

# SCIT/SLIT: *a Head-to-Head Comparison*



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# Disclosures for Linda Cox, MD

For the 12 months preceding this CME activity, I or my spouse/partner disclose the following types of financial relationships:

- Grant/Research Support from: None
- Consultant for: Greer
- Speaker's Bureau for: None
- Major Stock Shareholder for: None
- Other Financial or Material Support from: Circassia SDMC, Medimmune Adjudication Committee, Novartis Adjudication Committee

I will be discussing products that are investigational or not labeled for use under discussion.



# SCIT and SLIT *a head-to-head comparison*

- SCIT and SLIT efficacy in terms of:
  - Direct and indirect comparisons, meta-analysis, systematic reviews
  - Dosing and dosing regimen
- SCIT and SLIT safety
  - Adverse reactions: types and frequency
  - Risk factors & risk reduction
  - Package insert warnings, epinephrine autoinjectors and patient instructions
- SCIT and SLIT practical considerations
  - Adherence , costs and other consideration

# SCIT > 100 years

Start date 1911

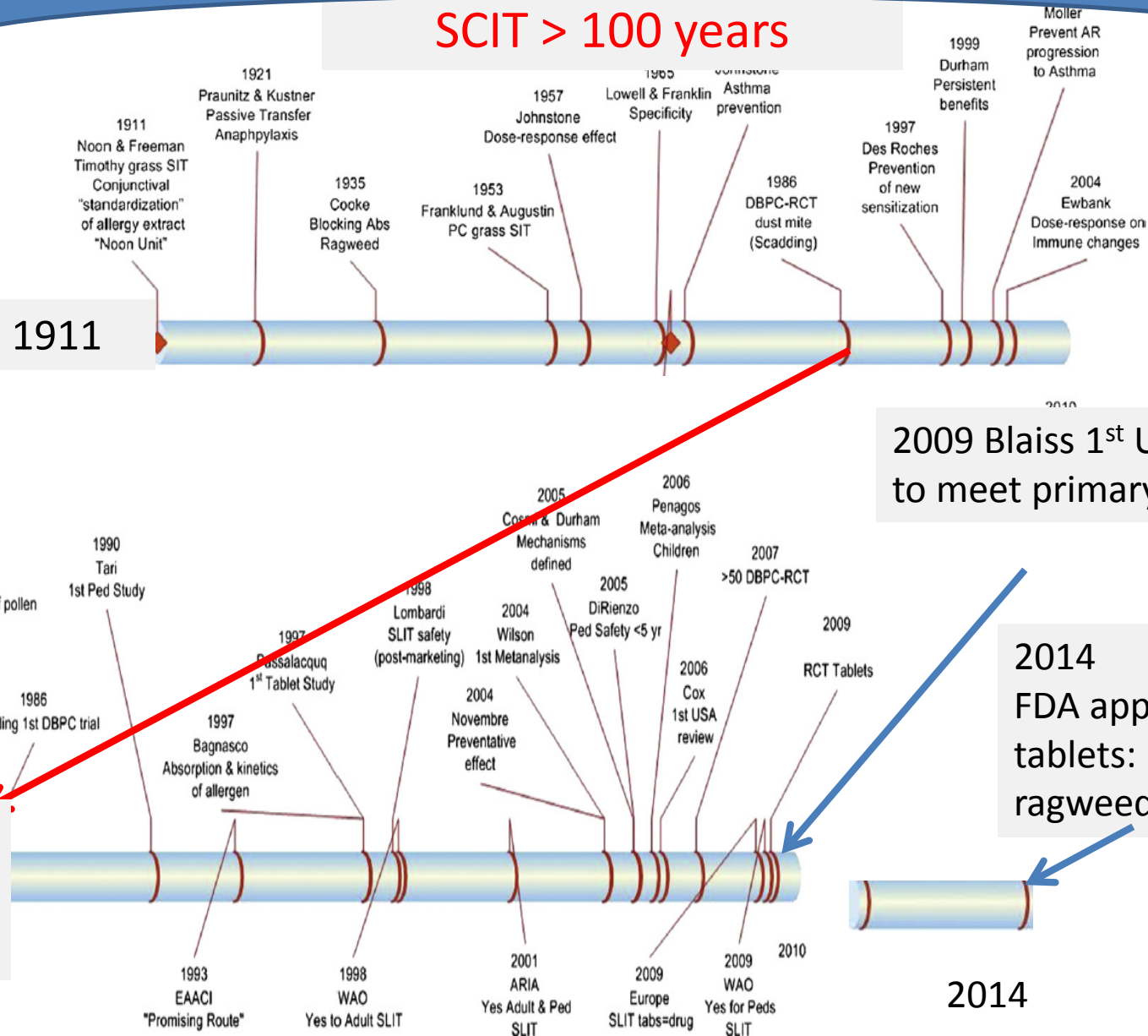
SLIT- 1<sup>st</sup>  
DBPC in  
1986

2009 Blaiss 1<sup>st</sup> US SLIT study  
to meet primary outcome

2014  
FDA approves 3 SLIT  
tablets: 2 grass & 1  
ragweed

2014

Cox L, Wallace D. Specific allergy immunotherapy for allergic rhinitis:  
subcutaneous and sublingual. Immunol Allergy Clin North Am. 2011;31(3):561-99.



## Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report

A. Wesley Burks, MD,<sup>a</sup> Moises A. Calderon, MD, PhD,<sup>b</sup> Thomas Casale, MD,<sup>c</sup> Linda Cox, MD,<sup>d</sup> Pascal Demoly, MD, PhD,<sup>e</sup> Marek Jutel, MD,<sup>f</sup> Harold Nelson, MD,<sup>g</sup> and Cezmi A. Akdis, MD<sup>h</sup> Chapel Hill, NC, London, United Kingdom, Omaha, Neb, Davie, Fla, Montpellier, France, Wroclaw, Poland, Denver, Colo, and Davos, Switzerland

### Efficacy of forms of AIT well established

TABLE E1. Symptom scores

| Disease          | Author                        | Studies<br>(no.) | Population          | Participants    |                  | Effect size, SMD (95% CI)* | Heterogeneity I <sup>2</sup> |
|------------------|-------------------------------|------------------|---------------------|-----------------|------------------|----------------------------|------------------------------|
|                  |                               |                  |                     | Active<br>(no.) | Placebo<br>(no.) |                            |                              |
| SCIT             |                               |                  |                     |                 |                  |                            |                              |
| Rhinitis         | Calderon, <sup>E1</sup> 2007  | 15               | Adults              | 597             | 466              | −0.73 (−0.97 to −0.50)     | 63%                          |
| Asthma           | Abramson, <sup>E2</sup> 2010  | 34               | Adults and children | 727             | 557              | −0.59 (−0.83 to −0.35)     | 73%                          |
| SLIT             |                               |                  |                     |                 |                  |                            |                              |
| Rhinitis         | Wilson, <sup>E3</sup> 2003    | 21               | Adults and children | 484             | 475              | −0.42 (−0.69 to −0.15)     | 73%                          |
| Rhinitis         | Penagos, <sup>E4</sup> 2006   | 10               | Children            | 245             | 239              | −0.56 (−1.01 to −0.10)     | 81%                          |
| Rhinitis         | Radulovic, <sup>E5</sup> 2011 | 49               | Adults and children | 2333            | 2256             | −0.49 (−0.64 to −0.34)     | 81%                          |
| Asthma           | Calamita, <sup>E6</sup> 2006  | 9                | Adults and children | 150             | 153              | −0.38 (−0.79 to 0.03)      | 64%                          |
| Asthma           | Penagos, <sup>E7</sup> 2008   | 9                | Children            | 232             | 209              | −1.14 (−2.10 to −0.18)     | 94%                          |
| Conjunctivitis   | Calderon, <sup>E8</sup> 2011  | 36               | Adults and children | 1725            | 1674             | −0.41 (−0.53 to −0.28)     | 59%                          |
| House dust mites | Compalati, <sup>E9</sup> 2009 | 8                | Adults and children | 194             | 188              | −0.95 (−1.77 to −0.14)     | 92%                          |
| Grass allergens  | Di Bona, <sup>E10</sup> 2010  | 19               | Adults and children | 1518            | 1453             | −0.32 (−0.44 to −0.21)     | 56%                          |

\*Effect size (SMD): poor, <-0.20; medium, -0.50; high, >-0.80.

†Heterogeneity (I<sup>2</sup>) = 0% to 40%, might not be important; 30% to 60%, might represent moderate heterogeneity; 50% to 90%, might represent substantial heterogeneity; 75% to 100%, considerable heterogeneity.

# IS SLIT MORE EFFECTIVE THAN SCIT?

- Paucity of well designed, well powered RC, DBPC trials comparing SCIT with SLIT so most 'head-to-head' comparisons are indirect
- Indirect comparisons tend to favor SCIT in terms of onset of improvement, asthma and immunological changes

# Cochrane Collaboration Systematic Reviews and Meta-analysis of SCIT and SLIT Compared to placebo

**TABLE II.** Cochrane Collaboration Systematic Reviews and meta-analyses of immunotherapy by the subcutaneous or sublingual approach (compared to placebo)

| Study                               | Method | No. of studies included | Allergens              | No. of subjects | Symptoms scores, SMD (95% CI) | Medication scores, SMD (95% CI) |
|-------------------------------------|--------|-------------------------|------------------------|-----------------|-------------------------------|---------------------------------|
| <b>Allergic rhinitis</b>            |        |                         |                        |                 |                               |                                 |
| Calderon et al <sup>1</sup> (2007)  | SCIT   | 51                      | Seasonal               | 2871            | -0.73 (-0.97 to -0.50)        | -0.57 (-0.82 to -0.33)          |
| Radulovic et al <sup>2</sup> (2011) | SLIT   | 49                      | Seasonal and perennial | 4589            | -0.49 (-0.64 to -0.34)        | -0.32 (-0.43 to -0.21)          |
| <b>Allergic asthma</b>              |        |                         |                        |                 |                               |                                 |
| Abramson et al <sup>3</sup> (2010)  | SCIT   | 88                      | Seasonal and perennial | 3459            | -0.59 (-0.83 to -0.35)        | -0.53 (-0.80 to -0.27)          |
| Calamita et al <sup>4</sup> (2006)  | SLIT   | 25                      | Seasonal and perennial | 1706            | -0.38 (-0.79 to 0.03) NS      | -0.91 (-1.94 to 0.12) NS        |

SMD, Standardized mean difference; NS, not significant.

