Title: Penicillin De-Labeling in the Pediatric Primary Care Setting; Protocol

NCT Number: 05010304

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PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

The goal of this project is to explore the feasibility of implementing a penicillin allergy delabeling protocol for low-risk pediatric patients in the primary care setting. Specifically, we seek to demonstrate risk-stratification of reported adverse reactions to penicillins and completion of direct amoxicillin challenge in low-risk subjects can be performed in the outpatient pediatric primary care setting.

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

Reported adverse drug reactions to penicillins are common; however, more than 90% of patients with a penicillin allergy label can safely tolerate penicillins (1, 2). Numerous adverse

outcomes are associated with an unverified penicillin allergy, and elective evaluation for penicillin allergy has been recommended (1, 3, 4).

There is a vast disparity between the number of patients with a penicillin allergy label and practicing allergists in the United States, with over 30 million penicillin-allergic labeled patients and less than 5000 practicing allergists (5, 6). With such a significant prevalence of labeled penicillin allergy, no single medical discipline can handle this burden alone; a coordinated effort across both primary care and subspecialists will be required to address this. As the majority of penicillin allergy labels occur in young childhood, pediatricians are uniquely situated to have a significant impact in reducing the long-term consequences of a penicillin allergy label through delabeling strategies (1, 5). Direct oral challenge in low-risk patients has been recommended as a delabeling strategy for this population (7-9). Cumulative studies have now evaluated the safety and efficacy of direct amoxicillin challenge in children with a penicillin-allergy label in over 1400 subjects (8-16); the majority of studies have taken place in the outpatient allergist setting. Across studies, positive challenge rates ranging from 0-13%. The largest study was a single center prospective study which defined low-risk allergy patients as an absence of severe cutaneous adverse reactions (SCARs); they reported on 818 patients and found a 6% positive challenge rate (8). Across the above studies, all reactions were mild and only required treatment with oral antihistamines, no epinephrine use was documented in any of these studies.

While there is significant evidence for the safety and efficacy of direct penicillin challenge in the evaluation of penicillin allergy, this has not yet been widely implemented in the primary care setting. There have been two pilot studies exploring direct amoxicillin challenge in the pediatric primary care setting. The first was a retrospective study of 42 children in Australia who included children greater than 18 months old. They performed direct amoxicillin challenges after 3 months had elapsed from the index reaction. There was a 3% positive challenge rate and all reactions resolved with only oral diphenhydramine. The second was a prospective study that included 102 children in Ireland and there no positive challenges to amoxicillin challenge. This approach has not been studied in the United States. A recent survey of US-based pediatricians identified perceived barriers to implementing penicillin allergy evaluations into their routine care (17). Significant gaps in knowledge exist regarding the feasibility of this approach involving direct amoxicillin challenge procedures in low-risk patients in the pediatric primary care setting.

1. Castells M, Khan DA, Phillips EJ. Penicillin Allergy. N Engl J Med. 2019;381(24):2338-51.
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3. Blumenthal KG, Shenoy ES. Is My Child Allergic to Penicillin? JAMA Pediatr. 2019;173(7):708.
4. Joint Task Force on Practice P, American Academy of Allergy A, Immunology, American College of Allergy A, Immunology, Joint Council of Allergy A, et al. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010;105(4):259-73.
5. Staicu ML, Vyles D, Shenoy ES, Stone CA, Banks T, Alvarez KS, et al. Penicillin Allergy Delabeling: A Multidisciplinary Opportunity. J Allergy Clin Immunol Pract. 2020;8(9):2858-68 e16.
6. American Academy of Allergy Asthma and Immunology Report on the Allergy and Immunology Physician Workforce (1999-2009/10). Rensselaer, NY: The Center for Health Workforce Studies; 2012 [Available from: https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/2012-AI- Physician-Workforce-Report.pdf.
7. Vyles D, Antoon JW, Norton A, Stone CA, Jr., Trubiano J, Radowicz A, et al. Children with reported penicillin allergy: Public health impact and safety of delabeling. Ann Allergy Asthma Immunol. 2020;124(6):558-65.
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12. Mustafa SS, Conn K, Ramsey A. Comparing Direct Challenge to Penicillin Skin Testing for the Outpatient Evaluation of Penicillin Allergy: A Randomized Controlled Trial. J Allergy Clin Immunol Pract. 2019;7(7):2163-70.
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16. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. J Allergy Clin Immunol. 2011;127(1):218-22.

