come to the clinic for 2 visits. Infant subjects will be required to come to the clinic for 6 visits. See Section 6.0 for details.

7.1.5.3 Post-Trial

This protocol does not require post trial visits.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as 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 adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of allocation/randomization through 14 days (42 days for live attenuated vaccines) following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days (42 days for live attenuated vaccines) thereafter, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is the administration of more than 1 dose of any individual study vaccine in any 24-hour period.

If an adverse event(s) is associated with (“results from”) the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology “accidental or intentional overdose without adverse effect.”

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic

reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 3 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following the last study vaccination, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event brought to the attention of an investigator who is a qualified physician at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is either:

1. A death that occurs prior to the subject completing the trial, but outside the time period specified in the previous paragraph.

or

2. A serious adverse event that is considered by an investigator who is a qualified physician to be vaccine related.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

No additional events of clinical interest have been identified for this program.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 3. The investigator's assessment of causality is required for each adverse event. Refer to Table 3 for instructions in evaluating adverse events.

Table 3 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities) **Injection site redness or swelling or hard lump (infants only) from the day of vaccination through Day 5 post-vaccination for adults and Day 14 post-vaccination for infants will be evaluated by maximum size.**
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose that:	
	†Results in death; or	
	†Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	†Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements; **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the test vaccine to be discontinued?	
Relationship to test vaccine	Did the test vaccine cause the adverse event? The determination of the likelihood that the test vaccine caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test vaccine and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the test vaccine and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test vaccine caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the test vaccine such as: reliable history, acceptable compliance assessment (e.g., diary), seroconversion or identification of vaccine virus in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test vaccine? Is the time of onset of the AE compatible with a vaccine-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to test vaccine (continued)	**The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)**	
	Dechallenge	(not applicable for vaccines)
	Rechallenge	Was the subject reexposed to the test vaccine in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose vaccine trial.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST VACCINE, OR IF REEXPOSURE TO THE TEST VACCINE POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Vaccine Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test vaccine or vaccine class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following criteria as guidance (not all criteria must be present to be indicative of a vaccine relationship).**	
Yes, there is a reasonable possibility of vaccine relationship.	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to the administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause.	
No, there is not a reasonable possibility of vaccine relationship	Subject did not receive the test vaccine OR temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the eDMC regarding the trial.

7.3.2 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

Safety Monitoring

The eDMC will include clinicians experienced in vaccinology, infectious diseases and/or pediatrics as well as a statistician; this is in addition to the unblinded MRL statistician who will be a non-voting member of the committee.

The eDMC will be provided with the following stopping rules as guidance for temporarily halting or terminating the study:

If any of the following events occurs, administration of study vaccine will be temporarily discontinued until a thorough review of accumulated safety data is undertaken by the eDMC, the investigators, and/or the SPONSOR's representative.

- Death in any subject, unless the cause of death is due to obvious alternative etiology;
- Unexpected life-threatening event in any subject, unless due to obvious alternative etiology. Event should not have been previously observed with similar pneumococcal vaccines, or vaccines administered concomitantly in this study;
- Any serious adverse event, unless due to obvious alternative etiology, with the exception of those already reported for pneumococcal conjugate vaccines or for other concomitantly administered vaccines and deemed related to those vaccines;
- Event in which in the opinion of the investigator and/or safety monitoring committee contraindicates further dosing of additional subjects.

Conclusions about the overall safety of the investigational product will otherwise be determined from any SAE and solicited systemic AEs with a severe intensity rating, regardless of relationship to vaccination. The relationship to study vaccine is determined by the study investigator.

The study site and SPONSOR's personnel involved in the conduct of the study (excluding the study statistician and statistical programmer) will remain blinded as to the treatment allocation of the study subject. The eDMC, unblinded statistician, and statistical programmer will be unblinded throughout the study. The EOC will be blinded, however it may be unblinded to evaluate the eDMC recommendations.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.11.

Study Design Overview	A Phase I-II, Randomized, Double-Blind, Study to Evaluate the Safety, Tolerability, and Immunogenicity of Different Formulations of V114 in Healthy Adults and Infants
Treatment Assignment	This is a double-blind study consisting of two cohorts. Stage 1 - Adult Cohort: Four (4) groups randomly assigned (1:1:1:1 ratio) to receive a single dose of either V114 medium, V114 high, V114 medium with an alternative carrier protein, or V114 high with an alternative carrier protein. Stage 2 - Infant Cohort: Five (5) groups randomly assigned (1:1:1:1:1 ratio) to receive either V114 medium, V114 high, V114 medium with an alternative carrier protein, V114 high with an alternative carrier protein, or Prevnar 13™ (control group).
Analysis Populations	Efficacy: Per-protocol (PP) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Stage 1 – Adult Cohort: There are no primary immunogenicity endpoints. Stage 2 – Infant Cohort: 1. The GMCs for the 15 serotypes in V114 and 13 serotypes in Prevnar 13™ based on the serotype-specific IgG responses as measured in the Pn ECL assay at 1 month PD3.
Key Secondary Endpoints	Stage 1 – Adult Cohort: 1. The GMCs and fold-rises from baseline for the 15 serotypes in V114 based on the serotype-specific IgG responses as measured in the Pn ECL assay at 1 month PD1. Stage 2 – Infant Cohort: 1. The proportion of subjects achieving IgG concentrations ≥0.35µg/mL as measured in the Pn ECL assay for the 15 serotypes in V114 and 13 serotypes in Prevnar 13™ at PD3, pre-dose 4, and PD4. 2. The GMCs for the 15 serotypes in V114 and 13 serotypes in Prevnar 13™ based on the serotype-specific IgG responses as measured in the Pn ECL assay at pre-dose 4 and PD4.
Statistical Methods for Key Immunogenicity Analyses	For the infant cohort, GMCs at PD3 along with two-sided 95% CIs will be computed for the 15 serotypes in V114 and 13 serotypes in Prevnar 13™. Additionally, GMC ratios (V114/Prevnar 13™) along with two-sided 95% CIs will be computed for the 13 serotypes in common between V114 and Prevnar 13™ for each V114 vaccination arm with Prevnar 13™. The CI for the ratio will be calculated using a 2-sample t-test approach based on the natural logarithm of the ratio.

Statistical Methods for Key Safety Analyses	For the adult cohort, within group summaries of safety (incidence rates and 95% CIs) will be provided for each V114 arm following a single dose. For the infant cohort, comparisons will be made between the V114 arms and Prevnar 13™ following each dose and across all doses. The analysis of safety results for the infant cohort will follow a tiered approach (Tier 1 through Tier 3). The Tier 1 safety endpoints in this study consist of the solicited injection-site (redness, swelling, and pain/tenderness) and solicited systemic (irritability, drowsiness, hives/welts, and appetite lost) AEs from the infant cohort and will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons (V114 versus Prevnar 13™). Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group (V114 versus Prevnar 13™) comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. These analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method.
Interim Analyses	Two interim analyses will be conducted during this study: (1) A first interim analysis will be performed when ~100% of the vaccinated subjects in the adult cohort and small infant cohort have completed postvaccination safety follow-up (single dose for adult cohort and postdose 3 for the small infant cohort) and ~100% of the immunogenicity results of IgG responses adult (postvaccination) and small cohort infant (postdose3) immunogenicity results of IgG responses are available; (2) A second interim analysis will be performed in this study when ~100% of PD3 immunogenicity results for all infants in Stage 2 (small and large cohorts) are available. An internal statistician and statistical programmer assigned to the protocol will be unblinded throughout the duration of the study to facilitate the performing of the interim analysis as well as creation of the eDMC safety reports for ongoing safety review. Results of the interim analysis will be provided and reviewed by the eDMC, and group summaries will be reviewed by the Sponsor's study team. The Sponsor's study team (except for the MRL statistician and programmer) will be blinded to the V114 formulation at the subject level. The Sponsor's study team will use the results to make scientific decisions regarding future studies. It may also inform certain scientific consultations.
Multiplicity	No multiplicity adjustment is planned since there are no formal hypothesis tests in this study.
Sample Size and Power	For the infant stage of the study, approximately 250 subjects will be enrolled, with approximately 50 subjects in each of the five vaccination arms. Assuming 90% evaluability at PD3 (~45 subjects per group), a standard deviation of the natural log antibody concentrations at PD3 of 1.0, and a one-sided alpha of 0.05, there is >90% power to detect a lower response (as measured by the GMC) in V114 for a given serotype if the true fold difference is 2-fold lower between any two vaccination groups.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

