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Intervention to Reduce Early (Peanut) Allergy in Children SHORT TITLE: iREACH

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STUDY SPONSORS: The National Institute of Allergy and Infectious Diseases (NIAID)

NIAID Funding Mechanism: *TBD*

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SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: AAABB-U01-LCH-002	**Version Number/Date:** **2.0/27-MAY-2021**
Protocol Title: Intervention to Reduce Early (Peanut) Allergy in Children (iREACH)	
IND/IDE Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	

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DAIT Regulatory Management Center
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[If PPD is not the Regulatory Management Center for this protocol, e.g., for an Investigator Initiated clinical trial, contact the DAIT Regulatory Officer for appropriate mailing address.]

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, 812 and in the International Conference for Harmonisation (ICH) document entitled *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

*[*The site Principal Investigator should print, sign, and date at the indicated location below. A written signature is acceptable, and an electronic signature is acceptable in a pdf version of the form.]*

_____

Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

Protocol Synopsis

Title	Intervention to Reduce Early (Peanut) Allergy in Children
Short Title	iREACH
Clinical Phase	Not applicable
Number of Sites	N=30-37; United States
IND Sponsor/Number	Not applicable
Study Objectives	To determine the effectiveness of iREACH in increasing adherence to the Addendum Guidelines for the Prevention of Peanut Allergy (PPA Guidelines) among pediatric clinicians.
Study Design	Practice-based, two-arm, cluster randomized controlled trial
Primary Endpoint(s)	• Percent of infants at *low risk for peanut allergy* whose pediatric clinicians adhered to the guidelines. • Percent of infants at *high risk for peanut allergy* whose pediatric clinicians adhered to the guidelines.
Secondary Endpoint(s)	• Percent of infants at low risk for peanut allergy who developed peanut allergy by age 2.5. • Percent of infants at high risk for peanut allergy who developed peanut allergy by age 2.5. (Exploratory Objectives) 1. Allergist adherence to the PPA Guidelines 2. Barriers/facilitators for PPA Guideline adherence among pediatric clinicians and caregivers. 3. Caregiver adherence to PPA Guidelines (peanut product introduction and feeding frequency).
Accrual Objective	Pediatric clinicians: 200; High-risk infants: 500; Low-risk infants: 10,000; Caregivers: 10,500
Study Duration	51 months for practices, maximum 23 months for pediatric clinicians, maximum 26 months for infants and caregivers
Treatment Description	The iREACH intervention consists of A) an education module on the PPA Guidelines and the research on which the guidelines were based; B) an EHR-integrated CDS tool in the 4- and 6-month WCC templates to support pediatric clinician decision-making around 1) proper triage of infants into peanut allergy risk categories, 2) allergy testing and interpretation and/or allergist referral for high-risk infants, and 3) caregiver counseling on peanut introduction including educational materials for families; and C) follow-up prompts in the 9-and 12-month WCC templates guiding pediatric

	clinicians to ask caregivers about inclusion of peanut products in their child's diet.
Inclusion Criteria	Practice sites • The practice utilizes a centrally-integrated EHR. • The practice has signed a legally-binding engagement agreement with Lurie Children's Pediatric Practice Research Group. • The practice employs at least one physician who has completed a residency in general pediatrics and is practicing as a general pediatrician. Pediatric Clinicians: • Clinician is a physician, physician assistant, resident, advanced practice nurse, family practitioner, or pediatric nurse practitioner working in a pediatric practice. • Clinician is employed by a practice that is a member of one of the participating practices in the study. • Clinician provides well child care to infants ages 4 or 6 months. Infants • Infant has been seen by a pediatric clinician in the intervention or control arm for a 4- and/or 6-month WCC. Caregivers • Is the caregiver of an infant seen for a 4- and/or 6-month WCC by a pediatric clinician in a practice belonging to the study's intervention or control arms. • Is ≥18 years of age or has parent or guardian permission to participate. • Is able to understand the study and provide informed consent for the 12- and 24-month (child's age) survey.
Exclusion Criteria	Practice Sites • Sees <50 newborn patients/year. • Has only temporary pediatricians on staff. • The practice prediatric clinicians do not use an EHR system. Pediatric clinicians • The clinician is a temporary employee. • The clinician begins employment at participating practice less than three months prior to end of the 18-month study enrollment period. Infants • The infant has a medical condition that chronically inhibits the ability to take food orally (i.e., dysphagia,

	muscular dystrophy, gastrostomy). • The infant has past or current medical problems that prohibit implementation of PPA Guidelines or may have impacted the quality or interpretation of the data obtained from the study. Caregivers • Caregiver's primary language is not English or Spanish.
Study Stopping Rules	• Breach of Confidentiality with Infant Personal Health-Related Information: The source of the breach will be investigated, identified, and resolved. If the source of the breach of confidentiality cannot be resolved, study will be placed on hold. • Change in PPA Guidelines that May Affect Study Procedures and Outcomes: The study will pause, and the study team will review implications and revise procedures as necessary.

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Table of Contents

Glossary of Abbreviations

AAP	American Academy of Pediatrics
BPA	Best Practice Advisory
CDS	Clinical Decision Support
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EEDI	Exploratory EHR Data Infant
EHR	Electronic Health Record
ETL	Extract Transform Load
FA	Food Allergy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
iREACH	Intervention to Reduce Early (Peanut) Allergy in Children
LEAP	Learning Early About Peanut
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
NLP	Natural Language Processing
PA	Peanut Allergy
PHI	Personal Health Information
PI	Principal Investigator
PPA	Prevention of Peanut Allergy
PEDI	Primary EHR Data Infant
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SEDI	Secondary EHR Data Infant
SFTP	Secure File Transfer Protocol

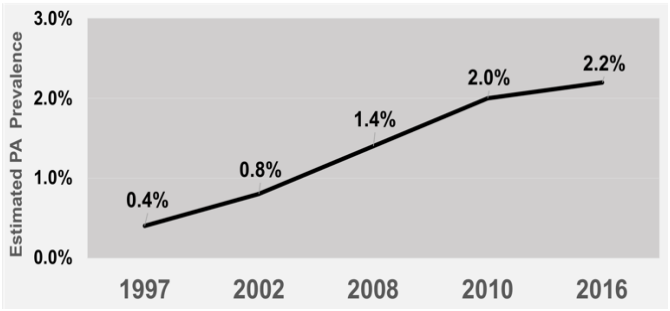
sIgE	Specific IgE
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction
WCC	Well Child Check

1. Background and Rationale

1.1. Background and Scientific Rationale

The Peanut Allergy Epidemic: Food allergy (FA) prevalence has increased sharply in recent decades[1] and is a major health concern. Previous work by our research group found FA to be common, affecting 8% of US children,[2] and costly—resulting in $24.8 billion dollars per year in expenditures by the healthcare system and US families.[3] Emergency department visits and hospitalizations for FA and food-induced anaphylaxis have increased steadily in the US over the past decade,[4] and in 2010 were estimated to exceed 200,000 visits annually.[5] Results from our latest prevalence survey confirm that peanut allergy (PA) remains the most common food allergy, affecting 2.2% of U.S. children[6] (**Figure 1**).[2,6-9] It is also one of the least frequently outgrown.[8] Prospective cohort studies in the US and Australia found that <20% of peanut-allergic infants outgrew their allergy. [10,11] Peanut is also a leading cause of fatal food-allergic reactions[12,13] and has been associated with substantially impaired quality of life among both peanut-allergic children and their families.[14,15]

Figure 1. Prevalence of US Childhood Peanut Allergy



Changing Recommendations for Timing of Peanut Introduction: Due to rising FA prevalence, the American Academy of Pediatrics (AAP) released guidelines in 2000 directing pediatricians to counsel caregivers of all infants to delay introduction of certain allergenic foods, including peanut, until age three.[16] These guidelines were substantially revised by AAP in 2008,[17] citing *"insufficient evidence to recommend any specific practices concerning introduction of these foods after 4-6 months for the prevention of allergic disease."* [17-19]

Growing Evidence for Earlier Peanut Introduction: In 2008 Du Toit et al. found that early peanut consumption was associated with a 10-fold reduction in PA prevalence among children aged 4-18 years.[20] Subsequently, the Learning Early About Peanut (LEAP) study (N=640) tested whether introduction of dietary peanut in high-PA risk infants 4-11 months of age would reduce PA incidence compared to high-risk infants counseled to avoid peanut until age 5 years.[21] Specifically, the LEAP protocol instructed caregivers in the early introduction arm to feed their infants at least 6g of peanut protein/week. The LEAP study found that early peanut introduction was safe and resulted in an 81% reduction in subsequent development of PA in high-risk children, as well as corresponding modulation of immune responses to peanuts at age 5. Overall, 92% of participants adhered to the intervention, demonstrating its feasibility. Moreover, the follow-up LEAP-ON study found that even after avoiding peanuts for a year, the children in the early introduction arm retained peanut tolerance.[22] These findings, in addition to emerging mechanistic evidence for its tolerogenic effects, [23,24] spurred a dramatic reversal of national guidelines to recommend early peanut introduction. The 2017 **NIAID-sponsored Addendum Guidelines for the Prevention of Peanut Allergy in the United States** (PPA Guidelines), stratified infants into three classes, each with its own evaluation protocol and recommendation for peanut product introduction (**Figure 2**). Based on these guidelines, pediatricians should assess PA risk for infants aged 4-6 months and advise accordingly.[25] Because the PPA Guidelines recommend peanut introduction for infants in both class 2 and 3

Figure 2. Summary of Addendum Guidelines for the Prevention of Peanut Allergy

Addendum Guideline	Infant Criteria	Recommendations	Earliest Age of Peanut Introduction
1	Severe eczema, egg allergy, or both	Strongly consider evaluation with peanut-specific IgE and/or skin prick test and, if necessary, an oral food challenge. Based on test results, introduce peanut-containing foods.	4 to 6 months
2	Mild to moderate eczema	Introduce peanut-containing foods.	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods.	Age-appropriate and in accordance with family preferences and cultural practices

(**Figure 2**), this protocol will refer to these infants as a single class of "low-risk" infants and will examine them separately from the "high-risk" infants in class 1.

While the provision of clinical practice guideline-consistent care has the potential to improve patient outcomes, uptake of the PPA guidelines by key stakeholders has lagged substantially.[26-29] Poor PPA guideline adherence was recently demonstrated by preliminary results of a large, NIAID-sponsored survey of pediatricians conducted from June-July 2018. Only 27% of pediatricians regularly adhered to all PPA Guideline recommendations, despite 92% being aware of the guidelines. Poor understanding of the PPA Guidelines and their application (35%) and lack of time in clinical encounters (30%) were commonly reported barriers to adherence.

A lack of adherence among pediatricians and residents was highlighted by Hoffman et al. Only 11% achieved the highest level of adherence to the PPA Guidelines.[30] Similarly, a survey of 53 residents found that while most reported familiarity with current guidelines for introduction of peanut-containing foods to infants, only 28% correctly identified the recommended age for introduction.[31] Nearly 75% chose answers that represented the currently-abandoned 2000 AAP guidelines; 83% reported that they often apply these outdated guidelines in practice. These data show that the PPA Guidelines are not being followed, even among young physicians who are currently under training.

There is also evidence that caregivers may be still unwilling to introduce allergenic foods during infancy. Data from a 2017 sample of caregivers revealed low willingness and questionable support for early allergenic solid food recommendations. Only 31% expressed willingness to introduce peanut before or around six months of age; 40% expressed willingness to introduce peanut after 11 months.[32] This reluctance from caregivers suggests that most are unlikely to spontaneously introduce peanut during the critical period identified by the PPA Guidelines.

