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Patient Satisfaction, Knowledge, Expectations and Perceptions on Allergen-Specific Immunotherapy: a survey

Ilaria Baiardini*, Francesca Puggioni°, Stefania Menoni§, Johan Diderik Boot#, Zuzana Diamant^, Fulvio Braido*, Giorgio Walter Canonica*, on behalf of SKEP study group.

* Allergy & Respiratory Diseases Clinic – DIMI - University of Genoa, IRCCS AOU San Martino-IST, Genova, Italy

° IRCCS Istituto Clinico Humanitas, Allergy and Respiratory Disease Department, Milano, Italy

§ University of Genoa, Biostatistic Unit, Department of Health Science, Genoa, Italy

# HAL Allergy BV, Medical Department, Leiden, The Netherlands

^ Skane University Lund, Dept of Respiratory Diseases and Allergology, Lund, Sweden

SKEP study group:

1. Fabio Agostinis, Osp. Riuniti Bergamo Unità Strutturale Complessa di Pediatria, Bergamo, fabioagostinis@yahoo.it;

2. Claudio Bombi, AZ. Osp. Bologna Policlinico S. Orsola Malpighi Dipartimento Cardio – Toraco – Vascolare U.O. Pneumologia Bologna, claudio.bombi@gmail.com;

3. Samuele Burastero – Osp. San Raffaele, Milano, s.burastero@hsr.it

4. Alberto Gasparini – Az. Osp. Melegnano Presidio Ospedaliero Cernusco sul Naviglio (MI), albert.gasparini@libero.it

5. Amhad Kantar – Centro Diagnosi, Cura e riabilitazione ell’Asma Infantile Istituto PIO XII Misurina (BL), kantar@tin.it
   Università A.O. Ospedaliera S. Orsola – Malpighi Bologna, Daniela.zauli@unibo.it

7. Paolo Pigatto – Dipartimento Tecnologie per la Salute -Clinica Dermatologica Università degli
   Studi di Milano Ospedale IRCCS R. Galeazzi – Milano, Paolo.pigatto@unimi.it

8. Marcella Pozzan –Servizio di Allergologia U.L.S.S. 16 Padova, marcella.pozzan@libero.it

9. Andrea Rapetti – Amb. Allergologia Presidio Ospedaliero Tradate (Va), parapetti@aubusto.it

10. Renato Enzo Rossi – Rete Regionale di Allergologia Cuneo, immunoway@libero.it

    (Mi), biagioscibi@libero.it

12. Anna Tosi –Unità Semplice di Allergologia A.O. Ospedale Civile Legnano (Mi),
    allergologialegnano@yahoo.it

**Corresponding Author:**

Zuzana Diamant, MD PhD

Skane University Lund, Dept of Respiratory Diseases and Allergology, Lund, Sweden;
University Medical Centre Groningen, Dept of General Practice, Groningen, The Netherlands

E-mail: z.diamant@gems.demon.nl

**Running title:** Patient evaluation of allergen-specific immunotherapy

**Keywords:** allergen-specific immunotherapy, allergy, perception, questionnaire, QoL, real life survey, satisfaction
INTRODUCTION

Assessing patient’s personal viewpoints on disease activity and treatment provides useful information enabling a customized therapeutic approach (1). The pivotal role of patient’s perspectives is now advocated by the Grade of Recommendations, Assessment, Development and Evaluation (GRADE) system (2), recently adopted by the World Health Organization (WHO), as a guideline for both quality of evidence and strength of recommendations. Along with traditional parameters of safety and efficacy, this system also includes patient’s preferences and values as cornerstones in the development of recommendations for therapeutic interventions, thus enabling the translation of scientific research into real life (2). Several aspects of allergen-specific immunotherapy (SIT) for the treatment of allergic rhinitis have been extensively investigated, including clinical efficacy (3), tolerability (4), effects on health-related quality of life (HRQoL) (4-6) and cost-effectiveness (7). However, besides HRQoL assessment, only few studies addressing patient’s perspective on this treatment modality have been published (8-10). In these studies, the population size was relatively small and the surveys took into account only one administration mode. This precludes a more general applicability of these findings.