This study that will be conducted in 2 stages which will enroll an adult cohort (Stage 1) and an infant cohort (Stage 2). Additionally, the infant cohort will be enrolled in 2 parts (I and II) in order to evaluate safety in a smaller group of infants prior to full enrollment of Stage 2. Prior to proceeding between Stage 1 and 2, as well as between Stage 2 part I and Stage 2 part II, the safety and tolerability of V114 will be carefully evaluated by the eDMC. For this Phase I-II study, an internal statistician and statistical programmer assigned to the protocol will be unblinded throughout the duration of the study to facilitate the interim reviews of the safety data by the eDMC. All other MRL employees directly involved with the conduct of this trial will remain blinded to the subject's treatment assignment until medical/scientific review of all safety and immunogenicity data has been performed, protocol deviations have been identified, and data have been declared final and complete.

The 2 planned interim analyses are described in Section 8.7. The results of each interim analysis will not be shared with the investigators prior to the completion of the study. Subject-level unblinding will be restricted to an internal unblinded statistician and an unblinded statistical programmer performing the interim analysis.

Results of the interim analyses will be provided by the unblinded statistician to the eDMC. Group summaries will be reviewed by the Sponsor's study team in order to make scientific decisions for future studies.

8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0. This is an estimation study and no formal hypothesis testing will be performed.

8.4 Analysis Endpoints

Immunogenicity and safety endpoints that will be evaluated for within- and between-treatment differences are listed below.

8.4.1 Immunogenicity Endpoints

Adult Stage

For the adult stage of the study, there are no primary immunogenicity endpoints. The secondary immunogenicity endpoints are the serotype-specific IgG GMCs and fold-rises from baseline as measured in the Pn ECL assay at 1 month postvaccination for the 15 serotypes in V114.

Infant Stage

For the infant stage of the study, the primary immunogenicity endpoints are the serotype-specific IgG GMCs as measured in the Pn ECL assay at 1 month PD3 for the 15 serotypes in V114 and 13 serotypes in Prevnar 13™.

The secondary immunogenicity endpoints include (1) the proportion of subjects achieving IgG concentrations ≥0.35µg/mL at 1 month PD3, pre-dose 4, and 1 month PD4, and (2) the GMCs at pre-dose 4 and 1 month PD4 for the 15 serotypes in V114 and 13 serotypes in Prevnar 13™.

The exploratory immunogenicity endpoints include the proportion of subjects with OPA titer ≥8 and OPA GMTs at 1 month PD3, pre-dose 4, and 1 month PD4 for the 15 serotypes in V114 and 13 serotypes in Prevnar 13™.

8.4.2 Safety Endpoints

Refer to Section 4.2.3.2 for the description of the safety measures in this study.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, within both the adult and infant cohorts. Tier 1 events for this study will consist of the solicited injection-site and solicited systemic AEs in the infant cohort.

8.5 Analysis Populations

8.5.1 Immunogenicity Analysis Populations

The primary immunogenicity analysis population will be the PP population. The PP population consists of those subjects who are not considered protocol violators. For the adult cohort, the violations include, but are not limited to: failure to receive the scheduled dose of correct clinical material, and lack of valid serology results available from 30 to 44 days following dose 1. For the infant cohort, the violations include, but are not limited to: failure to receive the scheduled doses (at least 28 days between doses 1 and 2 and between doses 2 and 3, and dose 4 at 12 months to 15 months of age) of correct clinical material, and lack of valid serology results available from 28 to 42 days following dose 3 or dose 4. The final determination on protocol violators will be made prior to unblinding of the database and will be documented in a separate memo.

The Full Analysis Set (FAS) population will also be used for supplementary analysis of the primary analyses. The FAS population consists of all randomized subjects who received at least one vaccination and have at least one serology result. Subjects will be included in the treatment group to which they are randomized for the analysis of immunogenicity data.

Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 Statistical Methods.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental SAP.

Analysis of the immunogenicity data from the infant stage of the study will be based on the combined data from Stage 2 Part I and Stage 2 Part II.

To address the primary infant immunogenicity objective #2, GMCs at 1 month PD3 along with two-sided 95% CIs will be computed for the 15 serotypes in V114 for V114 medium, V114 high, and 13 serotypes in Prevnar 13™. Point estimates of GMCs are the exponentiated estimates of the mean $\log_e$ concentrations. The confidence intervals for GMCs are the exponentiated confidence intervals for the mean $\log_e$ concentrations, based on 1-sample t-distributions. Additionally, GMC ratios (V114/Prevnar 13™) along with two-sided 95% CIs will be computed for each of V114 medium and V114 high relative to Prevnar 13™ for the 13 common serotypes. The CI for the ratio will be calculated using a 2-sample t-test approach based on the natural logarithm of the ratio.

To address the secondary infant immunogenicity objective #1, the proportion of subjects achieving the serotype-specific threshold value of $\geq$ 0.35µg/mL for the 15 serotypes at 1 month PD3 along with the 95% CI will be calculated for V114 medium, V114 high, and the 13 serotypes in Prevnar 13™. The one-sample two-sided CIs will be computed using the exact CI method for a single binomial proportion given in Collett [7]. Additionally, the

difference (V114 minus Prevnar 13™) in the proportion of subjects achieving an IgG concentration ≥0.35µg/mL along with two-sided 95% CIs will be computed for each of V114 medium and V114 high relative to Prevnar 13™ for the 13 serotypes in common. The CI for the difference will be computed using the method of Miettinen and Nurminen [8].

The additional secondary infant immunogenicity objective (#2) as well as the secondary adult immunogenicity objective #1 will utilize similar statistical methods as those outlined above.

Reverse cumulative distribution functions for both IgG and OPA levels at PD3 and PD4 will be graphically displayed by serotype in the CSR.

Table 4 summarizes the key immunogenicity analyses.