17. Cherk E, Morris K, Collins CA. Partnering with general pediatricians to delabel penicillin allergies in children. Ann Allergy Asthma Immunol. 2020.

b. Current practice

Currently there is no standard protocol in the Children's Health pediatric primary care clinic for evaluation of penicillin-allergy labels. Most often, children with a penicillin allergy label are referred to the Children's Health pediatric allergy clinic for evaluation of penicillin allergy regardless of their risk status based on the history of their index reaction to penicillin.

3. Study Design.

Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

This study is a prospective, descriptive, single arm study of a convenience sample of children from age 2-18 with a history of parent reported penicillin allergy who present to an outpatient pediatric clinic for a routine healthcare maintenance visit.

4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,

2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.

3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

Patients will be recruited from the pediatric primary care clinic at the Children's Health Specialty Center Dallas campus who are scheduled for a routine healthcare maintenance visit, have a penicillin allergy listed in the electronic medical record, and have consented to participate in research activities. Patient caregivers will receive a telephone call, where in a study member will introduce the topic of penicillin allergy and delabeling through direct

amoxicillin challenge and obtain verbal consent to administer a risk-stratifying questionnaire evaluating the index reaction and their interest in proceeding with the amoxicillin challenge, including reasons for hesitancy and perceived barriers. Subjects with a history of reactions consistent with severe cutaneous adverse reactions will be excluded. The study member will review the oral amoxicillin challenge procedure and assess caregiver and patient's interest in proceeding with oral amoxicillin challenge.

Subjects who are classified as low-risk and are interested to proceed with direct amoxicillin challenge will be sent the consent form through the caregiver's preference of encrypted email, mail, or patient portal MyChart for their review. Caregivers will be provided the option to sign the electronic consent form, using an encrypted, secure platform provided through UTSW (Docusign/REDCap), and if they choose this option, will be contacted via telephone to review the consent form and answer applicable questions. Alternatively, when presenting for their healthcare maintenance visit at the pediatric primary care clinic at the Children's Health Specialty Center Dallas campus, the written consent form will be reviewed.. Patients will be screened for acute dermatitis or respiratory symptoms. Subjects with acute dermatitis or respiratory symptoms at time of evaluation will be excluded. A point of care urine pregnancy test will be performed on adolescent female subjects who have begun menstruation; subjects who have a positive pregnancy test or who are breastfeeding will be excluded.

A single dose of amoxicillin 50 mg will be administered at the start of the healthcare maintenance visit. Subjects will be observed for 10 minutes and if no reaction, will be given a second 200 mg dose and observed for a further 50 minutes for immediate reactions, defined as onset of urticaria, angioedema, cough, wheezing, rhinitis, repetitive vomiting, diarrhea, protracted abdominal pain, or hypotension, and managed accordingly. This direct amoxicillin challenge testing is the recommended evaluation for low-risk patients, and the investigatory component of this study is if it can be performed in conjunction with a routine healthcare maintenance visit in the pediatric primary care setting. During this observation period, subjects will have their healthcare maintenance visit with the primary pediatric provider. Subjects who have a negative oral challenge will be provided documentation of their immediate tolerance of penicillin. Upon completion of challenge, a survey will be administered to families to assess the quality of their experience and identify areas for improvement. If immunizations are indicated per the CDC vaccination schedule, they will be administered after this 60-minute period of observation from the challenge. Subjects will be discharged with instructions to contact the pediatrician and study team for any delayed symptoms. We will also measure the duration of each subject's time in the clinic from check in to check out. A follow up encounter will occur over the phone at 7-10 days after the date of oral challenge to assess for delayed reactions. At 1 year post-challenge, subjects' penicillin allergy status will be assessed in the electronic medical record, and patients who have had penicillin allergy label added back to their allergy list will be contacted via telephone to assess reasons for the

