Statistical Analysis Plan for the Pragmatic Removal of Penicillin Allergy Electronic Health Record Labels (PROPEL) trial

A single center, stepped wedge, randomized, pragmatic, clinical trial of an intervention to remove low risk penicillin allergy labels

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1. INTRODUCTION

This document describes the statistical analysis plan (SAP) for a single center, stepped wedge, randomized, pragmatic, clinical trial of an intervention to remove low risk penicillin allergy labels using a single dose amoxicillin challenge. The intervention is deployed at the medical unit level, led by a unit pharmacist. Persons on the unit with a penicillin allergy label undergo a risk assessment, and low risk patients who consent to the procedure are presented with an oral amoxicillin challenge.

At the study outset, all participating units were naïve to the process for removing penicillin allergies. After the run-in period, medical units transitioned from the control condition to the intervention condition at monthly intervals. Medical units at VUMC will be randomized to determine the order in which they start the intervention.

This SAP describes the approach to analyzing the primary and secondary endpoints, as well as safety endpoints, once the trial is stopped.

2. PARTICIPANTS AND TREATMENT ARMS

Adult patients admitted to hospital during the 12-month study period who had 24-hour exposure to any of the study units will be included if they are not known to be pregnant. Pregnancy status is based on either documented known pregnancy via ObGyn status or BhCG results that are classified as positive using VUMC laboratory cutoffs.

Participants will be in either the control group or the intervention group, depending on when they presented to the hospital, and which hospital unit they were exposed to. Specifically:

- Control Group: Any patient who did not have a 24-hour exposure to a study unit where the intervention was active but did have at least 24-hour exposure to a control unit. The current standard of care in hospitalized patients with reported penicillin allergy is to do nothing, with all care at the discretion of the primary team. Hence, no intervention will be provided.
- Intervention Group: Any patient who had a 24-hour exposure to a study unit at any time where the intervention was active. The intervention includes systematic identification those with a penicillin allergy, application of a penicillin allergy risk stratification tool, and use of an oral amoxicillin test dose challenge order set for patients who stratify as low risk. The risk stratification tool has been demonstrated retrospectively to have a >99% (95% CI 96.4,99.9) negative predictive value for the presence of penicillin allergy in those who stratify as low risk. Test dose challenges with amoxicillin are a recommended part of routine practice in patients who report allergy but have symptoms that are low risk for true or ongoing allergy. When a unit crosses over and becomes a “live” unit with the intervention, a patient who was already admitted on the unit needs to be present for 24 hours afterward to be considered exposed to the intervention.

3. ENDPOINTS

Primary endpoint

The primary endpoint for this trial is the proportion of penicillin allergy labels that are listed at admission in the chart (allergy box or problem list) but are removed from the chart before discharge (from both the allergy box and the problem list).

The primary outcome is a binary variable, either penicillin allergy label removed yes or penicillin allergy label removed no.

Key secondary endpoints

The secondary endpoints for this trial include the following:

1. Tolerance of an amoxicillin oral challenge, which will be documented using a smart phrase to indicate tolerance or intolerance. This outcome is a binary variable, either yes= tolerated, or no =not tolerated, with relevant symptoms to be determined by chart review.
2. Uptake of the risk stratification tool: This is determined by whether patients with a penicillin allergy label in their chart receive a risk assessment. This is a binary variable, either the patient did or did not receive a risk assessment of their penicillin allergy.
3. Amoxicillin adverse events: In patients who did not tolerate their amoxicillin oral challenge, we will assess the types of adverse events that were reported.
    a. An immediate allergic amoxicillin challenge adverse event will be defined as an adverse event reported in association with the amoxicillin challenge that includes symptoms of anaphylaxis or rash, with onset within 6 hours of the challenge dose being given.
    b. A non-immediate allergic amoxicillin challenge adverse event will be defined as an adverse event such as rash that is potentially consistent with allergy, occurring within 24 hours of the dose being given.
    c. A non-allergic amoxicillin challenge adverse event will be defined as an adverse event, such as gastrointestinal upset, reported in association with amoxicillin challenge, within 6 hours of the challenge dose being given.
4. Communication about penicillin allergy label removal in the discharge summary: This is determined by the presence of language about the penicillin allergy evaluation, challenge, and removal, in those patients who underwent penicillin allergy challenge. The outcome is a binary variable, as this information is either present, or absent.
    a. This data will be obtained by manual chart review.
    b. A smart phrase has previously been created that was encouraged to be used for this purpose, and its utilization will be extracted.
5. Longer term penicillin allergy label removal, over 3 months and 18 months of follow up. Among those who underwent a penicillin allergy label removal, whether the allergy remains out of the chart or is “ever/never” re-entered into the chart. The outcome is a binary variable at either 3 months or at 18 months.
6. Time to penicillin allergy return: for those participants who underwent an allergy label removal, we will compare the time to return of the allergy label based on the date the label first re-appeared in the chart.
7. Antibiotic utilization: This is based on the presence of qualifying penicillin or cephalosporin treatment doses, during the same hospitalization, and at 3 months and 18 months of follow up.
    a. Same hospitalization: Utilization of these antibiotics will be defined as “yes” or “no” during the initial hospitalization in which amoxicillin challenge could have occurred, as a binary variable.
    b. Subsequent utilization: Utilization of these antibiotics will be defined as “ever/never” by 3 months and ever/never by 18 months of follow up, as a binary variable.
    c. Drugs included in the definition of penicillins are predefined as:
        i. Ampicillin
        ii. Ampicillin/sulbactam (unasyn)
        iii. Amoxicillin
        iv. Amoxicillin/Clavulanate (augmentin)
        v. Cloxacillin
        vi. Dicloxacillin

