Validate an Easy to Administer Algorithm to Define Penicillin (B-lactam) Allergy Status in STD Outpatients

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- International Conference on Harmonisation (ICH) GCP E6; 62 Federal Register 25691 (1997); and future revisions
- National Institutes of Health (NIH) Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator Signature:

Signed: _____ Date: _____

Name, Credentials
Title

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reactions
AE	Adverse Event
B-lactam	Beta-lactam antibiotics
BP	Blood pressure
CDM	Center for Data Management
CDMS	Clinical Data Management System
CFR	Code of Federal Regulations
CRF	Case Report Form
DHHS	Department of Health and Human Services
DM	Data Management
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DOC Group	Direct Oral Challenge Group
eCRF	Electronic Case Report Form
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GBS	Group B streptococcus
GCP	Good Clinical Practice
GI	Gastrointestinal
HAART	Highly Active Antiretroviral Therapy
HEENT	Head, ears, eyes, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgE	Immunoglobulin E
IM	Intramuscular
IRB	Institutional Review Board
IRT	Item Response Theory
mg	Milligram
ml	Milliliter
N	Number (typically refers to subjects)

NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
NPV	Negative Predictive Value
PCN	Penicillin
PD	Protocol Deviation
PE	Physical Exam
PN	Participant Number
PST Group	Penicillin Skin Test Group
SAP	Statistical Analysis Plan
SI	Site Investigator
STD	Sexually Transmitted Disease
U/ml	Units per milliliter
UK	United Kingdom
UPIRISO	Unanticipated problems involving risks to subjects or others
US	United States
USP	United States Pharmacopeia

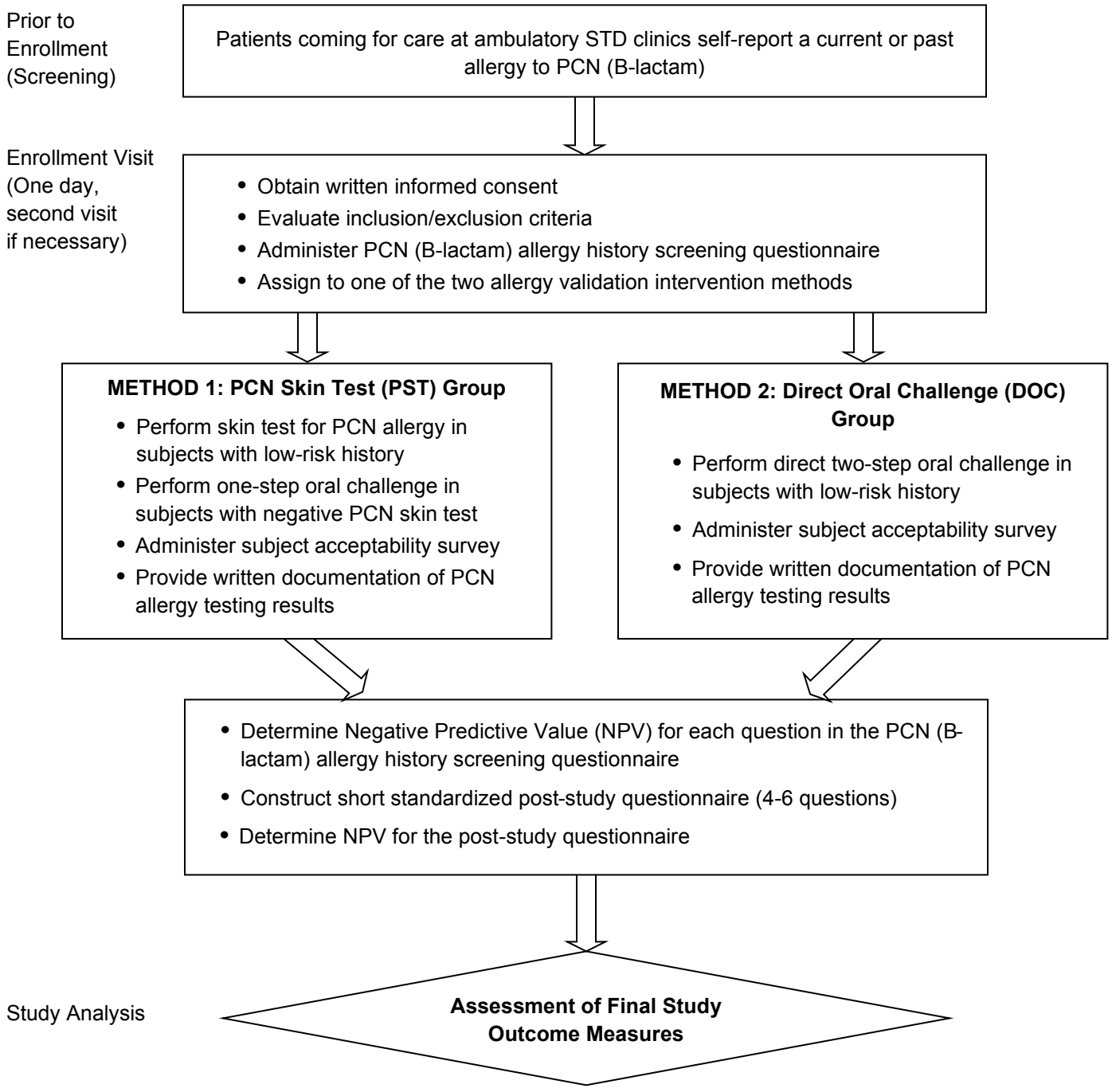
PROTOCOL SUMMARY

Title:	Validate an Easy to Administer Algorithm to Define Penicillin (B-lactam) Allergy Status in STD Outpatients
Population:	Approximately **5000** patients coming for care at Sexually Transmitted Disease (STD) clinics, emergency departments or ambulatory clinics will be screened to achieve **1000** evaluable subjects.
Number of Sites:	**Four**
Study Duration:	Approximately **27 months** from implementation of field activity through closure and analysis.
Participant Duration:	**One or two-visit study:** screening for eligible subjects with history of penicillin (PCN) (B-lactam) allergy; enrollment; same day administration of PCN (B-lactam) allergy history screening questionnaire. Each site will perform two allergy validation methods using a sequential enrollment design. **Method 1**: skin testing of subjects with low-risk history; one-step oral challenge of subjects with **negative** skin tests. **Method 2:** direct two-step oral challenge of subjects with low-risk history. If subject cannot stay to complete all study procedures, skin test and/or oral challenge may be completed another day.
Objectives:	Primary: • Validate an algorithm which incorporates a PCN (B-lactam) allergy history screening questionnaire followed by an allergy validation intervention — 1) skin testing and oral challenge or 2) direct two-step oral challenge — to produce a short standardized post-study questionnaire (4-6 questions) for use in ambulatory STD settings. • Determine how many subjects who report PCN (B-lactam) allergy can be treated with PCN or B-lactam drugs. Secondary: • Assess subject and provider acceptability of a PCN (B-lactam) allergy testing algorithm.

	• Determine the feasibility of implementing PCN skin testing followed by oral challenge for those who skin test negative or direct two-step oral challenge in an ambulatory STD setting.
Estimated Time to Complete Enrollment:	Approximately **14-16 months** for screening and enrollment.

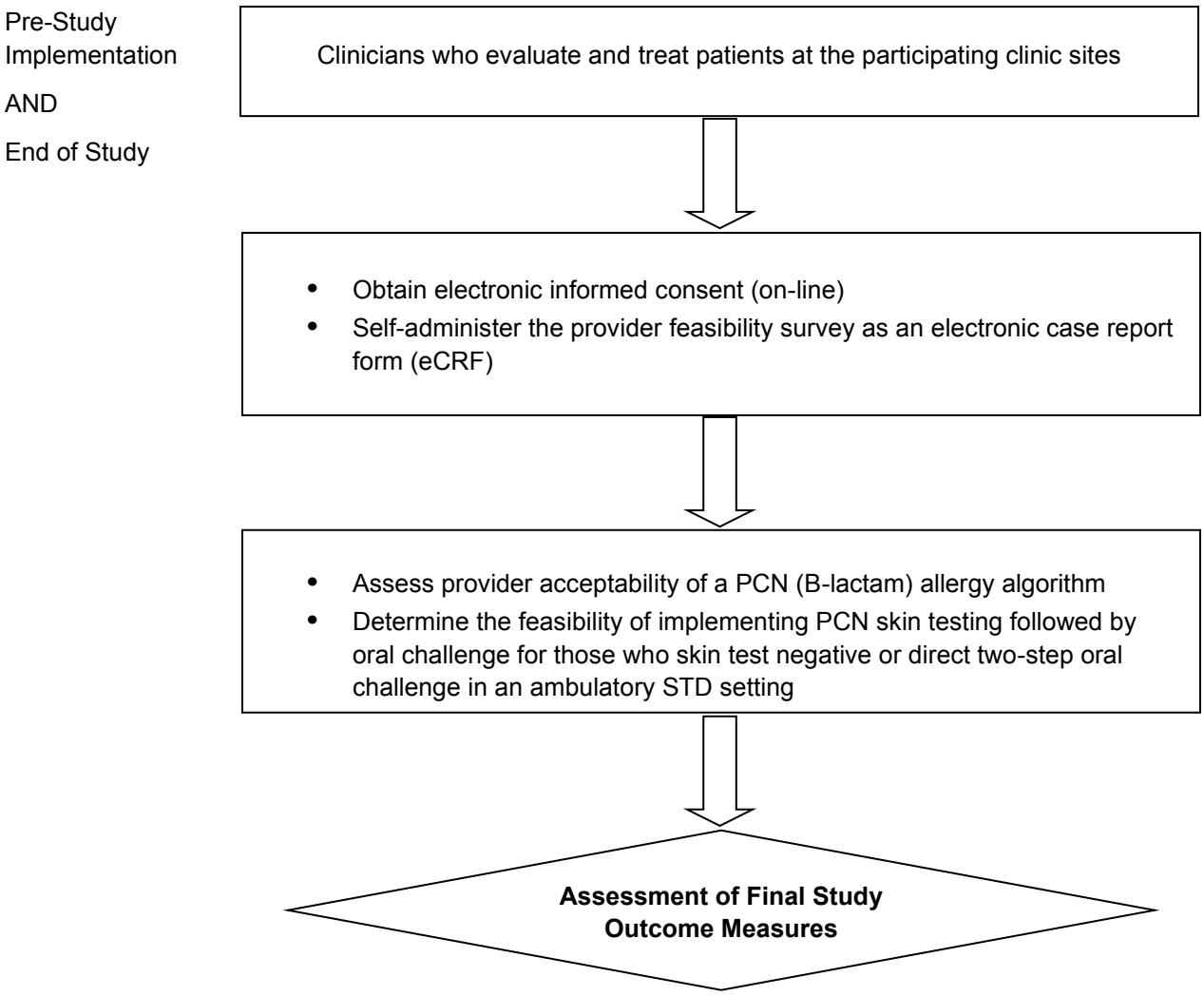
SCHEMATIC OF STUDY DESIGN

Total N: Approximately 5,000 patients screened to achieve 1,000 evaluable subjects.



SCHEMATIC OF PROVIDER FEASIBILITY SUB STUDY DESIGN

Total N: Up to 150 clinicians from the five participating clinics.