- Significant Clinical and Methodological Heterogeneity
  - Age, severity of disease, allergens,
  - Outcomes assessed, dosages (too low), schedules

# Evidence from Systematic Reviews

|                             | Indirect  |  | Head-to-Head  |  |
|-----------------------------|---|--|---|--|
|                             | Di Bona<br>Grass AR<br>2012   | Dretzke<br>2013  | Chelladurai<br>2013<br>AR & Asthma  | Kim<br>2013 Pediatric AR &<br>Asthma           |
| <b>No of RCTs</b>           | 17 SCIT vs Placebo<br>22 SLIT vs Placebo  | 17 SCIT vs Placebo<br>11 SLIT vs Placebo                           | 8 SCIT vs SLIT  | 3 SCIT vs SLIT<br>Paediatric only              |
| <b>Symptom<br/>Score</b>    | SMD= SCIT vs Placebo<br>-0.92 [-1.26 to -0.58]<br>SMD SLIT-D vs Placebo<br>-0.25 [-0.45 to -0.05]<br>SMD = SLIT-T vs Placebo<br>-0.40 [95% CI -0.54 to -<br>0.27] | SCIT vs SLIT<br>0.35[0.13 to 0.59]<br><b>Favoring SCIT</b>         | Moderate grade<br>evidence<br><br><b>Favoring SCIT</b>  | Low grade evidence<br><br><b>Favoring SCIT</b> |
| <b>Medication<br/>Score</b> | SMD= SCIT vs Placebo<br>-0.58 [-0.86 to -0.30]<br>SMD SLIT-D vs Placebo<br>-0.37 [-0.7 to 0.0]<br>SMD = SLIT-T vs Placebo<br>-0.30 [-0.44 to -0.16]               | SSD: SCIT vs SLIT<br>0.27[0.03 to 0.5]<br><br><b>Favoring SCIT</b> | Low grade evidence,<br>no difference in<br>treatment<br>effectiveness<br>between SCIT and<br>SLIT | Low grade evidence<br><br><b>Favoring SCIT</b> |

SMD= Standardized Mean Difference SSD= Standardised Score Difference, CI =confidence interval, Crls =credible intervals



# Randomized Studies for Asthma and Rhinitis

## SCIT vs SLIT

| Study<br>(population)     | AIT<br>allergen<br>(duration) | Patients<br>enrolled/ drop outs   | Outcome<br>(score)               | Before AIT    |               | After AIT     |               |
|---------------------------|-------------------------------|---|----------------------------------|---------------|---------------|---------------|---------------|
|                           |                               |   |                                  | SCIT          | SLIT          | SCIT          | SLIT          |
| Mungan 1999<br>Adults     | Dpt and Df<br>(1 yr)          | SCIT = 15/0<br>SLIT = 10/0<br>Placebo = 11/0                              | Asthma Symptom<br>Score (0-3)    | 1.20          | 0.63          | 0.59          | 0.41          |
|                           |                               |   | Rhinitis Symptom<br>Score (0-3)  | 0.84          | 0.87          | 0.45          | 0.50          |
| Eifan 2010<br>Children    | Dpt and Df<br>(1 yr)          | SCIT = 11/1<br>SLIT = 16/2<br>Pharm = 16/2                                | Asthma Symptom<br>Score (0-12)   | $0.9 \pm 0.7$ | $1.4 \pm 1.5$ | $0.4 \pm 0.6$ | $0.2 \pm 0.4$ |
|                           |                               |   | Rhinitis Symptom<br>Score (0-12) | $1.8 \pm 0.9$ | $1.3 \pm 0.9$ | $1.2 \pm 0.9$ | $1.5 \pm 1.0$ |
| Yukselen 2011<br>Children | Dpt and Df<br>(1 yr)          | SCIT+placebo = 10/0<br>SLIT+placebo = 11/1<br>Placebo drops+inj =<br>10/1 | Asthma Symptom<br>Score (0-12)   | 2.4           | 3.7           | 1.0           | 2.7           |
|                           |                               |   | Rhinitis Symptom<br>Score (0-12) | 4.6           | 4.3           | 3.0           | 3.8           |
| Keles 2011<br>Children    | Dpt and Df<br>(1 yr)          | SCIT = 11/2<br>SLIT = 13/2<br>SCIT+SLIT = 14/0<br>Pharm = 12/0            | Asthma Symptom<br>Score (NR)     | 0.25          | 0.12          | 0             | 0             |
|                           |                               |   | Rhinitis Symptom<br>Score (NR)   | 0.21          | 0.36          | 0.06          | 0.27          |

- No statistical power, outcomes (AR+AA), low doses

# A novel approach in SIT: combination of SLIT and SCIT

- Study 51 dust-mite asthmatic children randomized to SCIT, SLIT, SCIT plus SLIT, or pharmacotherapy for 18 months (ALK Alutard SQ & glycerinated extract)
- Build-up and maintenance phases was
  - 1.5 and 52.8 mcg of Der p 1 in SLIT group,
  - 16.2 and 44.1 mcg of Der p 1 in the SCIT group
  - 16.2 and 43.2 mcg of Der p 1 in the SCIT plus SLIT

**TABLE E1.** Immunotherapy schedule of the groups for 1 year

|                   |                           | SLIT group                           | SCIT group                            | SCIT + SLIT group                     |
|-------------------|---------------------------|--------------------------------------|---------------------------------------|---------------------------------------|
| Build-up phase    | Dose scheduled            | Vial 0: 1-5 drops                    | Vial 1: 0.2, 0.4, 0.8 mL              | Vial 1: 0.2, 0.4, 0.8 mL              |
|                   |                           | Vial 1: 1-5 drops                    | Vial 2: 0.2, 0.4, 0.8 mL              | Vial 2: 0.2, 0.4, 0.8 mL              |
|                   |                           | Vial 2: 1-5 drops                    | Vial 3: 0.2, 0.4, 0.6, 0.8 mL         | Vial 3: 0.2, 0.4, 0.6, 0.8 mL         |
|                   |                           | Vial 3: 1-5 drops                    | Vial 4: 0.1, 0.2, 0.4, 0.6, 0.8, 1 mL | Vial 4: 0.1, 0.2, 0.4, 0.6, 0.8, 1 mL |
|                   |                           | Vial 4: 1-5 drops                    |                                       |                                       |
|                   | Duration                  | 30 d                                 | 16 wk                                 | 16 wk                                 |
|                   | Cumulative dose (Der p 1) | 1.5 µg                               | 16.2 µg                               | 16.2 µg                               |
|                   | Cumulative dose (Der f 1) | 1.5 µg                               | 22.9 µg                               | 22.9 µg                               |
|                   |                           | 750.7 STU                            | 331.540 SQ-U                          | 331.540 SQ-U                          |
| Maintenance phase | Dose scheduled            | 5 drops of vial 4 three times a week | 1 mL of vial 4 per month              | 5 drops of vial 4 three times a week  |
|                   |                           | Cumulative dose (Der p 1)            | 52.8 µg                               | 44.1 µg                               |
|                   |                           | Cumulative dose (Der f 1)            | 52.8 µg                               | 62.1 µg                               |
|                   |                           | 26.400 STU                           | 900.000 SQ-U                          | 21.600 STU                            |

*SQ U*, Standard quality unit; *STU*, skin test unit.

## A novel approach in SIT: combination of SLIT and SCIT

- Asthma attacks and ICS decreased compared with baseline values at the months 4, 12, and 18 in the SCIT and SCIT plus SLIT groups but only at month 12 in SLIT group
- Rhinitis VAS was significant only in the SCIT plus SLIT group.
- Increases in the levels of regulatory and TH1 cytokines were observed both in the SCIT and SLIT groups, with some differences in dynamics.
- Antigen-specific IgG4 levels increased in the SCIT and SCIT plus SLIT groups but not in the SLIT group

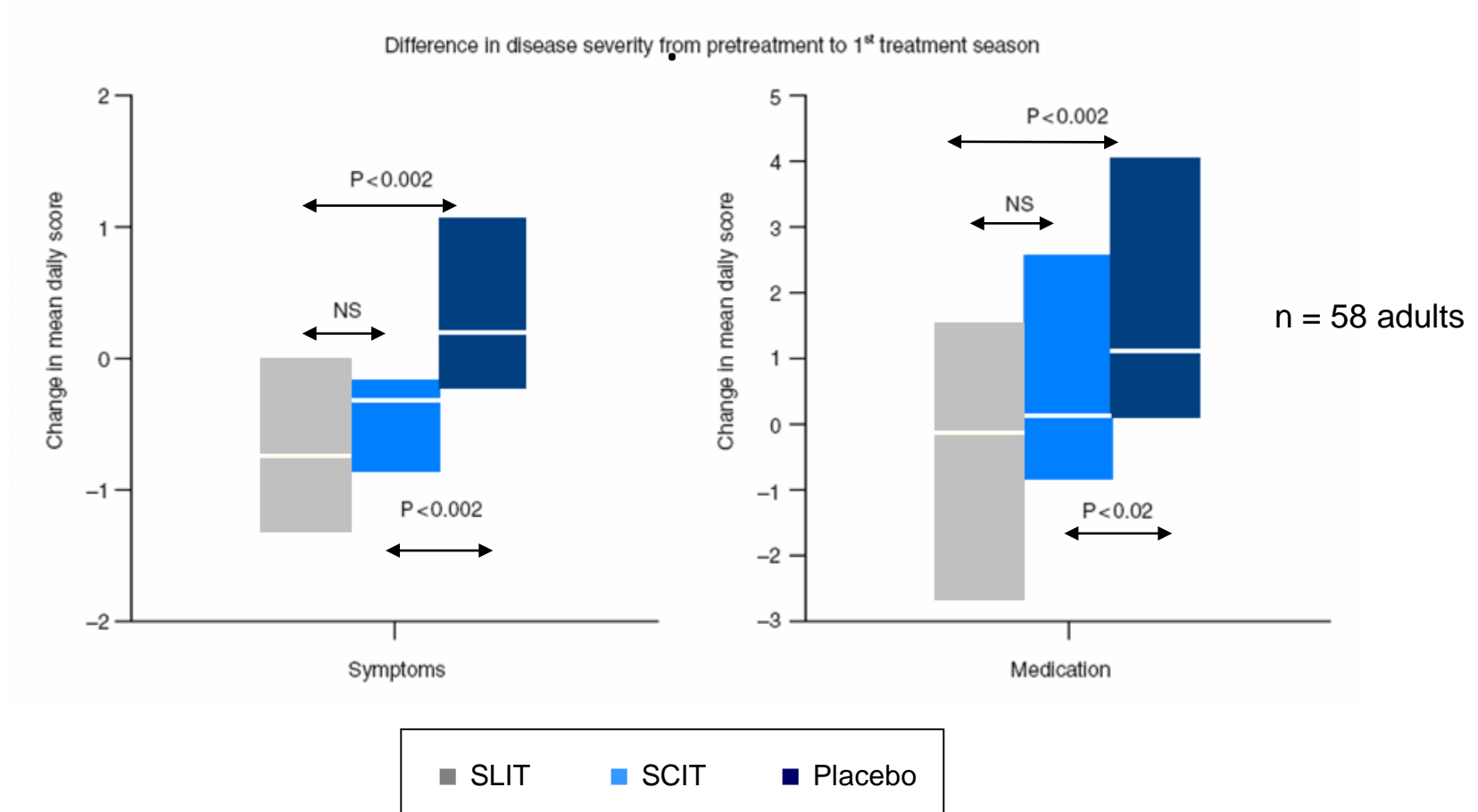
# Randomized Studies for Allergic Rhinitis

## SCIT vs SLIT

| Study population                         | AIT allergen (duration )             | Patients enrolled/ drop outs                | Outcome (score)                         | Before AIT |           | After AIT   |             |
|--|--------------------------------------|---|---|------------|-----------|-------------|-------------|
|  |                                      |   |   | SCIT       | SLIT      | SCIT        | SLIT        |
| <b>Piazza 1993 Children &amp; Adults</b> | Dpt (2 yrs)                          | SCIT = 14/0<br>SLIT = 17/0                  | Symptom medication score (0-14)         | 162        | 145       | 80          | 120         |
| <b>Khinchi 2004 Adults</b>               | Birch tree pollen (2 yrs)            | SCIT = 23/9<br>SLIT= 24/5<br>Placebo = 24/9 | Symptom score<br>Medication score (0-3) | NR         | NR        | 0.75        | 0.36        |
| <b>Mauro 2007 Adults</b>                 | Birch, alder, hazel tree pollen (NR) | SCIT = 20/5<br>SLIT = 20/1                  | Symptom medication score (0-18)         | NR         | NR        | 4.77 ± 1.41 | 3.63 ± 1.08 |
| <b>Tahamiler 2008 Adults</b>             | Dpt and Df (3 yrs)                   | SCIT = 97/NR<br>SLIT = 96/NR                | Symptom score (0-15)                    | 2.5 ± 0.4  | 2.4 ± 0.2 | 0.5 ± 0.1   | 0.9 ± 0.8   |

# SLIT vs SCIT for Birch Pollen RCT PC DB DD 24 months

Second year: 11.2 mg in SLIT vs. 51 µg in SCIT corresponds to a difference in dose of 175-219 times.