The aim of the present multicentre cross-sectional survey was to explore the patients’ subjective viewpoint on SIT including satisfaction, knowledge, expectations and perception in a large cohort of patients treated with either subcutaneous (SCIT) or sublingual immunotherapy (SLIT). In addition, the physicians’ viewpoint (in terms of satisfaction and perception) and its association to the patients’ perspectives were also explored.

MATERIALS AND METHODS

A cross-sectional observational survey was conducted across 13 specialized medical centers in North Italy from March to September 2010. Thirteen participating physicians (allergologists, pulmonologists, dermatologists, pediatricians) invited 30 consecutive patients with allergic rhinitis with or without
concomitant asthma treated with SIT to fill out a questionnaire related to their satisfaction, knowledge, expectation and perception of their treatment with SIT. Patients were invited to answer 28 questions while waiting for their control visit. The treating physicians were requested to collect clinical data of all participating patients (including disease severity, allergy sensitization, type of SIT). In addition, all physicians answered 3 questions related to their own satisfaction with the respective SIT for each patient enrolled in the survey. Both the patient and the physician were requested to complete the survey independently. The study was conducted in accordance with national legislation pertaining to confidentiality and data protection.

**Patients**

In all, 455 patients with allergic rhinitis with or without concomitant asthma treated with SIT (PURETHAL® or SUBLIVAC® HAL Allergy BV, Leiden, The Netherlands) were invited to participate in the survey. The inclusion criteria comprised the comprehension of written and spoken Italian language and the availability to participate in the survey. Exclusion criteria were the presence of evidently impaired cognitive functions and visual-auditory deficit and/or a physical inability to autonomously answer the questions.

**Surveys**

The questionnaires were developed by an expert panel on the basis of experience and literature review (11-13). Prior to application, the questionnaire was tested by 10 patients and 5 physicians to ensure the word choice and content of the questions were widely understood.

The patient questionnaire consisted of 28 items evaluating the knowledge (6 questions), perception (12 questions), expectations (5 questions) and satisfaction (5 questions) regarding SIT. There were 20 multiple choice and yes/no questions (where the patient had to choose 1 answer among those indicated)
and 8 visual analogue scale (VAS) questions (where the answer had to be indicated on a 10 cm horizontal scale ranging from 0 - not at all - to 100 - very much).

The physician questionnaire documented the physician’s satisfaction with the therapeutic efficacy of the SIT in each enrolled patient, whether there had been a change in the clinical condition since the start of SIT and if, in retrospect, he/she would prescribe the same type of SIT. Both questionnaires are presented in the Online Supplementary material (Appendix).

**Statistical Analyses**

It was planned to include 35 patient questionnaires from all participating physicians. Descriptive statistics were performed on demographic and clinical data and on patients’/physicians’ answers to the questions. In addition, the following analyses were performed with the aim to evaluate:

- potential association between patients’ education level (primary school and secondary school = low education level; high school, academic degree and postgraduate = high education level) and answers given to the survey and potential differences in answers between the two treatment modalities (SCIT and SLIT) (Chi Square Test);

- correlation and concordance among patients’ and physicians’ answers (Spearman Rho correlation, Cohen’s Kappa coefficient).

**RESULTS**

Of the 455 patients invited, 449 patients filled in the questionnaire. Only the questionnaires with more than a 95% completion rate (434) were considered for analysis.

Patient demographics, clinical data and duration of SIT are provided in Table 1.
The most frequently administered allergens were grass pollen (37.1%), followed by mites (26.6%), tree pollen (17%), weed and flower pollen (9.2%), moulds (5.6%), epithelia (2%) and other allergens (2.5%) administered alone or, in a minimal percentage, in mixture.

**Patients’ survey**

**Knowledge**

Almost 3 out of 4 patients claimed to have heard of SIT for the first time from a physician (48.4% from a specialist and 24.4% from a GP), 14.6% from their relatives and 8.6% from the mass media (4% did not remember). Accordingly, patients’ current knowledge on SIT was acquired through the information given by the specialist (86.3%), the GP (8.7%), some friends (3.1%) and the media (1.9%). With regard to treatment effect, 7.9% of patients believed it to be immediate, 31.5% thought it would start after a few months, 28.5% after one year, 26.5% after 2 years while 5.6% declared they did not know. The majority of patients (70.6%) believed that SIT should be continued for more than two years, while lower percentages of patients indicated shorter periods (only a few months (1.4%), one year (4.2%), two years (13%), respectively) while 10.8% declared they had no idea how long the treatment would last.