1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Penicillin and cephalosporins both belong to the B-lactam class of antibiotics. These antibiotics play a critical role in treatment of STDs such as syphilis and gonorrhea. Current first line therapy for syphilis is intramuscular benzathine penicillin and for gonorrhea it is the third-generation cephalosporin ceftriaxone. Although there is only limited cross reactivity between PCN allergy and third generation cephalosporins such as ceftriaxone, many clinical settings will not administer this drug to patients reporting PCN (B-lactam) allergy. Second line treatments for gonorrhea are not as effective, especially at non-genital sites of exposure.

There are no first line therapy options for syphilis patients who have B-lactam allergy. These patients are usually treated with doxycycline for a prolonged course. Treatment options for anorectal and pharyngeal gonorrhea are even more limited.

Up to 20% of patients seeking medical care report a history of PCN or B-lactam allergy.[1,2] However, when these patients are tested for allergy with formal skin testing, only a small minority of them are found to be allergic with immunoglobulin E (IgE) mediated hypersensitivity.[1,2] The term allergy is often conflated with any type of drug intolerance or intolerance history.[3] Most providers will not routinely administer B-lactam drugs to patients who report PCN allergy.[1,2] Over-reported penicillin allergy can adversely impact care in settings where STD care is provided.

It has been nearly three decades since PCN allergy was evaluated in the STD clinic setting by Gadde and coauthors[4] who studied this issue in Baltimore in the early 1990s. Of the 776 patients (among 5063 screened) who reported a PCN allergy history, only 55 (7.1%) had skin test reactivity, compared to 1.7% of 4287 with no allergy history. Higher skin reactivity rates were found in patients who reported anaphylaxis (17%) or urticaria (12%). Atopy rates were similar in both skin test positive and negative groups and was not useful as a predictive marker. No similar contemporary data are available.

More recently, the crisis of multiple drug resistant organisms and increased appreciation of PCN (B-lactam) allergy overdiagnosis has raised awareness of the issue. Overdiagnosis of PCN (B-lactam) allergy has been increasingly seen as a critical policy issue[5] related to antibiotic stewardship and health care costs.[6,7] Because patients with PCN (B-lactam) allergy are often administered second line drugs that are more broad spectrum and less efficacious, there are clear associations between patients with reported PCN (B-lactam) allergy and increased rates of *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus*,[8] surgical site infection for elective procedures,[9] overall length of stay and overall health care costs in a large Kaiser managed care population[10] and United Kingdom (UK) teaching hospitals.[11]

Although the impact of PCN (B-lactam) allergy on patient outcomes is substantial, in practice, few patients with reported allergy, when evaluated, have confirmed allergy.[5,7,10,12,13] Furthermore, anaphylaxis to penicillin and cephalosporins is rare. Macy[13] recently reviewed all penicillin and B-lactam use between 2009-2017 in the Kaiser Permanente Southern California system. Of 6,144,422 unique health plan members, 2,114,406 members received 4,558,1965 courses of oral PCNs, and 192,925 persons received 285,984 parenteral PCN courses. Of these, there were 32,133 new PCN allergy reports (0.66%) within 30 days. Anaphylaxis occurred in only 22 patients (1 in 207,191) with oral B-lactam exposures; there were only 2 severe cutaneous reactions, both of whom also had had exposure to cotrimoxazole. The clinical impression is that anaphylaxis is less common now than in the early B-lactam era, which may be due to purer preparations of drug, less parenteral administration and increased use of later generation B-lactams.[1,2]

The most reliable way to objectively define the presence of PCN allergy is by skin testing. Skin testing for PCN allergy can be easily performed as an outpatient with commercially available reagents (PRE-PEN® AllerQuest LLC, Plainville CT) and commercially available penicillin G. However, allergy referral and testing are typically either not available or difficult to access in most busy clinical settings, both inpatient and outpatient. Furthermore, the standard of care for STDs requires that patients be treated at the time of diagnosis or as soon as possible after exposure, which makes referral for allergy testing impractical. Therefore, patients who are being treated for syphilis or gonorrhea or contact exposure and who also report B-lactam allergy, are often treated with second line, and potentially less effective, therapy options, even though >90% may not have true allergy.

In clinical practice, because of the increasing demand for PCN (B-lactam) allergy evaluation and the lack of available allergist resources, various models to extend PCN skin testing have developed in both inpatient and outpatient settings. These models include testing and evaluation performed by hospitalists,[14] infectious diseases physicians,[15] pharmacists[16] and as part of routine pre-operative evaluations.[12]

The currently approved PRE-PEN® kits contain only the PCN major determinant (penicilloylpolylysine) and one minor determinant. Since some patients may react only to the PCN minor determinants, which may occur in up to a quarter of true allergic cases, the current kits are estimated to have a sensitivity of about 75%.[17] Skin testing itself is safe, even in sensitized subjects. In a large 2018 review, Adkinson[17] summarized 54 studies, which included 19,259 patients, and found a reported adverse event (AE) rate of 0.16%, none of which were serious or life threatening.

Therefore, absent approval of the newer comprehensive kit, there is consensus within the allergy community that to define an individual as PCN-allergy negative, skin testing should be supplemented by a single dose oral challenge (usually with amoxicillin 250 mg).

Because of the increased appreciation of the overreporting of PCN allergy, investigators have developed PCN allergy evaluation approaches that bypass the skin testing step[18] using risk

stratification criteria to identify patients with reported allergy who have a high negative probability of being truly reactive. Low risk was identified as having GI reaction only (nausea, vomiting), having family history without a direct personal history, having had a history of taking a B-lactam drug and having an ill-defined allergic reaction in the distant past (>5 years).

Higher-risk groups were described as having the following symptoms within a year: hives or other pruritic rash, blister or bullous skin eruption after B-lactams, or IgE related symptoms (swelling/angioedema, syncope, dyspnea/wheezing or hypotension).

The smaller clinical trials found that if patients had low-risk symptoms only (i.e., no higher-risk symptoms), then direct oral challenge was safe. Furthermore, on an institutional basis, these protocols are being adopted in practice settings, and have been implemented in a number of large health systems such as Kaiser Permanente in California and Partners Health in Massachusetts. There have also been smaller reports of similar risk stratification being used to optimize pre-operative prophylaxis.

2.2 Scientific Rationale

2.2.1 Predictive Model Approaches

There has been increased interest in developing predictive models for PCN (B-lactam) allergy. Santurino[19] employed a retrospective model to assess 466 patients from Salamanca, Spain who were evaluated for *any* adverse drug reaction (ADR) (only 27% were B-lactams). A multivariate model was constructed which found that the significant variables were age at time of reaction and symptoms suggestive of allergic disease. However, this study is limited because it was a relatively small sample, retrospective, assessed older patients with multiple comorbidities and medications, and assessed ADRs in general, not specific to B-lactams. It also started from the vantage point of individuals who were already diagnosed with an ADR, as opposed to those who had histories which are more likely to be remote.

A more robust approach was undertaken by Chiriac[20] who attempted to design a predictive model more specifically for B-lactam allergy, using patient populations with high prevalence of confirmed B-lactam allergy (26-31%). In the initial phase of the model development, they used retrospective patient data (training set) with 1991 patients. Of these, urticarial/angioedema was the most common symptom (43.5%). Interestingly, in the multivariate analyses, atopy and asthma were not associated. The significant factors for B-lactam allergy were immediate reaction, age (younger) at time of reaction, anaphylaxis and multiple episodes. After the model was developed, the authors adapted this to a prospective sample of 200 patients (validation set). Optimizing the model using different variable weights found that the model with the highest sensitivity was 98% in both the training and validation sets, but with an NPV of 77% in the retrospective training set and 85% in the prospective sample. Although this study highlights present dilemmas in accurate diagnosis of allergy without clinical testing, Blumenthal in, an

accompanying editorial,[21] points out that 1) this was a population with very high prevalence of true allergy; and 2) in typical outpatient clinic populations, the allergy prevalence is much lower than Chiriac's populations. Therefore, we would anticipate that the NPV would be much higher. Since our intent in this study is to develop algorithms which have high NPVs, this supports our hypothesis.

2.2.2 Development of Algorithms to Increase Use of B-lactams

Chiriac[22] recently reviewed the standardized drug allergy algorithms that were promulgated during the 2018 International Drug Allergy Symposium. These incorporated multiple algorithms, including large experiences from the Massachusetts General Hospital/Partners Health, Dartmouth, Mayo Clinic, Jacksonville, Rush University, University of Nebraska, University of Texas and groups from the UK and other systems. The authors noted that most patients report low risk allergy histories and, thus, many B-lactams are likely safe for use. Furthermore, standardized allergy algorithms can be used by trained personnel beyond allergy specialists, including medical doctors from other specialties, advanced practitioners, and pharmacists. The consensus algorithms included a series of elements:

- Definition of high-risk and low-risk phenotypes.
- Clinical practice guidelines for patients who had mild reactions were to use a different generation cephalosporin, to perform a test dose procedure or to provide access to skin testing.
- Recommendation to go directly to an oral challenge test dose without skin testing for low-risk patients whose reported "allergy" was more consistent with a non-allergic reaction (e.g., mild gastrointestinal (GI) distress). These algorithms are being increasingly adopted.

2.2.3 Oral Challenge Approaches

The approaches recommended in the increasingly used algorithms, in many cases, advise bypassing skin testing and going directly to an oral challenge in low-risk patients. Two recent studies evaluated the impact and safety of this approach.

Iammatteo[23] instituted a direct oral challenge procedure in drug allergy clinics at Montefiore Hospital in the Bronx, NY. This study enrolled subjects >7 years old with non-life-threatening reported reactions to PCN. The exclusions included bronchospasm, anaphylaxis, non-IgE syndromes such as Stevens Johnson, cutaneous and/or mucosal blisters, hypersensitivity vasculitis, nephritis, hepatitis or anemia. Of 165 patients screened, 159 were enrolled and 156 completed a graded challenge without skin testing but which also incorporated a placebo. Of those challenged, 19 had reactions of which only 4 were determined to be allergy mediated and all were mild. It should be noted that this study skipped skin testing entirely.

Macy instituted a large PCN allergy management protocol at Kaiser Permanente San Diego.[3] Between January 2017-December 2018, 806 patients had a direct oral challenge (no skin testing). Of these patients, 2 (0.2%) had an acute reaction, 9 (1.1%) had a delayed reaction; all were managed on-site with oral antihistamines or IM epinephrine; there were no hospitalizations. An additional 23 subjects (2.9%) had subjective reactions, such as mild nausea or headache.

Similarly, Blumenthal[24] implemented a risk-based algorithm in a large Boston based health system, and in a small study, directly challenged 83 low-risk patients in an outpatient setting. Of these patients, 3.6% experienced an immediate reaction (hives and rash), all resolved with treatment. In a larger antimicrobial stewardship-oriented intervention[25] which was performed in 5 acute care hospitals in 2016-17, patients with prior B-lactam allergy histories were evaluated using an EMR-based decision support tool and allergist consultation. A test dose of the prescribed B-lactam was administered in 1,045 instances to 942 patients with allergy histories considered low-risk. 96% of these cases did not have skin tests. Forty (3.6%) of patients had hypersensitivity reactions, 14 of which occurred within an hour of dosing. All were minor and treated successfully. Reactions were most frequent with late generation cephalosporins.

Mustafa evaluated[26] outpatients presenting to a Rochester allergy/immunology center in 2018. 363 patients reported PCN allergy of which 189 consented to evaluation.159 were randomized to either skin test evaluation or direct oral challenge. This study used a shorter observation period than previous investigators (30 minutes), and no adverse reactions were encountered.