# Subcutaneous Immunotherapy Versus Sublingual Immunotherapy: Which Is More Effective?

**TABLE IV.** Summary of randomized studies comparing SCIT with SLIT: double-blind, double dummy (n = 4)

| Significant improvement versus placebo | Symptom or combined scores | Medication scores | Immunologic and challenge outcomes (no. of studies) |
|--|----------------------------|-------------------|---|
| SCIT only                              | 1*                         | 1*                | SPT (1), IgG4 (2), BAC (1)                          |
| SLIT only                              | 0                          | 0                 | 0   |
| Both                                   | 3                          | 1                 | SPT (1), nasal eos (1), NAC (1), ↑ IL-10 (1)        |

**TABLE V.** Summary of randomized studies that compares SCIT with SLIT: randomized, open (n = 7)

| Significant improvement versus placebo | Symptom scores or combined score | Medication scores | Immunologic and challenge outcomes (no. of studies)                |
|--|----------------------------------|-------------------|--|
| SCIT only                              | 3*                               | 1                 | SPT (2), IgG4 (5),*<br>NAC (1), ↑CD4+CD25+ T cells (1)             |
| SLIT only                              |                                  |                   | 0  |
| Both                                   | 4                                | 1                 | SPT (1), NAC (1),<br>↓ IgE/IgG4 ratio (1),<br>↓ TNF-α and IL-2 (1) |

*SPT*, Skin prick test; *NAC*, nasal allergen challenge; ↑, increased; ↓, decreased.

\*Indicates one study in which improvement with SCIT is greater than SLIT.

## **Subcutaneous Immunotherapy Versus Sublingual Immunotherapy: Which Is More Effective?**

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Harold S. Nelson, MD *Denver, Colo*

“The relative clinical efficacy of SCIT and SLIT remains to be defined. When each is compared with placebo, results of meta-analyses suggest greater efficacy of SCIT. In the limited number of randomized, head-to-head studies, SCIT has more often provided greater clinical and immunologic responses.

However, head-to-head studies with well-defined effective doses by the 2 routes are urgently needed.”

# Is SLIT more effective than SCIT?

## Indirect Comparisons

- Inconsistent.
- Significant Clinical and Methodological Heterogeneity.
- When each is compared to placebo, suggest greater efficacy of SCIT.

## Direct Comparisons

- Limited number of randomized head-to-head studies.
- Design of the study (?)
- Power of the survey (?)
- Broad range of effective doses (?)
- SCIT provides greater clinical response.



## SLIT Practice Parameter Draft

*Question: How does SLIT efficacy compare with SCIT?*

Summary Statement 7:

- There are insufficient studies directly comparing subcutaneous and sublingual immunotherapy to make a definitive statement regarding relative efficacy. However, available studies suggest that SCIT is more effective in the short-term than SLIT. Strength of recommendation:

## Meta-analyses suggest the size of the treatment effect for AIT and Pharmacotherapy for AR is comparable

| Meta-analysis                                 | Standardised Mean Difference | 95%CI        | Number of subjects |
|---|------------------------------|--------------|--------------------|
| SCIT -Cochrane (Calderon 2007)                | -0.73                        | -0.97; -0.50 | 2871               |
| SLIT -Cochrane (Radulovic 2010)               | -0.49                        | -0.64; -0.34 | 4589               |
| Intranasal Mometasone Furoate (Penagos 2008)* | -0.49                        | -0.60; -0.38 | 2998               |

\*Systematic review

Note: One Cochrane MA on Nasal CS in pediatric SAR/PAR: 3 trial 79 pts data analysis 'was flawed in 2 and in the third trial it was incomprehensible.' *Sayyad et al Cochrane Database Syst Rev. 2007(1):CD003163.*

# Comparison of Magnitude of Improvement Between SLIT and SCIT with same allergen

|                                 | <b>SCIT<sup>1</sup></b><br>20 µg Phl p 5T<br>n = 187 SLIT<br>n = 89 placebo | <b>SLIT<sup>2</sup></b><br>~15 µg Phl p<br>n = 282 SLIT<br>n = 286 placebo | <b>SLIT<sup>3</sup></b><br>~ 25 µg group 5<br>n = 136 SLIT<br>n = 148 placebo |
|---------------------------------|---|--|---|
| <b>Symptom scores</b>           | <b>- 29%</b>  | <b>- 30%</b>   | <b>- 37%</b>  |
| <b>Rescue medication scores</b> | <b>- 32%</b>  | <b>- 38%</b>   | <b>- 46%</b>  |

**Approximately 30% improvement over placebo with SCIT & SLIT**

1. Alum-precipitated grass pollen extract (Alutard SQ<sup>®</sup>, ALK-Abello). Frew et al, JACI 2006;117:319-25.
2. Lyophilized grass pollen tablet (Grazax<sup>®</sup>, ALK-Abello) Dahl et al, JACI 2006;118:434-40.
3. Lyophilized grass pollen (Oralair<sup>®</sup>, Stallergenes) Didier et al, JACI 2007;120:1338-45

# Magnitude of SMS Improvement in large patient population SLIT RCT

| Study           | Active | Placebo | Allergen                   | Daily Dose  | Symptom Scores<br>(Mean % Change) | Medication<br>Scores<br>(Mean % Change) |
|-----------------|--------|---------|----------------------------|-------------|-----------------------------------|---|
| <b>Adults</b>   |        |         |                            |             |                                   |   |
| Durham 2006     | 153    | 150     | <i>Phleum<br/>pratense</i> | 75,000 SQ-T | -16 %                             | -28 %                                   |
| Dahl 2006       | 316    | 318     | <i>Phleum<br/>pratense</i> | 75,000 SQ-T | -31 %                             | -39 %                                   |
| Didier 2007     | 155    | 156     | 5-Grasses                  | 300-IR      | -27 %                             | -35 %                                   |
| Nelson 2011     | 213    | 225     | <i>Phleum<br/>pratense</i> | 75,000 SQ-T | -18%                              | -26%                                    |
| Creticos 2012   | 194    | 198     | <i>Ambrosia</i>            | 2,800 BAU   | -17%                              | -45%                                    |
| Nolte 2012      | 187    | 188     | <i>Ambrosia</i>            | 2,800 BAU   | -18%                              | -36%                                    |
| <b>Children</b> |        |         |                            |             |                                   |   |
| Bufe 2009       | 126    | 128     | <i>Phleum<br/>pratense</i> | 75,000 SQ-T | -28 %                             | -65 %                                   |
| Wahn 2009       | 131    | 135     | 5-Grasses                  | 300-IR      | -28 %                             | - 24 %                                  |
| Blaiss 2011     | 175    | 169     | <i>Phleum<br/>pratense</i> | 75,000 SQ-T | -28%                              | -41%                                    |

## **Subcutaneous Immunotherapy Versus Sublingual Immunotherapy: Which Is More Effective?**

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When each is compared with placebo, results of meta-analyses suggest greater efficacy of SCIT. In the limited number of randomized, head-to-head studies, SCIT has more often provided greater clinical and immunologic responses.

However, head-to-head studies with well-defined effective doses by the 2 routes are urgently needed.”

# SLIT Practice Parameter Draft

***Question: How does SLIT efficacy compare with SCIT?***

## **Summary Statement XX:**

There are insufficient studies directly comparing subcutaneous and sublingual immunotherapy to make a definitive statement regarding relative efficacy. However, available studies suggest that SCIT is more effective in the short-term than SLIT. Strength of recommendation:\_\_\_\_\_

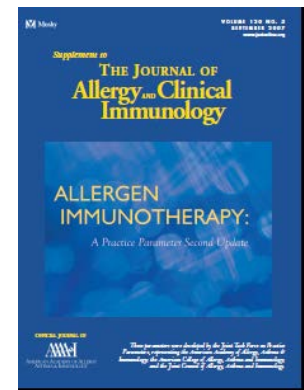
# Determinants of AIT Efficacy and Reasons For Lack of Efficacy

**SCIT efficacy** (and lack of) depends on several factors:

- **Quality of allergen extract** (mold/fungi)
- **Missing allergen:** some aeroallergens not available
- **Continued high exposure to allergens** due to:
  - home environment, occupational or other exposures
- Continued exposure to **nonallergen triggers** (e.g, tobacco smoke)
- **Duration of immunotherapy**
  - Optimal duration not defined but some suggestion 5 years > 3 years
- **Allergen dose:** range in multiple studies/allergens 5 to 20 mcg of major allergen

**SLIT efficacy** probable depends on all of the above but a consistent relationship with dose and efficacy has not been established

# Probable Effective Dose Table for SCIT



**TABLE IX.** Probable effective dose range for standardized and nonstandardized US- licensed allergen extracts

| Allergenic extract                                      | Labeled potency or concentration       | Probable effective dose range        | Range of estimated major allergen content in US-licensed extracts   |
|---|--|--------------------------------------|---|
| Dust mites: <i>D farinae</i> and <i>D pteronyssinus</i> | 3,000, 5,000, 10,000, and 30,000 AU/mL | 500-2,000 AU                         | 10,000 AU/mL<br>20-160 µg/mL Der p 1, Der f 1*<br>2-180 µg/mL Der p 2, Der f 2*<br>78-206 µg/mL Der p 1, Der f 1†<br>13-147 µg/mL Der p 2, Der f 2† |
| Cat hair  | 5,000 and 10,000 BAU/mL                | 1,000-4,000 BAU                      | 10,000 BAU/mL<br>20-50 µg/mL Fel d 1*†<br>30-100 µg/mL cat albumin§   |
| Cat pelt  | 5,000-10,000 BAU/mL                    | 1,000-4,000 BAU                      | 10,000 BAU/mL<br>20-50 µg/mL Fel d 1*†<br>400-2,000 µg/mL cat albumin§  |
| Grass, standardized                                     | 100,000 BAU/mL                         | 1,000-4,000 BAU                      | 100,000 BAU/mL<br>425-1,100 µg/mL Phl p 5*<br>506-2,346 µg/mL group 1   |
| Bermuda   | 10,000 BAU/mL                          | 300-1,500 BAU                        | 10,000 BAU/mL<br>141-422 Cyn d 1 µg/mL*   |
| Short ragweed   | 1:10, 1:20 wt/vol, 100,000 AU/mL       | 6-12 µg of Amb a 1 or 1,000-4,000 AU | 1:10 wt/vol<br>300 µg/mL Amb a 1†<br>Concentration of Amb a 1 is on the label of wt/vol extracts  |



# Dose-response study that is basis for SCIT dosing recommendation

DBPC study of 74 asthmatics treated with HDM SCIT for 24 months  
Monitored medication, PEFr & bronchial challenge in response to 3 doses of *D. pteronyssinus*:

- **0.7 mcg, 7.0 mcg and 21 mcg of Der p 1**
- Combination of SR rate and Bronchial Challenge determined optimal dose

| Maintenance dose  | Bronchial challenge | Systemic reactions % of injections* |
|-------------------|---------------------|-------------------------------------|
| Control (placebo) | p=0.6               | 0                                   |
| 0.7 mcg           | p=.003              | 0.56%                               |
| 7.0 mcg           | p=.0005             | 3.3%                                |
| 21.0 mcg          | p=.0007             | 7.1%                                |

\*systemic reaction defined as a fall of 15% in FEV<sub>1</sub>.

