**Online Repository Materials:**

| | Jones et al | Varshney et al | DEVIL |
|---|---|---|---|
| **N** | 36 | 26 | 49 |
| **Age** | 1-16 years | 1-6 years | 1-3 years |
| **Enrollment Criteria** | Reaction History<br>Peanut SPT ≥3mm<br>Peanut IgE≥15 kU/L *or* Peanut IgE≥7 kU/L if reaction within 6 months of enrollment | Reaction History<br>Peanut SPT ≥3mm<br>Peanut IgE≥15 kU/L *or* Peanut IgE≥7 kU/L if reaction within 6 months of enrollment | Positive entry challenge |
| **Arms** | Open Label | Active<br>Placebo<br>2:1 | Low Dose<br>High Dose |
| **Initial escalation: Initial & Final Dose Peanut protein** | 0.1 mg to 50 mg | 0.1 mg to 6 mg | 0.1 mg to 6 mg |
| **Starting Buildup Dose** | 50 mg | 6 mg | 6 mg |
| **Dose Escalation Frequency** | 2 weeks | 2 weeks | 2 weeks |
| **Maintenance Dose** | 300 - 4000 mg | 4000 mg | 300 or 3000 mg |

**Table E1. Comparison of Three Pooled Trials**

**Figure E1: Histogram of Rates and Counts of AEs.** Subjects A, B, and C experienced the top three highest counts of AEs, while Subjects C, D, E experience the top three highest rates of AEs. Modeling the number of AEs based on the total count (left) captures the elevated rates of AEs experienced by individuals A, B, and C. Evaluating total counts, however, misses individuals D and E who experienced low numbers of AEs over a short period of time, leading to early dropout. By adjusting for the time on therapy, modeling the rate of AEs (right) appropriately captures the experience of those individuals like D and E whose symptoms led them to discontinue OIT.

| *Variable* | *Overall AEs* | | *Buildup AEs* | | *Maintenance AEs* | |
|---|---|---|---|---|---|---|
| | *IRR (95% CI)* | *P-value* | *IRR (95% CI)* | *P-value* | *IRR (95% CI)* | *P-value* |
| **Sex (female compared to male)** | 0.76 (0.44, 1.33) | 0.34 | 0.71 (0.39, 1.29) | 0.27 | 1.10 (0.52, 2.34) | 0.80 |
| **Age (per year)** | 1.02 (0.92, 1.14) | 0.66 | 1.05 (0.94, 1.18) | 0.36 | 1.14 (1.00, 1.29) | 0.047 |
| **Asthma** | 0.94 (0.56, 1.60) | 0.83 | 0.91 (0.52, 1.59) | 0.73 | 2.45 (1.08, 5.57) | 0.03 |
| **Atopic Dermatitis** | 1.34 (0.69, 2.61) | 0.39 | 1.17 (0.58, 2.36) | 0.65 | 1.37 (0.54, 3.49) | 0.51 |
| **Allergic Rhinitis** | 2.82 (1.63, 4.88) | <0.001 | 2.15 (1.23, 3.76) | 0.01 | 7.59 (2.82, 20.4) | <0.001 |
| **Peanut SPT (per 5 mm)** | 1.46 (1.16, 1.83) | 0.001 | 1.42 (1.11, 1.80) | 0.005 | 1.42 (1.02, 1.99) | 0.04 |
| **Log Peanut IgE (per log increase)** | 0.91 (0.19, 4.34) | 0.91 | 0.73 (0.16, 3.41) | 0.69 | 8.23 (0.66, 102) | 0.10 |

**Table E2: Unadjusted Incidence Rate Ratios (IRR) of the Influence of Baseline Characteristics on Rates of AEs Overall, during the Buildup Phase, and Maintenance Phase.**

**Online Repository Methods:**

*Study Designs and Subject Recruitment*

We compiled data from three OIT studies conducted at Duke University Medical Center (DUMC), University of North Carolina at Chapel Hill (UNC), and the University of Arkansas for Medical Sciences/Arkansas Children's Hospital (ACH). The underlying objective of all three studies was to demonstrate the efficacy of peanut OIT in achieving desensitization in peanut-allergic children and to determine if sustained unresponsiveness could be achieved. The Jones et al. study (NCT01891136, n=39) was an uncontrolled pilot study of peanut OIT (10, 11), while the Varshney et al. study (NCT00815035, n=28) was a randomized, placebo-controlled trial of peanut OIT, with an open label arm for all placebo subjects after 1 year (12). Both of these multicenter studies were conducted in collaboration between DUMC/UNC and ACH. From these two studies, only data from participants enrolled at DUMC/UNC were used in this analysis, and data collection spanned April 2004 to June 2013. Inclusion and exclusion criteria are as previously published. The third trial, the DEVIL study (NCT00932828, n=49), is an ongoing randomized single-center trial initially at DUMC and later at UNC, comparing a low and high maintenance dose of peanut OIT, in a younger age range of 9 months to 36 months. Inclusion and exclusion criteria were similar for this study with the exception of target age and the use of a positive entry oral food challenge (Table E1).