Tucker[27] evaluated 402 US Marine recruits at a basic training site who reported PCN allergy. In the military basic training setting, PCN allergy has substantial impact because of the wide use of benzathine penicillin prophylaxis for epidemic Group A streptococcal diseases. By history, most of the reported reactions (76%) were cutaneous. 74 were skin tested negative and had amoxicillin challenge. The remaining 328 went directly to amoxicillin challenge and only 1.5% had cutaneous reactions, no anaphylaxis.

Over the past 3 years, there has been a marked increase in the number of reports of managing PCN allergy by stratifying risk and performing skin testing or direct challenge. When direct challenge is performed, the approach has typically involved using amoxicillin. The initial dose is 25mg of oral amoxicillin as a test dose, and after 30 minutes observation, followed with a 250mg dose, followed by 30–60-minute observation.

In almost all cases, even when adverse events or hypersensitivity reaction occurred, these were managed easily with oral antihistamines or IM epinephrine, with rapid resolution. These protocols are also increasingly being implemented in ambulatory clinics. Therefore, PCN allergy management can be implemented in most ambulatory STD settings.

2.2.4 Cephalosporin Challenge in Surgical Patients

One of the unique aspects about the STD setting is that antibiotic therapy is either single dose or very short term. This is especially true with gonorrhea, which is treated with a single dose of ceftriaxone. An analogous situation is perioperative antibiotic prophylaxis, in which cefazolin is almost universally recommended as first line therapy. Because of data demonstrating that surgical site infection is higher in patients treated with non-B-lactam regimens,[9] there has been interest in this area. Vaisman[28] evaluated 485 patients with reported PCN allergy. Using a conservative (sensitive) approach to identify allergy by history, he implemented a process to go directly to intravenous cefazolin surgical prophylaxis in low-risk patients. This was done in 267 patients (55%) without adverse reactions. Vorobeichik[29] recently performed an extensive review of the anesthesia literature. He concluded that overall anaphylaxis rates were extremely low (.0004%), and cited studies which found only 3 cases of cephalosporin anaphylaxis in >65,000 cases where patients had a history of PCN allergy and were administered perioperative cephalosporins. These rates were not significantly higher than patients who report no prior allergy history.

2.2.5 Cross Reactivity Between Penicillin and Cephalosporins

There is an extensive literature on the chemistry of B-lactams and the cross reactivity of penicillin and cephalosporin allergy. From a chemical basis, the key issue is the “R” group modifying the B-lactam ring. The literature is consistent in concluding that cross reactivity in clinical practice is highly overestimated. The most extensive recent review (2018) by Zagursky[30] reviewed cross reactivity in PCN allergy, including an extensive review of the chemical structures and a review of studies, which showed that there was limited cross reactivity between PCN and cephalosporins, even early generation cephalosporins compared to later generation cephalosporins. They concluded that “*there is ample evidence to allow the safe use of all but a few early generation cephalosporins in patients with penicillin or amoxicillin allergy. Patients with a history of penicillin allergy do have a general elevated risk of allergic reaction and may develop an allergic response to cephalosporins by coincidence, but the risk is comparable to that of receiving a sulfonamide antibiotics”.*

2.2.6 Moving Forward: Extending PCN (B-lactam) Allergy Testing and a Path to Improve STD Care

Increased interest in PCN (B-lactam) allergy testing and defining patient status has been driven by parallel trends which have included:

- Recognition that most patients who report PCN (B-lactam) allergy are actually not allergic;
- The public health crisis of antimicrobial resistance and recognition that alternative therapies for B-lactam drugs are often more broad-spectrum and may facilitate development of resistance;

- Recognition that overall clinical care costs may be higher in patients who are treated with alternative regimens;
- Recognition that alternative regimens are not as effective as B-lactam primary regimens.

As a result, there has been an explosion of interest in extending PCN (B-lactam) testing outside the traditional allergy office. In December 2018 and January 2019 alone, major reviews of this topic were published in the Lancet[1] and Journal of the American Medical Association,[2] both publications accompanied by educational materials to facilitate increased diagnostic testing.

Many experienced clinicians attempt to differentiate hypersensitivity from non-allergic reactions (i.e., non-allergic drug toxicity) by taking a careful history of the drug toxicity event(s). However, in the STD clinic setting, this may not be practical because of the wide variety of skills sets and expertise in these clinics. Because many clinics may not have physicians on staff 100% of the time and are ambulatory sites, there is a clear need to develop a path for an easy to administer instrument and testing algorithm that can be administered to patients who report a history of PCN (B-lactam) allergy. The instrument should have high sensitivity (for discerning which patients have true hypersensitivity) and a high NPV in clinic settings (important for clinicians and management) to enable B-lactam use to optimize treatment for a meaningful percentage of subjects who do not have allergy.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The risks associated with participation in the study are small. PCN skin tests are generally safe for adults and children of all ages, including infants. In certain circumstances, though, skin tests are not recommended. Skin testing with limited reagents may not be advised if:

- There is a strong history of a severe allergic reaction, e.g., anaphylaxis, within the past 10 years.
- The subject is taking medication that could interfere with test results. Antihistamines are the drugs most commonly associated with suppression of the skin test response.
- The subject has certain skin conditions which interfere with test interpretation, such as diffuse eczema or psoriasis.

The most common side effect of skin testing is slightly swollen, red, itchy bumps (wheals). These wheals may be most noticeable during the test. In some people, though, an area of swelling, redness and itching may develop a few hours after the test and persist for as long as a couple of days. These reactions can be treated with antihistamines, steroids or both.

Rarely, allergy skin tests can produce a severe, immediate allergic reaction such as swelling of the throat, difficulty breathing, a fast heart rate, or low blood pressure. These reactions are

largely eliminated by doing a preliminary prick (puncture) skin test which is part of the standard of care. Uncommonly, these symptoms can require immediate medical treatment with epinephrine.

Similarly, in people who skin test negative and are given an oral amoxicillin challenge, on rare occasions there can be an immediate or rapid development (within 6 hours) of a mild allergic reaction. This may include pruritis, rash or hives. In the vast majority of cases, these can be effectively treated with antihistamines.

Rarely, an oral challenge in an individual who skin tests negative can produce IgE-associated symptoms which can include rash, urticaria, bronchoconstriction and anaphylaxis requiring emergency care. Study staff at each site will be trained in managing these signs and symptoms and response kits will be available on site. The risk of this is estimated to be no different than that of an individual who does not have an allergy history.

2.3.2 Known Potential Benefits

Subjects may benefit from this study by finding out whether they have a true hypersensitivity to B-lactam drugs.

For many illnesses, PCN antibiotics are the best treatment options available. PCN antibiotics are often less expensive than other antibiotics. Other kinds of antibiotics may cause side effects. Antibiotics without PCN may lead to drug resistance which may make antibiotics less effective in the future.

3 OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objectives

- Validate an algorithm which incorporates a PCN (B-lactam) allergy history screening questionnaire followed by an allergy validation intervention — 1) skin testing and oral challenge or 2) direct two-step oral challenge — to produce a short standardized post-study questionnaire (4-6 questions) for use in ambulatory STD settings.
- Determine how many subjects who report PCN (B-lactam) allergy can be treated with PCN or B-lactam drugs.

3.1.2 Secondary Objectives

- Assess subject and provider acceptability of a PCN (B-lactam) allergy testing algorithm.
- Determine the feasibility of implementing PCN skin testing followed by oral challenge for those who skin test negative, or direct two-step oral challenge in an ambulatory STD setting.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

- Algorithm / PCN (B-lactam) allergy history screening questionnaire performance in ambulatory STD populations, specifically the NPV of the algorithm on true PCN (B-lactam) allergy.
- In ambulatory STD patients who report a history of PCN (B lactam) allergy and who have low-risk histories, determine the prevalence of PCN reactivity validated either by skin test or by direct oral challenge.

3.2.2 Secondary Outcome Measures

- Acceptability
  - Proportion of study subjects who find the testing procedures to be helpful.
  - Reasons why study subjects refuse to participate in the study or find the testing procedures to be of no value.
  - Proportion of study subjects who were negative on oral challenge who now feel confident in taking PCN or similar antibiotics.

- Proportion of study providers who will not offer PCN allergy assessment in the future.

- Feasibility
  - Proportion of study providers who will offer PCN allergy assessment in the future.
  - Reasons why study providers will not offer PCN allergy assessment in the future.
- Both acceptability and feasibility
  - Types and frequencies of elicited reactivity to PCN through skin testing and oral challenge among study subjects.

4 STUDY DESIGN

This will be a multicenter study screening approximately 5,000 men and women (to achieve 1,000 evaluable participants) from different geographic areas of the US over a 14-16-month recruitment period (200 participants per site over the recruitment period). We will screen and enroll eligible individuals coming for care at ambulatory STD clinics and similar venues who self-report a history of PCN allergy.

Two methods of validating PCN allergy will be used:

- **Method 1 – PCN Skin Test (PST) Group:** skin testing of subjects with low-risk history followed by one-step oral challenge of subjects with negative skin tests.
- **Method 2 – Direct Oral Challenge (DOC) Group:** direct two-step oral challenge of subjects with low-risk history.

Each site will perform both methods, using a sequential enrollment process (See Section 4.1). All participants will be administered the same PCN (B-lactam) allergy history screening questionnaire.

4.1 Assignment to Intervention Group (PST or DOC)

Each site will perform both allergy validation interventions, Method 1 PST Group and Method 2 DOC Group. The anticipated enrollment at each site will be 200 subjects overall; 100 in each group. Since each intervention has different logistical considerations, sites will enroll subjects in sequential block groups of 25. Sites will be assigned the order of block groups randomly.

For example, sites that are assigned to begin with PST will enroll the first 25 subjects into the PST group, then follow with 25 subjects in the DOC group, then PST, etc. until the full 200 are enrolled. Similarly, sites assigned to start with the DOC intervention will enroll the first 25 subjects using the DOC, followed by 25 in PST, then DOC etc., until the full 200 are enrolled. Therefore, each site will enroll 8 block groups, 4 in each allergy validation intervention.

Method 1: Enrollment in the PST Group

Site staff will review the responses from the allergy history screening questionnaire to identify subjects who have low-risk criteria for immediate hypersensitivity (see Sec 6.1.2.1). These subjects will receive penicillin skin testing. All subjects who have negative skin tests will be offered a one-step oral challenge for final validation. Subjects who report higher-risk criteria will be referred to an allergy provider.

Method 2: Enrollment in the DOC Group

Site staff will review the responses provided on the allergy history screening questionnaire to identify subjects who have low-risk criteria for immediate hypersensitivity (see Sec 6.1.2.1).

These subjects will be offered a two-step direct oral amoxicillin challenge to validate absence of allergy. Subjects who report higher-risk criteria will be referred to an allergy provider.

We anticipate that screening, consenting, enrollment of subjects with a history of PCN (B-lactam) allergy and all study procedures will take place during one or two clinic visits. Study sites can also choose to do oral or electronic consents and complete initial screening assessments (including the Allergy History Questionnaire) by telephone. The length of the study visit will be about 1-3 hours in addition to the clinical appointment depending into which method of PCN allergy validation the participant is enrolled. All participants will be screened for study interest and eligibility. Once participants have given their written, oral, or electronic consent and been enrolled, study staff will administer the PCN (B-lactam) allergy history screening questionnaire. All participants who complete the skin testing and/or oral challenge will be asked to complete an acceptability survey on the PCN testing procedures at the end of the study visit. See the table below for the anticipated length of time the study visit will take for both the PST and the DOC Groups.