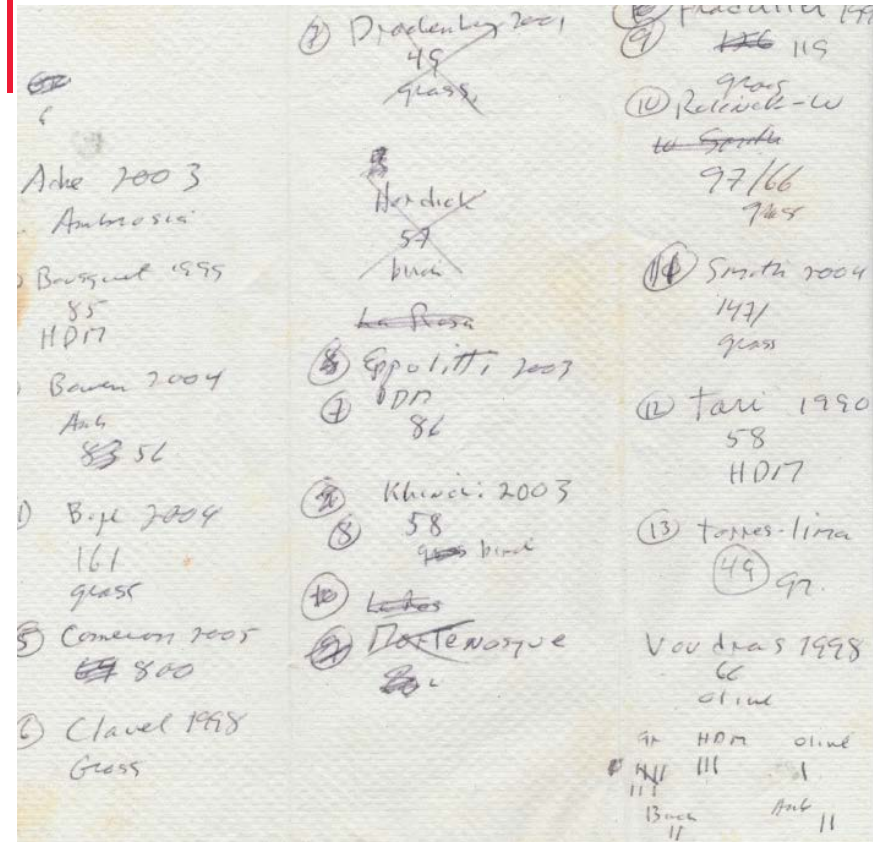
## Sublingual immunotherapy: A comprehensive review\*

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First draft: Aspen, Colorado  
July 2005

## Paper Towel Hal Nelson's SLIT Review Outline



- Individual dose, frequency of dosing & efficacy found over a very wide range of allergen doses
- A consistent relationship between allergen dose, treatment duration and clinical efficacy has not been established.

Hurricane WILMA is moving northeast at 25mph with max sustained winds of 110mph and gust of 145mph.  
Tropical Depression ALPHA moving north at 23mph with max sustained winds of 35mph and gust of 52mph.

Credit: NOAA

GOES-12 RGB-CH(1.4) 10/24/2005 12:45 UTC

# Sublingual Immunotherapy

## *Tracking The Progress To The US*

April 2, 2014: FDA approves first sublingual allergen extract Greer/Stallergene's ORALAIR®

Apr 14, 2014 - FDA Approves Merck's GRASTEK®

Apr 18, 2014 - - FDA Approves Merck's RAGWITEK®

SLIT



Sublingual immunotherapy (SLIT) under the tongue

## *Are We In The Eye Of The Storm?*



# SCIT and SLIT Efficacy and Dose

- Effective dosing range between 5 and 375 times SCIT Equivalent monthly dose
- SCIT narrow effective dosing range- 5-25 mcg of major allergen per injection for many allergens
- In contrast, SLIT effective dose may vary by extract and formulation
- *SLIT PP questions being considered: Does the effective dose vary with extract formulation? Is multiallergen SLIT effective?*
- 

| Allergen  | Tablet                           | Extract Solution   |
|-----------|----------------------------------|--|
| Grass     | 15-25 mcg Phl p 5                | ?? 10- 40 mcg  |
| Dust mite | Mixed Der p 1/Der f 1<br>148 mcg | <i>D farinae</i> 2800 AU ( 20 mcg) or<br>4200 AU (70 mcg ) |
| Ragweed   | 12 mcg                           | ~50 mcg Amb a  |

# Grass-pollen tablets

- Two grass-pollen tablets studied in 1000's of patients in multiple, multi-center trials. Five published studies conducted in U.S.
  - Grastek® (EU-registered as Grazax® 2006) Timothy ~15 mcg Phl p 5
  - Oralair® (EU-registered 2008, US) 5-grass pollen ~25 mcg Phl p 5

| Author (refs) | Number          | Preparation                           | Duration                           | Primary outcome               | Systemic TRAE                   |
|---------------|-----------------|---------------------------------------|------------------------------------|-------------------------------|---------------------------------|
| Nelson 2011   | 439 18–65 years | Timothy 15 µg Phl p 5, 2800 BAU daily | 4-month preseasonal and coseasonal | TCS entire GPS 20%, $P=0.005$ | 1 grade 1 anaphylactic reaction |
| Blaiss 2011   | 345 5–17 years  | Same                                  | Same                               | Same 26% $P=0.001$            | Urticaria 3<br>Asthma 1         |
| Maloney 2013  | 1501 5–65 years | Same                                  | Same                               | Same 23% $P<0.001$            | 2 moderate                      |
| Cox 2012      | 453 18–65 years | 5-grass 25 µg group 5 daily           | Same                               | Same 28.2% $P=0.0003$         | No anaphylaxis                  |

\*Adapted from Nelson HS. Sublingual immunotherapy: the U.S. experience. Curr Opin Allergy Clin Immunol. 2013;13

# SLIT Grass Extract U.S Licensed extracts

No dose-response study but studies examining other questions suggest efficacy at a dose of 2800 BAU daily

- **Multiallergen:** Timothy alone vs timothy and 9 other allergens. 19 mcg Phl p 5 q day or 2800 BAU effective per multiple 'relevant outcomes'.<sup>1</sup>
- **Dual SLIT:** Compared efficacy of dust mite + grass. 2800 BAU effective per immunological, nasal provocation, titrated SPT<sup>2</sup>
- Estimated costs of timothy-pollen extract 2800 BAU daily<sup>3</sup>
  - 100,000 BAU/ml , 50 mL vial = \$428
  - 2800 BAU daily =~ \$7.33 permonth

1. Amar et al, , J Allergy Clin Immunol. 2009;124(1):150-6 e1-5.
2. Swamy et al, 2. J Allergy Clin Immunol. 2012;130(1):215-24 e7.
3. Cox L.. Allergy Asthma Proc. 2014;35(1):34-42.



# Ragweed in U.S. Clinical Trails



Estimated costs of extract: if 50 mcg Amb a 1 effective dose; 1:20 w/v = ~150 mcg Amb a 1/ml , \$6.6/ml ~10 ml month= ~\$66

| Study         | Patient         | Treatment initiation           | Dose/ formulation                                    | Outcome                                       | Systemic AE   |
|---------------|-----------------|--------------------------------|--|---|---|
| Nolte 2013    | 565 Adults: ARC | 4 months before total 52 weeks | 6 and 12 mcg Amb a 1 tablet                          | CS reduced<br>12 mcg: 26%<br>6 mcg: 21%       | Epinephrine<br>6 mcg SLIT- ER visit<br>"severe pharyngeal edema" day 22         |
| Skoner 2010   | 115 Adults: ARC | 8-10 weeks before              | 4.8 and 48 mcg of Amb a 1 extract solution           | 15% reduced Symptoms in both groups (p> 0.10) | No asthma related AE<br>One each: eye swelling, skin rash, and GI symptoms      |
| Creticos 2013 | 429 Adults      | At least 8 weeks before        | Maximum tolerated dose up to 50 mcg extract solution | CS reduced 43% compared with baseline         | " no patient experienced anaphylaxis or required administration of epinephrine" |

Adapted from Cox L. Sublingual immunotherapy for aeroallergens: Status in the United States. Allergy Asthma Proc. 2014;35(1):34-42.

# SLIT Practice Parameter Draft

***Question: Is multiallergen SLIT effective?***

**Summary statement xx**

Almost all studies of sublingual immunotherapy have employed administration of a single allergen extract. A few studies have reported efficacy administering two unrelated allergen extracts. One study that has examined administration of an extract in a mixture of more than two allergen extracts suggested that there was reduced efficacy in the mixture compared to the same dose administered as monotherapy.



# Kaiser Clinical Question: Can we give two SLIT antigens?



- **Is monoallergen SLIT effective in polysensitized patients?**
  - Several monoallergen SLIT studies have demonstrated efficacy in polysensitized patients (dust mite and grass)<sup>2</sup>
- **Is multiallergen SLIT effective?**
  - **Dual allergen SLIT:** (2) efficacy when administered separately (dust mite & grass, birch & grass)
  - **Multiallergen SLIT** (timothy vs. timothy + 9 allergens) suggest clinical efficacy may be reduced with addition of multiple allergens

# Efficacy of SLIT with a Single Extract or as part of a Multi-Allergen-Extract Mixture in Patients with Grass SAR

| MAT Group, Allergen Extract | Amount |
|-----------------------------|--------|
| Timothy                     | 1.0 mL |
| Maple, Box-Elder            | 1.0 mL |
| Ash, White                  | 1.0 mL |
| Juniper, Western            | 1.0 mL |
| Elm, American               | 1.0 mL |
| Cottonwood, Common          | 1.0 mL |
| Firebush (Kochia)           | 1.0 mL |
| Ragweed, Western            | 1.0 mL |
| Sagebrush, Common           | 1.0 mL |
| Russian Thistle             | 1.0 mL |

| TM Group, Allergen Extract | Amount |
|----------------------------|--------|
| Timothy                    | 1.0 mL |
| Diluent                    | 9.0 mL |
| Caramelized Sugar          |        |

| Placebo Group     | Amount |
|-------------------|--------|
| Diluent           | 10 mL  |
| Caramelized Sugar |        |

- 54 randomized patients treated for 10 months
- CMD : Timothy ~ 30 x SCIT dose (19 mcg Phl p 5 qday), others 15-20x
- SCIT dose: 0.25-0.28 ml q am, held under tongue for 2 minutes, then swallowed

## Efficacy of SLIT with a Single Extract or as Part of a Multi-Allergen-Extract Mixture

- No significant difference in the symptom or medication scores in either treatment groups compared with placebo
  - Perhaps due to very low grass pollen season 2008
- Timothy alone: significant improvement in tSPT, NC, sIgG<sub>4</sub>, and decreased IFN- $\gamma$  levels compared to placebo
- Multiallergen: significant improvement in tSPT compared to placebo, but less than with TM
- Timothy alone arm demonstrated efficacy with 19 mcg Phl p 5 daily