*OIT Protocol*

OIT administration consisted of gradually escalating doses of allergen, administered orally in a food vehicle every day over months, with the goal of desensitization. Protocols for the Jones et al and Varshney et al studies are as previously published, and the DEVIL study shares this protocol with changes as described in Table E1 (10, 12). While the trials varied in their study design (Table E1), they all share the same features in terms of dose escalation, comprising

three phases: initial escalation day, buildup with clinic visits every 2-3 weeks, and maintenance. Buildup lasted approximately 1 year, though this varied by subject. Doses were increased in this fashion until the goal maintenance dose was achieved, which ranged from 300-4000 mg of peanut protein depending on the study (Table E1). At this point, the maintenance phase began, in which the subject continued to take the maintenance dose on a daily basis for approximately 3-4 years.

*Safety Data Collection*

Safety data was collected in three different ways: records of symptoms occurring during dose escalation at the clinic, symptom diaries of home AEs and adverse event reports of home AEs. During dose escalation, research staff recorded the symptoms and timing of all reactions, as well as treatment administered. With home doses, parents recorded any symptoms typically associated with allergic reactions, such as rash, mouth itch, sneezing, coughing, vomiting, and diarrhea, in daily symptom diaries, along with the timing of the event and the treatment administered. Furthermore, parents were instructed to report all events whether perceived as related or unrelated to study coordinators, in order to capture all events potentially associated with therapy. These reported events were catalogued in an adverse event (AE) database (MS Access). All events were evaluated at the time of occurrence by study personnel for their possible relatedness to the therapy, based on the timing and characteristics of symptoms, and assigned one of 3 possible relationships to OIT: likely related, possibly related, or unrelated. All analyses primarily focus on events that were deemed likely related to therapy after subjects had tolerated the initial escalation day. We did not include any symptoms occurring during the food challenges that were part of the screening process or required for testing desensitization or sustained unresponsiveness.

*Treatment of Reactions at Home*

The families of all study participants received extensive standard-of-care teaching in the recognition and treatment of allergic reactions and anaphylaxis. Subjects or their caregivers were instructed to administer antihistamines for any mild reactions (generally only affecting one body system) that developed within 2 hours of dosing. Reactions that involved more than one body system or were associated with systemic symptoms were considered to be moderate or severe, and subjects/caregivers were advised to administer epinephrine promptly and to call 911 for emergency assistance. The study team ensured that all families had in-date epinephrine autoinjectors and food allergy action plans. A study physician was available by pager and phone at all times throughout the study, and parents were strongly encouraged to call with any questions about a given reaction.

*Statistical Methods*

We computed means, standard deviations, frequencies and proportions for all clinical history and immunological variables. Comparisons were made by t-tests or paired t-tests, and chi-square tests or Fisher's exact tests where appropriate. AE reports, symptom diary reports, and reactions during dose escalations were compiled for all subjects who received OIT, in order to generate counts and rates of likely-related events experienced by every individual during the buildup phase, during the maintenance phase, and in total. For all analyses (unless specified otherwise), home AEs and research unit AEs were grouped together to best represent the overall risk experienced by participants receiving OIT. Based on the descriptions and symptoms reported, we retrospectively sorted events into a variety of categories, and the multiple symptoms category was reserved for events that included more than one allergic symptom.

Some subjects from the Varshney et al. study were originally enrolled in a placebo arm and then transferred over to an open label section of this trial after one year. Events during these

placebo periods were not included, but events from the open label period were included in the analysis. Because the number of subjects who received placebo was limited both in sample size (8 of the original 111 subjects) and time on placebo (1 year for each subject), we did not formally compare the treatment group to the placebo group.

We assessed the baseline predictors of AE outcomes (sex; age at starting therapy, as a continuous variable; current and past history of asthma, atopic dermatitis, or allergic rhinitis; baseline peanut IgE, baseline peanut skin prick test (SPT)) using principal component analysis, finding no collinearity that would require removal of a particular variable. These variables were chosen based on their clinical relevance. We then fit a generalized linear model, assuming a Poisson distribution with scaled deviance, to determine the influence of the covariates listed above on the counts of AEs. These Poisson models were fit with and without adjusting for the other covariates. Because each individual may spend a different duration of time on therapy, we used the time on therapy on a log scale as an offset to adjust for this variable exposure to OIT. We then fit a similar Poisson model for AEs during the buildup period as well as AEs during the maintenance period to determine if there were any differences between the phases. Finally, we fit a Poisson model focusing solely on any AEs that involved gastrointestinal side effects, and another focusing on systemic reactions. From these models, we presented the incidence rate ratios for each of the variables, after adjusting for the other covariates in the model. For the covariates studied, missing data was limited. For one subject, baseline IgE was missing and this value was imputed with the 3 month IgE.