Table 4 Analysis Strategy for Key Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Objectives			
PD3 GMCs, for the 15 serotypes in V114 and the 13 serotypes in Prevnar 13™ [V114 medium, V114 high, Prevnar 13™] (Infant Primary Objective #2)	• Within-group GMCs and 95% CI • GMC ratio (V114 arm/Prevnar 13™) and 95% CI (2-sample t-test) for common serotypes	Infant Per-Protocol	Missing data will be dropped
PD3 GMCs, for the 15 serotypes in V114 and the 13 serotypes in Prevnar 13™ [V114 medium, V114 high, Prevnar 13™] (Infant Primary Objective #2)	• Within-group GMCs and 95% CI • GMC ratio (V114 arm/Prevnar 13™) and 95% CI (2-sample t-test) for common serotypes	Infant FAS [Supportive]	Missing data will be dropped
Secondary Objectives			
PD3, pre-dose 4, PD4 %≥0.35, for the 15 serotypes in V114 and the 13 serotypes in Prevnar 13™ [V114 medium, V114 high, Prevnar 13™] (Infant Secondary Objective #1)	• Within-group %≥0.35 and 95% CI • Difference in %≥0.35 (V114 arm-Prevnar 13™) and 95% CI (M&N) for common serotypes	Infant Per-Protocol	Missing data will be dropped
Pre-dose 4 and PD4 GMCs, for the 15 serotypes in V114 and the 13 serotypes in Prevnar 13™ [V114 medium, V114 high, Prevnar 13™] (Infant Secondary Objective #2)	• Within-group GMCs and 95% CI • GMC ratio (V114 arm/Prevnar 13™) and 95% CI (2-sample t-test) for common serotypes	Infant Per-Protocol	Missing data will be dropped
PD1 GMCs and fold-rises from baseline, for 15 serotypes in V114 and the 13 serotypes in Prevnar 13™ [V114 medium, V114 high] (Adult Secondary Objective #1)	• Within-group GMCs and 95% CI • Within-group fold-rises from baseline and 95% CI	Adult Per-Protocol	Missing data will be dropped

The strategy to address multiplicity issues is described in Section 8.7, Interim Analyses and in Section 8.8, Multiplicity.

8.6.2 Statistical Methods for Safety Analyses

Analysis of the safety data from the infant stage of the study will be based on the combined data from Stage 2 Part I and Stage 2 Part II.

There are no safety hypotheses for this study. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, within both the adult and infant cohorts. For the adult cohort, within group summaries of safety (incidence rates and 95% CIs) will be provided for each V114 arm following a single dose. For the infant cohort, comparisons will be made between the V114 arms and Prevnar 13™ following each dose, and across all doses as outlined below.

The analysis of safety results for the infant cohort will follow a tiered approach (Table 5). The tiers differ with respect to the analyses that will be performed. The Tier 1 safety endpoints in this study consist of the solicited injection-site (redness, swelling, and pain/tenderness) and solicited systemic (irritability, drowsiness, hives/welts, and appetite lost) AEs from the infant cohort and will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons (V114 versus Prevnar 13™). Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group (V114 versus Prevnar 13™) comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences.

For this protocol, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a vaccine related AE, a serious AE, an AE which is both vaccine-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. For Tier 2, 95% confidence intervals will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method (1985) [8], an unconditional, asymptotic method.

Table 5 Analysis Strategy for Infant Cohort Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Solicited Injection-Site and Solicited Systemic AEs	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Vaccine-Related AE		X	X
	Any Serious and Vaccine-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs (incidence ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X

†Adverse Experience references refer to both Clinical and Laboratory AEs.
Note: SOC=System Organ Class; X = results will be provided.

8.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

Two interim analyses will be conducted during this study: (1) A first interim analysis will be performed when ~100% of the vaccinated subjects in the adult cohort and small infant cohort have completed postvaccination safety follow-up (single dose for adult cohort and postdose 3 for the small infant cohort) and ~100% of the immunogenicity results of IgG responses for adults (postvaccination) and small infant cohort (postdose 3) are available; (2) A second interim analysis will be performed in this study when ~100% of PD3 immunogenicity results for all infants in Stage 2 (small and large cohorts) are available. An internal statistician and statistical programmer assigned to the protocol will be unblinded throughout the duration of the study to facilitate the performing of the interim analysis as well as creation of the eDMC safety reports for ongoing safety review. Results of the interim analysis will be provided to the eDMC, and group summaries will be reviewed by the Sponsor's study team. The Sponsor's study team (except for the MRL statistician and programmer) will be blinded to the V114 formulation at the subject level. The Sponsor's study team will use the results to

make scientific decisions regarding future studies. It may also inform certain scientific consultations. No multiplicity adjustments will be made in either interim analysis as the conduct of the study will not be altered.

The endpoints, timing, and purpose of the interim analyses are summarized in Table 6.

Table 6 Summary of Interim Analysis Strategy

Interim Analysis	Key Endpoints of Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
Adult and small infant cohort	• Adult GMC ratios for each of the 15 serotypes contained in V114. • Adult GMCs at baseline and1 month postvaccination, GMFR and % of subjects who achieved at least 4-fold rise at 1 month postvaccination for each of the 15 serotypes contained in V114. • Adult percentage of subjects with any AE, a vaccine related AE, a serious AE, an AE which is both vaccine-related and serious, and who discontinued due to an AE. • Small infant cohort PD3 GMCs and GMC ratios, for the 15 serotypes contained in V114. • Small infant cohort PD3 proportion of subjects of subjects achieving concentrations ≥0.35 µg/mL and differences, for each of the 15 serotypes in V114. • Percentage of infants in the small cohort with any AE, a vaccine related AE, a serious AE, an AE which is both vaccine-related and serious, and who discontinued due to an AE after each vaccination.	~100% of the adult cohort and small cohort of infants have completed safety follow-up (postvaccination for adult cohort and postdose 3 for small infant cohort) and ~100% of the immunogenicity results (IgG responses) for adult (postvaccination) and small infant (postdose 3) cohorts are available.	Inform scientific decisions for future studies

Interim Analysis	Key Endpoints of Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
All Infant Cohorts	• Infant PD3 GMCs and ratios, for the 15 serotypes contained in V114. • Infant PD3 proportion of subjects achieving IgG concentrations ≥0.35 µg/mL and differences, for each of the 15 serotypes in V114. • Infant PD3 percentage of subjects with any AE, a vaccine related AE, a serious AE, an AE which is both vaccine-related and serious, and who discontinued due to an AE.	~100% of PD3 immunogenicity results (IgG responses) for all infants (small and large cohorts) are available.	Inform scientific decisions for future studies

8.8 Multiplicity

Since there are no formal hypothesis tests in this study, no adjustment will be made for multiplicity.

8.9 Sample Size and Power Calculations

For the adult stage of the study, a total of 80 subjects will be randomized to one of four vaccination groups in order to evaluate the safety of a single vaccination of V114.

For the infant stage of the study, approximately 250 subjects will be enrolled, with approximately 50 subjects in each of the five vaccination arms. The probability of detecting a lower response (as measured by the GMC) for a given serotype between 2 vaccination groups depends on the variability of the natural log antibody concentrations and the true difference between the groups. In Table 7, the powers for detecting a lower response for various standard deviation estimates and true fold difference are displayed assuming 45 evaluable subjects per group (90% evaluability) and a one-sided alpha of 0.05. Given the standard deviation of the natural log antibody concentrations at PD3 is 1.0 and the true fold difference is 2-fold lower between any two vaccination groups, there is >90% (94.7%) power to detect a lower response (as measured by the GMC) in V114 for a given serotype.