To understand key barriers to guideline adherence, an influential review by Cabana et al. (1999) demonstrated that non-adherence is rooted in lack of awareness, knowledge, and attitudes towards guideline content.[33] A review affirming Cabana's findings highlighted electronic Clinical Decision Support (CDS) tools as an effective strategy to improve guideline-consistent care by incorporating them into physicians' clinical workflow.[34]

1.2. Rationale for Selection of Investigational Product or Intervention

The iREACH intervention is designed to address the following identified barriers in the implementation of the PPA Guidelines: Poor understanding of the PPA Guidelines and their application, lack of time in clinical encounters, and caregiver concerns about allergic reactions.

Improving Clinical Guideline Adherence through CDS-based Interventions: Adherence to the PPA Guidelines involves new clinical responsibilities for pediatricians in all primary care encounters with 4- and 6-month-old infants. While data show that CDS-based interventions can improve guideline adherence across diverse settings,[37] such interventions are particularly important in the pediatric setting where a growing number of recommendations compete for clinicians' time and attention.[38]

As part of national efforts to support efficient and effective use of health information technology to improve health care outcomes, the *Agency for Healthcare Research and Quality* endorses the "CDS Five Rights" approach. This approach asserts that CDS-supported health care improvement can be achieved via CDS interventions that communicate:

- *The **right information***: evidence-based, suitable to guide action, pertinent to the circumstance
- *To the **right person***: considering all stakeholders, including clinicians, patients, and caregivers

- *In the **right intervention format***: such as a best-practice alert or order set
- *Through the **right channel***: for example, a clinical information system such as an EHR
- *At the **right time** in the workflow*: for example, at time of clinical decision/action/need

In the context of the AHRQ-endorsed Five Rights approach, iREACH was developed through strategic engagement of pediatric clinicians, allergists, caregivers, and information technology experts working to ensure that iREACH provides:

The right information: Leveraging data from the landmark LEAP trial[21] and other research reviewed by the expert panel responsible for the PPA Guidelines, the iREACH CDS will provide pediatric clinicians with a decision aid and resources to support PPA Guideline-adherent patient care.

To the right person: The iREACH CDS will directly engage pediatric clinicians explicitly targeted by the PPA Guidelines.

In the right CDS format: The iREACH CDS will employ best practice alerts, which encourage pediatric clinicians to provide guideline-consistent care during the clinical encounter.

Through the right channel: The iREACH CDS will be delivered through the EHR, integrating its functions into charting systems already utilized by physicians.

At the right time in workflow: The iREACH CDS will prompt clinicians to offer PPA Guideline-consistent care at the appropriate moment in the patient encounter in a manner that is minimally disruptive to existing workflows.

To our knowledge, no CDS tools currently exist to support decision-making related to peanut introduction recommendations for infants. The iREACH tool that we will apply in this trial has the advantage of being integrated into existing EHR workflow templates for the 4-, 6-, and 9-month WCCs that are recommended by the American Academy of Pediatrics and almost universally well-utilized by US pediatric clinicians.

Assessing Adherence Among Caregivers

The pediatric clinician's adherence to the PPA guidelines and subsequent recommendation to caregivers will influence the caregiver's decision to introduce peanut products early to their infant. Exploratory analyses will be conducted to measure caregivers' adherence ot the guidelines which will be assessed in the form of a survey.

1.3. Preclinical Experience

Not applicable

1.4. Clinical Studies

A pilot study of iREACH was conducted in a pediatric network at Ann and Robert H. Lurie Children's Hospital of Chicago to assess the utility and effectiveness of the clinical education module and CDS tool components of the intervention. Pediatric clinicians in one practice received both components (clinical education and CDS tool), and infants in this iREACH practice were compared with infants in a second Lurie Children's practice that did not have the intervention. The study population included all infants seen for a 4- or 6-month routine WCC during the study period. Results were obtained through EHR data extraction and chart review. We analyzed the proportion of infants whose pediatric clinicians adhered to the PPA Guidelines—characterized by appropriately recommending peanut introduction or completing sIgE testing or allergy referral.

From 06/2017-03/2018, 463 infants were seen for 4- or 6-month WCC visits. We found that far more pediatric clinicians in the iREACH clinic adhered to PPA Guidelines than did infants in a comparison clinic without iREACH, supporting the efficacy of the education module and CDS tool ($p<0.001$, low-risk infants). Additionally, over 90% of pediatric clinicians in the iREACH clinic partially adhered to the PPA Guidelines by distributing handouts to caregivers on how to introduce peanut products.

	iREACH Clinic	**Non-iREACH Clinic**
	#adherent/total (%)	# adherent/total (%)
Low-risk Infants Adherent to guidelines	75/143 (52.4)	44/311 (14.1)
High-risk Infants Adherent to guidelines	5/8 (62.5)	0/1 (0.0)

This pilot also included a survey of pediatric clinicians using the iREACH CDS tool to assess acceptability. Electronic surveys were sent to all 37 enrolled pediatric clinicians and 86% responded. Pediatric clinicians who saw low-risk children cited multiple positive aspects of the CDS tools. The majority (72%) noted the prompts were easy to use, and 86% felt the caregiver handout on solid food and peanut product introduction was easy to use. Respondents also noted that the caregiver handout helped them counsel families. Time spent using the tools varied, but the most common response (30%) was that iREACH neither saved nor added time. In summary, data from pediatric clinicians using a pilot version of the iREACH CDS supported its feasibility and acceptability.

2. Study Hypotheses/Objectives

2.1. Hypotheses

Primary:

High-risk infants (those with severe eczema and/or egg allergy) and low-risk infants (those with mild to moderate eczema and no egg allergy as well as those with no eczema or any food allergy) in the iREACH intervention arm will have higher rates of pediatric clinician adherence to PPA Guidelines compared to the respective infants in the non-intervention arm.

Secondary:

High-risk and low-risk infants in the iREACH intervention arm will have a lower incidence of peanut allergy by age 2.5 years compared to the respective infants in the non-intervention arm.

2.2. Primary Objective

To determine the effectiveness of iREACH in increasing adherence to the PPA Guidelines among pediatric clinicians.

2.3. Secondary Objective

To determine the effectiveness of iREACH in decreasing the incidence of peanut allergy by age 2.5.

2.4. Exploratory Objectives

a. To determine allergists' adherence to the PPA Guidelines
b. To identify common barriers/facilitators for PPA Guideline adherence among pediatric clinicians and caregivers
c. To determine caregiver adherence to the PPA Guidelines

3. Study Design

3.1. Study Populations

This study involves three study populations: 1) pediatric clinicians, 2) infants seen for a 4- and/or 6-month WCC by the pediatric clinicians, 3) caregivers of these infants.

3.2. Description of Study Design

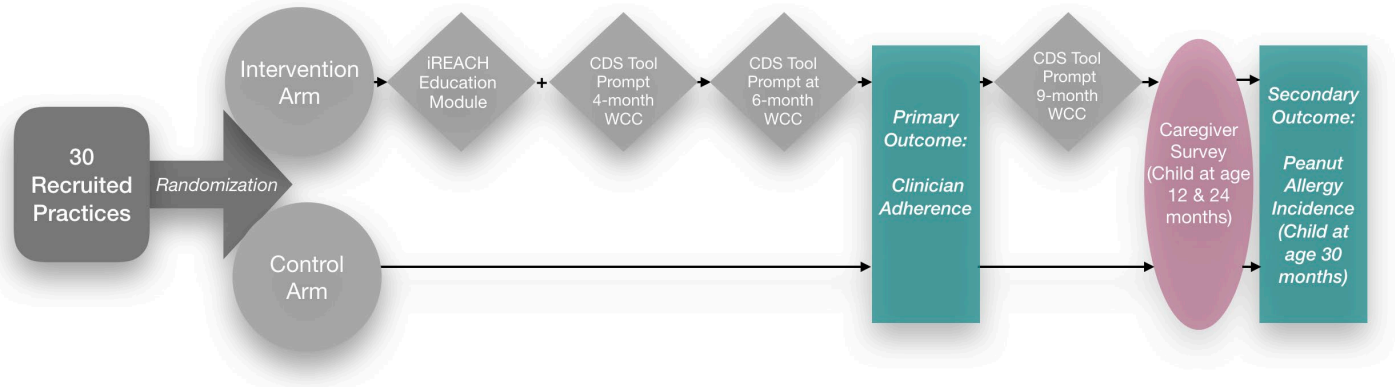
This study is a two-arm, cluster-randomized, controlled clinical trial. A minimum of 30 pediatric practice sites will be randomized to the iREACH intervention arm or to the control arm (**Figure 3**). All pediatric clinicians within each participating practice (n≈200 total) will be assigned to the arm to which their practice is randomized. Pediatric clinicians in the intervention arm will 1) receive the iREACH education module, 2) have the iREACH CDS tool integrated into the EHR templates for use at the 4-, 6-, 9-, 12-month WCC, and 3) will be reminded by EHR-embedded prompts at the 9-month WCC to ask caregivers whether peanuts were introduced and tolerated.

No study procedures will be implemented in the non-intervention, control practices, and their pediatric clinicians will not receive extra PPA Guidelines education, nor will any EHR modifications be made in their practices to support adherence to PPA guidelines. The trial will be conducted over an 18-month period. During this time, approximately 500 high-risk infants and 10,000 low-risk infants are expected to be seen for 4- and 6-month WCC. The primary outcome, pediatric clinician adherence to the PPA Guidelines, will be assessed using EHR data for each infant following the 6-month WCC.

Data for the secondary outcome will be obtained by a combination of EHR data extracted after the infant's 6-month WCC and data collected from caregivers. EHR data extraction will be performed to obtain data from the infant's 9-, 12-, 15-, 18-, 24-month WCC and any sick visits and allergist progress notes entered from 4-30 months of age. Caregivers' data will be collected via surveys of caregivers of children seen for 4- or 6-month WCC visits during the study period. Caregivers will be recruited and asked to provide informed consent at the time of the child's first birthday and questions will be asked to determine the incidence of peanut allergy. A follow-up survey will be sent to caregivers after the child's second birthday.

Data for exploratory outcomes will be obtained through EHR data extraction and surveys of pediatric clinicians and the caregivers of infants seen for 4- or 6-month WCC. Pediatric clinicians in the intervention arm will be asked to provide informed consent and will complete three surveys over approximately 21 months. Pediatric clinicians in the control arm will be asked to provide informed consent following completion of data collection for the primary outcome and will complete one survey. Finally, caregivers, through the two surveys conducted at the time of their child's first and second birthdays, will provide information for exploratory outcomes.

Figure 3. iREACH Study Design



3.3. Primary Endpoint(s)

The primary endpoint is the percentage of infants within each trial arm whose pediatric clinician adhered to the guidelines regarding peanut introduction assessed after completetion of either a 4- or 6-month WCC. The primary endpoint concerns only the peanut introduction recommendation by the treating pediatric clinician and not additional behavior by the treating allergist or by caregivers. The primary endpoint will be measured separately by risk category as follows:

- % of infants at *low risk for peanut allergy* whose pediatric clinician adhered to the guidelines for that infant.
- % of infants at *high risk for peanut allergy* whose pediatric clinician adhered to the guidelines for that infant.

