Outcomes: Efficacy for any AIT: who, what, when and how?

How is it measured?

- Regulatory Authority Requirements: new allergen products must demonstrate efficacy & safety
- **Primary outcome**: clinical efficacy measured via symptoms + medication scores with ‘natural exposure’ (e.g. pollen season or collected throughout the year for perennial)
  - Environmental chamber challenge may be accepted for Phase II dose response
- Similar requirement for existing US-licensed product if seeking a Product Information change – e.g. SCIT extract licensed for subcutaneous use to be changed to include sublingual use
- **WAO recommendation**: the primary outcome measure be a combined symptom + medication score \(^1\)
  - Efficacy inferior to antihistamines not considered acceptable
  - Magnitude: “minimal clinically relevant efficacy should be **at least 20% higher** than placebo”
- **Usual symptom scoring system**
  - 0-3, with 3 being worse
  - 6 symptoms: 4 nasal, 2 eye
  - Some scoring systems include bronchial
- **Medication scoring** varies with study: e.g., US grass tablet trials
  - Grastek®: antihistamine= 6, oral CS 1.6\(^2\)
  - Orolair®: antihistamine =1, oral CS 3\(^3\)
- **When** is it measured?
  - AIPP 3\(^{rd}\) update recommends: **Summary Statement 23**: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy.\(^4\)
- **Who** research vs. ‘real-life’ patient- Does the measurement tool change with the setting?
  - Research- combined symptom medication scores. Clinical practice no standard outcome assessment. AIPP recommends in Measures of efficacy. **Summary Statement 15**: Clinical parameters, such as symptoms and medication use, might be useful measures of the efficacy of immunotherapy in a clinical setting; however, repetitive skin testing of patients receiving immunotherapy is not recommended.\(^4\)
- **What is meaningful to the patient?**
  - Magnitude of improvement-clinically meaningful vs. statistically significant. “A statistically significant difference between treated and control groups does not necessarily mean that the difference is also of clinical importance. Clinical importance refers to the magnitude of the difference between the two treatments, whereas statistical significance indicates the probability of being able to reject the hypothesis of “no difference.” .......We use patient
perception of a meaningful change in quality of life as the anchor to calculate the minimal important difference (MID) for our questionnaires. We have defined the MID as “the smallest difference in score in the domain of interest that patients perceive as beneficial and would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management.”

Figure 1 AIT Effectiveness in Clinical Trials

<table>
<thead>
<tr>
<th>Disease</th>
<th>Author</th>
<th>Studies (n)</th>
<th>Population age</th>
<th>Participants</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Active (n)</td>
<td>Placebo (n)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>Calderon MA 2007</td>
<td>15</td>
<td>Adults</td>
<td>597</td>
<td>466</td>
</tr>
<tr>
<td>Asthma</td>
<td>Abramson MJ 2010</td>
<td>34</td>
<td>Adults and children</td>
<td>1284</td>
<td></td>
</tr>
<tr>
<td>SCIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>Wilson D 2003</td>
<td>21</td>
<td>Adults and children</td>
<td>484</td>
<td>475</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>Penagos M 2006</td>
<td>10</td>
<td>Children</td>
<td>245</td>
<td>239</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>Radulovic S 2011</td>
<td>49</td>
<td>Adults and children</td>
<td>2333</td>
<td>2256</td>
</tr>
<tr>
<td>Asthma</td>
<td>Calamita Z 2006</td>
<td>9</td>
<td>Adults and children</td>
<td>150</td>
<td>153</td>
</tr>
<tr>
<td>Asthma</td>
<td>Penagos M 2008</td>
<td>9</td>
<td>Children</td>
<td>232</td>
<td>209</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Calderon MA 2011</td>
<td>36</td>
<td>Adults and children</td>
<td>1725</td>
<td>1674</td>
</tr>
<tr>
<td>House Dust Mites</td>
<td>Compalati E 2009</td>
<td>8</td>
<td>Adults and children</td>
<td>194</td>
<td>188</td>
</tr>
<tr>
<td>Grass Allergens</td>
<td>Di Bona D 2010</td>
<td>19</td>
<td>Adults and children</td>
<td>1518</td>
<td>1453</td>
</tr>
</tbody>
</table>