Study Procedures	**Anticipated Length of Time**
PST Group	
• Screening, informed consent, enrollment	30 minutes
• Allergy history screening questionnaire*	30 minutes
• Skin testing (if qualified to receive)	30-60 minutes
• Oral challenge observation (if qualified to receive)	60 minutes
• Acceptability survey on the PCN testing procedures	10 minutes
TOTAL	1 to 3¼ hours
DOC group	
• Screening, informed consent, enrollment	30 minutes
• Allergy history screening questionnaire*	30 minutes
• Oral challenge 1st step observation (if qualified to receive)	30 minutes
• Oral challenge 2nd step observation (if qualified to receive)	30 minutes
• Acceptability survey on the PCN testing procedures	10 minutes
TOTAL	1 – 2¼ hours

* If subjects have a higher-risk history of allergy based on responses to the questionnaire, their study participation will be complete after 1 hour.

If enrolled subjects cannot complete all study procedures for which they are qualified during the clinic visit, study staff will give them the option to return at a later date (within six weeks from the

screening visit) to complete the skin testing and/or oral challenge and subject acceptability survey.

This study will assess reported PCN (B-lactam) allergy. Although the ultimate goal is to optimize therapy for patients with syphilis and gonorrhea who report PCN allergy, for this study patients attending the clinic venues for any reason (visit or diagnosis) will be eligible.

We recognize that clinics have operational and throughput concerns. Since we are assessing allergy issues only, the procedures outlined in this protocol can be conducted at any time during the clinic visit, including after treatment has been administered. Usual clinical management, including treatment and partner services, will not be modified because of the study.

At some clinic visits, subjects may require treatment for STDs with medications that could confound the evaluation of the oral challenge test results. In these cases, the clinicians may opt to either delay administration of therapy in the clinic until after the oral challenge is completed or provide STD treatment, administer the PCN (B-lactam) allergy history screening questionnaire, perform the skin test and then ask the subject to return to the clinic within the next 6 weeks for the oral challenge.

5 STUDY POPULATION

5.1 Selection of the Study Population

Approximately 5,000 males and females, 18 years and older, from participating STD clinics, emergency departments or ambulatory clinics in different regions of the US will be screened to enroll 1,000 evaluable participants who meet all eligibility criteria. The target study population will be patients coming for care at the participating clinic sites who self-report a current or past allergy to PCN or B-lactams.

Study staff will inform potential participants of the study, obtain informed consent, and determine study eligibility. Individuals who meet all study eligibility criteria and agree to participate will be enrolled.

5.2 Inclusion/Exclusion Criteria

5.2.1 Subject Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible to participate in the study:

- 18 years of age or older
- Be able to provide informed consent
- Report having a history of allergy to PCN or B-lactam drugs

5.2.2 Subject Exclusion Criteria

Subjects meeting any of the following criteria at baseline will be excluded from study participation:

- Not able to stay for testing and challenge (1-3 hours) on day of clinic visit (or return within 6 weeks to complete study procedures)
- Other exclusion criteria, per clinical judgment, which prohibits enrolling in study

5.3 Pregnant Subjects

There is no contraindication to enrolling pregnant subjects and administering the questionnaire or performing skin testing. PCN skin testing is safe in this population and is frequently performed. Pregnant women will not undergo the direct oral challenge with amoxicillin to verify PCN allergy. Pregnant women will be enrolled in the PST Group, complete the questionnaire, and have skin testing performed. If necessary, pregnant women may return to the clinic within 6-weeks to complete the skin testing. Pregnancy will be determined by self-report and/or the

standard procedures employed in the participating clinic to diagnose pregnancy when clinically indicated. All clinics have access to point-of-care pregnancy tests.

There is substantial benefit in pregnancy of “delabeling” a PCN (B-lactam) allergy since PCN is the only recommended therapy for syphilis in pregnancy, and B-lactam drugs are the preferred treatment for bacterial infections, such as amoxicillin for Group B streptococcus (GBS) and ceftriaxone for gonorrhea. The ambulatory STD settings in this study service patient populations at higher risk of GBS.

5.4 Provider Feasibility Sub Study Population

At each site, we will conduct a short feasibility Sub Study among the clinicians to determine the practicality of performing PCN (B-lactam) skin testing and oral challenge in the ambulatory STD setting (see secondary objective). Since this is an operational feasibility assessment, the sampled population will be clinicians who evaluate and treat patients at the participating clinic sites. The surveys will be administered once at the beginning of the study and again at the end. We estimate that there will be 15-30 eligible clinicians per site over the course of the study. Accounting for personnel turnover, we anticipate that the total sample will be no more than 150 individual respondents.

6 STUDY PROCEDURES/EVALUATIONS

6.1 Study Procedures

Operational implementation of study screening, enrollment and testing procedures will vary across the study sites. For example, depending on the operational considerations of the site, individuals may be screened in the waiting area, by the clinician and study staff during the actual clinic visit, or by study staff after the clinic visit has been completed. In some clinics it may be possible to perform the clinic visit procedures during the 30 to 60-minute ± 10 minutes oral amoxicillin challenge observation period.

Clinical exams will be conducted as appropriate for the visit, but the clinic procedures are not included as part of the protocol. Study staff will emphasize to potential subjects that the expected time commitment involved in completing the study procedures is in addition to the time for the standard of care clinic procedures. A key operational study outcome is discovering if the time commitment involved is a barrier for both subjects and/or providers to allergy testing in ambulatory STD settings.

6.1.1 Screening

Screening will occur through mechanisms allowable at the individual sites including virtual screening and/or referral of individuals who have a prior history of reporting PCN allergy. If waiting room recruitment is permitted, study staff will approach potential subjects systematically, inform them that we are doing a study to optimize antibiotic use in ambulatory STD settings and ask if they were ever told they had an allergy to PCN or similar antibiotic. Subjects who report an allergy will be asked if they are interested in participating in the study. If the subject expresses interest, study staff will review the inclusion/exclusion criteria checklist to ensure the subject is eligible for enrollment. We will use standardized and Institutional Review Board (IRB)-approved screening scripts at all sites. All participants who are eligible for enrollment will be assigned a unique 5-digit participant number (PN). The same PN will be used if the participant is enrolled.

In some clinics, direct recruitment in the waiting room is not permitted. In these cases, we will post study advertising materials in the clinic waiting area promoting a study for individuals who have a history of PCN or B-lactam allergy. The clinic receptionist can also provide information to patients at time of registration. The recruitment materials will ask, “Do you have a history of penicillin or other antibiotic allergy?” or, “Have you ever been told that you are allergic to penicillin or other antibiotics?” Patients will be instructed to contact study staff in the clinic. Clinic providers may also refer patients to the study team.

Some clinics collect drug allergy information in the pre-visit medical history form. In these settings we will use a Health Insurance Portability and Accountability Act (HIPAA) Waiver of

Authorization to pre-screen potential subjects' medical records for drug allergy. Interviewers will confirm that the drug allergy is to PCN or B-lactam.

If a potential participant meets all inclusion/exclusion criteria but declines to consent or enroll in the study, study staff will record the reason they are not interested in participating in the study on a case report form (CRF). No identifying participant information will be collected unless the participant consents for enrollment.

6.1.2 Enrollment Visit (One Visit, Second Visit if Necessary)

After the participant provides informed consent, study staff will note the date the informed consent form (ICF) was signed and appropriate eligibility information on a CRF. Study staff will discuss basic demographic information with each participant and record the information on a CRF. Study CRFs will be maintained in the participant's research study record. Study staff will then administer the PCN (B-lactam) allergy history screening questionnaire to all participants using an iPad. Concomitant medication information will be collected.

All participants successfully screened, consented, and enrolled in the study will undergo the following procedures:

- Written, oral, or electronic informed consent to participate in this study
- Assessment of eligibility
- Enrollment in the study
- Assignment to allergy validation method
- Collection of demographic information (age, gender, race/ethnicity)
- Collection of contact information
- Administration of PCN (B-lactam) allergy history screening questionnaire
- Collection of concomitant medication information
- If antibiotic allergy history shows a low-risk history of PCN (B-lactam) allergy, option to receive skin test (if assigned to PST Group) or direct oral challenge (if assigned to DOC Group)

6.1.2.1 Subject Classification after Administration of PCN (B-lactam) Allergy History Screening Questionnaire (Appendix B)

Subjects will be classified as having a Low-Risk History or a Higher-Risk History for PCN allergy based on their responses to the PCN (B-lactam) allergy history screening questionnaire. These allergy history categories are defined based on positive responses to the questionnaire elements[13,18,24,26].

Low-Risk History

- Isolated GI upset (*diarrhea, nausea, vomiting, abdominal pain*)
- Chills (*rigors*)

- Headache
- Fatigue
- Itching (pruritus), self-limited
- Rash (including maculopapular rash)
- Hives (greater than 5 years ago)
- Flushing / redness
- Family history
- Patient denies allergy history but is in medical record

Higher-Risk History

- Angioedema or swelling of lip, tongue, or around eyes
- Wheezing / chest tightness moderate or severe shortness of breath
- Throat tightness which affected ability to breathe
- Hypotension without rapid recovery
- Arrhythmia / irregular heartbeat or palpitations
- Syncope / pass out / dizzy
- Anaphylaxis or sudden drop in blood pressure
- Hives (5 years or less)

Late effects (higher-risk events which occurred >24 hours after drug administration)

- Stevens-Johnson syndrome (Loss >10% of skin)
- Organ injury (liver, kidney)
- Low Platelets
- Drug reaction eosinophilia and systemic symptoms (rash with eosinophilia and organ injury)
- Acute generalized exanthem (rash with pustules)
- Dystonia or muscles became very stiff or very weak
- Serum sickness (rash with joint pain, fever, myalgia)
- Anemia
- Documented drug fever
- Erythema multiforme (rash with target lesions)
- Hives (5 years or less)

6.1.2.2 Procedures After Defining Risk Category

Subjects classified with a low-risk history will progress to either skin testing (PST Group) or direct oral challenge (DOC Group), depending on which method of validating PCN allergy they are assigned. Subjects who meet the higher-risk classification will be advised that further elucidation of their allergy status will require a formal allergy evaluation. Referral resources will be provided.