Table 7 Power for Detecting a Lower Response for Varying Standard Deviation and True Differences with 45 Evaluable Subjects

SD of natural log concentrations†	True Fold-Difference Between Groups for a Given Serotype		
	1.5	2.0	2.5
0.8	77.1%	99.3%	>99%
1.0	60.4%	94.7%	99.6%
1.2	47.8%	85.9%	97.4%
1.4	38.9%	75.3%	92.4%
†The standard deviation (SD) estimates are representative of those observed in V114-003.			

The widths of the 95% CIs for the serotype-specific GMCs depend on the sample size, variability of the natural log concentrations, and the magnitude of the GMC. It is assumed that 90% (45 subjects) of the subjects in each group will have evaluable immunogenicity results at 1 month PD3. In Table 8, the 95% CIs for various hypothetical GMCs and standard deviation estimates for the natural log concentrations are displayed.

Table 8 95% CIs for Varying Standard Deviation and GMC Values with 45 Evaluable Subjects

SD of natural log concentrations†	Serotype-specific GMC†		
	1.0	2.0	3.0
0.8	(0.79, 1.27)	(1.57, 2.54)	(2.36, 3.81)
1.0	(0.74, 1.35)	(1.48, 2.70)	(2.22, 4.05)
1.2	(0.70, 1.43)	(1.39, 2.87)	(2.09, 4.30)
1.4	(0.66, 1.52)	(1.31, 3.05)	(1.97, 4.57)
†The standard deviation (SD) and GMC estimates are representative of those observed in V114-003.			

8.10 Subgroup Analyses and Effect of Baseline Factors

No analyses for these factors will be performed.

8.11 Extent of Exposure

The number of subjects vaccinated at each vaccination visit will be summarized by vaccination group.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 9.

Clinical supplies will be packaged to support enrollment as required.

Table 9 Product Descriptions

Product Name & Potency	Dosage Form
V114 medium	0.5 mL dose sterile suspension for I.M. injection
V114 high	0.5 mL dose sterile suspension for I.M. injection
V114 medium with an alternative carrier protein	0.5 mL dose sterile suspension for I.M. injection
V114 high with an alternative carrier protein	0.5 mL dose sterile suspension for I.M. injection
Prevnar 13™	0.5 mL dose sterile suspension for I.M. injection

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Sites will receive open label, single dose syringe kits. Each kit will contain 1 syringe.

9.3 Clinical Supplies Disclosure

This trial is blinded but provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Vaccine identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are provided.

The emergency unblinding call center will use the randomization schedule for the trial to unblind subjects and to unmask vaccine identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask

treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Vaccine identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign vaccine to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will

be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main

paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.2

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.2

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.2 – Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced

to any specimens, test results, or medical information once the specimens have been rendered de-identified

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of patient consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Buccal swab specimens for DNA isolation will be obtained at a time when the subject is having other trial procedures conducted. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and

privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox (PPD and a form will be provided by Merck to

obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database

maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

Buccal swab specimens will be collected inside the cheek with no associated venipuncture to obtain the specimen. Therefore, there will not be an additional risk for the subject.