Concerning their knowledge of the properties of SIT, 38.4% of patients expected it to cause side effects, 35% believed it could prevent the development of new allergies and 15.2% thought it would be necessary to stop other anti-allergy medications.

**Perception**

When asked to evaluate the relevance of their physician’s opinion in their choice of starting with SIT on a 0-100 VAS, the patients gave a mean score of 82 (SD 21.03). Patients’ perception regarding SIT treatment properties are summarized in Table 2.
Moreover, 2.3% of patients reported that SIT caused them severe side effects, 19% reported annoying but not severe side effects, while the remainder had no side effects related to SIT.

As for additional pharmacotherapy, 81.5% of patients declared they used fewer anti-allergy drugs once they started immunotherapy, and 35% thought the benefits exceeded the costs. Almost all patients reported an improvement of their allergic condition since they started SIT (Table 3).

**Expectations**

Most patients expected, when starting with SIT, that it would help them to recover from their allergy (38.1%), HRQoL improvement (21.4%), symptoms reduction (22.6%), lower consumption of anti-allergy medication (10.5%) worsening avoidance (6.4%) while 1% of patients did not specify their expectations. Using a 0-100 VAS, patients expected an overall SIT success rate of 83.4 (SD 13.8, VAS-score range 35-100) and rated their level of confidence in SIT by on mean 77.7 (SD 21.3, VAS-score range 0-100).

**Satisfaction**

The mean satisfaction degree for SIT effects with regard to symptoms was 74 (SD 21.5; VAS-score range 0-100), and the mean global satisfaction degree for the treatment was 77.7 (SD 21.3; VAS-score range 0-100).

No difference in the degree of satisfaction was noticed between mono- and poly-sensitized patients. The vast majority of patients (81.5%) declared they used fewer anti-allergic medication since the start of SIT. Based on their personal experience, the majority of patients (60.7%) were convinced they would “surely start SIT again”, 32.2% answered “I would probably start”, while 2.3% would not engage on treatment with SIT again and 4.7% did not specify their answer. With regard to the
administration modality, 38.4% of patients would like to change it, 39.6% would not and 22% did not answer.

**Physicians’ answers**

Physicians’ satisfaction score regarding SIT results was on mean 77.7 (SD 16.3, VAS-range 5-100). The improvement in allergy symptoms and signs was equally positive and similar to the patient reported answers (Table 3). Over 90% of physicians answered they would prescribe the same type of SIT for that specific patient again (68% of them would surely prescribe it, 27.5% probably) whereas 1.7% declared that they would not (1.2% probably not and 0.5% surely not) and 2.8% did not know.

**Concordance between patients’ and physicians’ answers**

There was a significant correlation between patients’ and physicians’ satisfaction scores regarding SIT, both in the SCIT group (r = 0.612, p <0.001) and in the SLIT group (r = 0.608, p <0.001) (Figure 1). Moreover, physicians and patients expressed a significant level of agreement in judging the clinical changes after starting SIT treatment, both in the SCIT group (Kappa = 0.318, p <0.001) and the SLIT group (Kappa= 0.380, p <0.001).

**Differences in answers based on patients’ educational level**

For this subgroup analysis, patients were divided into two groups according to their educational level (high or low) at the start of the survey. In the entire survey, only for the question “In your opinion, can SIT prevent the development of new allergies?” an association between education level was found (Chi-Square 4409, p= 0.029) where a higher percentage of patients with a high education agreed with this statement (64% vs. 53%).
**Difference in answers between the two SIT formulations (SCIT versus SLIT)**

The majority of patients were taking SLIT (313, 74%) while 110 patients were administered SCIT. For some questions statistically significant associations were found between the treatment groups. A significantly higher percentage of patients treated with SLIT, compared to those with SCIT, reported that SIT is easy to take (Chi Square 5.772, p=0.016), does not induce side effects (Chi Square 5.205 p=0.023), can prevent the development of new allergies (Chi Square 10.952 , p<0.001) and that the benefits obtained with this treatment exceed its costs (Chi Square 4.491, p=0.034), while a higher percentage of patients treated with SCIT preferred to change the administration mode of their SIT (Chi Square 39.076, p< 0.0001).