All participants classified as low-risk and who meet additional qualification criteria to receive allergy testing (See Sec 6.1.3) will undergo the following procedures:

ASSIGNED TO PST GROUP

- Administration of skin test (prick test first and, if indicated, intradermal test)
- If skin test results are negative, option to receive oral challenge of 250 mg of amoxicillin
- Pre-oral challenge brief PE, assessment of vital signs and measurement of peak flow
- Administration of oral challenge
- Post-oral challenge brief PE, vital sign assessment and peak flow measurement

ASSIGNED TO DOC GROUP

- Pre-oral challenge brief PE, assessment of vital signs and measurement of peak flow
- Administration of oral challenge (first step) of 25 mg of amoxicillin, vital sign assessment and, if indicated, administration of oral challenge (second step) of 250 mg of amoxicillin
- Post-oral challenge brief PE, vital sign assessment and peak flow measurement

All participants will undergo the following procedures after allergy validation methods are offered or completed:

- Administration of subject acceptability survey on PCN testing procedures for all subjects who were offered skin testing (with or without oral challenge) or direct oral challenge
- Written documentation of PCN allergy testing results for all subjects who received skin testing (with or without oral challenge) or direct oral challenge to share with subject's medical care providers

6.1.3 Additional Subject Qualification Criteria to Receive Allergy Testing

Subjects classified as low-risk after administration of the PCN (B-lactam) allergy history screening questionnaire and who meet any of the following criteria will be ruled out for skin testing and/or direct oral challenge:

- Known (per medical record or self-report) Human Immunodeficiency Virus (HIV) which is not controlled (defined as any of the following):
  - Not on Highly Active Antiretroviral Therapy (HAART)
  - CD4 <200 in the last 6 months
- Use of oral antihistamines within 1 week of visit. (Subjects can be advised to stop antihistamines and return after 7 days)
- Diffuse eczema, psoriasis, tattoos or other skin condition that would preclude skin testing
- Tachycardia: Pulse >100
- Tachypnea: Respiration rate >16

- Elevated blood pressure (BP) defined as either systolic >160mm or diastolic >100mm
- Uncontrolled asthma or wheezes present on physical exam (PE)
- Angioedema present on PE
- Stridor of throat, tonsils or uvula, or stridor present on PE
- Maculopapular rash or disseminated pruritis on >2 body areas which developed within 1 week prior to the visit.*

  Note: This exclusion does not apply to subjects with psoriasis or other chronic skin conditions. These subjects qualify if the forearm where the skin testing is performed is uninvolved.

6.2 PCN Skin Testing

Depending on the outcome of the PCN (B-lactam) allergy history screening questionnaire, participants may qualify to receive the PCN skin test.

- Participants with a higher risk of PCN allergy will not proceed to the PCN skin test or oral challenge. Their study participation will be complete. Subjects will be provided with a written referral to local allergy providers.
- Participants with a low risk of PCN allergy and assigned to the PST intervention group will be offered the PCN skin test.

Staff will verify that qualified participants do not meet any additional criteria that would preclude them from skin testing using the Skin Test Qualification Checklist. Study staff will explain the skin testing procedures to participants who may decide to accept or decline skin testing. If they decline, they will be asked to complete the subject acceptability survey and their study participation will be complete. Staff will note the reason(s) they declined to be skin tested on the appropriate CRF.

Study staff will perform the allergy skin testing for PCN allergy in accordance with standard allergy testing procedures and instructions provided in the PRE-PEN® kit package insert.[31] Prick (Puncture) tests will be performed before proceeding to intradermal testing. Prick testing is performed at marked sites on the inner volar aspect of the forearm. Testing for controls and each reagent is performed singly.

Reagents and controls for prick and intradermal tests include:

1. Controls:
   a.) Negative Control: Sodium chloride solution without preservative

* e.g., patients presenting with secondary syphilis

b.) Positive Control: Histamine:
   i. Prick testing: histamine base 1 mg/ml
   ii. Intradermal testing: histamine base 0.1 mg/ml

2. Reagents:
   a.) PRE-PEN® (major determinant)
   b.) Penicillin G 10,000 U/ml (minor determinant)

Intradermal testing will not be performed if there is a positive or uninterpretable reaction to PRE-PEN® and/or Penicillin G during the prick test. If the prick skin test results are negative the participant is qualified for intradermal testing. Study staff will perform duplicate intradermal skin testing of each reagent and single intradermal skin testing of the positive and negative controls on the inner volar aspect of the forearm. The same arm will be used for both prick and intradermal testing.

If there is a positive reaction to PRE-PEN® and/or Penicillin G during the prick test or the intradermal test, the participant is ruled out of the oral challenge with amoxicillin 250 mg. They will be counseled that their PCN allergy history was confirmed. Written documentation will be provided to the subject with instructions to share with their medical provider(s).

If the result of the intradermal test is ambiguous (equivocal), the intradermal test will be repeated with both reagents and the negative control in duplicate or, depending on each study clinic's procedures, the subject will be referred to a local allergy consultant or clinic. If the repeat intradermal test is positive or ambiguous or the initial reaction was uninterpretable, the participant will not proceed to the oral challenge and will be referred to an allergist for further evaluation.

Study staff will photograph the subject's arm to document the results of the skin test reactions using an iPad. No identifiers except a label containing the PN and a measuring guide will be included in the photograph. The images will be uploaded to the clinical database. Complete skin test responses (both prick and intradermal) will be recorded on the PCN skin test results CRF.

Occasionally, allergy skin tests can produce a severe, immediate allergic reaction. These are largely eliminated by doing the preliminary prick skin test. These can be treated with antihistamines, steroids or both. Infrequently, these symptoms this can require immediate medical treatment with epinephrine.

6.2.1 Oral Challenge Following a Negative Skin Test

In PST group subjects with negative skin test results, the absence of allergy will be confirmed by administering a single oral dose of amoxicillin 250 mg followed by one hour of observation to ensure that an immediate reaction does not occur.

6.3 Amoxicillin Oral Challenge

Study staff will explain the oral challenge testing procedures to all qualified participants in both allergy validation intervention groups who may decide to accept or decline the oral challenge. If they decline, they will be asked to complete the subject acceptability survey and their study participation will be complete. Staff will note the reason(s) a subject declined to take the oral challenge on the appropriate CRF.

For those who consent to oral challenge, study team will perform a focused PE and record vital signs (including peak flow) on the oral challenge testing results CRF before the oral challenge is performed. The focused PE will include:

- Eyes: Documentation of no angioedema
- Pharynx: Documentation of no stridor
- Lungs: Documentation of no wheezing or uncontrolled asthma
- Skin: Documentation of no maculopapular rash, disseminated pruritis or urticaria

Staff will verify that qualified participants do not meet any additional criteria that would preclude them from oral challenge using the Oral Challenge Qualification Checklist. At baseline, if subjects have pulse >100, respiration rate >16, or elevated BP (defined as systolic >160mm or diastolic >100mm), the oral challenge will not be performed. Additional reasons assessed during the focused PE for not receiving the oral challenge are listed in Section 6.1.3 and summarized in the listing above.

6.3.1 One-step Oral Challenge (PST Group)

After confirming the participant is qualified, amoxicillin 250 mg will be administered, and time of administration will be recorded. The subjects will be observed for 60 minutes± 10 minutes, after which vital signs, the PE and peak flow will be repeated. Note that each observation time point has a time window of +/- 10 minutes.

If subjects report the presence of difficulty breathing, swelling in lip/mouth/tongue/throat, eye itchiness/tearing, skin hives/itchiness or abdominal pain/nausea/vomiting while they are waiting for final evaluation, study staff will include the reactions with the post-oral challenge vital signs and the focused PE assessment performed after the 60-minute observation period ± 10 minutes. Standard treatment will be provided, including antihistamines, steroids and/or epinephrine, if indicated and dependent on the specific medical condition that arises.

If vital signs (including peak flow) and focused PE are within reasonable limits after the 60-minute ± 10 minutes waiting period, the subject will be counseled that they do not have an allergy to PCN (B-lactams). They will be provided with written documentation that they will be encouraged to share with their medical providers, including the STD clinic and their primary care physician (if they have one).

6.3.2 Two-step Direct Oral Challenge (DOC Group)

Preliminary Dose

After confirming the participant is qualified, amoxicillin 25 mg will be administered, and time of administration will be recorded. The subjects will be observed for 30 minutes ± 10 minutes, after which vital signs including peak flow will be repeated.

Administration of Full Challenge Dose

If vital signs are within reasonable limits after the 30-minute ± 10 minutes waiting period, the subject will be given the full challenge dose of 250 mg amoxicillin. The subject will be observed for an additional 30 minutes ± 10 minutes , after which vital signs, the PE and peak flow will be repeated.

If subjects report the presence of difficulty breathing, swelling in lip/mouth/tongue/throat, eye itchiness/tearing, skin hives/itchiness or abdominal pain/nausea/vomiting while they are waiting for final evaluation, study staff will include the reactions with the post-oral challenge vital signs and the focused PE assessment performed after 30-minute ± 10 minutes observation period. Standard treatment will be provided, including antihistamines, steroids and/or epinephrine, if indicated and dependent on the specific medical condition that arises.

6.3.3 Final Outcomes and Determination of Allergy Status

If vital signs (including peak flow) and focused PE are within reasonable limits after the applicable observation periods, subjects will be counseled that they do not have an allergy to PCN (B-lactams). They will be provided with written documentation that they will be encouraged to share with their medical providers, including the STD clinic and their primary care physician (if they have one).

Final outcomes of the oral challenge will be recorded on a CRF as no reaction (negative), reaction (positive) or unevaluable (if the participant leaves the clinic before the applicable observation period is completed). If there is a reaction, after providing standard treatment, study staff will record the type of reaction, severity and how long after the amoxicillin was administered it occurred on the oral challenge testing results CRF.

If reactions to the amoxicillin oral challenge occur, they will be graded and documented using the Toxicity Table (Appendix C).

Rarely, an oral challenge in an individual who skin tests negative can produce an acute reaction (e.g., anaphylaxis) requiring emergency care. Unexpected reactions that place a subject at increased risk will be treated as necessary and reported to the IRB and DMID as required.

6.3.4 Managing STD Treatment and Oral Challenge

In some cases, subjects will require treatment for STDs at the visit with medications which may have side effects. This could confound the results from the oral challenge. If there are concerns, the clinicians may opt to delay administration of therapy until after the oral challenge is completed in the clinic or provide STD treatment, administer the PCN (B-lactam) allergy history screening questionnaire, perform the skin test and have the subject return to clinic for the oral challenge within 6 weeks of the clinic visit.

6.4 Study Completion and Documentation of Allergy Testing Results

After the skin testing and/or oral challenge is completed, the participants will be asked to complete the subject acceptability survey to get their opinion of the PCN testing procedures conducted during the study, their results, and the subject's confidence that they will be able to take PCN (B-lactam) drugs in the future.

The subjects will be provided written documentation of the PCN (B-lactam) allergy testing procedures performed including a description of the skin testing and oral challenge, and verification of their PCN allergy test results (negative, positive or referral to allergist for further testing), which they will be encouraged to share with their medical providers.

In addition, we will provide the local STD clinic with the results, and these can be inserted into the medical record, as appropriate.

Subjects who have higher-risk histories which preclude skin testing and direct oral challenge or have ambiguous or uninterpretable results will be provided with a referral to local allergy providers. Each research site will maintain a list of local allergy providers for referral.

There are no follow up visits required. Subjects will be given instructions to contact study staff in the unlikely event of complications.

Incentives for a participant's time, transportation, and other expenses will be provided according to local IRB approval. Study staff will provide incentives depending on what procedures from the study visit the participant completed.

6.5 Provider Feasibility Sub study

A key operational question is provider acceptability and feasibility of PCN allergy evaluation including the allergy history screening questionnaire, skin testing and oral challenge in busy ambulatory STD settings. We will administer a brief electronic survey to providers at each of the clinics before implementation of the study and again at study conclusion. Since these are short surveys, and focus exclusively on clinical practice characteristics, consent will be obtained using either on-line consent or through an oral consent process.