Merck has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

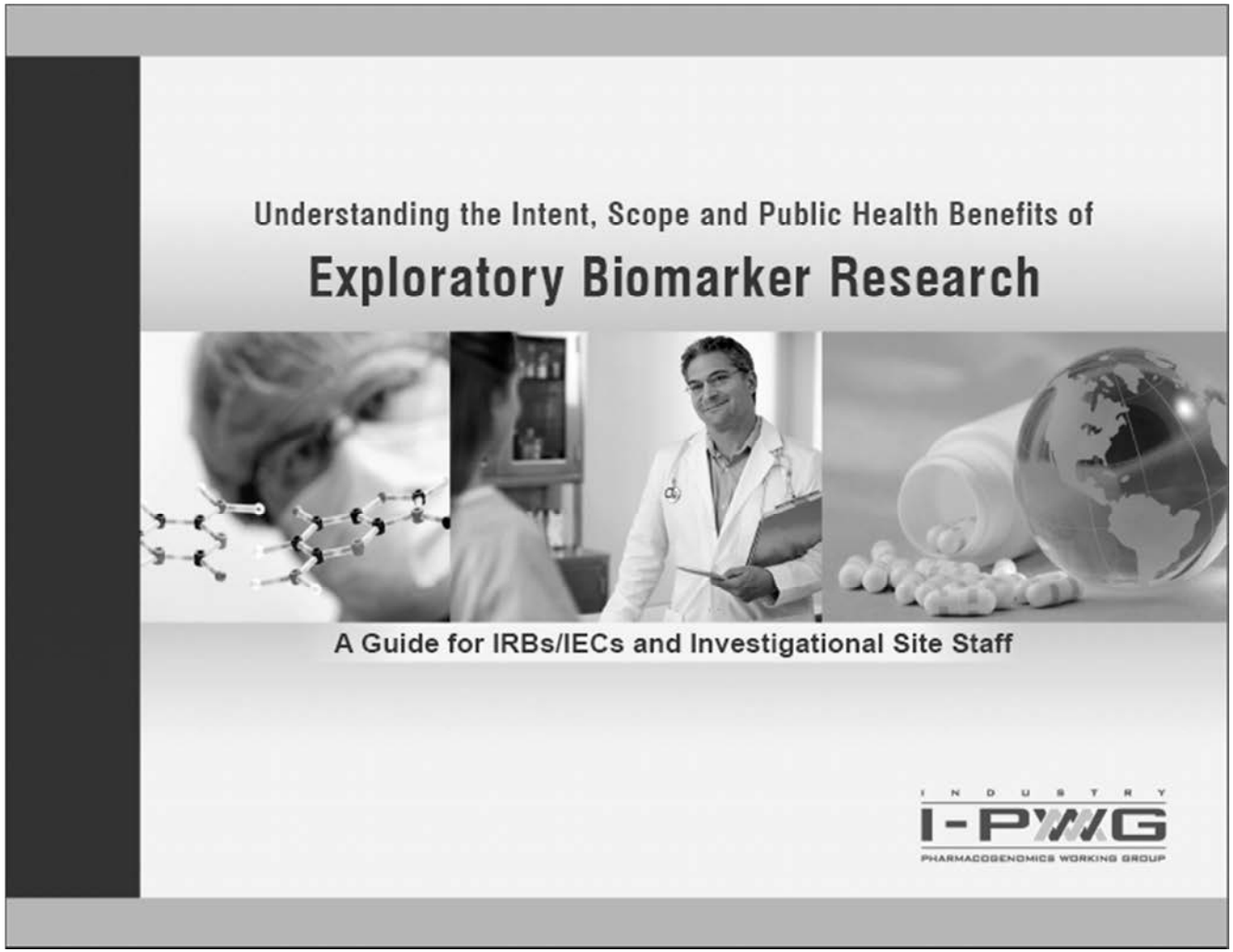
13. Questions

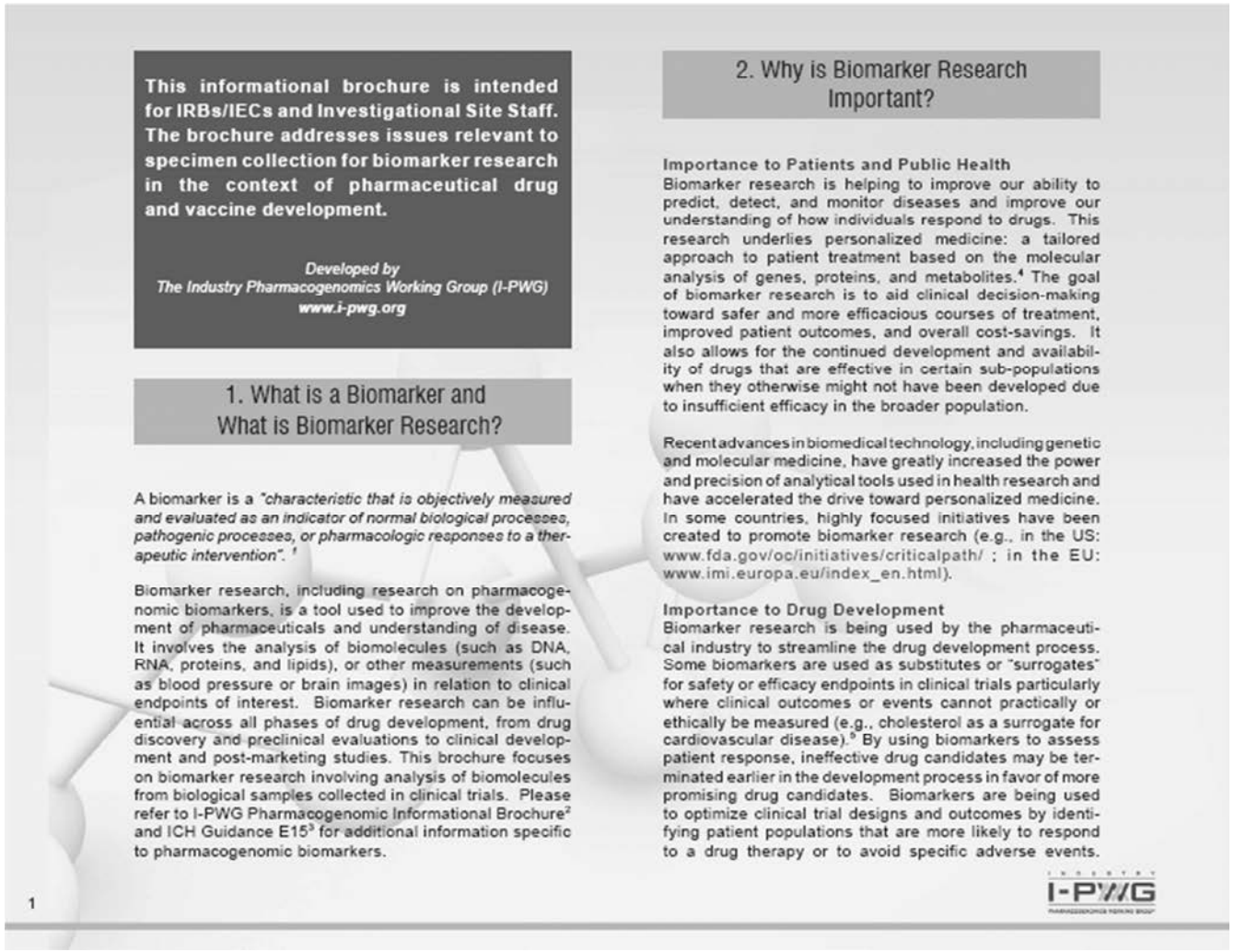
Any questions related to the future biomedical research should be e-mailed directly to PPD

14. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development

Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[9] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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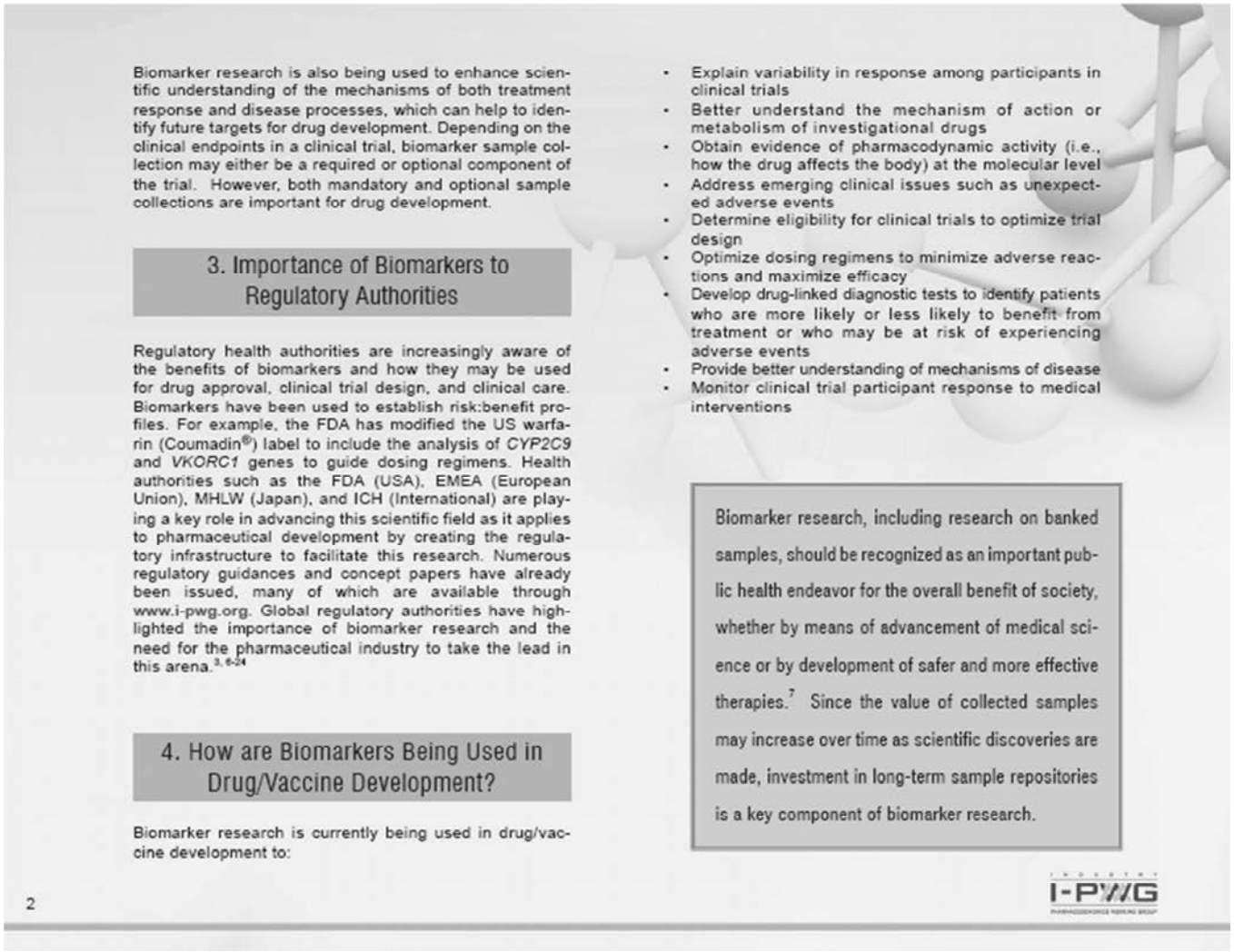
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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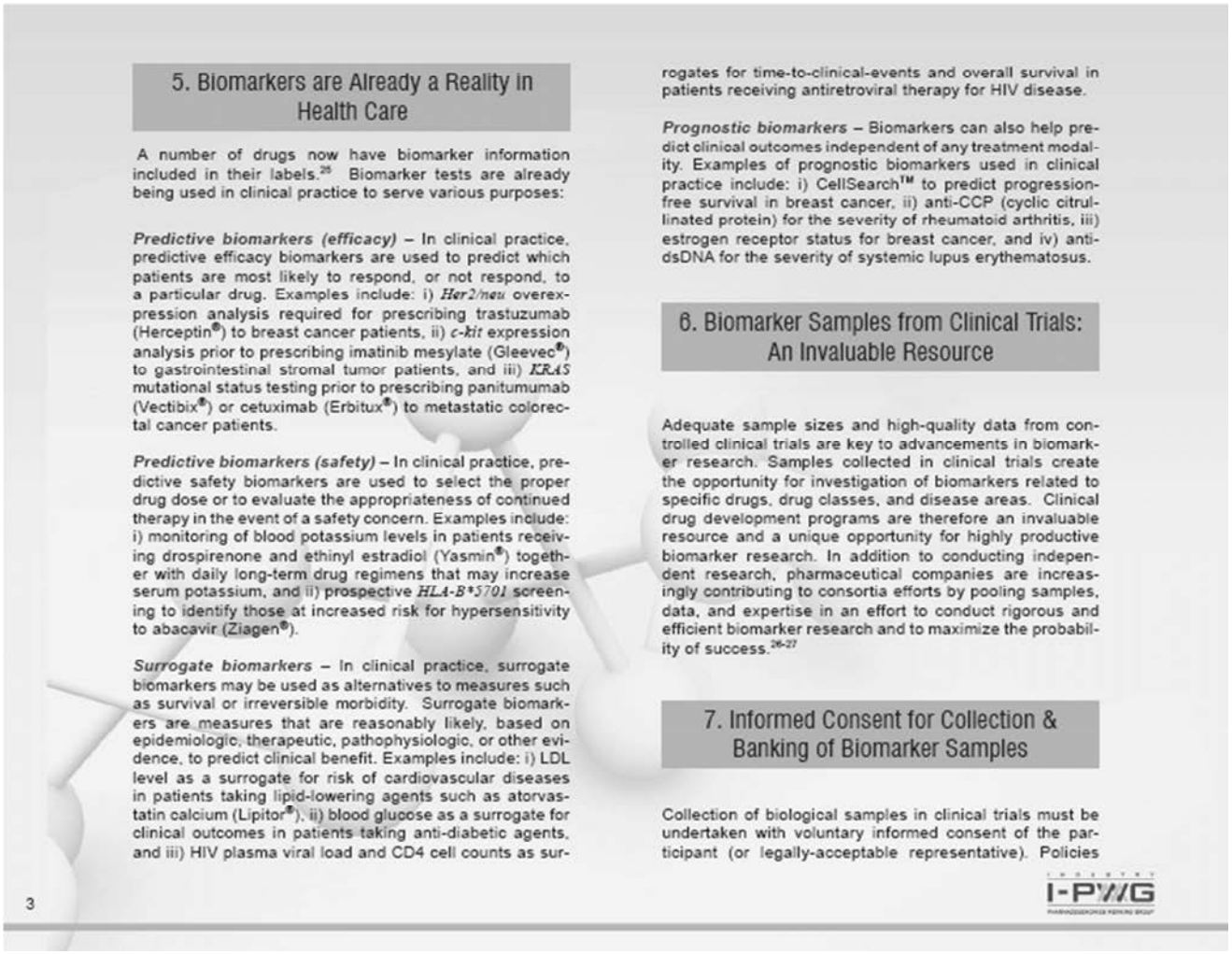