vii. Nafcillin
viii. Penicillin G
ix. Penicillin VK
x. Piperacillin
xi. Piperacillin/Tazobactam
xii. Ticarcillin
xiii. Ticarcillin/Clavulanate (timentin)

d. Drugs included in the definition of cephalosporins are predefined as:
i. Cefadroxil
ii. Cefprozil
iii. Cefaclor
iv. Cephalexin
v. Cephalothin
vi. Cefazolin
vii. Cefoxitin
viii. Cefotetan
ix. Cefamandole
x. Cefuroxime
xi. Cefepime
xii. Ceftriaxone
xiii. Cefpodoxime
xiv. Ceftazidime
xv. Cefdinir
xvi. Cefixime
xvii. Ceftaroline
xviii. Ceftobiprole
xix. Ceftozolane-Tazobactam

Safety endpoints

The key safety endpoints for this trial are potentially associated adverse events with the amoxicillin challenge, these are prespecified as:

- Anaphylaxis
- Other potentially allergic symptoms during/after amoxicillin challenge- e.g. rash
- Nausea/Vomiting/GI symptoms only
- Other symptoms during amoxicillin challenge

For reactions to penicillin given during the hospital stay, the same events will be captured:

- Anaphylaxis
- Other potentially allergic symptoms during/after penicillin administration- e.g. rash
- Nausea/Vomiting/GI symptoms only
- Other symptoms during penicillin administration

Due to the nature and clinical course of patients receiving routine hospital care, a substantial number of adverse events are expected among participants, including but not limited to:

- Death
- Sepsis
- Renal failure

- Respiratory failure
- Heart failure
- Pneumonia or other / new infection
- DVT or PE
- Complications related to ICU procedures
- Arrhythmia
- Delirium
- Bowel ischemia
- Ileus
- Leukopenia or leukocytosis
- Anemia or thrombocytopenia
- Coagulopathy (DIC)
- Hypoglycemia
- Electrolyte abnormalities

These adverse events are common in hospitalized patients and are thus not expected to reflect safety of the treatment regimen. There is no plan to summarize or report these events.

8. DESIGN CONSIDERATIONS

Randomization

During the trial, randomization will occur at the level of the medical unit. A single medical unit will serve as a cluster. Twelve medical units were selected for inclusion, and the order of starting the intervention was randomized, staggered by one-month intervals.

Adaptations and stopping

No adaptations are anticipated, and no stopping rules are implemented.

Power and Sample Size

To power this study, we assumed 0.5% of patients would have their penicillin allergy label intentionally removed or would receive a test dose challenge in the control condition, based on our observation of usual care for a six-month period at the participating units. Preliminary data further suggest that around 100 patients per month are admitted and discharged from each participating medical unit, and that 10-15% of all patients admitted have a penicillin allergy listed in their chart. Hence, approximately 10-15 penicillin allergic patients would be eligible for inclusion in the intervention group, per unit, per month.

Our sample size was selected to detect a clinically meaningful difference of 20 additional penicillin-allergic patients per 100 having their penicillin allergy label removed using our intervention. Assuming pessimistically that a minimum of 10% of patients randomized to intervention will undergo risk stratification leading to an allergy label removed, and that 0.5% of patients in the control group will have a penicillin allergy label removed during current practice, 1:1 allocation of participants, an alpha of 0.05, power of 0.8 and a two-sided test of differences in proportions, we would need a minimum of 35 patients per group (70 total) to detect a minimally clinically meaningful 20% increase in penicillin allergy label removals. Much smaller sample sizes will be needed to see effects if higher engagement

and utilization is observed. By running this study with one year of intervention (12 medical units with one month step lengths), we will greatly exceed the sample size needed for the main analysis, and we will have sufficient data to report on the secondary outcomes with precision.