Effect size (SMD): poor < -0.20; medium = -0.50; high > 0.80

Heterogeneity: low = I² < 25%; moderate I² = 50%; high I² > 75%
Table 1: Magnitude of improvement in Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Preparation</th>
<th>Total Combined Scores</th>
<th>Symptom Score</th>
<th>Medication Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox 2011&lt;sup&gt;3&lt;/sup&gt;</td>
<td>5-grass 25 mcg Grp 5 SLIT tablet</td>
<td>28%</td>
<td>23%</td>
<td>47%</td>
</tr>
<tr>
<td>Maloney 2014&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Timothy 15 μg Phl p 5 SLIT tablet</td>
<td>23%</td>
<td>20%</td>
<td>35%</td>
</tr>
<tr>
<td>Frew 2006&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Timothy 20 μg Phl p 5 SCIT</td>
<td>n/a</td>
<td>29%</td>
<td>32%</td>
</tr>
<tr>
<td>Varney 1991&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Timothy 20 μg Phl p 5 SCIT</td>
<td>n/a</td>
<td>61%</td>
<td>79%</td>
</tr>
<tr>
<td>Howarth 2012&lt;sup&gt;10&lt;/sup&gt;</td>
<td>5-grass 25 mcg Grp 5 SLIT tablet</td>
<td>42% (AAdSS)</td>
<td>40%</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Selected Patient Populations**

<table>
<thead>
<tr>
<th>Study</th>
<th>Preparation</th>
<th>Total Combined Scores</th>
<th>Symptom Score</th>
<th>Medication Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘extremely or very hypersensitive’</td>
<td>Timothy 20 μg Phl p 5 SCIT</td>
<td>n/a</td>
<td>61%</td>
<td>79%</td>
</tr>
<tr>
<td>Centers with highest placebo score</td>
<td>5-grass 25 mcg Grp 5 SLIT tablet</td>
<td>42% (AAdSS)</td>
<td>40%</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**AAdSS**= Average Adjusted Symptom Score based on the RTSS and adjusted for the use of rescue medication

**Unmet Need: Patient-centered AIT Outcome Assessment Tool (in development-AAAAI presidential initiative)**

- All patients to enter the information themselves
- Capture outcomes important to the patient
- Measure clinical impact on quality of life, economic impact
- Validated against AIT clinical outcomes, patients satisfaction, reliability, etc.
- Could also be used in research
- Extract data from EHR systems, and the AIT Registry
- Provide tracking during the AIT process
- Prepare a clinically useful report for physicians
- Available for free
Figure 2: Example of a Patient-centered AIT Outcome Assessment Tool

**Patient Symptom Profile**

**Name:** Jeremy Wildfire  
**Telephone Number:** 919-408-8000  
**Age:** 15  
**Diagnosis:** Seasonal Allergic Rhinitis  
**Parents:** Wilma and William Wildfire

Jeremy was first seen in March, 2013. He presented with watery and itching eyes and frequent sneezing. In his self-reported symptom profile, Jeremy was most concerned that his allergies led to frequent sneezing and caused him to be in a bad mood. He also expressed concern regarding his allergies interfering with his social life.