A subgroup analysis based on the different allergens used for SIT was not possible due to too low numbers in one or more subgroups.

**DISCUSSION**

This real life cross-sectional survey aimed to evaluate the personal perspectives during treatment with either subcutaneous or sublingual SIT in a large number of Italian patients recruited from various medical centres. To this end, a survey consisting of 28 questions assessing patient’s satisfaction, knowledge, expectations and perception, was developed by an expert panel. The survey was readily accepted by the patients: 449 out of 455 decided to participate, and, it was deemed easy to understand and to complete. In addition, correspondence with the physician’s view was assessed. Our data confirm and extend previously published experience with SIT (8, 10, 14).

Allergen specific immunotherapy is a valuable causal treatment for respiratory allergies. However, it is a lengthy therapy and not without certain risks. Therefore, patient knowledge should be adequate when following SIT therapy. Although over 70% of patients showed adequate knowledge of SIT, this survey identified some gaps and misconceptions in patients, independent of their educational level.
Approximately 40% of the patients expected immediate results from SIT, about one out of five patients was convinced that the treatment should be pursued for a short period and 15% thought that SIT and regular pharmacotherapy are incompatible. Our findings are in agreement with the results of Rathkopf et al (14), who reported adequate knowledge in 77% of 158 patients receiving aeroallergen and/or venom immunotherapy before the start of therapy. On the other hand, Sade et al (10) found “a serious” lack of knowledge and numerous misconceptions among substantial numbers of patients receiving aero-allergen immunotherapy. Both these studies only evaluated SCIT. Since the treating physician, and in particular the specialist, represents the most important reference point for all treatment information, a standard “check list” to ensure patients receive all the required information before engaging on SIT could help to minimize knowledge gaps and misconceptions. Ensuring adequate knowledge and personal evaluation on SIT for each patient both when therapy is prescribed and during is crucial. It may prevent misunderstandings and inadequate expectations and may even increase compliance (15).

When asked to indicate their degree of agreement with a series of statements regarding their perception of SIT treatment, the majority of patients were positive towards integration of SIT in their everyday lives. More than 8 patients out of 10 considered SIT safe, easy to take, easy to remember, feasible to integrate in daily routine, and capable of improving allergy control. Other perceived benefits by patients included a reduced use of anti-allergy medications and an improvement of their allergic condition.

Regarding their expectations towards SIT, all patients had high confidence that the treatment would successfully affect several aspects of their allergic disorder.

Independently of the duration and the kind of SIT modality, patients indicated a high level of satisfaction with the effects of SIT, both on symptoms, need of additional medications and HRQoL. Similarly, the majority of physicians also expressed a high level of satisfaction with the efficacy of SIT,
inducing relevant improvement. If patients and physicians are of one mind concerning these two relevant issues regarding treatment management, this could help to build a real partnership favoring compliance and treatment efficacy. Adequate monitoring of treatment effect and sharing a long-time treatment plan represent hard to reach objectives if physicians and patients evaluate SIT benefits differently.

The comparison between patient’s evaluations of SLIT and SCIT revealed that SLIT was frequently considered easier to take and superior in terms of costs/benefits, although a similar degree of satisfaction was reported in both treatment groups.

Our study should be viewed in the light of its limitations. The cross-sectional design, the use of self-report tools, the differences in clinical and therapeutic aspects (including the presence or absence of any co-sensitisations or concomitant asthma, administration modality, treatment duration) can be considered as the main weak points. Moreover, our results refer to the patients’ personal point of view with regards to a specific product and treatment regimen and thus cannot be generalized to other SIT products or to other administration modalities. We acknowledge that the correlation we found between patient and physician satisfaction towards treatment may be somewhat influenced by the doctor – patient relationship. In patients with a chronic condition, the choice of treatment by the treating physician may positively affect the patient’s view and satisfaction towards this treatment. Conversely, a patient’s satisfaction towards treatment will positively affect the physician’s judgement. However, patients and physicians scored the questions independently, and since in our study strong correlations between patient and physician satisfaction scores were found over the entire VAS scale reflecting several aspects of satisfaction, we believe this reinforces the positive value of our findings.