9. DEFINITION OF ANALYSIS SETS

Intent-to-treat Analysis Set

All participants who were present on a study unit for at least 24 hours during the 12-month study period will be included in the intent-to-treat analysis set. The intent-to-treat participants will be used for all primary, secondary, and other efficacy analyses. All participants will be included in the intent-to-treat analysis set, regardless of what interventions or challenges were given.

Safety analysis set

Participants who received a dose of amoxicillin as a challenge will be included in the safety analysis set related to the safety of the intervention. All other participants will be classified as not having received an intervention with oral challenge to disprove their allergy label, and thus there are no adverse events potentially associated with the control group.

In addition to reporting the safety of the challenge itself, we also intend to compare the incidence of safety events from use of penicillin between the two groups. This analysis will include the intent-to-treat analysis set.

10. ANALYSIS

Timing of Analysis

The primary analysis is based on outcomes at discharge. Secondary outcomes include outcomes at 3 months and 18 months. The main analysis will proceed after all units have crossed over to the study group for 30-days, and have contributed 3 months of follow up time, i.e. four months after the last unit begins intervention. Secondary analyses focused on 18-month outcomes will occur after 18 full months of follow up, i.e. at least 19 months after the last unit cross-over to the intervention condition.

Blinding

There is no blinding in this study.

Descriptive analysis

Initial analysis will be descriptive in nature. First, we will describe the flow of participants into the study and allocated to the two arms using a CONSORT diagram. Then, the study participants will be characterized based on demographic and clinical variables measured at the time of eligibility, unless otherwise indicated. Variables will be described using median and interquartile range or using count and percent (proportion). No statistical testing will be done to compare characteristics between groups. The following variables will be described by study arm and overall:

- Age (years)- Date of presentation-birthdate in years
- Race (categories same as for Clinical Trials.gov reporting: American Indian/Alaska Native, Asian, Native Hawaiian or Pacific Islander, Black or African American, White, More Than One Race, Unknown or Not Reported)- patient self-reported in EHR
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown or not reported)- patient self-reported in EHR

- Sex (Male or female, other, unknown)- patient self-reported in EHR
- Charlson comorbidity index
- Health literacy score- VUMC instruments- standard of care to collect for inpatients
- Unit admitted to at the time of study inclusion- first study unit on which patient spends at least 24 hours during the admission.
    - Unit on which challenge was performed- For those who received amoxicillin challenge, unit on which the testing was done.
- Penicillin allergy listed under allergies/problem list on day of admission
    - Proportion reporting allergy to any of the following indicated in Allergy field in eStar:
        - Ampicillin
        - Ampicillin/sulbactam (unasyn)
        - Amoxicillin
        - Amoxicillin/Clavulanate (augmentin)
        - Cloxacillin
        - Dicloxacillin
        - Nafcillin
        - Penicillin G
        - Penicillin VK
        - Piperacillin
        - Piperacillin/Tazobactam
        - Ticarcillin
        - Ticarcillin/Clavulanate (timentin)

Next, we will describe the fidelity of applying the intervention as follows:

- Penicillin allergy labeled patient completed risk assessment (as n (proportion) of total Penicillin Allergy Labels (PALs)
    - Highest- as n (proportion of risk assessed)
    - Higher- as n (proportion of risk assessed)
    - Low-risk allergy- as n (proportion of risk assessed)
- Patient received amoxicillin challenge as n (proportion of total PALs)
    - After qualifying as low-risk -as n (proportion of low-risk PALs)
- For each participant, duration of exposure to control environment versus intervention environment.

Main Analysis

Prior to modeling the data, we will describe the presentation of the amoxicillin challenge, the response, any adverse events, the rate of penicillin allergy removal, and subsequent use of penicillin as follows:

- Patient response to amoxicillin challenge -as n (proportion of total PALs)
    - Pass/Fail
        - as n (proportion) of total challenges done

        - Proportion of failed challenges in which hypotension was present
            - as n (proportion) of challenges failed
                - Hypotension defined as systolic blood pressure decrease of 30% compared to pre-challenge blood pressure.
- Patient allergy removed from the chart's allergy box- absent at discharge
    - as n (proportion of total PALs)
- Same hospitalization use of a penicillin antibiotic,
    - as n (proportion of total PALs)
- Adverse events associated with amoxicillin challenge,
    - as n (proportion) of total challenges
- Adverse events associated with same hospitalization use of a penicillin antibiotic
    - as n (proportion of total PALs),
- Allergy evaluation information present/absent in discharge summary,
    - as n (proportion of completed PALs assessed as low-risk)
- Number of subsequent VUMC healthcare encounters after the initial hospitalization
    - Outpatient
        - average n per patient
    - ED/observation
        - average n per patient
    - Hospitalization/Inpatient
        - average n per patient
    - Surgical
        - average n per patient
- Ratio of penicillin treatments per total patient healthcare encounters since study entry