**Self-reported Problem Scores**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Initial Problem Score March 1, 2013</th>
<th>Change in Problem Score as of October 1, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sneezing</td>
<td>4.5</td>
<td>1.1 (-3.4)</td>
</tr>
<tr>
<td>Bad Mood</td>
<td>4.3</td>
<td>2.0 (-2.3)</td>
</tr>
<tr>
<td>Social Life</td>
<td>3.5</td>
<td>3.0 (-0.5)</td>
</tr>
<tr>
<td>Itchy Eyes</td>
<td>3.4</td>
<td>2.0 (-1.4)</td>
</tr>
</tbody>
</table>

**Self-reported Symptom Change**

- **Sneezing**  
  - Visit 1: 4.5  
  - Visit 2: 2.8  
  - Visit 3: 1.1

- **Bad Mood**  
  - Visit 1: 4.3  
  - Visit 2: 2.4  
  - Visit 3: 2.0

- **Interferes in Social Life**  
  - Visit 1: 3.5  
  - Visit 2: 3.0  
  - Visit 3: 1.8

- **Itchy Eyes**  
  - Visit 1: 3.4  
  - Visit 2: 3.4  
  - Visit 3: 2.7  
  - Visit 4: 2.0
### Table 2: Comparing SCIT vs SLIT

<table>
<thead>
<tr>
<th>Study</th>
<th>Allergen</th>
<th>Design</th>
<th>Duration</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yukselen, 2011</td>
<td>HDM</td>
<td>Ran, DB, PC, DD</td>
<td>1 year</td>
<td>30</td>
<td>SCIT = SLIT (except for asthma scores when SCIT &gt; SLIT)</td>
</tr>
<tr>
<td>Keles, 2011</td>
<td>HDM</td>
<td>Ran, open, PG, Con</td>
<td>1.5 years</td>
<td>50</td>
<td>SCIT &gt; SLIT (rhinitis and total symptom and medication scores)</td>
</tr>
<tr>
<td>Eifan, 2010</td>
<td>HDM</td>
<td>Ran, DB, PG, Con</td>
<td>1 year</td>
<td>43</td>
<td>SCIT = SLIT</td>
</tr>
<tr>
<td>Ventura, 2009</td>
<td>Cypress</td>
<td>Ran, DB, PC</td>
<td>1 year</td>
<td>40</td>
<td>SCIT = SLIT</td>
</tr>
<tr>
<td>Tahamiler, 2008</td>
<td>HDM</td>
<td>Ran, open, PG</td>
<td>3 years</td>
<td>193</td>
<td>SCIT &gt; SLIT (symptom score)</td>
</tr>
<tr>
<td>Mauro, 2007</td>
<td>Trees</td>
<td>Ran, open, PG</td>
<td>1 year</td>
<td>34</td>
<td>SCIT = SLIT</td>
</tr>
<tr>
<td>Khinchi, 2004</td>
<td>Birch</td>
<td>Ran, DB, DD</td>
<td>2 years</td>
<td>71</td>
<td>SCIT = SLIT</td>
</tr>
<tr>
<td>Mungan, 1999</td>
<td>HDM</td>
<td>Ran, SB, PG, PC</td>
<td>1 year</td>
<td>36</td>
<td>No comparisons of SLIT/SCIT vs placebo or SLIT vs SCIT were made</td>
</tr>
<tr>
<td>Quirino, 1996</td>
<td>Grass</td>
<td>Non-Ran, DB, DD</td>
<td>2 years</td>
<td>20</td>
<td>SCIT = SLIT</td>
</tr>
<tr>
<td>Piazza, 1993</td>
<td>HDM</td>
<td>Ran, open, PG, Con</td>
<td>2 years</td>
<td>43</td>
<td>SCIT &gt; control (combined symptom medication)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SLIT = control (combined symptom medication)</td>
</tr>
</tbody>
</table>

Provided with permission for Cheryl Hankin, PhD
Hankin et al Systematic literature review OF patterns and outcomes of allergy immunotherapy for the treatment of patients with allergic rhinitis .2014 manuscript in preparation
Linda Cox, MD, FAAAAI AAAAI 2014 Annual Meeting Saturday Plenary Saturday, March 1st, AIT Outcomes Examining the Data for Efficacy, Safety, Adherence, and Costs