**Clinical implications: The clinical efficacy of SLIT may be reduced with the addition of multiple allergens, potentially limiting its use in polysensitized individuals.**

# SLIT DOSING REGIMENS AND TREATMENT BE INITIATED

*Daily? QOD? Once a week? Before season? At start of season? Updosing or no updosing?*

*Once starting continuous or discontinuous treatment?*



When

Where  
do I **START?**



# SLIT Maintenance Dosing Schedule



- Optimal maintenance dosing frequency of SLIT has not been established
- Dosing regimens in published studies and extract manufacturers PI vary from daily to once week
- Very few studies have compared dosing frequency
- Daily dosing is the most frequently used in recent studies-better adherence is cited rationale
- Treatment costs will be linked with dosing regimen



# SLIT Allergen Extract Solution Considerations When Prescribing



- Limitations related to sublingual absorptive capacity
  - Can all allergens be sufficiently absorbed? e.g., cockroach?
  - How much can be absorbed in the 2 minutes?
  - Mixtures may result in inconsistent and incomplete of the different allergens
- Extract storage conditions will be dependent on patient
- Higher dose requirement may make multiallergen cost prohibitive



# SCIT AND SLIT



**SAFETY: ADVERSE EFFECTS & RISK FACTORS  
AND CLINICAL PRACTICE TO MINIMIZE BOTH**

# Local SCIT reactions



- Erythema, pruritus and swelling at the injection site
- Very common: ranging from 26% to 82% of patients and 0.7% to 16% of injections.<sup>1</sup>
- 92% of A/I adjust for LR in concern for LR/SR or pt will discontinue<sup>2</sup>

Table 1 Local reaction size definitions

---

|   |
|---|
| •“A” reaction: induration 15-20 mm  |
| •“B” reaction: induration 20-25 mm  |
| •“C” reaction: induration >25 mm or 12 h [2]  |
| •Small local reaction <40 mm and large local reaction ≥40 mm [1]  |
| •>20 mm and >24 h are significant [1]   |
| •Early local reaction ≤30 min and late local reaction >30 min [3]   |
| •Local reaction ≥40 mm [4]  |
| •Small local reaction <20 mm and large local reaction ≥20 mm [5]  |
| •Local reaction no larger than the size of the palm of the patient’s hand and large local reaction larger than the size of the patient’s palm (8-10 cm) [6] |

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Table 2 Historical local reaction grading and recommended dose adjustments

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|   |
|---|
| •“A” reaction: induration 15-20 mm; repeat dose                       |
| •“B” reaction: induration 20-25 mm; return to dose without a reaction |
| •“C” reaction: induration >25 mm or 12 h; reduce dose 50%             |

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# SCIT Local reactions '*pearls/myths*'

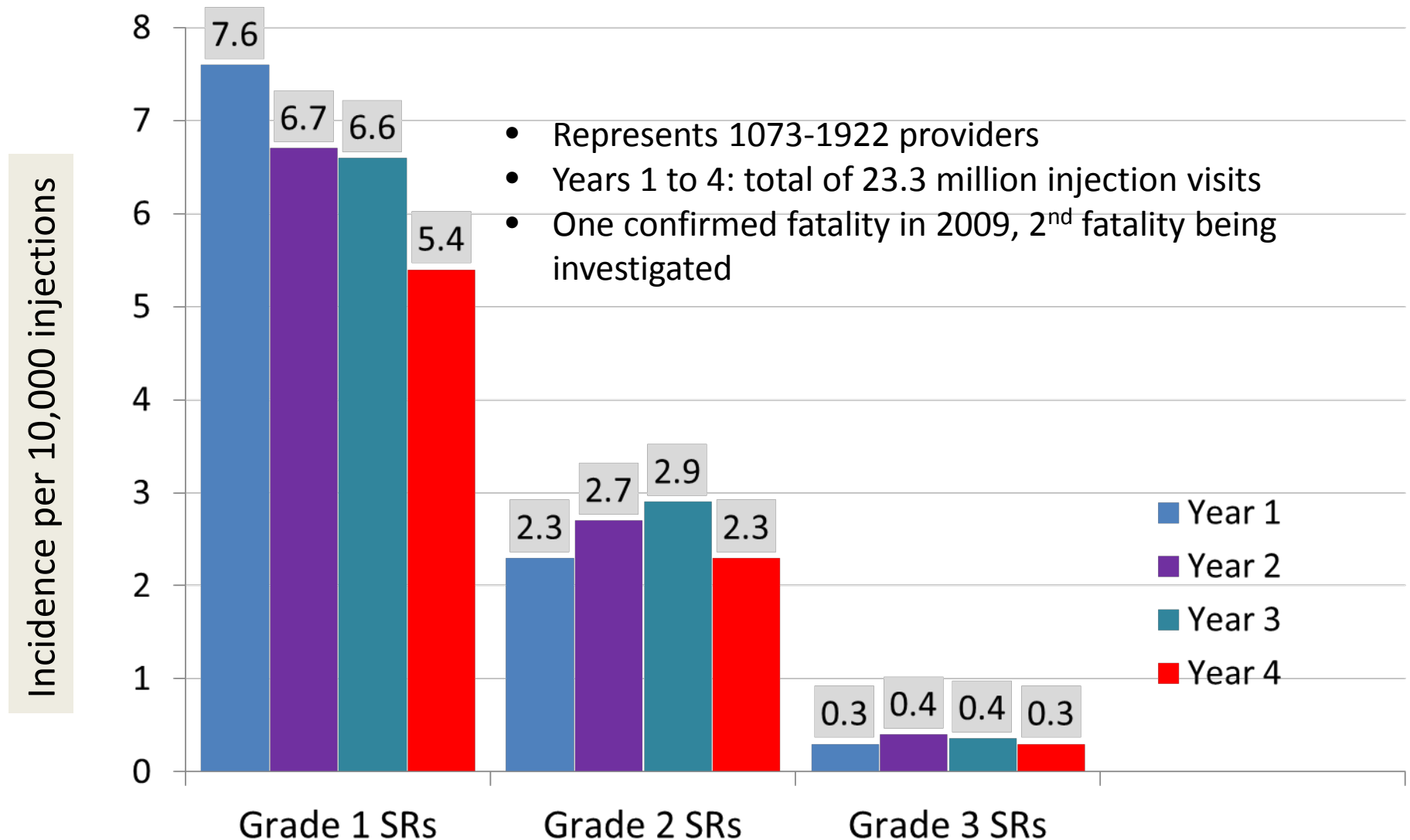


- Small or large LR rate defined as  $\leq$  or  $>$  palm of hand) .<sup>1</sup>
  - Not related to glycerin content but
  - Small LR rate higher with increasing allergen content.
- LLR found not to be predictive of local or systemic reactions with subsequent injections <sup>2-4</sup>
- Survey of 249 SCIT patients-those who experienced LR<sup>5</sup>
  - 81.9% deemed LR not to be bothersome.
  - 96.0% stated they would not stop SCIT because of these LR

1. Calabria et al., J Allergy Clin Immunol. 2008;121:222-6. 2. Calabria et al., J Allergy Clin Immunol. 2009;124:739-44. 3. Tankersley et al, J Allergy Clin Immunol. 2000;106(5):840-3. 4. Kelso Ann Allergy Asthma Immunol. 2004;92(2):225-7. 5. Coop et al, Ann Allergy Asthma Immunol. 2008;101(1):96-100

# Prospective annual electronic survey AAAAI/ACAAI AIT

## Overall 0.1% of injection visits



## Anaphylaxis vs. Systemic Reaction



- Unlike the multidisciplinary group's criteria for defining anaphylaxis, a symptom/sign representing a single organ system would be considered an SR in this grading system, as included in the epinephrine statement by the WAO

# WAO Subcutaneous Immunotherapy Systemic Reaction Grading Systems

- **5 Grades:** based on organ system involved and severity.
- Organ systems are defined as:
  - Cutaneous, conjunctival, upper respiratory,
  - Lower respiratory, gastrointestinal, cardiovascular and other.
- **Grade 1:** single organ system such as cutaneous, conjunctival, upper respiratory, **but not** asthma, gastrointestinal or cardiovascular
- **Grade 2 & 3.** Symptoms from >1 organ system or asthma, gastrointestinal, cardiovascular
- **Grade 4:** Respiratory failure, hypotension  $\pm$  loss of consciousness
- **The Grade is determined by the physician's clinical judgment after the event is over.**

Endorsed by AAAAI, ACAAI, the Latin American Society of Allergy and Immunology, the Asia Pacific Association of Allergy, Asthma and Clinical Immunology,

# Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

**TABLE I.** World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)

| Grade 1  | Grade 2  | Grade 3  | Grade 4   | Grade 5      |
|--|--|--|---|--------------|
| <p><i>Symptom(s)/sign(s) of 1 organ system present*</i></p> <p><u>Cutaneous</u><br/>Generalized pruritus, urticaria, flushing, or sensation of heat or warmth†<br/>or<br/>Angioedema (not laryngeal, tongue or uvular)<br/>or<br/><u>Upper respiratory</u><br/>Rhinitis - (eg, sneezing, rhinorrhea, nasal pruritus and/or nasal congestion)<br/>or<br/>Throat-clearing (itchy throat)<br/>or<br/>Cough perceived to originate in the upper airway, not the lung, larynx, or trachea<br/>or<br/><u>Conjunctival</u><br/>Erythema, pruritus or tearing<br/><u>Other</u><br/>Nausea, metallic taste, or headache</p> | <p><i>Symptom(s)/sign(s) of more than 1 organ system present</i></p> <p>or</p> <p><u>Lower respiratory</u><br/>Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV<sub>1</sub> drop, responding to an inhaled bronchodilator)<br/>or<br/><u>Gastrointestinal</u><br/>Abdominal cramps, vomiting, or diarrhea<br/>or<br/><u>Other</u><br/>Uterine cramps</p> | <p><u>Lower respiratory</u><br/>Asthma (eg, 40% PEF or FEV<sub>1</sub> drop<br/>NOT responding to an inhaled bronchodilator)<br/>or<br/><u>Upper respiratory</u><br/>Laryngeal, uvula, or tongue edema with or without stridor</p> | <p><u>Lower or upper respiratory</u><br/>Respiratory failure with or without loss of consciousness<br/>or<br/><u>Cardiovascular</u><br/>Hypotension with or without loss of consciousness</p> | <p>Death</p> |

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

# SCIT Safety Summary

- **SCIT:**
  - Local reactions very common; not a common reason for discontinuation
  - Incidence of SRs dependent on multiple factors at a rate
    - ~0.1- 0.2% of injections and 2-5% of patients
  - Delayed & biphasic 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, none confirmed from 2008 to 2012 survey

# SLIT Practice Parameter Draft

## Summary statement 9:



- The majority of SLIT adverse events are local reactions (oral, pharyngeal, or abdominal). Most local reactions occur during the first week of therap. They usually disappear within a few days to weeks without treatment or dosing modification. However, some local reactions can be severe and/or bothersome enough to discontinue treatment. SLIT systemic allergic reactions are very uncommon..