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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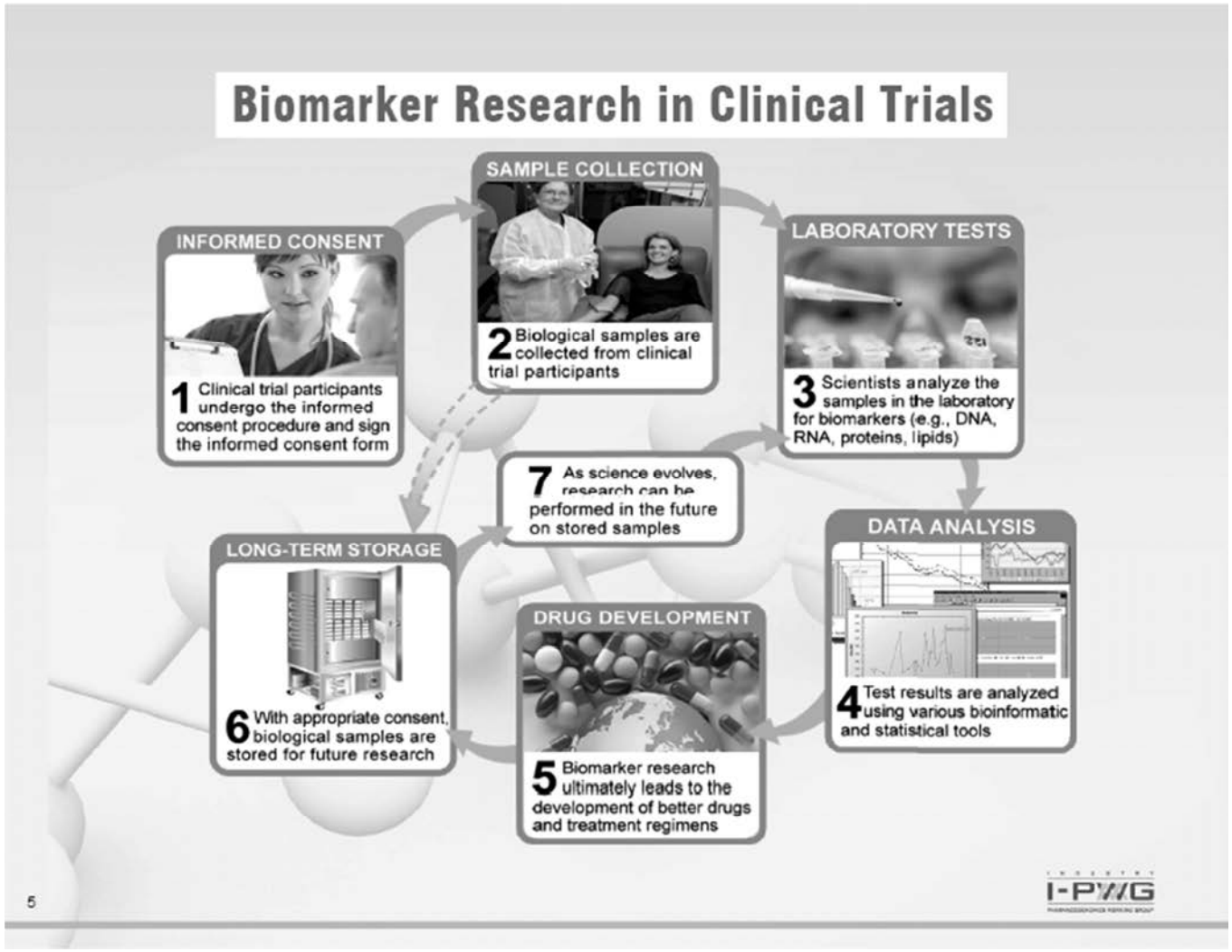
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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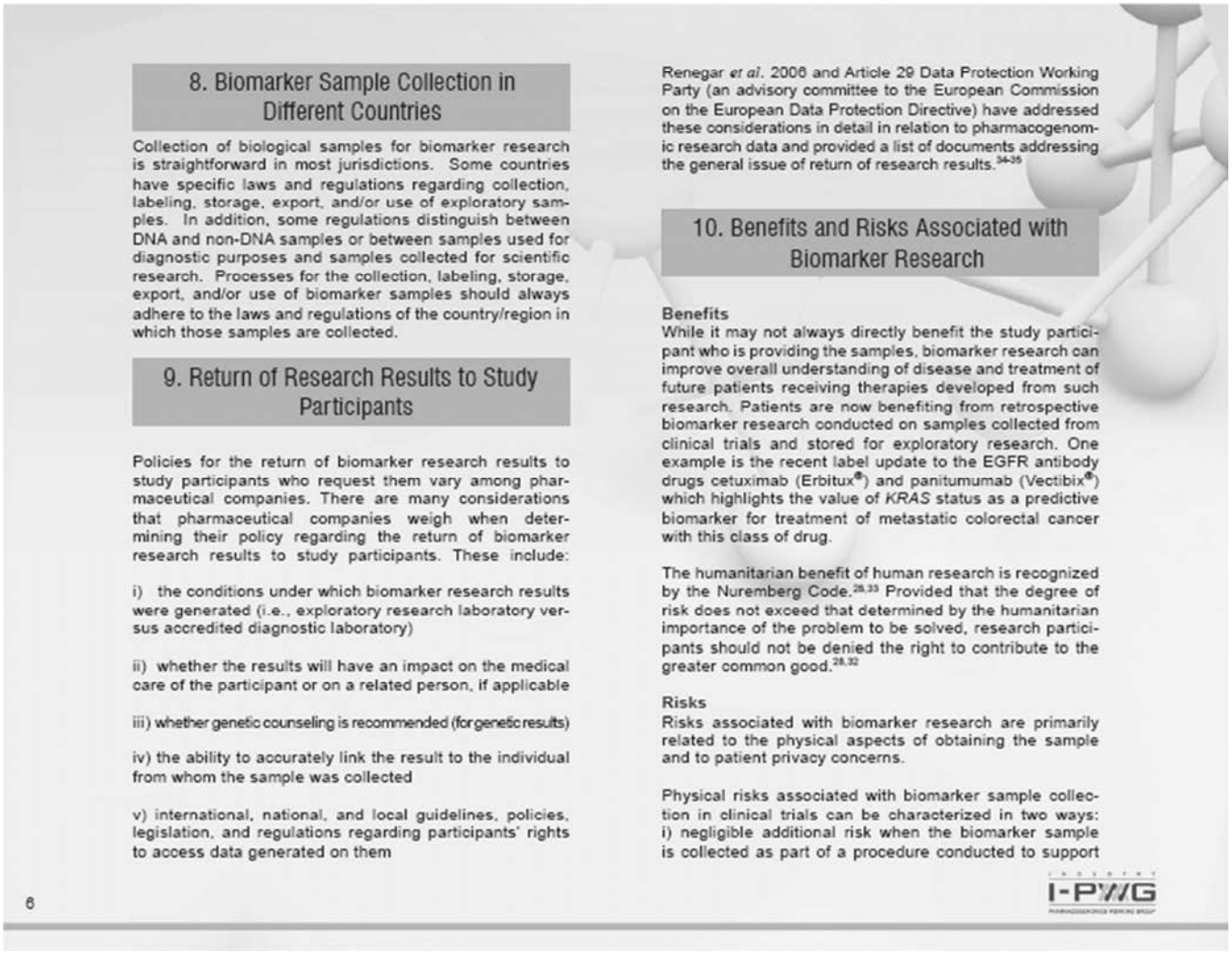