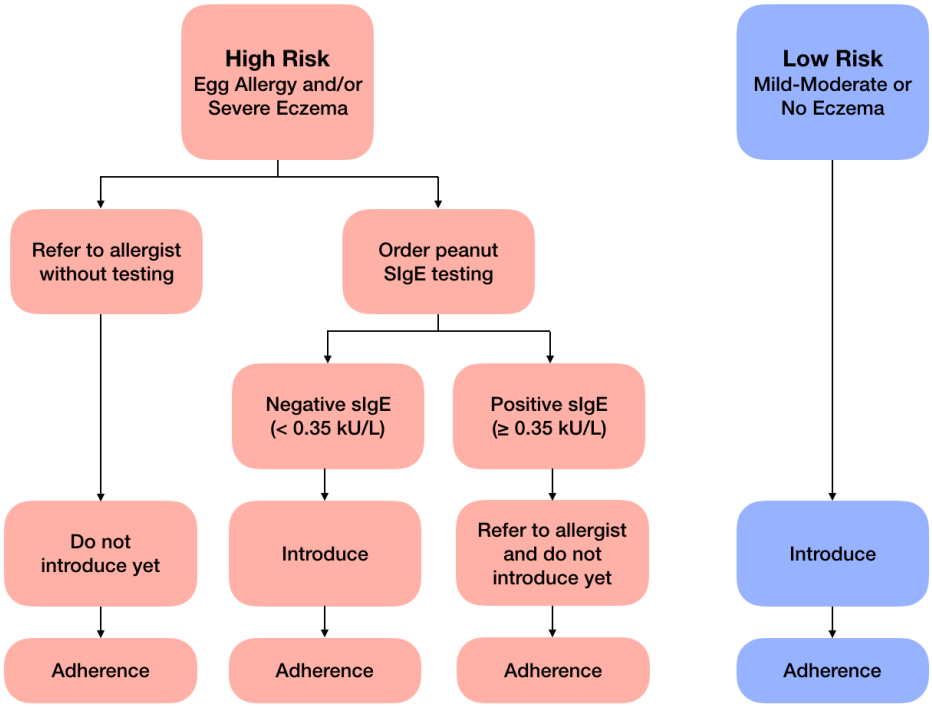
Adherence will be determined as follows: Infants will be stratified into high- versus low-risk categories based on the presence of severe eczema and/or egg allergy. Egg allergy and eczema diagnoses will be obtained from the "problem list" and "encounter diagnosis" sections of the EHR. Severe eczema will be further identified by the presence of prescriptions for topical corticosteroids, calcineurin inhibitors or other anti-inflammatory agents and/or clinician documented eczema classification (i.e., use of word "severe" and lack of words "mild or moderate") found in the encounter notes through natural language processing (NLP).

For high-risk infants, pediatric clinician adherence will be determined as indicated in **Figure 4** by:

1. Actions taken by the pediatric clinician (peanut sIgE testing, referral to an allergy specialist, or neither). The information on these actions will be obtained from laboratory test and referral orders entered into the EHR.
2. Peanut sIgE testing results, if applicable (negative when IgE <0.35 kUA/L versus positive when IgE ≥ 0.35 kU/L). The information on these results will be obtained from laboratory test results entered into the EHR.
3. Dietary peanut introduction recommendation (recommendation to introduce or no recommendation). This information will be obtained from mentions of peanut introduction extracted from the encounter note using NLP (if sIgE ordered). If the information is absent from these sources, other sources will be utilized (i.e., parent- caregiver surveys and/or pediatric clinician surveys) to complement EHR data.

For low-risk infants, pediatric clinician adherence will be determined based on whether a recommendation for dietary peanut introduction was given. This information will be obtained from pediatric clinician notes made in the anticipatory guideance section using NLP. If the information is absent from these sources, other sources will be utilized (i.e., caregiver surveys) to complement EHR data.

Figure 4. Pediatric Clinician Adherence



3.4. Secondary Endpoint(s)

The secondary endpoint is the incidence of peanut allergy by age 2.5 years and is assessed through a combination of parent survey data and extracted EHR data. Secondary endpoints will be measured separately by risk category as follows:

- % of infants at low risk for peanut allergy who developed peanut allergy by age 2.5.
- % of infants at high risk for peanut allergy who developed peanut allergy by age 2.5.

Peanut allergy determination will follow a hierarchy based on the source of information (tiers). This hierarchy will offer the first level of diagnostic confidence. If the diagnosis was made by an allergist, we will consider this as the highest confidence for peanut allergy (Tier 1). If the diagnosis was made by a pediatric clinician, we will consider it as Tier 2 and if it was only based on information from a caregiver (through the surveys that we will conduct at when the child is age 12 and 24 months), Tier 3.

Within each tier, there are diagnostic categories that reflect a decision algorithm based on tier-specific data. The diagnostic categories are as follows:

- Confirmed Diagnosis
- Convincing Diagnosis
- Questionable Diagnosis
- No Peanut Allergy (PA)

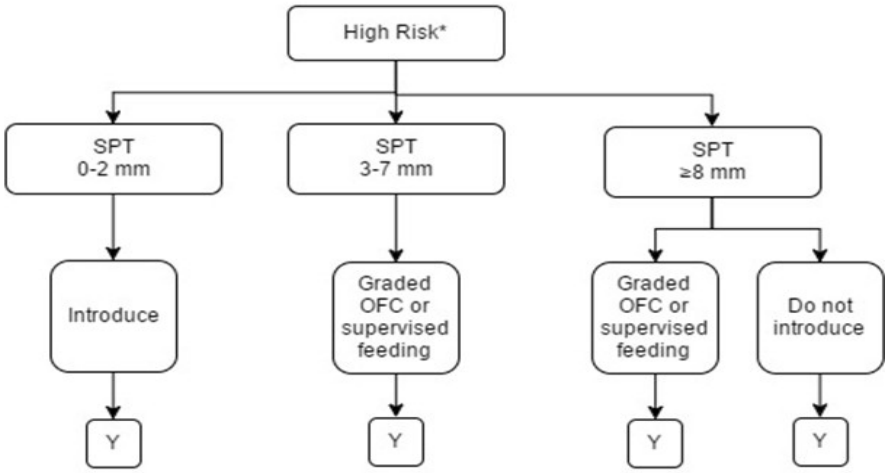
This double system approach (tiers and diagnostic categories) will offer substantial transparency for diagnosis and will allow us to evaluate whether the impact of our intervention can be evidenced at a particular level of diagnostic certainty. The details of the algorithm can be found in the Manual of Procedures.

3.5. Exploratory Endpoint(s)

Allergist Adherence to the PPA Guidelines (**Figure 5**). Allergist adherence will be assessed once progress notes by the allergist to whom the infant was referred to have been added to the patient EHR and will be determined based on the following four data elements:

1) Skin Prick Test result (0-2 mm, 3-7mm, ≥8 mm), 2) peanut sIgE results, 3) results of in-office supervised feeding of peanut products or oral food challenge with peanut products and 4) peanut product introduction/feeding recommendation. These data will be extracted from laboratory test results, if available, and the allergist progress note entered into the patient EHR. If any data elements are missing, however, the allergist adherence will be adjudicated by an expert panel of allergists from the study advisory board.

Figure 5. Allergist Adherence



*We assume that allergists will evaluate any child who is referred to them.

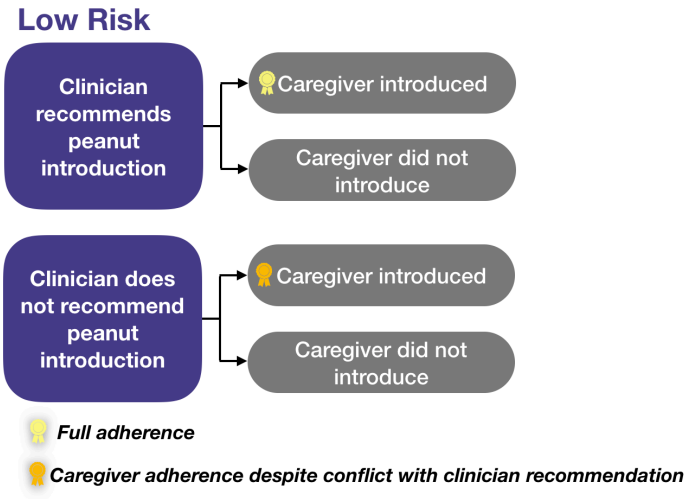
Barriers/facilitators for PPA Guideline adherence among pediatric clinicians and caregivers. Barriers and facilitators will be assessed through survey of pediatric clinicians and caregivers.

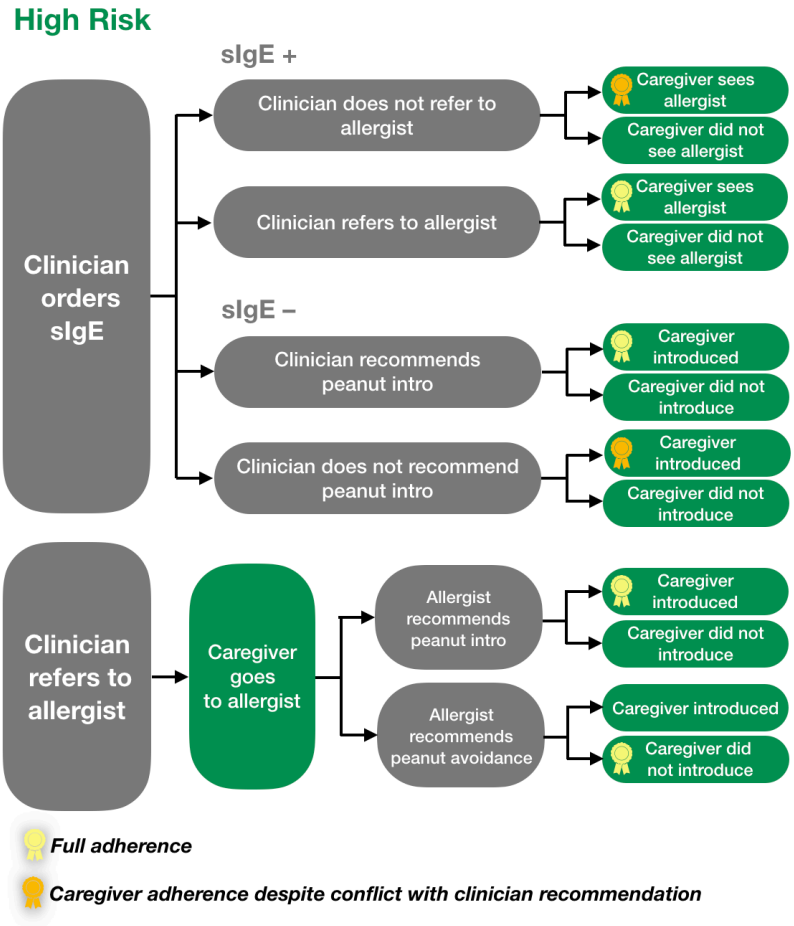
Caregiver adherence (peanut product introduction and feeding frequency) **(Figure 6)**. Caregiver adherence is conceptualized to be independent of the clinician's adherence. All pathways to adherence (whether full adherence, meaning the clinican and the caregiver adhere, or caregiver adherence despite conflict with clinician recommendation) are described in Figure 6. Caregiver adherence to the PPA Guidelines will be assessed through the caregiver survey completed around the child's first and second birthdays, as well as through the child's EHR records.