Recommendation strength strong Evidence A

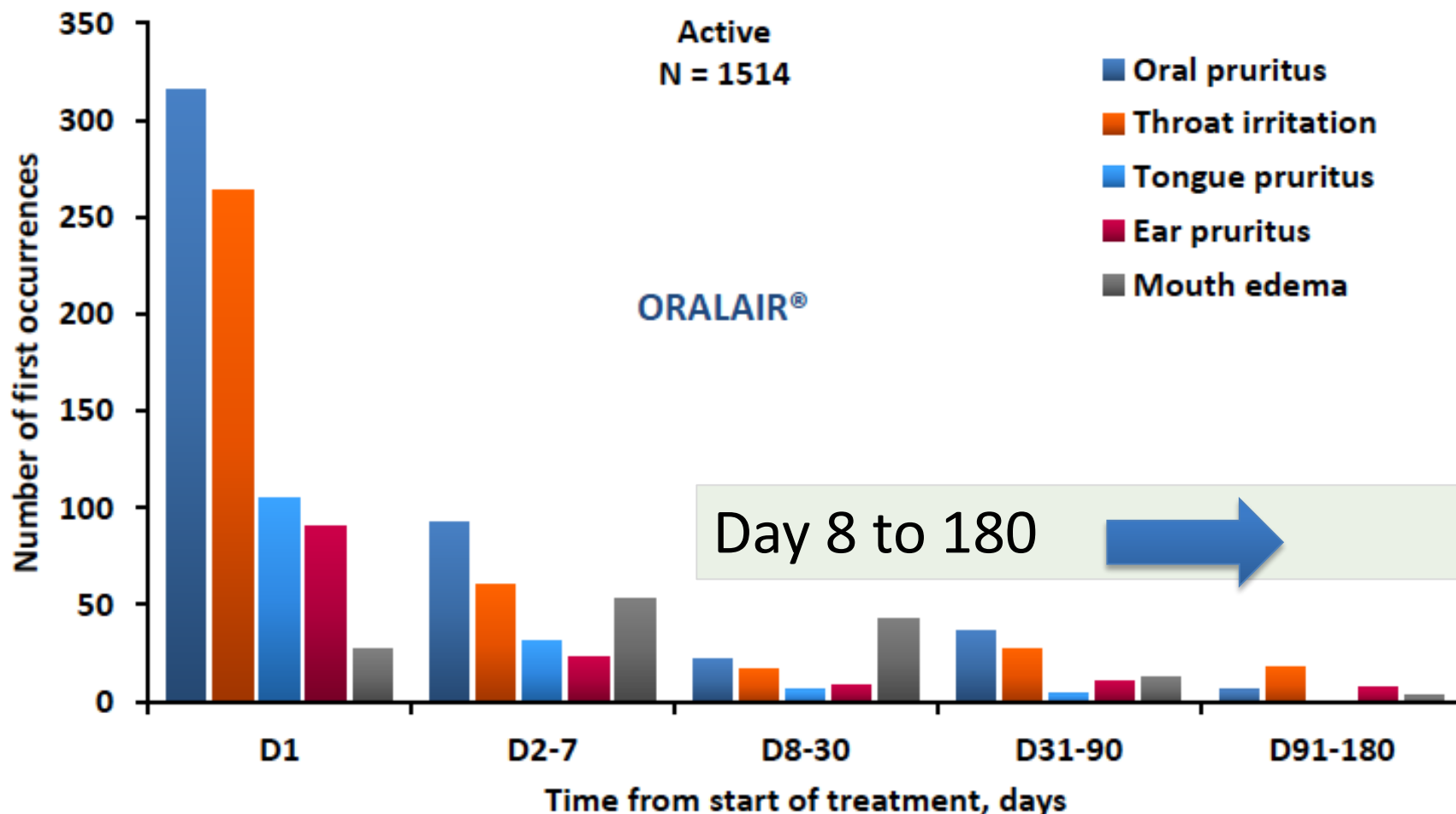
- Effect of AH premedication not known
- Few reported cases of anaphylaxis (at least 11)
- No relationship with pattern with up dosing schedule
- No clear risk factors: a few prior SCIT SR\* one after eating dry food \*\*
- Two case reports of EoE with pollen SLIT

\* Calderon et al,,Allergy. 2012 Mar;67(3):302-11.

\*\*Van Dyken et al, Clinical case of anaphylaxis with sublingual immunotherapy: house dust mite allergen. *JACI: In Practice*, 2(4): 485-486.

# Randomized Controlled Trials Safety :

Time to Onset of TEAEs – Active Treatment, All Doses





## Grading System for SLIT Local Reactions

A similar grading system is also necessary for the local side effects of SLIT because they most commonly occur in clinical practice and their severity, persistence, or both can result in discontinuation of SLIT.

There are no objective parameters, such as changes in FEV1 or blood pressure, to quantify the severity of the local AE; therefore a certain degree of subjectivity is unavoidable in grading these reactions.

In general, the severity of local side effects depends on the signs and symptoms and their duration

Local reactions leading to discontinuation included in criteria

# Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language

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

| Symptom/sign<br>(see Table I)   | Grade 1: Mild  | Grade 2: Moderate  | Grade 3: Severe  | Unknown severity  |
|---|--|--|--|---|
| Pruritus/swelling of mouth, tongue, or lip; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema | <ul style="list-style-type: none"> <li>• Not troublesome AND</li> <li>• No symptomatic treatment required AND</li> <li>• No discontinuation of SLIT because of local side effects</li> </ul> | <ul style="list-style-type: none"> <li>• Troublesome OR</li> <li>• Requires symptomatic treatment AND</li> <li>• No discontinuation of SLIT because of local side effects</li> </ul> | <ul style="list-style-type: none"> <li>• Grade 2 AND</li> <li>• SLIT discontinued because of local side effects</li> </ul> | Treatment is discontinued, but there is no subjective, objective, or both description of severity from the patient/physician. |

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

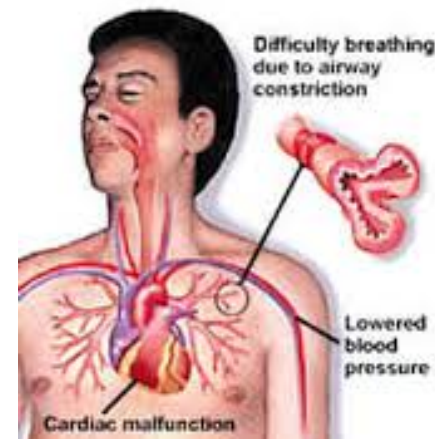
\*See Table I for the MedDRA code that applies to exactly report and describe the AE.

**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

# GI Symptoms Associated with SLIT

- Lower gastrointestinal tract symptoms associated with SLIT are generally are generally classified as local reactions
- But if GI symptoms occur with other systemic manifestations would be considered a system reaction and would be classified per the WAO SR Grading System
- US tablet PI PI recommends treatment discontinuation in patients experience severe or persistent gastro-esophageal symptoms



## US Licensed SLIT Tablet PI Warnings

\_\_\_\_\_ is contraindicated in patients with:

- ☐ Severe, unstable or uncontrolled asthma
- ☐ A history of any severe systemic allergic reaction
- ☐ A history of any severe local reaction after taking any sublingual allergen immunotherapy
- ☐ A history of eosinophilic esophagitis
- ☐ Hypersensitivity to any of the inactive ingredients [gelatin, mannitol and sodium hydroxide] contained in this product [*See Description (11)*].

April 02, 2014

[FDA Approvals > Medscape Medical News](#)

FDA Oks First US Sublingual Allergy Immunotherapy

*So where are the practice parameter guidelines to provide guidance to US practitioners???*



## Immunotherapy for Inhalant Allergens: Current and Emerging Treatments CME

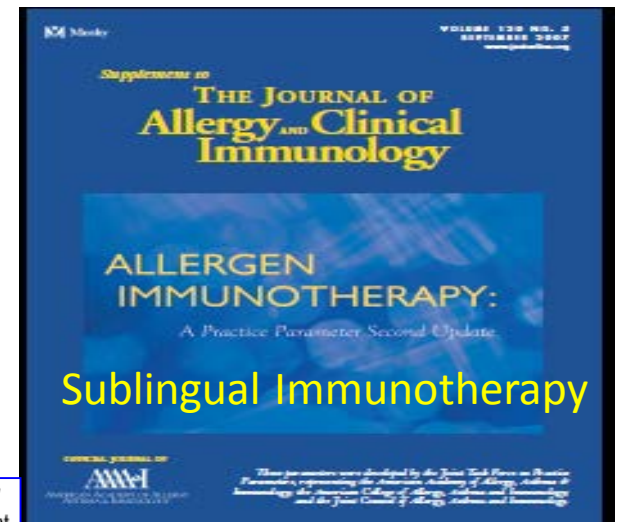
Linda S. Cox, MD; Harold S. Nelson, MD Faculty and Disclosures

CME Released: 07/19/2013; Valid for credit through 07/19/2014

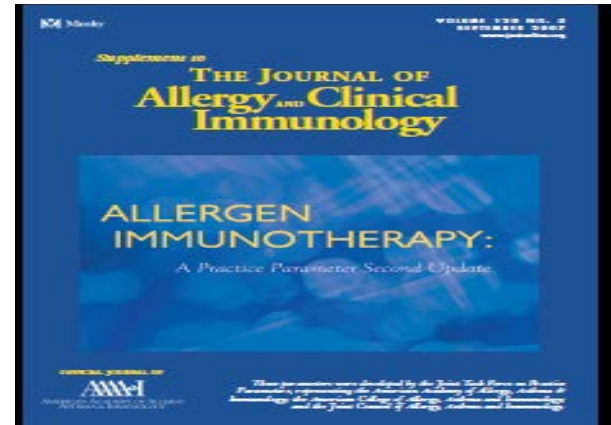
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# SCIT Relative Contraindications



**Summary Statement 18:** Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications for allergen immunotherapy. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease. C

# SLIT Practice Parameter Draft

## **SLIT contraindications, warnings and age limitations**

- Summary statement 10: Medical conditions that reduce the patient's ability to survive a systemic allergic reaction (SR) or the resultant treatment are relative contraindications for SCIT. Although, associated with a lower risk of systemic allergic reactions, such medical conditions are also considered relative contraindications for SLIT. Factors that may increase the incidence or severity of adverse reactions are noted in the product prescribing information of the three SLIT tablets available for use in the United States. The contraindications listed in the FDA-approved SLIT tablets include, patients who currently have severe, unstable or uncontrolled asthma, any history of a severe systemic allergic reaction; a history of any severe local reaction to sublingual allergen immunotherapy; or hypersensitivity to any of the inactive ingredients of the preparation. None of these listed contradictions are based on direct evidence but rather are derived from known SCIT risk factors or the exclusion criteria of the clinical trial. Strength of recommendation ?

# Fish-derived Gelatin

## Product

**Name:** bovine  
kosher gelatin



fish gelatin

- Gelatin is derived from a skin of cold-water fish source such as cod, pollock, or haddock. Gelatin constitutes a fraction of the 28 mg tablet weight. In one study, commercial, food-grade fish gelatin derived from the skins of codfish was evaluated in a double-blind, placebo-controlled food challenge.
- None of the 30 fish-allergic patients reacted adversely to the ingestion of cumulative dose of 3.61 g fish gelatin. Investigators concluded with a 95% certainty that 90% of fish-allergic consumers will not react to ingestion of a 3.61 g cumulative dose of fish gelatin.