All clinic providers who complete the provider feasibility survey will undergo the following procedures:

- Electronic informed consent (on-line or oral) to participate in the sub study
- Self-administration of the provider feasibility survey as an eCRF both pre-study implementation and at the end of the study

Although pre/post evaluation data will be available in aggregate, all clinic-based providers will be assigned a 5-digit Provider ID number which will be used to compare responses for individual providers at the beginning and end of the study. We anticipate that among the 5 participating clinics, we should be able to generate 50-100 surveys from staff who were present at the beginning and at the end of study. We anticipate that the total number of respondents will be no more than 150.

6.6 Data Handling, Data Quality Control and Record Keeping

For this study the FHI 360 Center for Data Management (CDM) will be responsible for all issues relating to data collection (forms, tools, and systems), quality control, and management. FHI 360 Biostatistics will provide statistical support for this study.

A detailed data management (DM) plan will be written prior to study initiation. The following is a summary of the plan.

6.6.1 Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS), that meets the technical requirements described in 21CFR Part 11, GCP and HIPAA. The CDMS will be validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data. Before using the CDMS, all study personnel will receive training on the system along with study specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the study site by appropriately designated and trained personnel. All screened participants who meet eligibility requirements will be assigned a PN. CRFs must be completed for each eligible participant. For eligible participants who decide not to enroll, data for the reason they declined enrollment will be collected on a refuser survey CRF. No identifying information will be collected on participants who do not consent for enrollment. Most of the data will be collected using paper CRFs. However, the PCN (B-lactam) allergy history screening questionnaire for participants and the provider feasibility survey for clinicians will be eCRFs. Data for the eCRFs will be collected using iPads.

No names or personal identifying information will be collected on the CRFs. Data will be verified by the site and reviewed for consistency by CDM using both automated logical checks and

manual review. Each site investigator (SI) or designee is responsible for the accuracy of data entered on the CRFs and will sign a statement on the final form for each participant acknowledging the review of all CRFs for that participant and certifying that all information on them is complete and accurate.

The completed CRFs will be scanned and emailed to CDM.

Digital images of the skin testing results will be collected and stored in the CDMS.

6.6.2 Data Quality Control

CDM is responsible for the accuracy, quality, completeness and internal consistency of the data from this study. Data handling, including data quality control, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality control, will be described in the DM plan.

Paper CRFs received at FHI 360 will be processed and entered, then queried for completeness, consistency and the presence of mandatory values. Logical checks will be implemented to ensure data quality and accuracy. Any necessary data changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Discrepancies found will be queried.

Data corrections will be made through the CDMS. The system audit trail captures the reason for each change, the previous and new data values, date and time and the username of the staff person making the change.

The statistician will request data freezes for all interim and final reports. Thorough cleaning and closure of participant data will be performed at study close-out according to the DM plan. Prior to closure, all participant data will be complete or accounted for.

At the conclusion of the study, the CDMS and all other study data will be locked to prevent further changes. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

6.6.3 Retention of Data

At study close-out, the CDM will archive all the final datasets, CRFs, design documentation, protocol and all other documents in a study data repository. Records may not be destroyed without written permission from NIAID/DMID.

Study sites will maintain study records and reports, including, but not limited to, CRFs, source documents, ICFs, test results, and medication inventory records for 3 years after study completion. The investigators may transfer custody of the records to another person who will accept responsibility for them. Notice of transfer must be given to the sponsor preferably before, but no more than ten days after, the transfer.

No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigators and FHI 360 CDM when these documents no longer need to be retained.

6.6.4 Protocol Deviations

A protocol deviation (PD) is any noncompliance with the study protocol, GCP or protocol-specific Manual of Procedures requirements. The noncompliance may be either on the part of the participant, the SI, or other study personnel. As a result of deviations, corrective actions will be developed though a plan agreed upon by the site, the study Principal Investigator and DMID and then implemented promptly.

It is the responsibility of the SI and other study personnel to use continuous vigilance to identify and report deviations within five working days of identification of the PD, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID using the approved DMID PD form and reporting methods.

All deviations from the protocol must be addressed in study participant source documents. A completed copy of the DMID PD form must be maintained in the Regulatory File. PDs must be sent to the local IRB/Independent Ethics Committee per their guidelines. The SIs and other study personnel are responsible for knowing and adhering to their IRB requirements.

7 SAFETY ASSESSMENT AND REPORTING

This clinical study poses only minimal risk to study subjects. Minimal risk is defined by 45 US CFR 46.102 (j) as follows:

“Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

Our experience indicates there will be infrequent problems with AEs. The PRE-PEN® (benzylpenicilloyl polylysine injection USP) kit was FDA approved in 2009 for the assessment of sensitization to PCN (benzylpenicillin or penicillin G) in those patients suspected of having a clinical hypersensitivity to PCN. Rarely, a systemic allergic reaction including anaphylaxis may follow a skin test with PRE-PEN®. To decrease the risk of a systemic allergic reaction, we will perform prick (puncture) skin testing first. Intradermal skin testing will be performed only if the prick test is entirely negative. Occasionally, patients may develop an intense local inflammatory response at the skin test site. Rarely, patients will develop a systemic allergic reaction, manifested by generalized erythema, pruritus, angioedema, urticaria, dyspnea, hypotension, or anaphylaxis. We will use standard of care treatment for any reactions. Study staff will be trained and anaphylaxis kits will be available at all sites. If necessary, subjects will be referred to local urgent care or emergency department facilities.

7.1 Safety Assessments

For the purposes of safety assessment and reporting, there are three potential safety checkpoints in this clinical trial:

1) Pre-skin testing
2) Post-skin testing
3) Oral challenge

These checkpoints are applicable to all subjects consented and enrolled after the initial screening questions.

7.1.1 Pre-Skin Testing

Prior to skin testing, study staff will verify that subjects:

- Have not responded ‘yes’ to any of the high-risk PCN allergy history questions on the PCN (B-lactam) Allergy History Screening Questionnaire
- Have not used oral antihistamines within the past week
- Do not have severe eczema, psoriasis, or other major skin conditions in the areas where testing will be done (usually the arms)

- Do not have large tattoos on their arms
- If HIV positive, are on HAART
- If HIV positive, CD4 not <200 in the past 6 months

7.1.2 Post-Skin Testing

- Subjects will be observed for 30 + 5 minutes and 60 + 5 minutes after skin testing. Assessment of elicited reactivity to PCN will include local skin reactions including erythema, induration and itching which will be evaluated both by self-report and physical exam. Systemic reactions are extremely rare.
- Subjects with positive skin tests will not progress to oral challenge step.

An impending generalized reaction to immediate hypersensitivity skin testing is unusual. If any acute reactions occur, they will be treated as necessary and reported to the IRB and DMID as required.

7.1.3 Oral Challenge

Pregnancy status will be verified. Pregnant women will not be enrolled in the DOC group.

Prior to the oral challenge, vital signs will be recorded (heart rate, respiratory rate, blood pressure and peak flow). A focused PE will be performed (eyes, pharynx, lungs and skin). Subjects will be observed for 60 minutes ± 10 minutes after the amoxicillin is administered. Vital signs, peak flow measurement and focused PE will be repeated after the 60-minute observation period ± 10 minutes.

After oral challenge, subjects will be assessed for the most common elicited reactions associated with amoxicillin which will be graded and documented using the Toxicity Table (Appendix C):

- Cardiovascular: lightheadedness, loss of consciousness
- Skin: urticaria, flushing, rash, angioedema
- HEENT: conjunctivitis, rhinitis, congestion
- Respiratory: shortness of breath, wheezing
- GI: nausea, vomiting, diarrhea

Data will be collected on reactions to amoxicillin as a diagnostic tool for defining an allergic reaction that was not identified by the skin testing. Unanticipated reactions that place the subject at increased risk will be recorded on the AE CRF and reported to the IRB and DMID according to their reporting guidelines.

Subjects will be provided with contact information for study staff to report the development of additional symptoms.

7.2 Reporting

Federal regulations require that institutions engaging in human subjects' research have written procedures to ensure investigators properly report certain events to the IRB. Events must be reported promptly after the event is discovered or within 10 working days after discovery of the event.

All potential unanticipated problems involving risks to subjects or others (UPIRSO) must be reported. An event is considered an UPIRSO when it meets all of the following criteria:

1. It is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the population being studied;

2. It is related or possibly related to participation in the research (i.e. there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

   and

3. It places subjects or others [e.g., study staff or relatives of a subject] at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Other events that require prompt reporting include potential breaches of confidentiality and unresolved participant complaints.

8 STATISTICAL CONSIDERATIONS

8.1 Study Outcome Measures

8.1.1 Primary Outcome Measures

The following primary outcome measures will be used to address the primary study objectives:

- Algorithm / PCN (B-lactam) allergy history screening questionnaire performance in ambulatory STD populations, specifically the NPV of the algorithm on true PCN (B-lactam) allergy.
- In ambulatory STD patients who report a history of PCN (B lactam) allergy and who have low-risk histories, determine the prevalence of PCN reactivity validated either by skin test or by direct oral challenge.

8.1.2 Secondary Outcome Measures

The following secondary outcome measures will be used to address the secondary study objectives:

- Acceptability
  - Proportion of study subjects who find the testing procedures to be helpful.
  - Reasons why study subjects refuse to participate in the study or find the testing procedures to be of no value.
  - Proportion of study subjects who were negative on oral challenge who now feel confident in taking PCN or similar antibiotics.
  - Proportion of study providers who will not offer PCN allergy assessment in the future.
- Feasibility
  - Proportion of study providers who will offer PCN allergy assessment in the future.
  - Reasons why study providers will not offer PCN allergy assessment in the future.
- Both acceptability and feasibility
  - Types and frequencies of elicited reactivity to PCN through skin testing and oral challenge among study subjects.

8.2 Sample Size Considerations

The sample size for this study was selected to have adequate study power to conclude a high NPV of the PCN (B-lactam) allergy history screening questionnaire in ruling out the presence of true PCN (B-lactam) allergy. To address the objective properly, we applied Steinberg's et al.[32] approach to obtain the minimal sample size needed to achieve a lower 95% confidence bound for NPV that exceeds the NPV with a useless test at a fixed level of significance with a given study power. Based on this approach, the sample size calculation depends on the prevalence of PCN allergy in the population and among observed study participants and the sensitivity and specificity of the PCN allergy diagnostic kit (PRE-PEN®). To target at least 85% power at 5% of significant level, the listed sample sizes (see table) provide lower 95% confidence bounds for NPV under the following various assumptions:

- The true population prevalence with PCN allergy: 1%, 3%, 5%
- The observed % of PCN allergy in this study: 1%, 3%, 5%
- The PCN allergy diagnostic kit with sensitivity at least 85% and specificity 95%
- 5% of participants who report a PCN allergy history will have a high-risk allergy history and therefore will not proceed to skin testing.

Population prevalence of PCN allergy	Observed % of PCN allergy in study	Estimated NPV	The lower 95% confidence bound for NPV						
			99.0%	98.4%	97.9%	97.5%	97.3%	97.0%	95.0%
1%	1%	99.84%	1259	796	635	556	526	488	351
	3%	99.51%	420	265	212	185	175	163	117
	5%	99.18%	252	159	127	111	105	98	70
3%	1%	99.84%	8119	2964	1958	1559	1421	1259	759
	3%	99.51%	2707	**988**	653	520	474	420	253
	5%	99.18%	1624	593	392	312	284	252	152
5%	1%	99.84%	113000	9519	4770	3378	2950	2483	1259
	3%	99.51%	37547	3174	1590	1126	984	828	420

	5%	99.18%	22533	1905	954	676	590	497	252

For example, with 3% PCN allergy prevalence in population and among observed study participants, the NPV for a useless test is 97%. A useful PCN (B-lactam) allergy history screening questionnaire should have the lower 95% confidence bound for NPV greater than 97%. Based on the list a minimum sample size of 988 subjects who reported to have PCN allergy history would provide an estimated NPV = 99.51% with 85% power to conclude that the NPV of the study allergy history screening questionnaire is least 98.4% at 5% significant level.

