Immunogenicity of PPSV-23 after PCV-13 Vaccination in Adult Asthmatic Patients

NCT03260790

6/7/2018

IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Avni Joshi

Study Title: **Immunogenicity of PPSV-23 after PCV-13 Vaccination in Adult Asthmatic Patients**

Protocol version number and date: Protocol version number 3. 06/07/2018

Research Question and Aims

Hypothesis:

1) Priming with PCV13 will result in increased immunogenicity of PPSV23 in asthmatic subjects
2) Priming with PCV13 will result in durable immunogenicity of the PPSV23 in asthmatic subjects

Aims, purpose, or objectives:
Aim 1 will compare the safety and immunogenicity of PPSV23 and PCV13 vaccines in asthmatic subjects. The vaccine response of randomized asthmatic patients to either PPSV 23 alone (Group A) or PCV13 with PPSV23 given 8 weeks later (Group B) will be compared. Immunogenic response will be assessed and compared between groups at 8 and 16 weeks after vaccination.

Aim 2 will compare the changing of immunologic response in the two arms over the subsequent 8 weeks' time frame in both Group A and Group B.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):
S pneumoniae is the leading bacterial cause of pneumonia and invasive pneumococcal disease and is a significant cause of morbidity and mortality in the United States with $16.2 billion dollars spent in healthcare-related costs in 2013[1]. The CDC currently recommends the polysaccharide PPSV23 vaccination (Pneumovax®) in all adults over the age of 65 as well as in individuals with chronic lung disease.

Pneumococcal conjugate vaccine PCV13 (Prevnar ®), initially developed for use in children, is currently recommended for immunocompromised adults and individuals with cerebrospinal fluid leaks and cochlear implants. There is some debate as to whether PPSV23 leads to a decrease in prevalence of disease caused by *S. pneumoniae*, indeed, a 2009 meta-analysis funded by the WHO found that the evidence supporting its use was poor.[2] In 2014, vaccination guidelines changed to support the use of PCV13 in patients over the age of 65 after it was found to be efficacious in preventing community acquired pneumonia and invasive pneumococcal disease in the elderly population.[3] The PCV13 vaccine contains polysaccharide antigens conjugated with a protein carrier whereas the PPSV23 contains polysaccharide antigens alone. It is proposed that the conjugate vaccine induces immunity via a T-cell dependent process. Given that patients with asthma are disproportionately affected by pneumococcal disease, it is imperative that the vaccination strategy for pneumonia be as immunogenic and efficacious at eliciting a robust immune response as possible.

To address this, we propose to compare the response to PPSV23 with a novel schedule of PCV13 followed by PPSV23 given eight weeks later in adult patients with asthma. We will assess the immune system at 8 weeks and 16 weeks post vaccination. Given that the PCV13 vaccine elicits immunity via a T-cell dependent mechanism, we hypothesize that giving PCV13 in conjunction with PPSV23 will lead to an enhanced immune response in asthmatic patients.

References

1. American Lung Association. Trends in Pneumonia and Influenza Morbidity and Mortality. November 2015.
2. Huss A, Scott P, Stuck A, Trotter c, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. *CMAJ*. 2009; 180(1):48-58.
3. Isturiz R, Webber C. Prevention of adult pneumococcal pneumonia with the 13-valent pneumococcal conjugate vaccine: CAPiTA, the community-acquired pneumonia immunization trial in adults. *Hum Vaccin Immunother*. 2015; 11(7):1825-1827.

Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:
Subjects: 50 adult patients diagnosed with asthma will be recruited from patients seen in the Division of Allergic Diseases and from Primary Care; volunteers will also be solicited with flyers and electronic announcements. The patients recruited will be between 19 and 64 years of age. Exclusion criteria include

research exemption requested, history of PCV-13 vaccination, age≤19 or ≥64, history of cochlear implant, CSF leak, CHF, DM, CKD, HIV, CVID as well as patients who have received the PPSV23 vaccine in the last 5 years. Women who are pregnant will also be excluded from the study. They will be contacted at the end of their visit to discuss enrollment in the study by the research coordinator.

Protocol: The patients will then be randomized into either Group A (standard of care) or Group B (experimental group). At the week 0 time point, the patients will receive either PPSV23 vaccine (Group A) or PCV13 (Group B) and undergo a blood draw of 5mL for assessment of pre-vaccination serotype titers. Group A will undergo a 5mL draw for assessment of titers at week 8, 16, and 24 following vaccination. Group B will undergo vaccination with PPSV23 at Week 8 with 5mL draw for pneumococcal serotype titers as well as a blood draw at Week 16 and Week 24. Immunogenicity will be analyzed by assessing for serotype-specific IgG as well as total IgG binding. Samples will be run at Mayo Rochester, and samples will additionally be shipped to a third party, The Binding Site, for further antipneumococcal binding assays. The samples will be identified to The Binding Site only by their study-specific identification number (i.e. A01, B01 etc). The Binding Site will not receive any patient identifying information.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:
This study is being conducted by A Joshi, M Park, K Bachmann, and C McNulty. C McNulty, PGY4, has 9 months of dedicated research time.

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 50

Subject population (children, adults, groups): Adults

Inclusion Criteria: Ages 19 to 64 with diagnosis of asthma

Exclusion Criteria: Exclusion criteria include research exemption requested, history of PCV-13 vaccination, age<19 or >65, history of cochlear implant, CSF leak, CHF, DM, CKD, HIV, CVID as well as patients

who have received the PPSV23 vaccine in the last 5 years. Women who are pregnant will also be excluded from the study by performing 2 point of care urine pregnancy tests (prior to vaccinations)

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. x☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. x☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☐ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☐ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _15___ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) __4 times per year_____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: __15___ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

(3) Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range:

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☐ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.

Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

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HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	x	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	x	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	x	x
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	x	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☐ None

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Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Data Analysis:
For each of the 23 serotypes, exact, unconditional, 2-sided 95% confidence intervals (CIs) on the single proportions will be calculated using the F distribution. The 95% CIs for the difference in proportions ([PCV-13+PPSV23] – [PPSV23]) will be computed using the non-inferiority procedure of Chan and Zhang, using the standardized test statistic and γ=0.000001. Non-inferiority is declared if the lower CI for the difference is >-0.10. Similar procedures will be used for the evaluation of antibody concentrations after 12 months.
For the secondary endpoints, the pneumococcal IgG serotype antibody concentrations will be logarithmically transformed for analysis. Within each treatment group and for each antibody concentration separately, geometric means of the antibody concentrations will be calculated for each vaccine group. Two (2)-sided 95% CIs will be constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results will be computed using the Student *t* distribution. To assess differences between the 2 vaccine groups, the 95% CIs for geometric mean ratio will be computed using the Student *t* distribution for the mean difference of the measures on the log scale ([PCV-13+PPSV23] – [PPSV23]) Non-inferiority will be declared if the lower limit of the CI for the ratio was greater than 0.5 (2-fold criterion). In addition, the geometric mean fold rises from baseline to 12 month following PPSV23 in each arm, and corresponding 2-sided 95% CIs, will be calculated for each of the serotype-specific pneumococcal IgG responses. For formulation decision analyses, 99.8% CIs will be calculated.