# Epinephrine Autoinjectors and SLIT

## FULL PRESCRIBING INFORMATION

### WARNING: SEVERE ALLERGIC REACTIONS

- **GRASTEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)**
- **Do not administer GRASTEK to patients with severe, unstable or uncontrolled asthma. (4)**
- **Observe patients in the office for at least 30 minutes following the initial dose. (5.1)**
- **Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)**
- **GRASTEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)**
- **GRASTEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)**

<http://www.fda.gov/downloads/BiologicsBloodVaccines/Allergenics/UCM393184.pdf>

*No established patient guidelines for for EAI use in response to SLIT AE because this is not a routine or recommended practice outside of US*

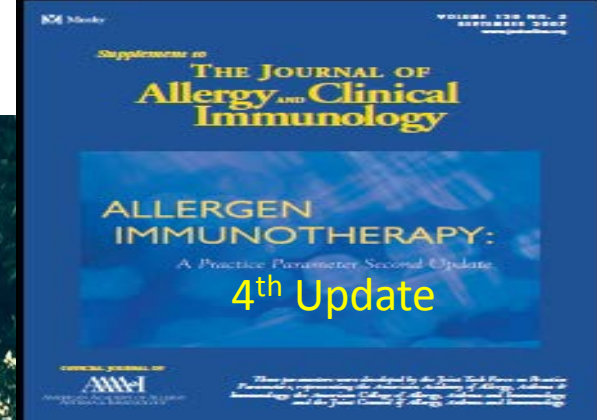
Have you seen the warning  
on the newly approve SLIT  
tablet?  
...epinephrines  
autoinjectors

>

Quite crazy in some points. Who  
prepared such a warning,  
> and on which scientific basis?  
> WOW!!! this is risky!!!  
Gianni

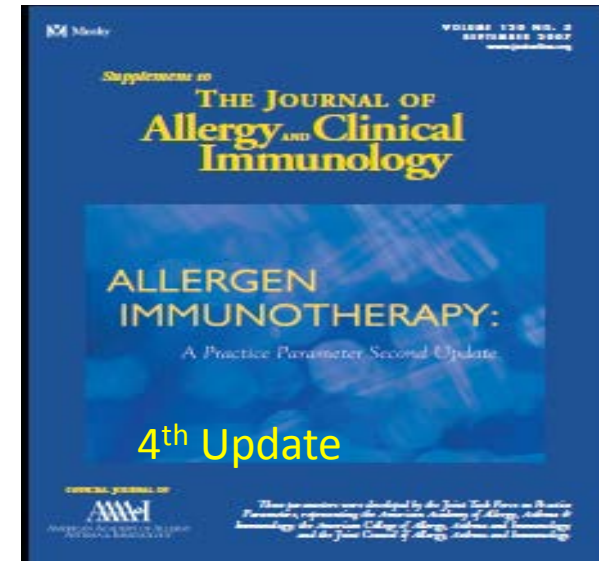


# AAAAI/EAACI Practall on Sublingual Immunotherapy Washington DC September 19, 2014 to be published in JACI 2015



# SLIT Practice Parameters safety questions to consider

- **Can premedication prevent local reactions?**
- **Risk of eosinophilic esophagitis?-PI warning**
- **Patient safety instructions**
  - What do for interruption of dosing
  - When to contact physician
  - What do you instruct pts to do after gap: Practall- 7 days then contact office, PP likely mention the PI recommendation
  - What time of day should take SLIT-again PP likely to cite PI
- **Provision or not of an epinephrine auto-injector**
  - What instructions should be given to patients regarding when to administer
  - Medications to be avoided in US listed in package insert.





# AAAAI IT/AS/ADT Committee SLIT Forms

Approved and scheduled to be posted on  
[www.aaaai.org](http://www.aaaai.org) in Jan 2015

- Patient instruction and information forms
- When to withhold SLIT
- How long to keep the tablet under tongue
- What not to do before administration
- Patient instructions for epinephrine autoinjector use with a SLIT reaction (this would be their “SLIT reaction action plan” or “SLAP” (sublingual action plan))

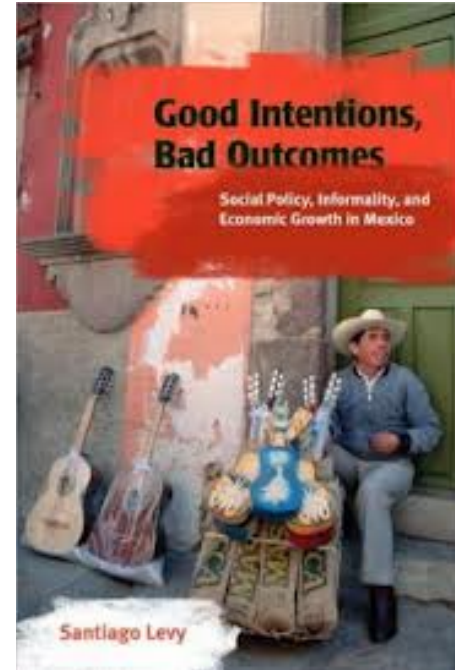
# FDA-Approved SLIT Tablet PI

Common  
to all  
three  
products

- Administer the first dose ... in a healthcare setting in which acute allergic reactions can be treated under the supervision of a physician with experience in the diagnosis and treatment of severe allergic reactions. After receiving the first dose of ORALAIR, observe the patient for at least 30 minutes ...
- Administer to children under adult supervision.
- Remove the tablet from the blister just prior to dosing.
- Place the tablet immediately under the tongue until complete dissolution for at least 1 minute before swallowing.
- Wash hands after handling the tablet.
- Do not take the tablet with food or beverage. To avoid swallowing allergen extract, food or beverage should not be taken for 5 minutes following dissolution of the tablet.

# SLIT Dosing Regimens Practical Consideration

## Adherence and Costs



- Both SLIT and SCIT require multiple year treatment courses and are associated with *very poor* adherence
- SLIT cost-efficacy: studies comparing vs. standard drug treatment with SLIT most show cost-efficacy per a calculated measure, e.g. QALY
- Extracts cost consideration may be a significant factor in deciding on continuous vs. pre-coseasonal or muliallergen treatment

# A systematic review and economic evaluation of SCIT and SLIT in adults and children with SAR

## Conclusions

- Based on a substantial number of RCTs, both SCIT and SLIT have been consistently shown to be significantly more effective than ST only.....
- It is uncertain to what extent this statistical significance translates to clinically significant differences across the different types of outcome measures used.
- An indirect comparison is suggestive of SCIT being more beneficial than SLIT based on SSs and MSs, but no such difference could be shown for combined SMSs or QoL, and firm conclusions cannot be drawn.
- **CEAs suggest that both SCIT and SLIT may become cost-effective per QALY from around 6 years.** However, these estimates were based on limited data and the use of a number of assumptions. Potential cost savings resulting from future cases of asthma avoided were not included in the analysis, but would likely lead to an increase in cost-effectiveness.



# National Institute for Health Research Health Technology Assessment

## Systematic Review: Economic Evaluation of SCIT In SAR

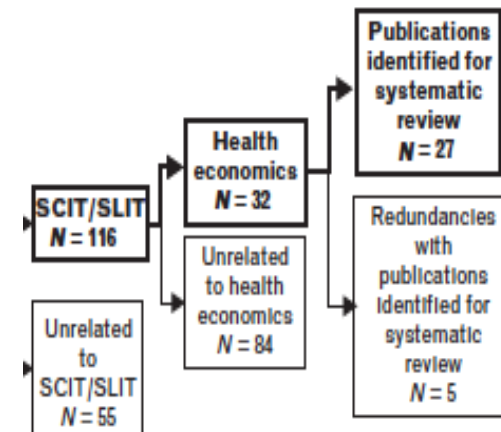
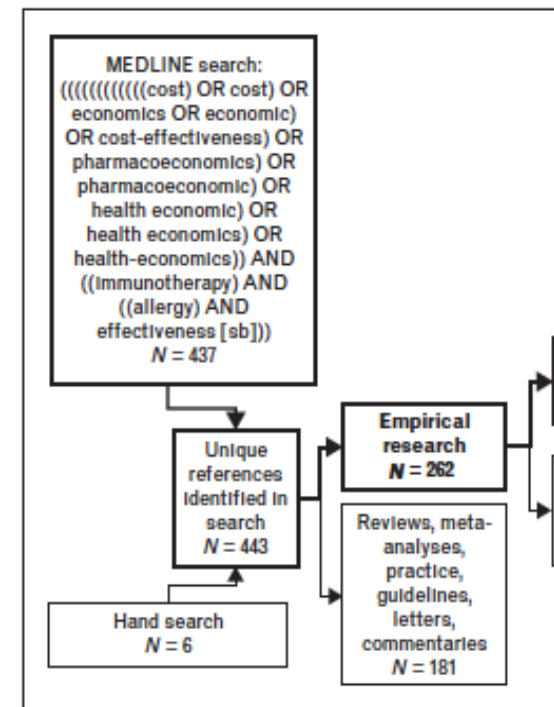
Standard methods for study selection, data extraction and quality assessment of DBPC trials of SCIT or SLIT, SCIT compared with SLIT identified 14 Economic Evaluations studies:

- Based on a substantial number of RCTs, both SCIT and SLIT have been consistently shown to be significantly more effective than STD only
- SCIT and SLIT may be cost-effective compared with SDT from around 6 years at a threshold of £20,000–30,000 per QALY
- Limited evidence indicated SCIT may more beneficial and less costly than SCIT
- Potential cost savings resulting from future cases of asthma avoided were not included but would likely lead to an increase in cost-effectiveness.
- Authors noted the challenges in comparing results across studies utilizing different outcome measures and encouraged further research to “establish the comparative effectiveness of SCIT compared with SLIT and to provide more robust cost-effectiveness estimates.”
- All of the studies in this systematic review employed single allergen AIT .

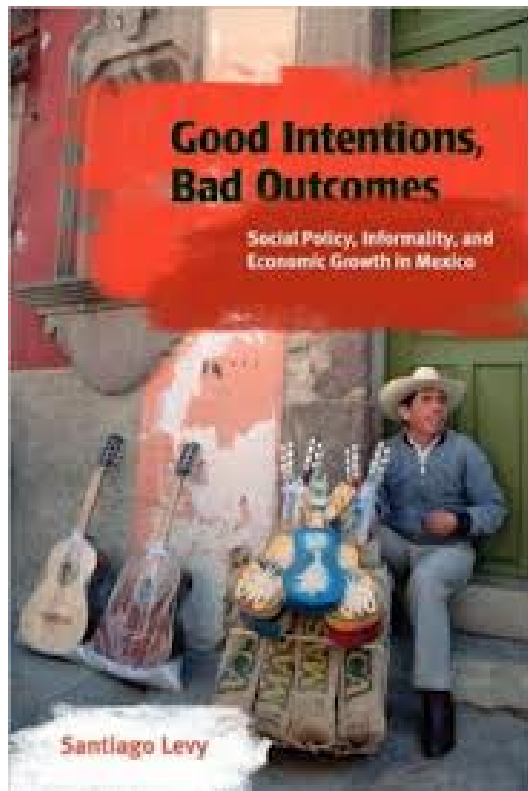
# Allergy immunotherapy: what is the evidence for cost saving?

Cheryl S. Hankin<sup>a</sup> and Linda Cox<sup>b</sup>

- Systematic review of the published studies indexed 3/2014 that reported health economic outcomes associated with AIT
- 23/24 comparative cost studies provided compelling evidence for the cost savings of AIT (SCIT or SLIT) over SDT.
- Of the six studies comparing the cost outcomes of SLIT to SCIT, the preponderance of findings favored SLIT



Hankin CS, Cox L. Allergy immunotherapy: what is the evidence for cost saving? *Curr Opin Allergy Clin Immunol* 2014, **14**(4): 363-370.

