Terminology Used in Food Oral Immunotherapy Including Clinical Trial Endpoints
Background

• Food allergy is an increasingly prevalent, costly, and potentially life-threatening condition.

• Peanut allergy among the most common childhood food allergies, affecting approximately 1 in 70 children and 1 in 160 adults in the United States.¹

• Peanut allergy is associated with substantial economic burden and reduction in quality of life.
  
  – Overall cost of food allergy is an estimated $24.8 billion annually.²
  
  – 4% of peanut allergic children have ≥1 allergic reaction/week due to accidental exposure to food products containing peanut.³

Background

• Currently, there is no FDA-approved therapy for peanut allergy, but recent Phase 3 data suggest that oral immunotherapy (OIT) could be a potentially safe and effective treatment for children and adolescents.4

• There is a lack of standardization in the terminology used for OIT, which is confusing for patients, caregivers, and even physicians.

What is OIT?

• OIT is a form of desensitization designed to treat patients with specific food allergies. It consists of daily ingestion of a specific food allergen (precisely measured) following a schedule starting with minimal quantities and slowly increasing the amounts over weeks to months, eventually progressing to doses approximating small food portions.

• Once these maintenance doses are achieved, the patient needs to continue to ingest the maintenance dose level of the allergen on a regular basis in order to maintain desensitization.
What is OIT?

• Treatments are typically started in a controlled setting (e.g., the doctor’s office, or hospital clinic) where gradually increasing doses of allergen are given up to a targeted dose.

• Example protocol for peanut OIT (1 peanut kernel = 250-300 mg of protein):
  – Peanut starting dose = 0.5 mg of protein
  – Peanut maintenance dose = 300 mg of protein
OIT for Food Allergy Schematic

- Initial dose escalation
- Early Desensitization Period
- Up-dosing
- Maintenance

Time

Dose
The Role of Food Challenges

• PRACTALL guidelines define a double-blind, placebo-controlled food challenge (DBPCFC) as the gold-standard when performing oral food challenges.\textsuperscript{5}

• An oral food challenge has dual roles:
  – Diagnosis of food allergy
  – Assessment to determine efficacy in clinical trials after OIT

• Historically, DBPCFC has been used only for diagnostic purposes, resulting in the use of specific terminology.

• When used as a clinical trial endpoint, interpretation of the results using this terminology may be different.

\textsuperscript{5}Sampson et al. J Allergy Clin Immunol 2012; 130: 1260-74.
There are significant gaps leading to potential misinterpretation of clinical trial and research results (clinical endpoints), which could impact patients, caregivers, physicians, payers, and advocates.

As potential new standards of care for food allergy evolve, a better understanding of clinical trial endpoints, including terminology, will be important to successful implementation, patient understanding, education, and safety.
• **Reactive Dose**: The dose given during a food challenge that induces the onset of unequivocal allergic symptoms; the dose that stops the challenge, i.e., is not tolerated.

*Occasionally referred to as “eliciting dose”

**For the reactive (not-tolerated)/stopping dose, the symptoms are typically objective and can range from mild to severe.*
• Single Highest Tolerated Dose:

– *The highest dose given during a food challenge that elicits either no symptoms or symptoms that are not clearly indicative of an allergic reaction*°

*For the tolerated dose, the symptoms should not be any worse than mild, are usually transient, and are typically subjective (examples include pruritus of the skin, nausea, throat/abdominal discomfort, etc.*
Terminology Used in Food Allergy Clinical Trials

• **Cumulative Tolerated Dose:**
  
  – *The sum of the tolerated doses, not including the reactive dose*

\[1 + 3 + 10 + 30 + 100 + 300 \text{ mg} = 444 \text{ mg}\]
Terminology Used in Food Allergy Clinical Trials

• **Cumulative Reactive Dose:**

  – *The sum of doses consumed, including the reactive (not tolerated) dose*

  \[1 + 3 + 10 + 30 + 100 + 300 + 1,000 \text{ mg} = 1,444 \text{ mg}\]

  *1+3+10+30+100+300+1,000 mg = 1,444 mg is the sum of all doses given including the last not tolerated dose, i.e., the reactive dose. This means that the actual tolerated dose is 300 mg, i.e., is the last dose prior to the reactive dose.*
A Hypothetical Situation with a Peanut Allergic Patient in a Clinical Trial: Question

• You have administered an active food challenge to Patient A at the end of the study in a clinical trial. In the food challenge to assess efficacy of therapy for this patient, the patient took the following peanut doses without dose-limiting symptoms*: 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, and 600 mg of peanut protein, but had dose-limiting symptoms at 1000 mg of peanut protein. When communicating the result, what would be the Single Highest Tolerated Dose by the patient?

*The highest dose given during a food challenge that elicits either no symptoms or symptoms that are not clearly indicative of an allergic reaction.
A Hypothetical Situation with a Peanut Allergic Patient in a Clinical Trial: Answer

A. 1000 mg is the Single Highest Tolerated Dose
B. 600 mg is the Single Highest Tolerated Dose
C. 1000 mg is the Reactive Dose
D. 600 mg is the Reactive Dose
Terminology Used in Food Allergy Clinical Trials

• Eliciting dose (ED):
  – The population threshold described in terms of percentages
    – Example: ED_{10}
      – The eliciting dose predicted to provoke a reaction in 10% of individuals with a specific food allergy
  – Useful for the comparison of the potency of one allergenic food vs. another
  – Useful in predicting how many individuals should respond to any specific exposure, e.g., a food contaminated with an undeclared allergen

• There is a need to standardize the terminology used in food allergy clinical trials.

• As new standards of care for food allergy evolve, an understanding of the differences between reactive dose, single highest tolerated dose, cumulative tolerated dose, and cumulative reactive dose as clinical trial endpoints will be critical to the successful implementation of new treatments.

• The evolving field of food allergy provides a novel opportunity to define clinical trial endpoints that are most meaningful for patients.