Caregiver adherence will be determined based on the following five data elements: 1) infant risk category (high- vs. low-risk based on the presence of an egg allergy and/or severe eczema), 2) peanut sIgE testing results, if applicable (negative vs. positive); 3) peanut skin prick test results (if applicable), 4) peanut product introduction (introduced or did not introduce), and 5) peanut product feeding frequency and quantity (feedings per week). These data will be obtained from the caregiver survey (which will assess the timing, amount, frequency, and modes of peanut product consumption by the infant) and from the infant's EHR records (risk category, testing recommended, and testing results).

For low-risk infants, the caregiver is adherent if the caregiver introduces peanut by 12 months of age. For high-risk infants, the caregiver is adherent if the clinician'stesting indicates the introduction of peanut and the caregiver introduced peanut products by 7 months of age and continued feeding at least 6g over ≥ 3 feedings per week as reported around the infant's 1st birthday or the clinician's testing indicates avoidance of peanut and the caregiver does not introduce peanut products as reported around the infant's 1st birthday. For high-risk infants, the caregiver is partially adherent if the pediatric clinician and/or allergist's testing supports the introduction of peanut, and the caregiver introduces peanut products but does not do so by 6 months of age or does not continue feedings with at least 6 gm of peanut protein or over ≥ 3 feedings per week as reported around the infant's 1st birthday.

Figure 6. Caregiver Adherence





3.6. Stratification, Randomization, and Blinding/Masking

Randomization will be accomplished through a password-protected, web-based, randomized system maintained by the Statistical and Data Coordinating Center. Practices will be randomized to intervention using a random number generator. Randomization will be stratified by size of the practice site, so that large volume practices are randomized to intervention separately from practices with fewer annual patients. Neither the control arm practice sites nor intervention sites will be blinded to their trial arm status.

3.6.1. Procedure for Unblinding/Unmasking

Not applicable.

4. Selection of Participants and Clinical Sites/Laboratories

4.1. Rationale for Study Population

- Primary care pediatric clinicians are the clinicians to whom the PPA Guidelines are primarily directed and who see the majority of infants during the time frame that peanut product introduction is recommended for high-risk infants (4-6 months).
- All infants, regardless of peanut allergy risk, are subject to the NIAID-sponsored PPA Guidelines. Infants seen by primary care pediatric clinicians working in study-participanting clinics will have their EHR data extracted to determine whether pediatric clinicians in the intervention arm adhered to the PPA Guidelines moreso than those in the non-intervention arm and to measure incidence of

peanut allergy.

- Caregivers are the final and most important conduits for PPA Guidelines implementation. Therefore, caregivers of infants seen at all participating practices at a 4- and/or 6-month WCC during the designated study period will be surveyed when their infants are 12 and 24 months in order to determine PPA Guidelines adherence regardless what their pediatric clinician's and/or allergist's recommendation was. In addition, caregivers will be surveyed for the presence of peanut allergy in their infant.
- Particularly for high-risk infants, allergists to whom the pediatric clinicians of the study refer infants for early dietary peanut product introduction are important for Guidelines implementation. Therefore, in order to assess adherence to the portion of the PPA Guidelines directed towards allergists, the study will review the specific management approach these allergists will use. It is anticipated that a given allergist will see patients referred by pediatric clinicians from both study arms.

4.2. Inclusion Criteria

For each of the following entities/individuals, all criteria need to be met for participation in the study:

a) Practice sites:
   a. The practice utilizes a centrally-integrated EHR.
   b. The practice has signed a legally-binding engagement agreement with Lurie Children's Pediatric Practice Research Group.
   c. The practice employs at least one physician who has completed a residency in general pediatrics and is practicing as a general pediatrician.

b) Pediatric Clinicians:
   a. Clinician is a physician, physician assistant, resident, advanced practice nurse, family practitioner, or pediatric nurse practitioner working in a pediatric practice.
   b. Clinician is employed by a practice that is a member of one of the participating practices in the study.
   c. Clinician provides well child care to infants ages 4 or 6 months.

c) Infants:
   a. Infant has been seen by a pediatric clinician in the intervention or control arm for a 4- and/or 6-month WCC. (Note: Because infants will be followed through EHR data extraction, inclusion of an infant's data in the study will not require caregiver consent.)

d) Caregivers:
   a. Is the caregiver of an infant seen for a 4- and/or 6-month WCC by a pediatric clinician in a practice belonging to the study's intervention or control arms.
   b. Is at least 18 years of age or has parent or guardian permission to participate.
   c. Is able to understand the study and provide informed consent for the 12- and 24-month (child's age) survey.

4.3. Exclusion Criteria

For each of the following entities/individuals, if any of the following criteria are met, they will be excluded from participation in the study:

a) Practice Site:
   a. The site sees <50 newborn patients/year.
   b. The site has only temporary pediatricians on staff (e.g., resident physicians).
   c. The practice prediatric clinicians do not use an EHR system.

b) Pediatric Clinicians:
   a. The clinician is a temporary employee.
   b. The clinician begins employment at participating practice less than three months prior to end of the 18-month study enrollment period.

c) Infants:
   a. The infant has a medical condition that chronically inhibits the ability to take food orally (i.e., dysphagia, muscular dystrophy, gastrostomy).
   b. The infant has past or current medical problems or findings that prohibit implementation of PPA Guidelines or may have impacted the quality or interpretation of the data obtained from the study. This will be identified from the caregiver survey and a post-hoc review of EHR data. .

d) Caregivers:
   a. Caregiver's primary language is not English or Spanish.
      i) The study is presently limited to participants fluent in English and/or Spanish because practice sites have not indicated a significant patient population with additional language needs. If a need is identified, the study team will allocate resources to develop appropriate materials and obtain any needed staff for translation(s).

4.4. Selection of Clinical Sites/Labs

Thirty-seven practices that are members of the Pediatric Practice Research Group (PPRG), a pediatric practice-based research network at the Ann and Robert H. Lurie Children's Hospital of Chicago (Lurie Children's Hospital) may participate in the study. In order to account for possible attrition prior to the start of the study, the study has been designed (see **Section 13.7**) for at least 30 randomized practice sites providing adequate statistical power to test the primary hypothesis. The PPRG will ensure that all engagement agreements with practice networks or practices are completed for the participating sites. The practices are part of networks that utilize a centrally-integrated EHR system. Practice networks include but are not limited to:

1. Lurie Children's Hospital of Chicago's multi-site primary care practice (Town & Country) and Community Connect Health Exchange network. These practices share the outpatient version of Lurie Children's Hospital Epic EHR.
2. AllianceChicago, a network of community health centers that share Centricity EHRs.
3. OSF HealthCare in Peoria, IL is a network of practices that share an Epic EHR system.
4. Unity Point Health in Peoria, IL is a network that has a history of participating in practice based

research with OSF HealthCare. The practices share an Epic EHR system.

5. Known and Potential Risks and Benefits to Participants

5.1. Risks of Investigational Product or Intervention as cited in Investigator Brochure or Package Insert

Not Applicable

5.2. Risks of Investigational Product or Intervention cited in Medical Literature

Not Applicable

5.3. Risks of Other Protocol Specified Medications

Not Applicable

5.4. Risks of Study Procedures

1. Pediatric clinicians: There are no risks to pediatric clinicians due to any procedure in this trial.
2. Infants/caregivers: There is a risk of breach of confidentiality. There are no additional risks to infants due to any procedure in this trial compared to not participating in the study (all clinical procedures outlined in the PPA Guidelines are considered standard of care and the infants are not subject to any of those procedures as a result of study participation).

5.5. Potential Benefits

1. The iREACH intervention may improve the clinical decision making process of pediatric clinicians around peanut allergy risk assessment and counseling of caregivers and may lead to increased implementation of guidelines-based peanut product introduction.
2. If the intervention improves adherence to the PPA Guidelines, the following benefits may be seen:
    a. Improved identification of infants at risk for peanut allergy by pediatric clinicians.
    b. Prevention of unnecessary referrals to allergy specialists for infants at low-risk for peanut allergy.
    c. Reduction in allergic reactions to peanut introduction in the home setting through improved identification of infants at risk for allergic reactions.
    d. Improved confidence of caregivers regarding peanut introduction for prevention of peanut allergy.
    e. Reduction in the incidence of peanut allergy in children.

6. Investigational Agent /Device/Intervention

6.1. Investigational Agents/Devices/Interventions

6.1.1. Investigational Intervention: Intervention to Reduce Early (Peanut) Allergy in Children (iREACH)

The iREACH intervention consists of **A) an education module** about the PPA Guidelines and the research on which the guidelines were based; **B) an EHR-integrated CDS tool** in the 4- and 6-month WCC templates to support pediatric clinician decision-making around 1) proper triage of infants into peanut allergy risk categories, 2) allergy testing and interpretation and/or allergist referral for high-risk infants, and 3) caregivers counseling on peanut introduction including educational materials for families

and a minor addition to the anticipatory guidance section of the note template to facilitate documentation of PPA Guidelines discussion; and **C) follow-up prompts** in the 9- and 12-month WCC templates guiding pediatric clinicians to ask caregivers about inclusion of peanut products in their child's diet. The components of the intervention are detailed below:

A. Education Module: Text- and video-based educational materials covering the PPA Guidelines, the research on which the guidelines were based, and instructions for using the iREACH CDS tool will be delivered as an online module. Pre-and post-test knowledge surveys will be embedded into the module and permits monitoring of provider compliance with the assigned training. Key study personnel will be available via email, phone, or in-person to answer any questions that arise after completion of the educational module posttests.

B. CDS Tool: A multi-component tool within the EHR that includes the following:

a. *A Best Practice Advisory (BPA)* will be triggered at 4- and 6-month well child visits to remind pediatric clinicians to evaluate child for peanut product introduction.

b. *A Smart List* within note template to remind pediatric clinicians to assess the infant for conditions that would classify the infant as high-risk for PA (i.e., egg allergy or severe eczema).

c. *A Smart Set* (order set) to guide the pediatric clinician in choosing peanut sIgE or allergist referral based upon PA risk status. The pediatric clinician selects orders based upon their assessment of PA risk. This Smart Set includes the option to print out a caregiver educational handout to assist with caregiver counseling on peanut product introduction.

d. *A BPA* triggered when the pediatric clinician views peanut sIgE results (for those patients for whom sIgE has been ordered. The BPA will provide the criteria for "positive" results (≥0.35 kU/L) and a recommendation to refer to an allergy specialist if results are positive.

Caregiver Handout on How to Introduce Peanut Containing Products: Handout adapted from the NIAID caregiver materials (English and Spanish versions). The handouts were simplified and tested with caregiver groups including low-literacy, underserved families. This handout can be used as part of pediatric clinician counseling and can go home with caregivers as a reminder.

C. Follow-up Prompts at 9- and 12-month WCC: *Smart Texts and Data Elements* that advise the pediatric clinician to ask caregivers and chart whether peanut products have been introduced into their infant's diet. If the caregiver reports that peanut products were introduced, the clinician will be directed to document whether introduction was tolerated. If caregiver reports that peanut products were not introduced, the clinician will be directed to ask the caregiver for reasons why they did not.
Note: For those practices that do not use an Epic-based EHR, Lurie Children's study team will facilitate and work with their informatics teams to implement an iteration of the CDS tool that is compatible with the practice EHR.

6.1.1.1. Formulation, Packaging, and Labeling

Not Applicable

6.1.1.2. Dosage, Preparation, and Administration

Not Applicable

6.1.2. Control Arm

Pediatric clinicians in practices that will be randomized to the control arm will provide standard care.