8.3 Participant Enrollment and Follow-Up

The final statistical report will include an accounting of all subjects screened, including the number enrolled, the number excluded, the number with high-risk history of PCN allergy, the number who refused to participate in skin testing, the number who received skin testing, the number excluded from oral challenge, the number who refused oral challenge, the number who received oral challenge and other key study status indicators. The reason for excluding any study subject during the study process will be documented. The study population flow chart will be provided.

8.4 Analysis Plan

A detailed statistical analysis plan (SAP) will be developed prior to performing any analyses. The following is a summary of the planned analyses. Any changes made to this summary plan will be documented in the detailed SAP.

8.4.1 Primary analysis

The primary analysis will estimate with corresponding exact 95% confidence intervals:

- The prevalence of PCN reactivity validated either by skin test or by direct oral challenge among those participants who report a history of PCN (B lactam) allergy and who have low-risk histories.
- The NPV on true PCN (B-lactam) allergy of the algorithm / PCN (B-lactam) allergy history screening questionnaire performance in the study population.

The NPV for each question will be estimated and its performance will be assessed.

To construct a short standardized post-study questionnaire (4-6 questions) from the PCN (B-lactam) allergy history screening questionnaire, we will use Item Response Theory (IRT) to evaluate each question item's discrimination ability of true PCN (B-lactam) allergy and use variable importance evaluation functions to indicate which questions are most useful for

predicting the true PCN (B-lactam) allergy. Based on the results of IRT and variable importance analyses, we will then apply machine learning approaches (e.g., random forest approach via R packages of caret)[33] to select a short post-study questionnaire that has the highest NPV among those possible short questionnaires with 4-6 selected questions.

8.4.2 Analysis of Secondary Endpoints

The frequency and the percentage of participants 1) who experienced elicited reactivity to PCN allergy skin testing in the PST Group and oral challenge in both groups; 2) who refused to participate the study; 3) who found the testing procedures of no value will be tabulated by study site. The proportions of participants 1) experiencing elicited reactivity to penicillin allergy testing; 2) reporting reasons for refusing to participate in the study or finding the testing procedures to be of no value; 3) describing confidence in taking PCN or similar antibiotics among those who were negative on oral challenge will be calculated with corresponding exact 95% confidence intervals.

The same approach will also be used to evaluate the feasibility of providers who will offer the PCN allergy assessment in the future and the reasons among those providers who will not offer the PCN allergy assessment in the future. The evaluation of the secondary endpoints will be conducted by intervention group and overall

9 SUBJECT CONFIDENTIALITY

The participating investigators, their staff, and the sponsor(s) and their agents hold participant confidentiality strictly in trust. This confidentiality includes clinical information relating to enrolled participants. All clinical information will be maintained at the sites.

The study protocol, documentation, data, and all other information generated during participation in the study will be held in strict confidence. No information concerning the study, or the data generated from the study, will be released to any unauthorized third party without prior written approval of the sponsor. Subject confidentiality will be maintained when study results are published or discussed at conferences. Authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator. The clinical study site will permit access to such records.

All records will be kept locked, and all computer entry and networking programs will be carried out with coded numbers only and with password protected systems. All evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

This research is covered by a Certificate of Confidentiality from the NIH. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify a subject in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless a subject has consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings); if a subject has consented to the disclosure, including for their medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

10 INFORMED CONSENT PROCESS

Federal regulations specify the elements of informed consent that must be conveyed to research participants through the informed consent process (see 21 CFR 50.20). It is the responsibility of the SI and his/her assigned staff to ensure that all required information has been provided to potential research participants. The consent forms for this study will be IRB approved.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Participants may withdraw consent at any time during the trial. Study staff will provide the potential participant consent forms (as approved by the IRB) which describe the study procedures and risks in detail. Documentation of obtaining informed consent will be noted. Staff will ask the potential participant to read and review the document, or have it read to them, and will also be available to answer any questions the participant may have. Those who administer consent will provide extensive discussion of risks and possible benefits to the potential participants. Informed consent can be obtained orally, written and electronically using procedures approved by the IRB. The potential participant will provide consent before any procedures are performed specifically for the study. The potential participants will have the opportunity to discuss the study prior to agreeing to participate. A copy (or electronically) of the applicable consent form will be provided to the participant. The consent will state that the administration and quality of their medical care will not be adversely affected if they decline to participate in this study.

The study staff's approach to study subjects will be compliant with HIPAA regulations.

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APPENDIX A: SCHEDULE OF EVENTS

Procedures	Enrollment Visit	Additional Visit (within 6 weeks as necessary to complete study procedures)
Written, oral, or electronic informed consent	X	
Assessment of eligibility criteria	X	
Review demographic information	X	
Administration of PCN (B-lactam) Allergy History Screening Questionnaire	X	
Review of concomitant medications	X	(X)
Allergy Validation Method 1: PST Group		
Assessment of PCN Skin Test qualification criteria	X	(X)
If additional criteria met, PCN Skin Test (prick and/or intradermal)	X	(X)
Photo documentation of skin testing (iPad)	X	(X)
Assessment of Oral Challenge qualification criteria	X	(X)
Assessment of vital signs (plus peak flow) and focused PE before and after Oral Challenge	X	(X)
If additional criteria met, Oral Challenge of 250 mg amoxicillin	X	(X)
Allergy Validation Method 2: DOC Group		
Assessment of Oral Challenge qualification criteria	X	(X)
Assessment of vital signs (plus peak flow) and focused PE before and after Oral Challenge	X	(X)
If additional criteria met, two-step Oral Challenge – initial dose of 25 mg amoxicillin followed by full dose of 250 mg	X	(X)
Completion of CRFs	X	(X)
Assessment of Adverse Events	X	(X)
Administration of subject acceptability survey	X	(X)
Provide written documentation of PCN allergy testing results or referral to allergist	X	(X)

At enrollment, all procedures will be completed unless participant cannot stay for skin testing and/or oral challenge.

(X) indicates procedures that may not have been completed during Enrollment Visit because of time constraints

APPENDIX B: PCN (B-LACTAM) ALLERGY HISTORY SCREENING QUESTIONNAIRE

Section 1: Allergy History

1) How long ago was the reaction to the antibiotic?

   a. < 6 months
   b. 6 months-1 year
   c. 2-5 years
   d. 6-10 years
   e. > 10 years
   f. Don't remember / Unknown

2) What was the name of the drug you reacted to?

   a. (Please list) _____
   b. Don't remember / Unknown

3) How was the antibiotic administered?

   a. Pill or Liquid by mouth
   b. Injection (a shot) into a muscle or through a vein
   c. Don't remember / Unknown

4) When did your allergic reaction to the antibiotic start?

   a. Less than 1 hour after the first dose
   b. Between 1 and 6 hours after the first dose
   c. More than 6 hours, but less than 24 hours after the first dose
   d. 24 hours or more after the first dose
   e. Unknown

5) How many days did you receive your antibiotic treatment?

   a. One day only
   b. About _____ days of treatment
   c. Don't remember / Unknown

6) People experience many different kinds of symptoms during an allergic reaction to an antibiotic. What were the symptoms of your allergic reaction? (OK to select more than one)

   a. Can't remember (check only after reading entire list)

b. Non-specific symptom(s) (e.g., “sick” “thought I was a goner” “high as a kite” “like I had the flu”

Responses to the symptoms listed below should be graded on a 5-point scale:

Don’t Recall /None / Mild / Moderate / Severe

Low-Risk Allergy History

a. Isolated GI upset *(diarrhea, nausea, vomiting, abdominal pain)*
b. Chills *(rigors)*
c. Headache
d. Fatigue
e. Itching (*pruritus*), self-limited,
f. Rash *(including maculopapular rash)*
g. Hives (greater than 5 years ago)
h. Flushing / redness
i. Family history
j. Patient denies allergy history but is in medical record

Higher-Risk Allergy History: Skin Testing and Oral Challenge Contraindicated

a. Angioedema or swelling of lip, tongue, or around eyes
b. Wheezing / chest tightness moderate or severe shortness of breath
c. Throat tightness which affected ability to breathe
d. Hypotension without rapid recovery
e. Arrhythmia / irregular heartbeat or palpitations
f. Syncope / pass out / dizzy
g. Anaphylaxis or sudden drop in blood pressure
h. Hives (5 years or less)

Late Effect Symptoms (higher-risk events occurred >24 hours after drug administration)

a. Stevens-Johnson syndrome *(Loss >10% of skin)*
b. Organ injury *(liver, kidney)*
c. Low Platelets
d. Drug reaction eosinophilia and systemic symptoms *(rash with eosinophilia and organ injury)*
e. Acute generalized exanthem *(rash with pustules)*
f. Dystonia or muscles became very stiff or very weak
g. Serum sickness *(rash with joint pain, fever, myalgia)*
h. Anemia

i. Documented drug fever
j. Erythema multiforme *(rash with target lesions)*
k. Hives (5 years or less)

7) What treatment did you receive for the allergic reaction on the day it started? (OK to select more than one)

a. No treatment
b. Went to the hospital emergency room or urgent care center
c. Was admitted to the hospital
d. Given epinephrine / adrenaline
e. Given steroid pills or injections
f. Given a steroid cream
g. Given an antihistamine (anti-itch pill)
h. Antibiotic discontinued
i. Fluids through a vein
j. Other (please list) _____
k. Unknown

8) Did you stop taking the antibiotic or did you finish the course?

a. Stopped after the reaction started
b. Continued to take the antibiotic after the reaction
c. Don't remember

9) Since you had the antibiotic reaction, have you ever taken any of the following antibiotics?

a. Amoxicillin/Clavulanate (Augmentin)
b. Cephalexin (Keflex)
c. Ceftriaxone (Rocephin)
d. Benzathine Penicillin (Bicillin) (injections)
e. Cefuroxime (Ceftin)
f. Cefadroxil (Duricef)
g. Ampicillin
h. Amoxicillin
i. Cefaclor (Ceclor)
j. Cefixime (Suprax)
k. Any other drug whose name ended with "cillin"
l. Any other drug whose name started with "cef"
m. Other (Please list) _____
n. Don't know or remember

10) Since you had the antibiotic reaction, have you ever been treated for gonorrhea, syphilis or strep throat?

a. Yes (please list medication) _____
b. No

Section 2: Skin Testing History
Questions to ask before skin testing is performed

11) Have you ever been skin tested for allergy to penicillin?

a. Yes (if Yes, go to Q12; otherwise skip to Q13)
b. No
c. Unknown

12) What were the results of the skin test?

a. Positive
b. Negative
c. Unknown

13) In the past week have you taken any of the following medications, including over the counter (OTC)? (***Include only medications that you have taken orally, no skin or eye medications)***

a. OTC cough and cold remedies containing antihistamines
b. Benadryl
c. Non-sedating antihistamines (Zyrtec, Allegra, Claritin, Xyzal)
d. Antivert / meclizine, Dramamine and Phenergan
e. Hydroxyzine (Atarax/Vistaril)
f. Other (please list) _____
g. None – I have not taken any of these medications

(If Yes to a, b, c, d or e, exclude from skin test))

Section 3: Subject Acceptability Survey
Questions to ask after skin testing and oral challenge procedures are completed

FOR ALL SUBJECTS

14) Did you find the penicillin testing procedures to be helpful?