AIT Safety

- **SCIT:**
  - Incidence of SRs dependent on multiple factors at a rate ~0.2% of injections and 2-5% of patients\(^{21}\)
  - Delayed\(^{22}\) & biphasic\(^{23,24}\) do occur and are not rare
  - Risk factors identified: symptomatic asthma, previous AIT SR
  - Fatalities rare per US survey data - ~1 in 2.5 million injections from 1945 to 2001,\(^{25-27}\) none confirmed from 2008 to 2012 survey\(^{28}\)

- **SLIT:**
  - SLIT appears to be better tolerated than SCIT
  - Majority of SLIT AE's are local reactions - oromucosal symptoms
    - Occur during the beginning of treatment
    - Resolve within a few days or weeks without any medication or intervention
  - Systemic reactions are uncommon and SAE rare
  - Risk factors for the occurrence of SLIT severe adverse events (SAEs) have not yet been established, although there is some suggestion that patients who have had prior systemic reactions to SCIT may be at increased risk
  - Because this treatment is administered in a medically unsupervised setting, specific instructions should be provided to patients regarding the management of adverse reactions, unplanned interruptions in treatment, and situations when SLIT should be withheld.
  - WAO grading system for AIT systemic reactions\(^{21}\) and SLIT local reactions\(^{29}\) (see figures below)
The final reaction grade will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the SCIT injection and

A letter that denotes if and when epinephrine is or is not administered: a, 5 minutes or less; b, greater than 5 minutes to 10 minutes or less; c, greater 10 minutes to 20 minutes or less; d, greater than 20 minutes; z, epinephrine not administered.

Final report: Grade a-d, or z ________________ First symptom_______Time of onset of first symptom______ e.g., Grade 2a: rhinitis: 10 minutes.

**TABLE IV. Grading system for SLIT local AEs**

<table>
<thead>
<tr>
<th>Symptom/sign (see Table 5)</th>
<th>Grade 1: Mild</th>
<th>Grade 2: Moderate</th>
<th>Grade 3: Severe</th>
<th>Unknown severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus/itching of mouth, tongue, or lip; bucal irritation, nausea, abdominal pain, vomiting, diarrhea, hives, or urticaria</td>
<td>Not troublesome AND No symptomatic treatment required AND No discontinuation of SLIT because of local side effects</td>
<td>Troublesome OR Requires symptomatic treatment AND No discontinuation of SLIT because of local side effects</td>
<td>Grade 2 AND SLIT discontinued because of local side effects</td>
<td>Treatment is discontinued, but there is no subjective, objective, or both description of severity from the patient/physician</td>
</tr>
</tbody>
</table>

Each local AE can be early (<30 minutes) or delayed.

*See Table 1 for the MedDRA code that applies to exactly report and describe the AE.

Mild: symptoms that persist for greater than 10 days and require no treatment and the patient does not regard them as bothersome

Moderate: troublesome symptoms that might or might not require treatment but not result in discontinuation

**Economics of AIT—see separate table in appendix**

- Various designs, outcomes and duration:
  - Designs: budget impact analysis; cost-consequence analysis; cost-effectiveness analysis; cost-utility analysis and retrospective claims
  - Outcomes: assessed which include ICER, QALY, asthma prevented, and, societal, payer, patient and actual cost

- 10 economic analysis compared SDT vs. AIT - only one showed greater costs with AIT vs AIT

- Different CER and ‘breakeven time points’ - from 3 months to 10 years
One 12 year large retrospective claims study (‘real-life’) involving Florida Medicaid Data which included ~7.5 million people found 18-month median total cost savings of 30% in adults and 42% in children with new onset AR who received AIT vs. matched controls that did not.  