Following the completion of data collection for the primary outcome, practice sites in the control arm will be offered the iREACH intervention. This will not affect the outcome of any of the primary, secondary, or exploratory analyses.

6.1.2.1. Formulation, Packaging, and Labeling

Not Applicable

6.1.2.2. Dosage, Preparation, and Administration

Not Applicable

6.2. Drug Accountability

Not Applicable

6.3. Assessment of Participant Compliance with Investigational Agent

Not Applicable

6.4. Toxicity Prevention and Management

Not Applicable

6.5. Premature Discontinuation of Investigational Agent

Not Applicable

7. Other Medications

7.1. Concomitant Medications

7.1.1. Protocol-mandated

Not Applicable

7.1.2. Other permitted concomitant medications

Not Applicable

7.2. Prophylactic Medications

Not Applicable

7.3. Prohibited Medications

Not Applicable

7.4. Rescue Medications

Not Applicable

8. Study Procedures

8.1. Enrollment/Screening

Screening and enrollment of practice sites, pediatric clinicians, infants, and caregivers will largely take place by collecting data from practice managers or via the EHR pull. Pediatric clinicians and caregivers will provide consent prior to completing any surveys. We have received a waiver of informed consent and written signed

consent for the pediatric clinicians to complete surveys. We have also receieved a waiver of informed consent and signed consent for caregivers to complete surveys. However, for those caregivers that give permission to link their survey responses with their child's medical records, written signed consent will be obtained.

1. Practice sites will have completed legally-binding engagement agreements with Lurie Children's PPRG prior to study activation. These agreements will describe how EHR data will be accessed, copied, used, and transmitted for research. Once agreements are signed, practices will sign a study-specific Memorandum of Agreement (MOA), which summarizes study procedures and expectations. In addition to the MOA, practices will complete a practice characteristic questionnaire that will document that practice inclusion and exclusion criteria are met.
2. Pediatric clinicians within participating practices will be engaged in the study via practice managers and/or study practice champions once engagement agreements are executed and the Memorandum of Agreements are signed by practice representatives. Practice champions will complete a CRF form ensuring each clinician within participating practice fulfills inclusion/exclusion criteria. The study will be activated and practices are assigned to the respective randomization arms. Prior to survey administration, pediatric clinicians will provide informed consent.
3. Caregivers will have signed a Notice of Privacy agreement (a HIPAA directed agreement) in the practice for which their child is a patient. This document describes how that practice will access, copy, use, and transmit PHI for research purposes. Aroundthe infant's first birthday, the study team will recruit caregivers of all children seen for 4- and/or 6- month WCC (caregivers and infants need to fulfill study inclusion/exclusion criteria) to take the caregiver survey. Caregiver survey will include consent for both 12- and 24-month questionnaires. Procedures for caregiver recruitment will vary across practices and fall into two broad categories: in-person recruitment or remote recruitment, based on practice preferences and policy.

   Around the child's first birthday,, an opt-out letter on practice letterhead will be sent to each caregiver whose child was seen at the 4- and/or 6-month WCC. This letter will provide the caregiver an opportunity to opt-out of being contacted for participation in the iREACH study. For those caregivers who do not opt-out, the method for follow-up contact will vary and be based on preference of the practice.

   In-person recruitment: This method will use study staff members to recruit caregivers on-site in the pediatric clinics. In coordination with clinic staff, the study staff will approach caregivers arriving for 12-month WCC appointments, collect informed consent, and provide access to the electronic survey instrument.

   Remote recruitment:

   - If the practices agree to sharing eligible caregiver contact information with the study team, the study team will email, text, and/or call to recruit caregivers. Caregivers have the option to complete the consent, screening questionnaire, and survey online or over the phone. Consent will be obtained and recorded in REDCap prior to administration of surveys.
   - For those practices who do not wish to share caregiver contact details, the practices will have a practice representative email and/or call caregivers. Consent will be obtained and recorded in REDCap prior to administration of surveys.
4. Infants seen for a 4- and/or 6-month WCC and who fulfill inclusion/exclusion criteria will be assigned a unique participant number. The caregiver's informed consent will include text allowing for the infant's EHR data to be linked to the caregiver's survey. Once caregivers provide informed consent to link their child's EHR data to the survey, both the survey data and EHR data will be linked to the participant number. If the caregiver wishes to complete the survey but does not want to

link their chid's EHR data to the survey, they can indicate this on the consent form and their survey responses will not be linked to their child's EHR record.

8.2. Study Assessments

The assessments for this study are the collection of information through questionnaires (surveys) (Table 8.2.1) and the EHR (Table 8.2.2).

8.2.1. Questionnaires/Surveys

8.2.1.1. Pediatric Clinicians

- Pediatric Clinician Characteristics Questionnaire
- Pediatric Clinician Knowledge, Attitudes, Barriers and Facilitators to Guideline Implementation Questionnaire (KABF)

8.2.1.2. Caregivers

- Caregivers Characteristics Questionnaire (English and Spanish versions)
- Caregivers Feeding, Outcomes, Attitudes, Barriers and Facilitators to Guideline Implementation Questionnaire (FOABF) (English and Spanish versions)

Table 8.1 Data To Be Collected

Topic	Data	When Collected
Pediatric Clinician Characteristics	Age, sex, years in practice, type of medical professional, patient volume	After informed consent
Pediatric Clinician Knowledge, Attitudes, Barriers, Facilitators to Guideline Implementation (KABF)	Knowledge of PPA Guidelines, attitudes towards guidelines, barriers and facilitators of guideline implementation	Intervention arm: After informed consent, mid-point of observation period & after 1˚ outcome data collection Control arm: after 1˚ outcome data collection
Caregiver Characteristics	Age, sex, ethnicity, education, income level, geographic location	After informed consent

Caregiver Feeding, Outcomes, Attitudes, Barriers, Facilitators to Guideline Implementation (FOABF)	Peanut introduction practices, attitudes towards PPA Guidelines and barriers/facilitators of guideline implementation	After informed consent
Caregiver Report of Child's Adverse Reactions	Any reactions to peanut, and infant's allergy status	After informed consent and when infant is around 24 months old
Caregiver Account of Clinician Peanut Recommendations, Testing and Introduction	Information shared with caregiver by pediatric clinician regarding peanut introduction, allergy testing, and/or allergist referrals	After informed consent
Caregiver Stress, Quality of Life	Perceived stress and psychosocial outcomes	After informed consent and/or when infant is around 24 months old
Child Food Frequency Questionnaire	Detailed peanut and total diet food frequency questionnaire	After informed consent and/or when infant is around 24 months

8.2.2. EHR Data Extraction

Data collection will take place at both the practice network (e.g., Lurie Community Connect, Peoria area-OSF and Unity Point, Alliance Chicago) or practice level for inclusion in the EHR study database.

Each practice will have an information technology analyst responsible for facilitating data extraction at the practice level. Data from participating practices' EHRs will be extracted on a weekly basis through an automated process established by Lurie Children's Data Coordinating Center team (DCC) and sent to DCC via a secure file transfer protocol (SFTP). Practices will be provided a data dictionary and natural language processing code to identify the appropriate elements and visits/services to extract. DCC will develop Extract Transform Load (ETL) scripts on behalf of the practice network (with the appropriate approvals from the practices). The ETL

scripts will be run weekly so that each week the Lurie Children's DCC data manager will have a complete EHR-based data file for reporting compliance and participation metrics. The weekly file will also be used to identify new providers hired by the practices who may need training in the intervention.

The EHR study database will include data from each of the following types of health care encounters documented in the EHR:

1. 4-month WCC
2. 6-month WCC
3. 9-month WCC
4. 12-month WCC
5. 15-month WCC
6. 18-month WCC
7. 24-month WCC
8. Additional sick visits until 30 months of age
9. Allergy visits until 30 months of age
10. Emergency department visits until 30 months of age

Table 8.2 presents the data elements that will be collected in the EHR study database. Partial PHI including the full date of birth, patient zip code, and date of service will be included.

Table 8.2 EHR Data Elements

EHR Activities	Data Collected
Infant characteristics	Gender, race, ethnicity, date of birth, height and weight over time, patient zip code at 4- month WCC, patient zip code at 6-month WCC, health insurance type at 4-month WCC, health insurance type at 6-month WCC
Problem list	Type of problem, date problem entered, date problem resolved
Medications list	Medications ordered, order date
Primary care visits (well or sick)	Date of service, peanut product introduction recommendation (NLP based), severe eczema (NLP based), eczema ICD-10 code, food allergy ICD-10 codes, date of allergy referral, CDS-specific fields (intervention arm only)
Allergy visits	Date of service, peanut product introduction recommendation (NLP based), severe eczema (NLP based), food allergy ICD-10 codes.
Peanut testing	Date of test, type of test (peanut sIgE or peanut skin prick test), test result
Emergency Department visits	Date of ED visit, food allergy or anaphylaxis ICD-10 codes

8.2.3. Education

iREACH training (intervention arm) occurs shortly after enrollment. Pediatric clinicians in the intervention arm will be sent a link to complete a web-based video training module covering the PPA Guidelines and use of the iREACH CDS tool. In-person training will be conducted by the study team as requested by the

practice.

8.3. Timeline for Study Activities

Study activities will begin with practice randomization and continue for 18 months of observation.

During the 18-month observation period, all infants that will be seen by pediatric clinicians in participant practices for at least one 4- or 6-month WCC will be considered eligible for EHR data extraction, as long as they (and their caregivers) fulfill inclusion/exclusion criteria. During this period, EHR data will be extracted as described above (Table 8.2). Additional study activities related to the pediatric clinicians that will take place during the same period are described in Table 8.5.1.

For each study infant, information will be obtained through EHR until age 30 months. In addition, activities related to the infant caregivers will take place at 11, 12 and 24 months of the infant's age, as described in Table 8.5.2.

Table 8.5.1. Schedule of Activities-Practice Sites, Pediatric Clinicians	**18-Month Study Observation Period**		
	Beginning	**Middle**	**End**
PRACTICES			
Randomization of Practice Sites	X		
INTERVENTION ARM PEDIATRIC CLINICIANS			
Pediatric Clinician Informed Consent	X		
Pediatric Clinician Characteristics Questionnaire	X		
Pediatric Clinician Knowledge Attitudes Barriers Facilitators Survey #1	X		
Pediatric Clinician Knowledge Attitudes Barriers Facilitators Survey #2		X	
Pediatric Clinician Knowledge Attitudes Barriers Facilitators Survey #3			X
CONTROL ARM PEDIATRIC CLINICIANS			
Obtain Pediatric Clinician Informed Consent			X
Pediatric Clinician Characteristics Questionnaire			X
Pediatric Clinician Knowledge Attitudes Barriers Facilitators Survey			X

Table 8.5.2. Schedule of Activities-Caregivers	**Age of Infant**		
		Around12-months	**Around 24-months**
CAREGIVERS			
Caregiver Opt-out Letter (if needed based on recruitment method)		X	
Caregiver Informed Consent and Consent to Link Survey with		X	X
Caregiver Characteristics Questionnaire		X	X
Caregiver Feeding, Outcomes Attitudes, Barriers, Facilitators		X	X
Caregiver Account of Clinician Peanut Recommendations, Testing and Introduction Survey		X	
Caregiver Stress, Quality of Life		X	X

Infant Food Frequency Questionnaire		X	X

9. Mechanistic Assays

Not Applicable

10. Biospecimen Storage

Not Applicable

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1. Participant Completion

Practice Sites: A practice site will be considered as having completed the study after the caregiver of the last infant that was observed though EHR during the 18-month practice observation period has been contacted before that infant reaches 12 months of age.