8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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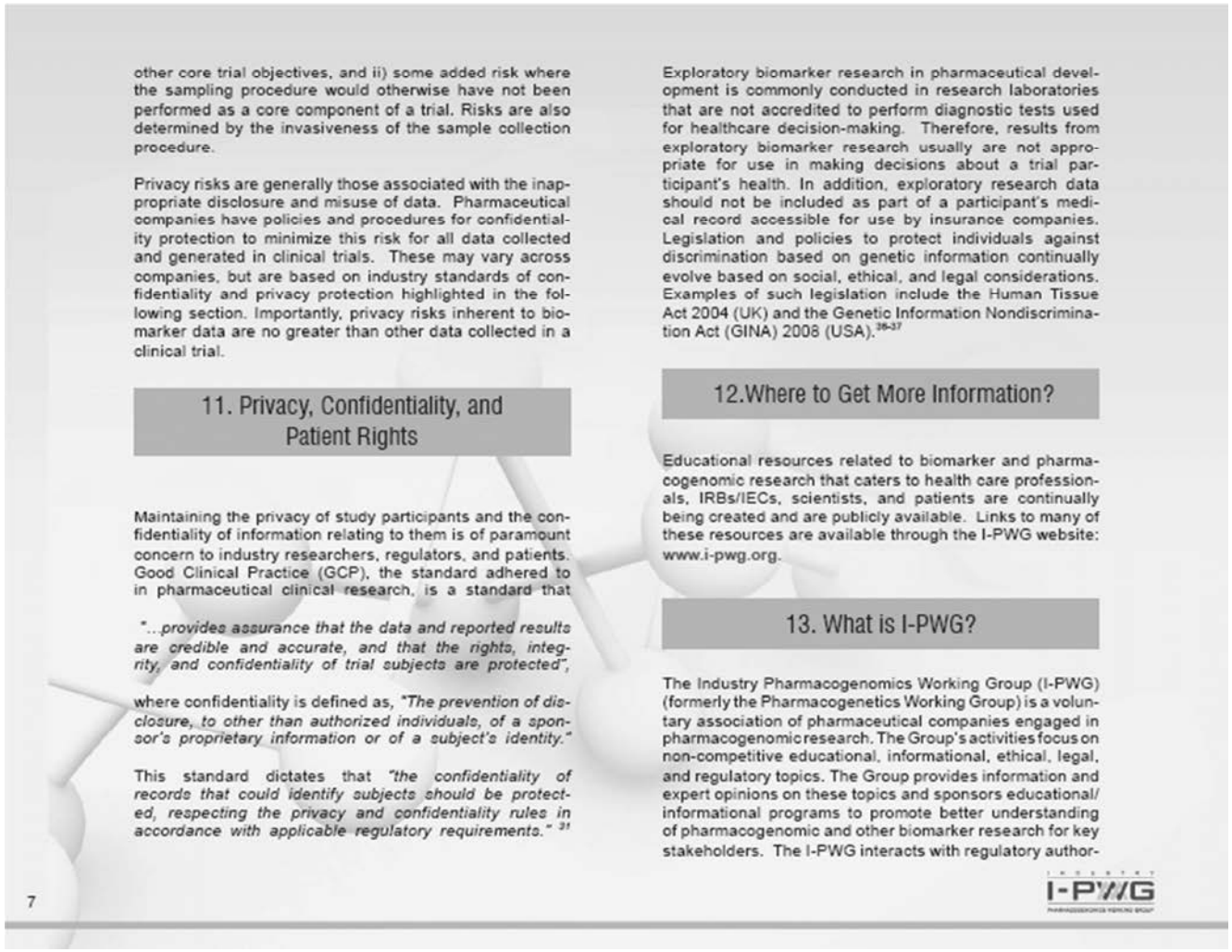