addition of the penicillin allergy label. Descriptive statistics will be used to describe the population completing amoxicillin challenge testing.

4.b. List of the study intervention(s) being tested or evaluated under this protocol			
☐	**N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.		
#	**Study intervention(s) being tested or evaluated under the protocol** *Add or delete rows as needed*	**Affiliate** Place a check next to institution(s) where the intervention will be performed	**Local Standard Practice?** Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	**Direct Amoxicillin challenge**	☐ UTSW	☐ Yes
		☐ PHHS	☐ Yes
		☒CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes
2	**Insert study intervention 2 here**	☐ UTSW	☐ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

4.c.

Study Intervention #1

Direct Amoxicillin Challenge

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
All groups/subjects	One benefit will be the accurate diagnosis of current penicillin tolerance status. If penicillin tolerant, would have the benefit of using penicillin-based antibiotic treatment for future infections and diminishing the harms associated with a penicillin-allergy label which include prolonged hospital stays, increased surgical site infections, increased rates of Clostridium Difficile infections, and increased healthcare utilization costs when compared to patients without a penicillin allergy label. Another benefit includes increased access to evaluation, as this evaluation would be included within patients' healthcare maintenance visit and not require a separate referral to an allergist with the associated barriers of time and cost with seeing another provider.

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).

(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)

Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious

Rare These risks are expected to occur in less than **5** subjects out of **100**		•

4.c.

Study Intervention #1

Insert name used in 4.b.

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).

(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)

Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

		4.d. List ALL other research procedures or components not listed in table 4.b. ***The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.*** Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)		
#	**Research component** • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Eligibility Assessments**			
	Questionnaire assessing Index Reaction and hesitancy and barriers to pursuing challenge		1	Not Serious and Less Likely
2	**Healthcare Maintenance Visit**			
	History and Physical	1		Not Serious and Less Likely
	Insert procedure here			
	Insert procedure here			
3	**Post-challenge Assessment**			
	Questionnaire assessing post-challenge status		1	Not Serious and Less Likely
	Insert procedure here			
	Insert procedure here			

4	**Urine Pregnancy Test**		1	Not Serious and Less Likely
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			

5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

NA

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

Risks of Protocol Specified Medications/Procedures

- Adverse reactions to amoxicillin include headache, diarrhea, nausea, vomiting, rash, and allergic reactions. Allergic reactions range from mild to severe, and if a patient has an allergic reaction, he/she may need oral, IM, or IV medications. The site investigators for this trial are credentialed advanced health providers who are trained to recognize and manage systemic reactions. Treatment will be available within 60 seconds in the event of a reaction. Emergency medications as listed below will be available to treat any allergic reactions.
- Treatment of individual acute allergic reactions during the conduct of the study may include antihistamines, epinephrine, β-adrenergic agonists, oxygen. The risks of these common medications include the following
    - Antihistamines: drowsiness, dizziness, constipation, stomach upset, blurred vision, dry mouth/nose/throat
    - Epinephrine: tachycardia, palpitations, nervousness, sweating, nausea, vomiting, trouble breathing, headache, dizziness, anxiety, tremors, pale skin
    - β-adrenergic agonists: nervousness, shaking, headache, dizziness
    - These risks will be minimized by appropriate dosing per guideline management of systemic allergic reactions.

c. Will the safeguards be different between/among groups?

☐ Yes ☒ No

If yes, describe here