Pediatric Clinicians: A pediatric clinician will be considered as having completed the study after having finished the last pediatric clinician survey, at the end of the study's 18-month practice observation period.

Infants: An infant will be considered as having completed the study after the last observations from her/his EHR record at 30 months of age are extracted.

Caregivers: A caregiver will be considered as having completed the study after participating in the study questionnaire and survey, when the child is 24 months of age.

11.2. Participant Stopping Rules and Withdrawal Criteria

Practice Sites:

1. A practice site may elect to withdraw from current or future study activities.
2. The investigator, with the NIAID medical monitor's approval, can terminate a practice site if it fails to fulfill its obligations in accordance to the iREACH protocol.

Pediatric Clinicians:

1. A pediatric clinician may withdraw consent from participating in surveys.
2. When pediatric clinician leaves the practice for any reason they will be withdrawn from the study.
3. The investigator, with the NIAID medical monitor's approval, can terminate a pediatric clinician from participating in study activities if the investigator believes that further participation compromises the integrity of the study.

Infants:

1. Because infant data are obtained through the EHR and are only observational, no stopping rules nor withdrawal criteria apply.

Caregivers:

1. A caregiver may elect to withdraw consent from all future study activities; in such case, the caregiver will not be contacted by study staff for any future surveys or questionnaires.

2. A caregiver is "lost to follow-up" and assumed withdrawn after five attempts to reestablish contact by study representatives have failed.
3. A caregiver is withdrawn if they die.
4. The investigator may opt to withdraw a caregiver if they believe further participation compromises the integrity of the study.
5. A caregiver may elect to withdraw their "notice of privacy agreement" with the practice of which their child is a patient. If this occurs and the study team is notified, the child's EHR data will be deleted from the EHR database.

11.3. Participant Replacement

Practice Sites: In the event the number of participating randomized study sites falls below the target of 30, additional practices will be approached and, if agree to study participation, will complete a practice characteristic questionnaire that will document that practice inclusion and exclusion criteria are met.

Infants or Caregivers: Not applicable. There is no target number of infants that are to be observed via EHR data extraction in this study.

11.4. Follow-up after Early Study Withdrawal

Caregivers will have no follow-up if they choose to withdraw from participating in any remaining study surveys and questionnaires. The data that have already been obtained from these individuals will remain in the iREACH study database.

11.5. Study Stopping Rules

The study may be prematurely terminated for the following reasons:

If a breach of confidentiality as it pertains to infant personal health-related information occurs, the source of the breach will be investigated, identified, and resolved. If the source of the breach of confidentiality cannot be resolved, study will be placed on hold. If this stopping rule is met, the DSMB will be asked to review the circumstances under which breaches occurred and provide an opinion whether the study should be terminated or whether specific changes will need to be made in order for the study to resume.

If there is a change in PPA Guidelines that may affect study procedures and outcomes, the study will pause, and the study team will review implications and revise procedures as necessary.

12. Safety Monitoring and Reporting

12.1 Overview

This is an educational intervention trial with the subjects of the intervention being pediatric clinicians. The objective of the intervention is to improve the implementation of the PPA Guidelines, which are now considered standard of care in the USA. As such, no adverse events (AEs) in the pediatric clinicians are expected or will be recorded.

It is possible that, as a result of implementing the standard of care PPA Guidelines, some infants under the care of the study's pediatric clinicians may experience reactions to the introduction and/or later use of peanut-containing food. These reactions will not be recorded as AEs because a) such reactions may or may not be captured by the clinician in the EHR and the study has no control over this factor, b) since the study team is blinded as to the identity of the child that may experience such a reaction, study staff has no means of

contacting the child's caregiver and obtaining any information about the reaction to allow appropriate grading, attribution and follow-up.

When the child reaches 12 months of age, and if the caregiver consents to participation in the survey, information on whether peanut-containing food was tolerated after early introduction and whether any allergic reactions occurred will be obtained by the study staff through a) the caregiver survey and b) linking the child's information extracted from the EHR to the caregiver'survey. At that stage of the study, immediate reactions to early introduction of peanut-containing foods or later reactions, after peanut-containing foods have been introduced into the child's diet, will be captured as a study outcome, but not as AEs, and reported as such to NIAID and to the Institutional Review Board (IRB) and the Data Monitoring Safety Board (DSMB) with routine reporting, in accordance with applicable regulations.

12.2 Definitions

12.2.1 Adverse Event (AE)

Not applicable to this study.

12.2.1.1 Suspected Adverse Reaction (SAR)

Not applicable.

12.2.2 Unexpected Adverse Event

Not applicable.

12.2.3 Serious Adverse Event (SAE)

Not applicable.

12.3 Grading and Attribution of Adverse Events

12.3.1 Grading Criteria

Not applicable.

Table 12.3.1. Grading of Adverse Events Related to Exposure to Peanut-Containing Foods

Not applicable.

12.3.2 Attribution Definitions

Not applicable.

Table 12.3.2 Attribution of Adverse Events

Not applicable.

12.4 Collection and Recording of Adverse Events

12.4.1 Collection Period

Not applicable.

12.4.2 Collecting Adverse Events

Not applicable

12.4.3 Recording Adverse Events

Not applicable.

12.5 Reporting of Serious Adverse Events and Adverse Events

12.5.1 Reporting of Serious Adverse Events to Sponsor (*[DAIT/NIAID or other Sponsor, if applicable]*)

Not applicable.

12.5.2 Reporting to Health Authority

Not applicable: This study, which does not involve an investigational product or device, is not regulated by a Health Authority.

12.5.2.1 Annual Reporting

Not applicable.

12.5.2.2 Expedited Safety Reporting

Not applicable.

12.5.3 Reporting of Adverse Events to IRBs/IECs

Not applicable.

12.6 Pregnancy Reporting

Not applicable.

12.7 Reporting of Other Safety Information

The study Principal Investigator shall promptly notify the SACCC, DAIT/NIAID, and the IRBs when an "unanticipated problem involving risks to subjects or others" is identified, which is not otherwise reportable as an adverse event. The Office for Human Research Protections considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:

Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

12.8 Review of Safety Information

12.8.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive periodic reports, at a frequency determined by DAIT/NIAID, from the study's Data Center compiling new and accumulating information on unanticipated problems. In addition, the Medical Monitor shall review and make decisions on the disposition of such problems.

12.8.2 DSMB Review

12.8.2.1 Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review the progress of the study and any available safety information at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported unanticipated problems.

12.8.2.2 *Ad hoc* DSMB Reviews

In addition to the pre-scheduled data reviews, the DSMB may be called upon for ad hoc reviews. The DSMB will review any event that potentially impacts safety at the request of the Principal Investigator or DAIT/NIAID. After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.8.2.2.1 Temporary Study Suspension of *<enrollment/drug dosing or both>* for *ad hoc* DSMB Safety Review

If an *ad hoc* safety review is triggered, the DAIT/NIAID will decide whether any aspects of the study should be temporarily suspended before an *ad hoc* DSMB review.

13. Statistical Considerations and Analytical Plan

13.1 Overview

Analysis of study data will be conducted to address all study objectives and to understand other interrelationships among all data elements of interest to the investigators and of relevance to the objectives of the study. Although the study has recruited 37 practice sites prior to protocol initiation, the analytical plan is based on 30 practice sites as a conservative estimate due to potential attrition.

13.2 Endpoints

Primary Endpoints:

- % of infants at *low risk for peanut allergy* whose pediatric clinician adhered to the guidelines for that infant.
- % of infants at *high risk for peanut allergy* whose pediatric clinician adhered to the guidelines for that infant.

Secondary Endpoint:

- % of infants at *low risk for peanut allergy* who developed peanut allergy by age 2.5.
- % of infants at *high risk for peanut allergy* who developed peanut allergy by age 2.5.

Exploratory Endpoint 1:

- % of infants at *high risk for peanut allergy* whose allergist adhered to the guidelines.

Exploratory Endpoint 2: Pediatric clinician and caregiver reported knowledge, attitudes, and barriers and facilitators to PPA Guideline adherence.

Exploratory Endpoint 3: Each of the following endpoints include infants that are fully adherent and those that are adherent despite conflict with the clinician recommendation as defined in Figure 6. The endpoints for high risk infants can only be determined for infants where clinician testing (e.g. IgE and/or skin prick tests) is available in order to determine guideline consistent caregiver behavior.

- % of infants at *low risk for peanut allergy* whose caregiver introduced peanut by 12 months of age.

- % of infants at *high risk for peanut allergy* whose caregiver introduces peanut products by 7 months of age and continues feedings with at least 6 g of peanut protein over ≥ 3 feedings per week as reported around the infant's 1st birthday in accordance with the peanut allergy prevention guidelines.% of infants at *high risk for peanut allergy* whose caregiver introduces peanut products but does not do so by 7 months of age or does not continue feedings with at least 6 g of peanut protein or over ≥3 feedings per week as reported around the infant's 1st birthday. 13.3 Measures to Minimize Bias

A minimum of 30 participating clinic sites will be randomized in a 1:1 ratio to the intervention arm (i.e., offering iREACH intervention) or standard care (i.e. without iREACH). Using a computerized random number generator, the randomization will be stratified by practice site size to achieve balanced allocation of participants into the intervention and standard care arms. This process will be performed by the Lurie DCC biostatistician, who is blinded to the intervention delivery and will not be aware of the identity of participating sites.

13.4 Analysis Plan

13.4.1 Analysis Populations.

Primary EHR data infant (PEDI) sample: All infants meeting inclusion/exclusion criteria for whom EHR data has been obtained at a 4-month or 6-month WCC in order to assess the primary endpoint of pediatric clinician adherence. Data regarding characteristics of the treating pediatric clinician are not required for an infant to be included in this population.

Secondary EHR data infant (SEDI) samples with pediatric clinician characteristics obtained: All infants meeting inclusion/exclusion criteria for whom EHR data has been obtained at a 4-month or 6-month WCC in order to assess the primary endpoint of pediatric clinician adherence and whose pediatric clinician has consented and completed the characteristics questionnaire information. In addition to characteristics obtained through the characteristics questionnaire information, data on completion of pre-study training for pediatric clinicians in the intervention arm will also be captured.

Exploratory EHR data infant (EEDI) samples

- With allergist adherence obtained (EEDI1): All high-risk infants meeting eligibility criteria who are referred to an allergist for testing and for whom data are obtained regarding the testing that was conducted, the outcome of the allergist testing and the recommendation provided by the allergist as to early introduction of peanut-containing food.

- With caregiver adherence obtained (EEDI2): All infants whose caregivers complete the FOABF and Caregiver Account of Clinician Peanut Recommendations, Testing and Introduction surveys at 12 and/or 24 months.

Pediatric clinician sample: All pediatric clinicians within the intervention group meeting consent and eligibility criteria who complete baseline and at least one follow-up knowledge, attitudes, or barriers and facilitators survey. Those clinicians in the control group will complete one follow-up knowledge, attitudes, or barriers and facilitators survey.

13.4.2 Primary Analysis of Primary Endpoint(s)

The primary endpoint is the percentage of infants in the PEDI sample within each trial arm whose pediatric clinician adhered to the guidelines regarding peanut introduction. The primary

endpoint concerns peanut introduction recommendation by the treating pediatric clinician only and not additional behavior by the treating allergist or by caregivers.