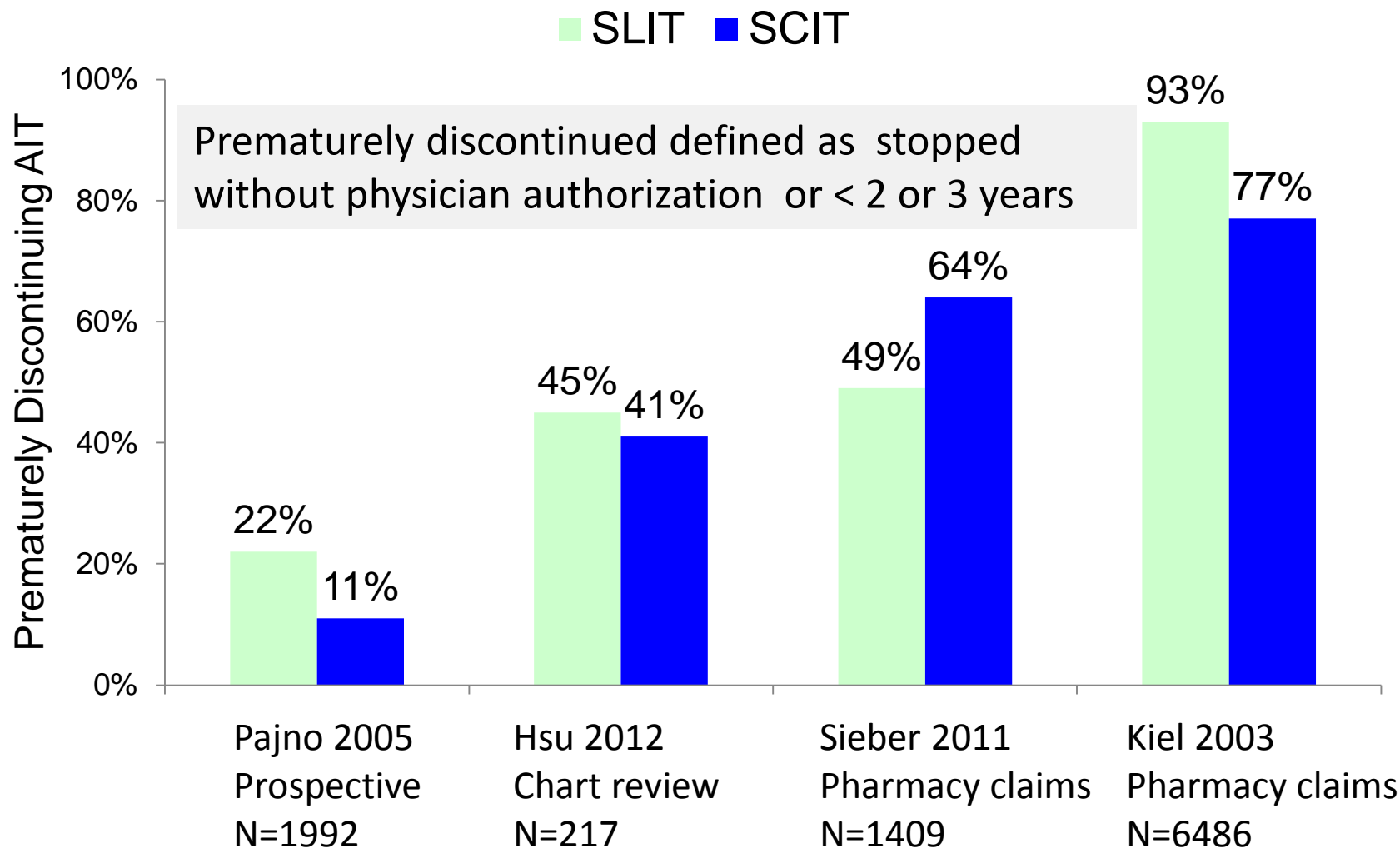


**ALLERGY IMMUNOTHERAPY**  
**ADHERENCE**  
**HOW DO SCIT AND SLIT COMPARE?**  
***QUITE POORLY***

Both SLIT and SCIT require multiple year treatment courses and are associated with *very poor* adherence

# Studies Directly Comparing SLIT and SCIT Adherence

## *Similar poor adherence rates*



Cox L , Hankin C, Lockey R Allergy Immunotherapy Adherence and Delivery Route: Location Doesn't Matter J Allergy Clin: In Practice 2014; March/April 2014 issue: Volume 2, (2).

## SLIT Extract Solution Some Considerations

- Drop standardized in the metric system to equal exactly 0.05 ml
- Official USP-NF medicinal dropper: 20 drops= 1 ml
- Number of drops required to deliver dose will vary
- Requiring multiple drops may affect compliance
  - patient may simple lose track while counting



Now where  
was I in my  
drop count ....  
how drops  
have I taken???



## Communicate and Educate Education can improve SLIT adherence

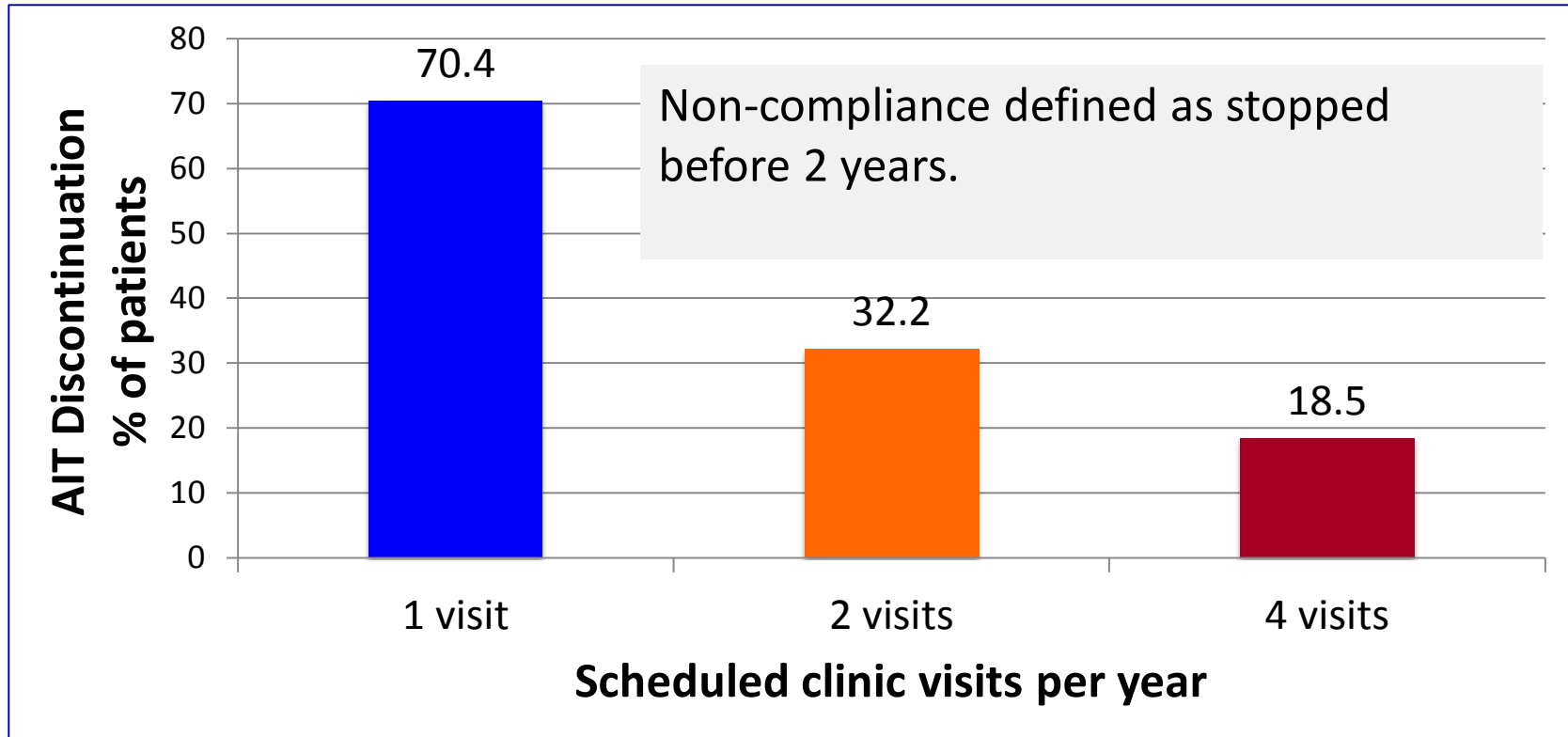


- Education plan with follow-up telephone calls from a nurse or no intervention found lower discontinuation rates with education plan.<sup>1</sup>
  - At one year adherence was 88% compared with 65% in no intervention group .
- 3-hours education program (EP) vs. standard verbal instructions (SV).<sup>2</sup>
  - Average adherence over 6 months: 96% EP vs.77% SV

Savi et al . Allergy. 2013;68(9):1193-5.

Incorvaia et al, Allergy. 2010;65(10):1341-2.

# Significantly Improved SLIT Adherence with More Frequent Clinical Monitoring



**Study:** 300 children 6-16 yrs prescribed SLIT and randomized to 3 scheduled clinic visit follow-up groups: 1, 2 and 4 visits per year (100 each).

# SCIT & SLIT Practical Considerations: initiation, adherence, barriers to care, and unmet needs

- Globally SCIT and SLIT prescribed at near equal frequency to a minority of allergic patients
  - ~2-9 % of US AR population receives SCIT<sup>1</sup>
  - Equally low usage in Europe ~5%
- Many factors likely account for low treatment initiation
  - Provider related: Access to A/I specialist
  - Patient factors:
    - Costs, SLIT extract >SCIT ,
    - Convenience; SCIT= requires more patient time
- SLIT cost-efficacy: studies comparing vs SDT with SLIT most show cost-efficacy per a calculated measure, e.g. QALY
- Both require multiple year treatment courses



1. Hankin et al, Allergy Clin Immunol. 2013;131(4):1084-912.
2. Cox L, Jacobsen L. Ann Allergy Asthma Immunol. 2009;103(6):451-59





# SLIT and SCIT in US



- **SLIT only three FDA approved products for two allergens**
  - **Effective dose** not established for most U.S. licensed extract solutions for SCIT or SLIT
  - **SLIT Costs** may be a significant if treated for multiple allergens
  - **Many treatment regimen questions for**
    - **when to initiate:** beginning of season, or 8 , 12 or 16 weeks before?
    - **schedule:** continuous vs. pre- vs pre-co, coseasonal, daily , QOD, etc, -but daily and pre-coseasonal seem to be most common
- **US PI warnings: epinephrine auto-injectors –no global guidance**
- **Adherence** with with SLIT likely as problematic as SCIT and pharmacotherapy-education, close f/u and education may help
- **More studies are needed:** effective dose & optimal duration/schedule, strategies to improve patient adherence

*Who is the winner? The is should determined by patient preference and physician judgment .*



- **Efficacy:** probably favors SCIT
- **Safety AIT:** favors SLIT but PI warnings challenging in term of patient directions & warnings
- **Economics:** cost of extracts less with SCIT but other factors as such indirect costs may change this balance
- **Adherence :** equally problematic with both routes-need strategies to improve



*SCLIT vs. SCIT: which is 'best' is for the physician and patient to decide*