- One study compared cluster vs conventional build-up and found cost-savings with cluster. Total cost per patient in the build-up phase amounted to €184.40 with accelerated SCIT and €429.35 with traditional SCIT. There was no difference between treatments in occurrence of side effects per patient and per injection.  
- Both SCIT and SLIT have been shown to be cost-effective compared with SDT for the treatment of AR.  
- Whereas the cost of SLIT allergen may be higher than SCIT, SLIT requires fewer physician visits than SCIT, resulting in lower treatment costs and indirect costs (travel, lost working hours).  
- Of the 4 economic studies comparing SLIT and SCIT, 3 found SLIT to be a more cost-effective treatment option and 1 found SCIT to be more cost-effective.  
- In general, the longer the time horizon the greater AIT cost-effectiveness compared with SDT.  

### Adherence:  

- Studies have reported widely varying rates of premature discontinuation for both SCIT and SLIT.  
  - **SCIT**: rates of SCIT premature discontinuation: ranged from 6% to 84% (15 studies). Seven studies reported discontinuation rates ranging from 6% to 30%, 5 studies from 31% to 50%, and 3 studies reported discontinuation rates greater than 50%.  
  - **SLIT adherence in short-term studies**: Studies that quantitatively measured adherence to SLIT over 1 year or less reported high adherence rates (84-97%).  
  - **SLIT long term studies** that assessed adherence quantitatively by measuring the amount of SLIT returned during clinical trials reported adherence rates of 72-91%.  
- **RCTs**: Rates of adherence to SLIT have been generally good (70-90%); however, adherence to SLIT is substantially lower when based on physician estimates (29%) and examination of pharmacy SLIT refill data (38%).  
- **Real-world SLIT adherence**  
  - The highest rate of SLIT premature discontinuation was reported in a retrospective analysis of pharmacy claims data in the Netherlands.
Among 3690 Dutch adults who initiated SLIT, only 7% completed 3 years of treatment.\(^4\)

- A study that examined sales data from 2 large SLIT manufacturers found that less than 20% of SLIT prescriptions were continued after 3 years.\(^6\)
- A study that examined SLIT prescription renewal rates, only 50% of patients who were prescribed SLIT renewed their prescriptions in the 2 subsequent years.\(^4\)

- **SCIT vs SLIT:** three of the 4 studies that compared rates of premature discontinuation to both SCIT and SLIT found higher rates of premature discontinuation in patients who received SLIT than in those who received SCIT.

- **Reason for discontinuation:** the most common reasons patients cite for discontinuing SCIT are inconvenience, concurrent illness, lack of efficacy, improvement in symptoms, change of residence, and adverse reactions.

- **The most common reasons patients cite for discontinuing SLIT are the inability to take the medication as scheduled/compliance, inconvenience, lack of efficacy, concurrent illness, cost, and adverse effects.**

- **Potential interventions to improve adherence**
  - **Improve patient education:** patients may have poor perception of what to expect from AIT Study surveying AIT patients knowledge found:\(^6\)
    - 60% unaware of any treatment duration
    - 33% did not know about the risk of side effects
    - 35% considered AIT to be entirely safe
    - 3% recognize all their allergens without mistakes
  - **Increase visit frequency**\(^6\)
Electronic messaging: Studies have demonstrated improved medication adherence and disease management with text messages and other forms of electronic reminders significantly increased medication adherence.

**AIT Outcomes: Efficacy, Safety, Cost-efficiency and Adherence**

- **AIT Outcome**: Essentially no ‘gold standard’ for AIT outcome
  - Most ‘accepted’ – 20% improvement in CMS score
  - But questions remain: what is clinically meaningful? Are we measuring what matters to the patient?
  - Need a patient-centered Allergy Immunotherapy Outcome Assessment Tool
- **Safety**: SLIT better safety profile compared with SCIT but both acceptable safety when administered appropriately (i.e., medically supervised setting)
- **Economics**: significant cost-savings seen with AIT in various study designs
- **Adherence**: In RCT adherence is generally good but problematic with both forms of AIT in real-life. Interventions to improve adherence are need