The primary endpoint will be computed using EHR data from the 4-month and 6-month WCCs as follows:

For low-risk infants:

- Adherence is achieved if the pediatric clinician recommends introduction of peanut products.
- Non-adherence is achieved if the pediatric clinician fails to recommend introduction.

For high-risk infants, adherence is assessed through three routes. A pediatric clinician is adherent if:

- The pediatric clinician does not order an sIgE test and refers the infant to an allergist.
- The pediatric clinician does order an sIgE test, the result is ≤0.35, and the pediatric clinician recommends introduction.
- The pediatric clinician does order an sIgE test, the result is >0.35, and the pediatric clinician refers the infant to an allergist.

A pediatric clinician is non-adherent if:

- The pediatric clinician does not order an sIgE test and does not refer the infant to an allergist.
- The pediatric clinician does order an sIgE test, the result is ≤0.35, and the pediatric clinician fails to recommend introduction.
- The pediatric clinician does order an sIgE test, the result is >0.35, and the pediatric clinician does not refer the infant to an allergist.

Analysis of the primary endpoint will be performed separately for high- and low-risk infants. The primary pediatric clinician (yes/no) adherence outcome will be compared between trial arms with generalized linear mixed models using infants as the unit of analysis using Kenward-Roger degrees of freedom. Fixed effect predictors will include the intervention arm and the categorical measure of practice volume used as a stratification variable for randomization. To account for correlation of treatment procedures within practices, a random effect for practices will also be included resulting in a compound symmetry covariance structure for infants within a practice. Compound symmetry is the only appropriate choice, since repeated measures of infants within a practice are exchangeable and have no natural ordering. Odds ratios will be computed to describe the odds of adherence for the iREACH intervention compared to the control intervention. In order to satisfy the ITT principle, pediatric clinician adherence will be imputed as non-adherent when the criteria for adherence defined earlier are not met.

13.4.3 Supportive Analyses of the Primary Endpoint(s)

Consistent with the intent-to-treat principle, infants seen by all clinicians in each participating practice are included in the primary analysis (PEDI sample). Recognizing that some clinicians in treatment arm practices might decline to participate in the pre-study training and/or decline to utilize the CDS tool, we will also perform sensitivity analyses to investigate any change in these results that would be associated with excluding infants seen by each of these categories of non-participating clinicians: (1) declines training/uses CDS, (2) has training/declines CDS, (3) declines training and declines CDS.

The primary analysis will be repeated in the PEDI sample to evaluate the impact of missing data,clinician-level clustering, and type of pediatric clinician. Sensitivity analyses will be performed where 1) missing adherence data are not imputed and are left missing and 2) where missing data are imputed as being adherent. It is not possible to have missing data in the context of low-risk infants but is possible for high-risk infants. For high risk infants, adherence can be incomplete and data missing, if peanut-specific IgE is ordered for an infant but never conducted. Sensitivity analysis with a clinician-level random effect will also be performed to evaluate the impact of clinician-level clustering. Finally, sensitivity analysis will be conducted to assess any potential differences between types of pediatric clinicians (pediatricians and advanced practice nurses).

The primary analysis will be repeated in the PEDI sample combining all infants from both the high- and low-risk groups. Risk group and the interaction of risk group and intervention group will be included as fixed effects predictors.

The primary analysis will be performed again using the SEDI infant sample and adjusting for relevant covariates from the pediatric clinician questionnaire and practice site enrollment data. All questions in these forms and questionnaires will be explored one at a time for possible inclusion as covariates. Infants will be excluded from these analyses if information was not collected for each particular question.

Exploratory analyses will be conducted using data collected from the practice characteristics and clinician surveys. Specifically, we will examine whether the primary analysis differs according to practice-level interest in peanut allergy or affiliation with an allergy practice. We will also examine the potential influence of additional clinician education received outside of the study (i.e. professional conferences, research results, other teaching conduits).

13.4.4 Analyses of Secondary and Other Endpoint(s)

Analysis of the secondary endpoint will be performed separately for high- and low-risk infants. Incidence of peanut allergy will be analyzed with generalized linear mixed models in the PEDI sample in the same manner as the primary pediatric clinician endpoint with infants as the unit of analysis.

Data for diagnosis of peanut allergy (yes/no) from the 4 month - 30 month EHR data collection time points will be combined into one binary variable describing whether (yes/no) diagnosis occurred at any time up through the 30-month time point. Data from caregivers FOABF surveys at 12 and/or 24 months will be used to determine the presence of a caregiver reported peanut allergy or physician diagnosed peanut allergy.

The peanut allergy endpoint will be determined by combining information from EHR and caregiver survey information as described in the MOP.

Exploratory analyses of the secondary peanut allergy endpoint will include the following. Analyses will be treated as exploratory and hypothesis- generating, so no formal correction for multiple testing will be applied.

- The primary analysis of the secondary endpoint will be repeated to evaluate the impact of missing data. Missing data will be classified in three ways as follows:
    - Missing data are not imputed via multiple imputation and are left missing.

- Missing data are imputed as non-peanut allergic.
- Missing data are imputed as peanut allergic.

- The primary analysis of the secondary endpoint will be repeated combining all infants from both the high- and low-risk groups. Risk group and the interaction of risk group and intervention group will be included as fixed effects predictors.
- The primary analysis of the secondary endpoint will be repeated in the PEDI sample including pediatric clinician adherence, allergist adherence (high-risk only), their interaction, and their interactions with intervention group as fixed effects predictors.
- The primary analysis of the secondary endpoint will be repeated in the EEDI2 sample including pediatric clinician adherence, allergist adherence (high-risk only), caregiver adherence, and all two- and three-way interactions with each other and intervention group, as fixed effects predictors.
  - The primary analysis of the secondary endpoint will be repeated in the EEDI2 sample including the presence and extent (e.g., duration and amount) of peanut exposure as predictors.

13.4.5 Analyses of Exploratory Endpoint(s)

All analyses will be provided separately for high- and low-risk groups as noted. The entire infant sample of both risk groups will also be analyzed together where noted. Analyses will be treated as exploratory and hypothesis- generating, so no formal correction for multiple testing will be applied.

Allergist adherence will be analyzed with generalized linear mixed models for high-risk infants in the EEDI1 sample in the same manner as the primary pediatric clinician endpoint with infants as the unit of analysis. The allergist adherence endpoint will be determined as follows:

An allergist is adherent if:

- The allergist recommends introduction following a sIgE test ≤0.35, a skin prick test 0-2mm, a successful supervised feeding or a successful oral graded food challenge.
- The allergist recommends avoidance and continued monitoring after a skin prick test ≥8 mm or a failed supervised feeding or oral graded food challenge.

An allergist is non-adherent if:

- The allergist fails to recommend introduction following a sIgE test ≤0.35, a skin prick test 0-2mm, a successful supervised feeding or a successful oral graded food challenge.
- The allergist recommends introduction following a skin prick test 3-7mm without performing a supervised feeding or oral graded food challenge.
- The allergist recommends introduction following a skin prick test of ≥8mm.

Caregiver adherence (yes/no) will be analyzed with generalized linear mixed models in the EEDI2 sample in the same manner as the primary pediatric clinician endpoint with infants as the unit of analysis. Only high risk infants with data on clinician and/or allergist testing will be used in the analysis of caregiver adherence. For the high risk infants in the primary analysis of the exploratory endpoint, partial caregiver adherence (as defined below) will be grouped with non-adherence. The caregiver adherence endpoint will be determined as follows:

For low-risk infants:

- A caregiver is adherent if the caregiver introduces peanut by 12 months of age, regardless of the pediatric clinician's recommendation.
- A caregiver is non-adherent if the caregiver does not introduce peanut by 12 months of age, regardless of the pediatric clinician's recommendation.

For high-risk infants:

- A caregiver is adherent if the pediatric clinician and/or allergist's testing supports the introduction of peanut, and the caregiver introduces peanut products by 7 months of age and continues feedings with at least 6 g of peanut protein over ≥ 3 feedings per week as reported around the infant's 1st birthday ..
- A caregiver is adherent if the pediatric clinician and allergist's testing supports the avoidance of peanut and the caregiver does not introduce peanut products as reported around the infant's 1st birthday.
- A caregiver is *partially adherent* if the pediatric clinician and/or allergist's testing supports the introduction of peanut, and the caregiver introduces peanut products but does not do so by 6 months of age or does not continues feedings with at least 6 gm of peanut protein or over ≥ 3 feedings per week as reported around the infant's 1st birthday.
- A caregiver is non-adherent if the pediatric clinician and/or allergist's testing supports the avoidance of peanut, and the caregiver introduces peanut products as reported around the infant's 1st birthday.

The primary analysis of the exploratory endpoint will be repeated in the EEDI2 sample including pediatric clinician adherence, allergist adherence (high-risk only) and two-way interactions with each other and intervention group, as fixed effects predictors.

The primary analysis of the exploratory endpoint will be repeated in the EEDI2 sample by combining adherence and partial adherence and comparing partial and non-adherence.

Pediatric clinician knowledge of guidelines, attitudes towards implementation, and barriers and facilitators of adherence will be summarized in the pediatric clinician sample with descriptive statistics using pediatric clinicians as the unit of analysis. A proportion adherent summary statistic will be computed for each pediatric clinician and will be related to KABF with generalized linear mixed models as described in the primary endpoint analysis. The final pediatric clinician KABF assessed after primary outcome data collection will be compared between trial arms. Pediatric clinician KABF after primary outcome data collection in the control group will also be compared to the KABF of pediatric clinicians in the intervention arm at initial informed consent. Pediatric clinician KABF in the intervention arm at 6 months after informed consent and after primary outcome data collection will be separately analyzed for change over time. Any pediatric clinician who did not see infants for 4- or 6-month WCC during the 18-month observation period will be excluded from the analyses.

Caregiver survey data on feeding practices, reaction history, and barriers and facilitators to guideline implementation will be summarized in the EEDI2 sample with descriptive statistics using infants as the unit of analysis.

13.4.6 Descriptive Analyses

The number and percent of infants in all infant analysis samples will be tabulated by high- and low-risk group. Number and percent of infants for whom EHR data is obtained at each visit in the 4-month through 30-month data collection period will be summarized. Number and percent of infants who are lost to followup from each analysis sample will also be

summarized. Number and percent of pediatric clinicians and caregivers responding to each survey will be summarized.

The disposition of all pediatric clinicians treating infants in any infant sample will be summarized in tables and listed. The numbers and percent of treating pediatric clinicians consenting to participate in the study, withdrawing consent from study participation, and who treated infants throughout the entire study data collection, will be presented. Any information regarding reasons for pediatric clinician withdrawal of consent will be summarized and listed.

Summary descriptive statistics for demographics and baseline characteristics will be reported for all infant analysis samples and will be compared across samples to check for consistency. Variables to be summarized include age, race, ethnicity, and sex, as well as all components included in the assessment of high- or low-risk status.

Two types of outcomes will be monitored for all children in the infant analysis sample based on EHR data and caregiver surveys. First, the number of infants who react to first exposure to peanut will be reported. Second, the number of infants who have been fed peanut more than once and report a reaction after the first exposure.

Responses to all questions in the practice site, pediatric clinician characteristics questionnaires will be summarized overall and by trial arm.

Protocol deviations will be listed by practice with information such as type of deviation, severity of the deviation (major or non-major), date of occurrence, and the reason for the deviation. Protocol deviations will be summarized in tabular format by type of deviation.