Primary model: Penicillin allergy label removal will be compared between the two groups using an adjusted logistic regression mixed effects model. In addition to study group assignment, the model will be adjusted for the following baseline covariates: time from start of study, age, race/ethnicity, sex, comorbidity index, health literacy, and intervention unit as a random effect. We will additionally include intervention unit general acuity level, defined based on the average APRDRG for patients discharged from the unit during the study period. The magnitude of effect will be reported as odds ratios with confidence intervals. A critical two-sided p-value of 0.05 will be used to draw conclusions on the main effect of intervention.

Subgroup analysis: We do not have evidence suggesting subgroups will respond differently to the intervention. However, such a possibility does exist. Differential treatment effect will be analyzed as detailed in https://hbiostat.org/bbr/ancova.html#strategy-for-analyzing-differential-treatment-effect. Briefly, the analysis will avoid subgroup analysis because it does not properly handle continuous baseline variables such as age, and because it does not inherit covariate adjustment. Each factor that potentially interacts with treatment will have its treatment interactions added to the model, one interacting factor at a time. Continuous interacting baseline factors will be modeled as restricted cubic splines with 3 default knots so as to not assume linearity. For each analysis a plot will be made with the baseline factor in question on the x-axis and the estimated treatment effect and its 0.95 confidence band on the y-axis, accompanied by a statistical test for non-flatness of the curve (lack of interaction). The same analysis will be used to construct a model-based forest plot where for

continuous interacting factors, treatment effects will be estimated at quartiles of interacting factors (or discrete levels for categorical factors), neither of which involves stratifying/subgrouping the data.

Sensitivity analysis: We will repeat the main analysis without covariate adjustment. In the presence of missing outcomes, a sensitivity analysis using multiple imputation for missing outcomes may be conducted.

Multiplicity: This study is designed with a single primary endpoint and no interim analyses. Therefore, no adjustments for multiple testing will be made. Secondary analyses will emphasize effect sizes over statistical significance.

Safety Analysis

This study is not designed to compare safety between study arms using inferential statistics. However, we do intend to report on safety of the amoxicillin challenge. Safety endpoints will be presented for the safety analysis set in tabular form using counts and proportions.

We will also report safety events observed from penicillin treatments grouped by whether the participant was randomized to intervention, and whether they received full active intervention or not. Statistical testing is not expected; differences in event rates between groups will be computed with 95% confidence intervals.

Reporting of Safety Events:

- Adverse events associated with amoxicillin challenge
    - as n (proportion) of total challenges
- Adverse events associated with same hospitalization use of a penicillin antibiotic
    - as n (proportion of total PALs)

Analysis of secondary endpoints

We will proceed with exploring the effect of low-risk penicillin allergy challenge on secondary endpoints in a similar manner as for the primary endpoints:

i) Endpoints will be described as medians and interquartile ranges or frequencies and proportions
ii) Binary variables will be compared using an adjusted logistic regression, and ordered or continuous variables will be compared using proportional odds logistic regression
iii) The odds ratios with confidence will be reported as estimates of effect size.
iv) Secondary endpoints will be modelled with adjustment for baseline covariates; sensitivity analyses will exclude adjustment and may include imputation for any missing outcomes.
v) Differential treatment effects will be evaluated using the interaction term, and consequent differential effects reported
vi) Time to return of penicillin allergy labels will be evaluated using a Cox proportional hazards model with covariate adjustment.

11. SUMMARY

The analyses described here are those necessary **to answer the trial's primary** question of whether an intervention to actively risk-stratify and challenge low-risk penicillin allergies is more effective at removing these allergies than the standard of care (which is to work around them).

Beyond our analysis exploring the effect of challenge on primary and secondary endpoints, we expect there to be multiple additional exploratory analyses conducted. It is not possible to predetermine the nature of such analyses. However, we are committed to preserving rigor and reproducibility and will pre-specify each subsequent analysis in the context of the specific question to be answered, cognizant of bias and missingness in the data.

Version and Revision Log

4/11/2022 Version 1: Developed with and approved by Christopher J. Lindsell, PhD

4/19/2023 Version 2: Developed with and approved by Frank E. Harrell, Jr., PhD

Revisions: The analysis for differential treatment effect language has been updated to fix problems with reliability and interpretability of subgroup analysis.