(Scale of 1-5, where 1 is extremely helpful, 5 is not helpful at all)
(if 4 or 5, go to Q15; otherwise skip to Q16)

15) Why were the penicillin testing procedures not helpful?

a. Took too long
b. Testing was uncomfortable
c. Other (Please list) _____

16) Were you comfortable with allergy testing conducted in settings where STD services are provided rather than by an allergist?

(Scale of 1-5, where 1 is extremely comfortable, 5 is not comfortable at all)

17) If a friend or family member had a history of penicillin allergy, would you refer them for testing?

(Scale of 1-5 where 1 is definitely yes, 5 is definitely no)

FOR SUBJECTS WHO HAVE BEEN SKIN TESTED AND ARE NEGATIVE FOR PCN ALLERGY

18) How confident are you that you can now take penicillin or similar antibiotics?

(Scale of 1-5 where 1 is very confident and 5 is not confident at all)

APPENDIX C: TOXICITY TABLE

Clinical Adverse Events			
NEUROLOGICAL/ CARDIOVASCULAR	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Pre-syncope/Syncope	Lightheadedness	Dizziness (pre-syncope), diaphoresis and sense of impending doom	Confusion, collapse, loss of consciousness
Hypotension			Decrease in systolic blood pressure greater than 30% from baseline
Pulse		Increase or decrease of 20bpm from baseline	Increase or decrease of 30bpm from baseline
CUTANEOUS	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Urticaria and angioedema	Flushing or sensation of heat or warmth	Generalized urticaria and/or periorbital edema or angioedema (not laryngeal, tongue or uvular)	Generalized urticaria and laryngeal, tongue or uvula swelling with or without stridor
HEENT	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Eyes, face and periorbital area	Conjunctival erythema, pruritus or tearing	Conjunctivitis plus rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion),	
Upper respiratory		Cough perceived to come from the upper airway (not the lungs, larynx, or trachea) without stridor	Upper respiratory symptoms and cough perceived to come from the lungs, larynx, or trachea with stridor
RESPIRATORY	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**

Shortness of breath (bronchospasm)	Transient; no treatment; 71% - 80% of baseline peak flow	Bronchospasm (dyspnea, hoarseness, wheeze) that requires medical intervention; normalizes with bronchodilator; 60% - 70% (of baseline peak flow)	<60% of baseline peak flow Bronchospasm that does not resolve or progresses to respiratory failure
GASTROINTESTINAL	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Abdominal cramps, vomiting or diarrhea	Transient abdominal cramps	Abdominal cramps, nausea, vomiting or diarrhea	Abdominal cramps, nausea, vomiting or diarrhea with signs/symptoms of dehydration that requires medical intervention

APPENDIX D: PROVIDER FEASIBILITY SURVEY

SECTION 1: PRE-TRIAL SURVEY

1. What is your practice setting? **Check (X) only one**
   a. Public health clinic ..... |___|
   b. Outpatient primary care clinic ..... |___|
   c. Outpatient specialty clinic ►**Specify**_____ ..... |___|
   d. Other clinic setting► **Specify:** _____ ..... |___|

2. What type of provider are you? **Check (X) only one**
   a. Physician (MD/DO) ..... |___|
   b. Nurse practitioner ..... |___|
   c. Physician assistant ..... |___|
   d. RN ..... |___|
   e. Other ► **Specify:** _____ ..... |___|

3. What is your specialty or defined area of practice? **Check (X) all that apply**
   a. Adult medicine ..... |___|
   b. Family medicine ..... |___|
   c. Infectious disease only ..... |___|
   d. Pediatric/Adolescent medicine ..... |___|
   e. OB-GYN ..... |___|
   f. Preventive medicine ..... |___|
   g. Other ► **Specify:** _____ ..... |___|

4. What is your current approach to penicillin (PCN) allergic patients? **Check (X) all that apply**
   a. Use alternative antibiotic ..... |___|
   b. Penicillin skin testing ..... |___|
   c. Oral challenge ..... |___|
   d. Referral to allergist ..... |___|
   e. Other ► **Specify:** _____ ..... |___|

5. Do you have access to PCN skin testing? ..|___|
   0=No (**Skip to Q8**)

1=Yes (**Continue to Q6**)

6. Do you offer/perform PCN skin testing on site?|___|
   0=No
   1=Yes

7. What are the barriers to offering / performing PCN skin test to your allergic patients? **Check (X) all that apply**
   a. Lack of training ..... |___|
   b. Cost of testing ..... |___|
   c. Length of time to perform test ..... |___|
   d. Fear of precipitating a severe allergic reaction in a patient ..... |___|
   e. I don't think PCN skin testing is necessary ..... |___|
   f. Not interested in offering / performing skin testing ..... |___|
   g. Other ► **Specify:** _____ ..... |___|

8. Do you have offer / perform oral challenge for your PCN allergic patients? ..... |___|
   0=No (**Skip to Q10**)
   1=Yes (**Continue to Q9**)

9. Who do you test? **Check (X) all that apply**
   a. Patients with low risk history and skip skin testing ..... |___|
   b. Patients who are negative on skin test..... ..... |___|
   c. Other criteria used ► **Specify:** _____ ..... |___|

10. What are the barriers to offering / performing oral challenge to your PCN allergic patients? **Check (X) all that apply**
    a. Lack of training ..... |___|
    b. Cost of testing ..... |___|
    c. Length of time to perform test ..... |___|
    d. Fear of precipitating a severe allergic reaction in a patient ..... |___|
    e. I don't think oral challenge is necessary ..... |___|
    f. Not interested in offering / performing an oral challenge ..... |___|
    g. Other ► **Specify:** _____ ..... |___|

SECTION 2: POST-TRIAL SURVEY

1. What is your practice setting? **Check (X) only one**
   a. Public health clinic ..... |___|
   b. Outpatient primary care clinic ..... |___|
   c. Outpatient specialty clinic ►**Specify**_____ ..... |___|
   d. Other clinic setting► **Specify:** _____ ..... |___|

2. What type of provider are you? **Check (X) only one**
   a. Physician (MD/DO) ..... |___|
   b. Nurse practitioner ..... |___|
   c. Physician assistant ..... |___|
   d. RN ..... |___|
   e. Other ► **Specify:** _____ ..... |___|

3. What is your specialty or defined area of practice? **Check (X) all that apply**
   a. Adult medicine ..... |___|
   b. Family medicine ..... |___|
   c. Infectious disease only ..... |___|
   d. Pediatric/Adolescent medicine ..... |___|
   e. OB-GYN ..... |___|
   f. Preventive medicine ..... |___|
   g. Other ► **Specify:** _____ ..... |___|

4. What is your current approach to penicillin (PCN) allergic patients? **Check (X) all that apply**
   a. Use alternative antibiotic ..... |___|
   b. Penicillin skin testing ..... |___|
   c. Oral challenge ..... |___|
   d. Referral to allergist ..... |___|
   e. Other ► Specify: _____ |___|

5. Prior to the trial, did you offer/perform PCN skin testing on site? |___|
   0=No
   1=Yes

6. Prior to the trial, did you offer/perform oral challenge for your PCN allergic patients? |___|
   0=No
   1=Yes

7. Which PCN allergy intervention did you perform? |___|
   0=PCN Skin Testing
   1=Direct Oral Challenge
   2=Both

8. Which method did you prefer? |___|
   0=PCN Skin Testing
   1=Direct Oral Challenge
   2=No preference

9. Please explain why you preferred the allergy intervention method you chose in Q8.
   Describe: _____
   _____

10. After participating in the trial, do you feel PCN allergy assessment can be performed safely and effectively in a setting which treats patients with STIs? **Check (X) only one**
    a. Strongly agree ..... |___|
    b. Somewhat agree ..... |___|
    c. Neither agree not disagree ..... |___|
    d. Somewhat disagree ..... |___|
    e. Strongly disagree ..... |___|

11. Do you think your clinic will offer this service in the future? ..... |___|
    0=No ►**Continue to Q7**
    1=Yes ►**End of survey. Skip to initials**

12. Please indicate the reasons you will not offer PCN allergy assessment in the future. **Check (X) all that apply**
    a. Lack of organizational support .... |___|
    b. Reimbursement .... |___|
    c. Local site training ..... |___|

d. Don't believe that the results will be useful .....|___|
e. Risk of adverse reaction .....|___|
f. Lack of time for providers to do the testing . .....|___|
g. Lack of access to reagents ....|___|
h. Other barriers to offering / performing this service ► **Describe:** _____ _____.....|___|

APPENDIX E: ASSESSMENT TOOL FOR OBSERVER

Validate an Easy to Administer Algorithm to Define Penicillin (B-lactam) Allergy Status in STD Outpatients

DMID Protocol Number (#18-0023)

PARTICIPANT I.D. _____

Assessment Tool for Observer

1. **Screening Procedure (Check all that apply)**
   - Staff approach subjects in waiting area ____
   - Flyers posted in waiting area ____
   - Recruitment materials provided at reception ____
   - Referral from Clinicians ____
   - Allergy identified in Medical Record ____
   - Other _____ ____

2. **Informed Consent Obtained (ICF)** _____
3. **Copy of ICF provided to participant** _____
4. **Questionnaire Administered** _____
5. **Defined as Low-Risk or High-Risk Group** _____
   a. If High-Risk Defined STOP
   b. If Low-Risk Continue
6. **Exclusion Criteria Assessed** _____
   a. If Excluded STOP

7. **SKIN TESTING GROUP**
   a. Verify skin test reagents correctly labeled _____
   b. Skin Prick Targets Marked appropriately _____
   c. Skin Pricks administered in the correctly labeled area _____
   d. Positive and Negative Controls Correct _____
   e. Intradermal Targets Mapped and Marked _____
   f. Intradermal Tests administered _____
   g. Waiting Time Appropriate _____
   h. Positive and Negative Controls Correct _____
   i. If positive, photograph and document _____

8. **Oral Challenge (After Skin Testing)**
   a. Physical assessment and Vital Signs time =0 *(Peak Flow: Use highest value of 3 successive readings)* _____
   b. Oral Challenge administered _____
   c. Physical assessment and Vital Signs time =60 min. _____
   d. Results Explained to Subject _____

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DMID Protocol Number (#18-0023)

PARTICIPANT I.D. _____

9. Direct Oral Challenge

Low Dose (25 mg)

- **a.** Physical assessment and Vital Signs time =0 _____
- **b.** Oral Challenge administered _____
- **c.** Physical assessment and Vital Signs time =30 min. _____
- d. Results Explained to Subject

Full Dose (250 mg)

- **a.** Physical assessment and Vital Signs time =0 _____
- **b.** Oral Challenge administered _____
- **c.** Physical assessment and Vital Signs time =30 min. _____
- **d.** Results Explained to Subject _____

10. Participant Accessibility Survey _____

11. Notification Letter Provided _____

12. Is Action Plan Required? ☐ Yes ☐ No

Comments: _____

_____

_____

_____

Completed By: _____ Date: _____

(Name, Observer Signature)

Reviewed By: _____ **Date:** _____

(Name, Site Investigator Signature)

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