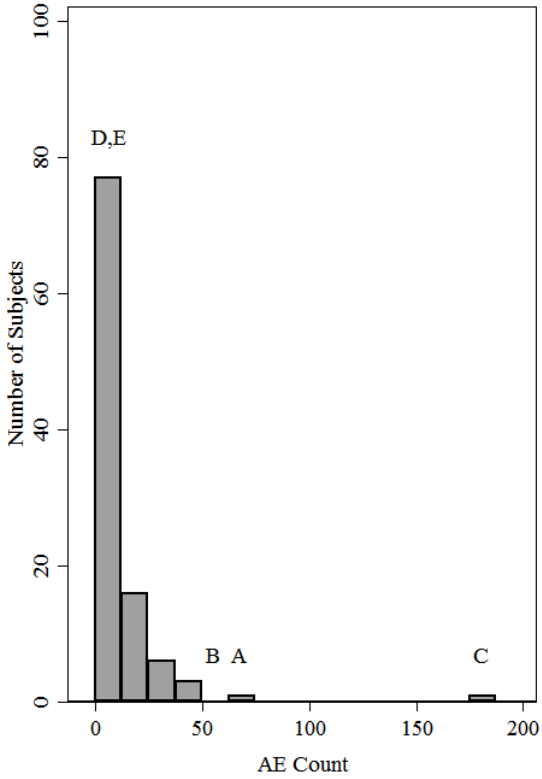
To assess seasonality of AEs between subjects with and without allergic rhinitis, we calculated the proportion of AEs occurring in each month. Chi-square test was used to determine if the counts of AEs by month were different between subjects with allergic rhinitis and those without. Relative risk ratio was calculated using rates of AEs during peak allergy months (April & September) compared to non-peak months (December).

To assess whether an event was indicative of a systemic reaction, we developed the following algorithm, based on the criteria for anaphylaxis established by the National Institute of Allergy and Infectious Diseases / Food Allergy and Anaphylaxis Network symposium (28). At the time that the AE was reported, each individual symptom was graded by the participants on a three point scale of mild (1), moderate (2), and severe (3). If an AE involved wheezing (mild, moderate, or severe), severe angioedema, whole body hives (severe), cough (moderate or severe), repeated vomiting (moderate or severe), or involved at least two body systems, then the event was labeled as a systemic reaction. For this analysis, we assumed that all systemic reactions should have been treated with epinephrine, and we compared this rate of predicted epinephrine use to the actual rate of epinephrine use.

Of note, reactions were also evaluated for their overall severity (based on the individual symptom severities assigned), and grouped into mild, moderate, and severe categories. Severe AEs were defined as involving hospitalization, ICU admission, or documented hypotension.

To assess parental patterns of epinephrine use, we identified five isolated symptoms that might trigger the use of epinephrine: moderate or severe coughing, wheezing of any severity, severe hives, and moderate or severe abdominal pain or vomiting. We then determined the proportion of times epinephrine was given in response to an event involving one of these symptoms.

All statistical analyses were performed with Stata/SE 13.1 (StataCorp LP, College Station, TX) and SAS 9.3 (SAS Institute, Cary NC).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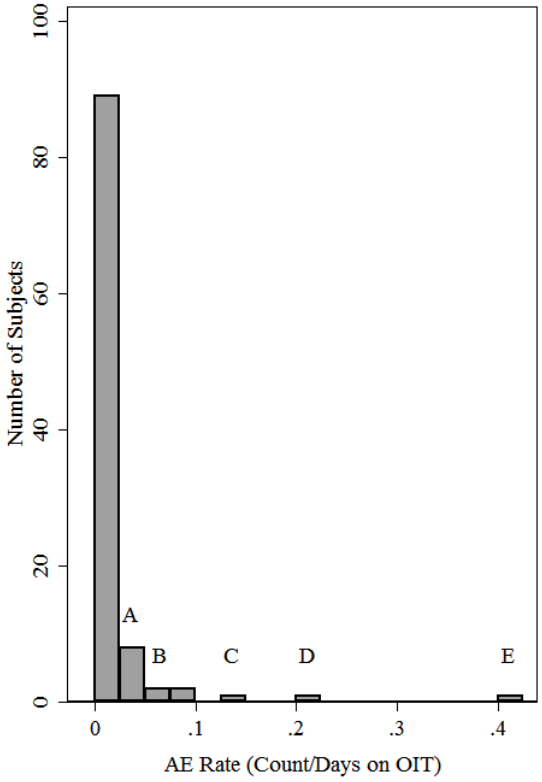
80
100
D,E
B
A
C
0
50
100
150
200
AE Count


Number of Subjects
0
20
40
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80
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E
0
.1
.2
.3
.4
AE Rate (Count/Days on OIT)