other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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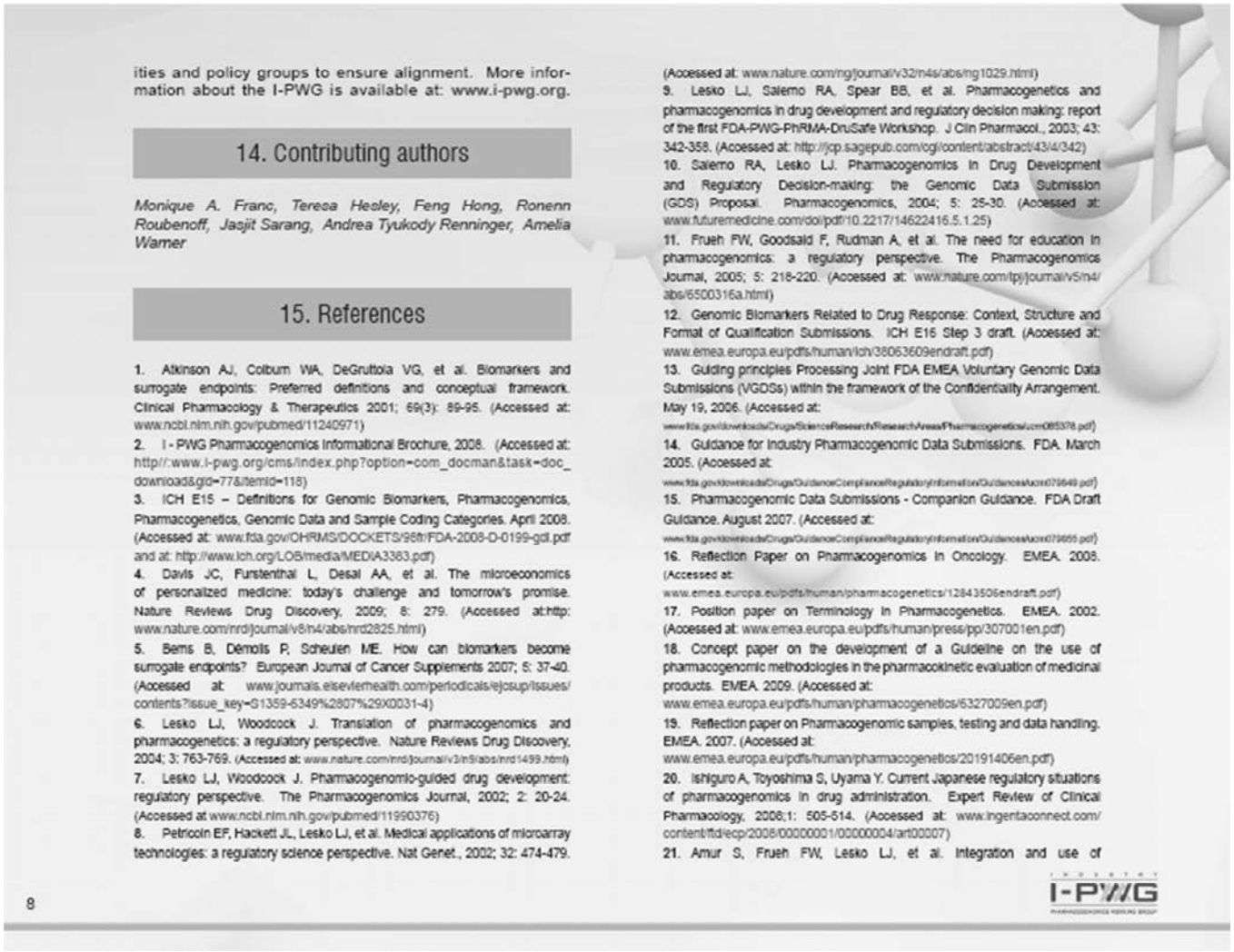

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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12.4 Approximate Blood Volumes Drawn by Trial Visit and by Sample Types

Adult Cohort

Trial Visit:	**Visits 1**	**Visit 2**
Blood Parameter	**Approximate Blood Volume (mL)**	
ECL/OPA Assay	40 mL	40 mL
Expected Total (mL)	40 mL	40 mL

Infant Cohort

Trial Visit:	**Visit 4**	**Visit 5**	**Visit 6**
Blood Parameter	**Approximate Blood Volume (mL)**		
ECL/OPA Assay	5 mL	5 mL	5 mL
Expected Total (mL)	5 mL	5 mL	5 mL

12.5 List of Abbreviations

ACIP	U.S. Advisory Committee on Immunization Practices
AEs	Adverse Events/Experiences
ASaT	All subjects as treated
CIs	Confidence Intervals
CSR	Clinical Study Report
DEG	Data Entry Guideline
eCRF	Electronic Case Report Form
eDMC	external Data Monitoring Committee
EOC	Executive Oversight Committee
ePRO	Electronic Patient Reported Outcome
ERC	Ethics Review Committee
EU	European Union
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
GCPs	Good Clinical Practices
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
HEENT	Head, Eyes, Ears, Nose and Throat
IB	Investigator's Brochure
ICF	Informed Consent Form
IPD	Invasive Pneumococcal Disease
IRB	Institutional Review Board
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
MAPA	Merck Aluminum Phosphate Adjuvant
MOPA-4	Multiplexed OPA Assay
MRL	Merck Research Laboratories
MSD	Meso-Scale Discovery
OPA	Opsonophagocytic Killing Activity

PCV	Pneumococcal Conjugate Vaccine
PD1	Postdose 1
PD3	Postdose 3
PD4	Postdose 4
Pn ECL	Pneumococcal Electrochemiluminescence
PnPs	Pneumococcal Polysaccharides
PP	Per-protocol
PRO	Patient Reported Outcome]
PS20	Polysorbate 20
PS80	Polysorbate 80
RCDC	Reverse Cumulative Distribution Curve
SAE	Serious Adverse Event/Experience
SAP	Statistical Analysis Plan
SOPs	Standard Operating Procedures
US	United States
VRC	Vaccination Report Card
WHO	World Health Organization

12.6 Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials

Protocol Specific Injection-Site AE Toxicity Guidance

Injection-Site AE Toxicity Grading Scale

Injection Site Reaction to Study Vaccine/Placebo*	Grade 1	Grade 2	Grade 3	Grade 4
Injection-site AEs occurring days 1 through 5 following receipt of study vaccine/placebo				
Pain/Tenderness	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Erythema/Redness	Size measured as B	Size measured as C or D	Size measured as E→	Necrosis or exfoliative dermatitis or results in ER visit or hospitalization
Induration/Swelling	Size measured as B	Size measured as C or D	Size measured as E→	Necrosis or ER visit or hospitalization
Other	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Any injection-site reaction that begins ≥ 6 days after receipt of study vaccine				
Pain/tenderness Erythema/Redness Induration/Swelling Other	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization

*Based upon information provided by the patient on the Vaccine Report Card (VRC) and verbally during VRC review. Erythema/Redness/Induration and Swelling are specific injection-site AEs with size designations of letters A through E→, based upon a graphic in the VRC. Size A is not assigned a toxicity grade; however, injection-site AEs that measure size A should be reported as adverse experiences. If the patient has an ER visit or is hospitalized for any injection-site AE, that AE is to be assigned a toxicity grade of 4, regardless of the size measured.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	