Number and percent of pediatric clinicians utilizing individual iREACH prompts will be summarized to describe overall utilization of the iREACH intervention.

13.5 Interim Analyses

Not applicable.

13.5.1 Interim Analysis of Efficacy Data

Not applicable.

13.5.2 Interim Analysis of Safety Data

Not applicable.

13.5.3 Futility Analysis

Not applicable.

13.6 Statistical Hypotheses

Primary hypotheses: In each of the high-risk and low-risk strata, the primary endpoint analysis performs a test of superiority to assess whether the proportion of infants whose pediatric clinician is adherent to PPA Guidelines is different in the intervention arm compared to the control arm. A multiplicity adjustment will not be applied to the primary analysis because high and low-risk children represent independent risk strata where pediatric clinicians must take different steps to achieve adherence.

Null hypothesis: P(intervention group) = P(control group) where P denotes the proportion adherent.

Alternative hypothesis: P(intervention group) ≠ P(control group)

13.7 Sample Size Considerations

Power has been computed for primary and exploratory binary adherence outcomes and secondary peanut allergy outcomes. In order to compute power, six quantities have been specified: the type 1 error rate, the number of practice sites, the number of patients expected per practice site, the within cluster correlation, the average proportion adherent (or peanut allergic) over all practice sites and intervention arms, and the difference in proportion adherent (or peanut allergic) between the intervention and control arms. Calculations assume a type 1 error of 0.05. In this study, investigators can control the number of practice sites invited to participate in the study but cannot control the number of infants assessed at each practice site. Since deployment of the intervention and data collection are through the EHR, inclusion of additional practice sites does not require significant additional budget. Therefore, the choice of number of practice sites is based primarily on the number expected to participate and not on budgetary or statistical power concerns. We estimate that at minimum 30 clinics will participate. Using a preliminary EHR data pull, we estimate being able to assess on average 17 high-risk and 333 low-risk per clinic in 18 months for a total sample size of approximately 500 high-risk and 10,000 low-risk infants.

Since investigators cannot control the number of infants assessed, power calculations describe the differences between intervention arms in study outcomes that are detectable with 80% power for our given study sample sizes, rather than the sample sizes needed to be able to detect given differences between intervention arms in study outcomes.

Statistical power for primary and exploratory adherence outcomes: We assume a within cluster correlation of 0.07 for the pediatric clinician adherence outcomes, estimated from a preliminary EHR data pull. Similar studies have assumed lower correlations in the range of 0.001-0.01 [39,40] however, so we expect this estimate to be conservative. To further be conservative, we assume the average proportion adherent over all practice sites and intervention to be 0.50. These and the previously described assumptions and sample sizes allow us to detect with >80% power an absolute difference in proportions of adherence of ≥18% in high-risk infants and ≥14% in low-risk infants.

Statistical power for secondary peanut allergy outcome: We assume a within cluster correlation of 0.02 for the peanut allergy outcome, estimated from a preliminary EHR data pull on general food allergy. Peanut allergy prevalence data referenced earlier in this document provide estimates of the incidence of peanut allergy at age 2 of 13.8% for high-risk infants and 1.5% in low-risk infants. In high-risk infants, these and the previously described assumptions and sample sizes allow us to detect with >80% power an absolute difference in proportions with peanut allergy of 8.2% in high-risk infants (intervention and control arm proportions 5.4% and 13.8%). In low-risk infants, we can detect an absolute difference in proportions with peanut allergy of 0.98% (intervention and control arm proportions 0.11% and 1.50%). In high-risk infants, the LEAP study showed a 14% absolute difference in proportions with peanut allergy contrasting early introduction of peanut to avoidance. Compared to this, we are powered to detect smaller reductions in peanut allergy that might be expected with a CDS intervention.

14. Identification and Access to Source Data, Monitoring Plan

14.1. Source Data

Source documents and source data are considered to be the original documentation where subject information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial. In this trial, the following source documents will be present:

- Paper source documents will be created when a study coordinator obtains an informed consent form, generates a log that links the child participants to a practice, pediatric clinician and caregivers, and links all participants to a unique study identification number.
- Electronic health records data

The completion of each online survey will create source electronic data on the survey vendor's

14.2. Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID, as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

14.3. Monitoring Plan for Consent Process

A copy of the caregiver survey information sheet will be provided to the participant and stored in the study records on a secure system. Every month, study staff will review study records to ensure that consent was obtained and documented. In the event of a failed consent documentation we will immediately pause study activity for the participant in question and document the protocol deviation and report it to the appropriate parties.

No monitoring is necessary for clinician survey consent forms as consent is implicit upon survey completion.

15. Quality Assurance and Quality Control

Data collection will take place at both the practice network (e.g., Lurie Community Connect, Peoria area, Alliance Chicago) and practice level. Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe each site's quality management processes. Each practice network PI will be responsible for organizing data collection at the practice level.

Data from participating practices' EHRs will be extracted through an automated process established by the DCC and sent via a secure file transfer protocol (SFTP). Practices will be provided a data dictionary to identify the appropriate elements and visits/services to extract. The DCC will develop Extract Transform Load (ETL) scripts on behalf of each practice network (with the appropriate approvals from the practices). The ETL scripts will be run on a regular basis so the DCC data manager will have a complete EHR-based data file for reporting compliance and participation metrics.

The DCC data manager will supervise data collection progress, consent and study enrollment, survey completion, identify potential data quality issues, alert study leadership and appropriate staff members to resolve any issues and will assure overall integrity of the data used for analysis. The DCC data manager will work with each practice network through the network PI and Informatics team to assure adherence to the study protocol and to implement quality control (QC) procedures. Data QC checks will be generated from the EHR database on a weekly basis.

The practice networks will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

16. Protocol Deviations

16.1. Protocol Deviation Definitions

Protocol Deviation: The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation): A Protocol Violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation: A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

16.2. Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

Upon determination that a protocol deviation has occurred, the study staff will a) notify the site Principal Investigator, b) notify the study data center, and c) will complete a Protocol Deviation form. The Protocol Chair will document all protocol deviations in the Trial Master File and promptly report the deviations to the DAIT/NIAID Medical Monitor and Project Manager. The DAIT/NIAID Medical Monitor and Project Manager will make the decision as to whether the Deviation is major or not and what the impact of the Deviation on the study participant or the entire study may be, and will review and approve the action plan that will be implemented as a result of the Protocol Deviation.

17. Ethical Considerations and Compliance with Good Clinical Practice

17.1. Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

17.2. Informed Consent Process

Caregiver Survey Consent

The informed consent process for caregiver survey participation will occur via phone or in-person to provide information about the study to a prospective participant and allow adequate time for review and discussion prior to his/her decision. The method of consent will be at the discretion of the prospective participant During both the phone and in-person consent process, research study staff will review the consent with the prospective

participant in the preferred language and answer any questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from their part at any time, for any reason. Consent materials will be presented to participants in English or Spanish. A copy of the information sheet will be provided to the participant.

The consent process will be ongoing. The information sheet will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

Pediatric Clinician Survey Consent

The pediatric clinician will only receive an online information sheet to complete the consent process. They will directly receive an email with the online survey invitation link and a statement of consent. The invitation will state:"Your participation in this survey is voluntary. Your individual answers will remain confidential and reported only in the aggregate." Consent of the invited respondent to participate will be implied when the participant opens the survey URL in their web browser and/or answers at least one question in the survey. While taking the survey, a participant may end the survey at any time by not answering any further questions. Once a participant provides any survey data, the data automatically enters the study database.

17.3. Privacy and Confidentiality

Participant (including caregivers, their children, and pediatric clinicians) privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives. Each pediatric clinician and caregiver survey will be coded with a unique identification number and stored on password protected computers and servers. Only aggregated data will be shared. Participant-specific data will not be shared with care providers or colleagues at the practice and no practice personnel will have access to survey responses. To further protect the confidentiality of pediatric clinicians, aggregated data by practice will not be shared.

18. Publication Policy

This trial will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

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19. Appendices

Figure 7. Clinician Pathway

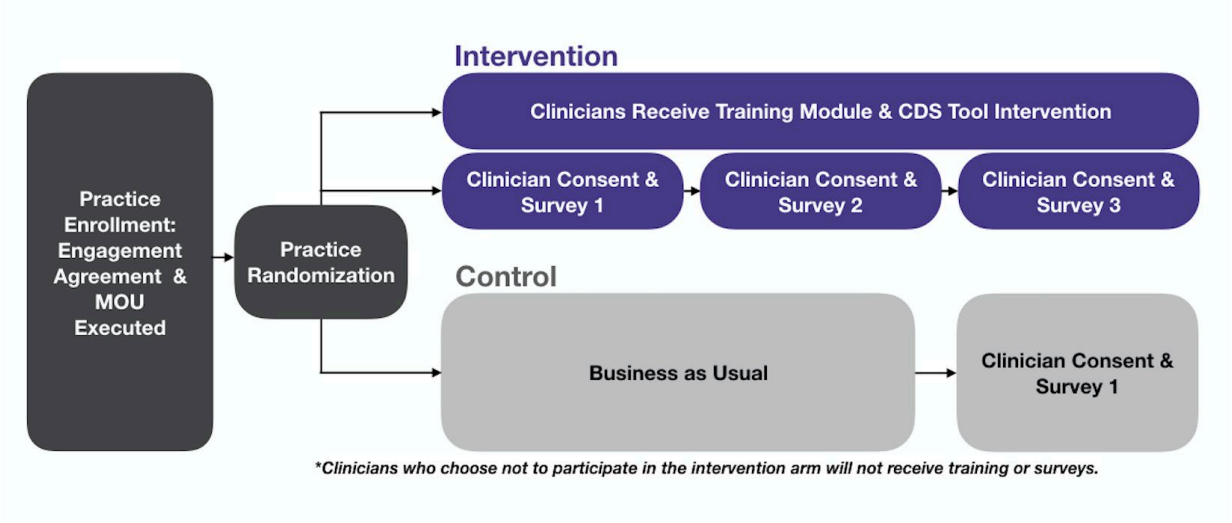
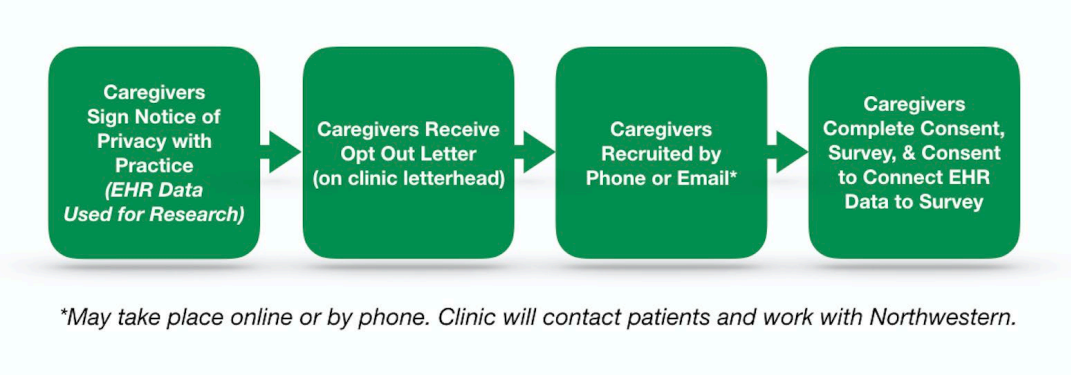


Figure 8. Caregiver Pathway



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