The main strength is that data collection was performed in real life in a large patient population, providing relevant data for clinical management of patients receiving SIT: this is in accordance
with the most recent guidelines, emphasizing the importance of the patient’s point of view on treatment. Our results can be considered as preliminary data that must be followed by further research involving other countries and longitudinal samples, before more solid conclusions can be drawn regarding the patients’ viewpoint about SIT.

Acknowledgements

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References


Table 1. Patient demographics and clinical data

<table>
<thead>
<tr>
<th>Demographic Characteristics (n= 434)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>238 Males / 192 Females</td>
</tr>
<tr>
<td>Mean age ± SD in years (range)</td>
<td>31.5 ± 12.2 (age range: 18-54)</td>
</tr>
<tr>
<td>Mean duration of treatment ± SD in years (range)</td>
<td>2.5 ± 1.3 (0-9)</td>
</tr>
<tr>
<td>Highest level of education</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>6.2%</td>
</tr>
<tr>
<td>Secondary school</td>
<td>15.2%</td>
</tr>
<tr>
<td>High school</td>
<td>50.7%</td>
</tr>
<tr>
<td>Academic degree</td>
<td>6.7%</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>20.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis - ARIA classification</td>
<td></td>
</tr>
<tr>
<td>Intermittent</td>
<td>40.6%</td>
</tr>
<tr>
<td>Persistent</td>
<td>59.4%</td>
</tr>
<tr>
<td>Mild</td>
<td>11.3%</td>
</tr>
<tr>
<td>Moderate - Severe</td>
<td>88.7%</td>
</tr>
<tr>
<td>Asthma- GINA Classification (N=266)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>29.7%</td>
</tr>
<tr>
<td>2</td>
<td>54.5%</td>
</tr>
<tr>
<td>3</td>
<td>14.3%</td>
</tr>
<tr>
<td>4</td>
<td>1.5%</td>
</tr>
<tr>
<td>Sensitization</td>
<td></td>
</tr>
<tr>
<td>Monosensitized</td>
<td>33.3%</td>
</tr>
<tr>
<td>Polysensitized</td>
<td>66.7%</td>
</tr>
<tr>
<td>Specific immunotherapy</td>
<td></td>
</tr>
<tr>
<td>SCIT</td>
<td>26%</td>
</tr>
<tr>
<td>SLIT</td>
<td>74%</td>
</tr>
</tbody>
</table>
Table 2. Patients’ perception about SIT properties

<table>
<thead>
<tr>
<th>Questions</th>
<th>Patients’ answers</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Completely True</td>
<td>Partly True</td>
<td>Partly false</td>
<td>Completely false</td>
<td>Don’t know</td>
</tr>
<tr>
<td>SIT is safe</td>
<td>54.5%</td>
<td>37.4%</td>
<td>0.2%</td>
<td>0.2%</td>
<td>7.7%</td>
</tr>
<tr>
<td>SIT is easy to take</td>
<td>68.6%</td>
<td>27.4%</td>
<td>0.5%</td>
<td>0</td>
<td>3.5%</td>
</tr>
<tr>
<td>SIT is handy to use in daily routine</td>
<td>47.2%</td>
<td>42.7%</td>
<td>1.8%</td>
<td>0.2%</td>
<td>8.1%</td>
</tr>
<tr>
<td>It is easy to remember to take SIT</td>
<td>50.8%</td>
<td>37%</td>
<td>2.8%</td>
<td>0.2%</td>
<td>9.2%</td>
</tr>
<tr>
<td>SIT allows to better control your allergy</td>
<td>56%</td>
<td>35.2%</td>
<td>0.7%</td>
<td>5.1%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Table 3: Patients’ and physicians’ perception of change in clinical conditions after SIT

<table>
<thead>
<tr>
<th>Possible answers</th>
<th>Patients’ answers</th>
<th>Physician’s answer’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much worse</td>
<td>1.4 %</td>
<td>0.2 %</td>
</tr>
<tr>
<td>Worse</td>
<td>1.2 %</td>
<td>0.2 %</td>
</tr>
<tr>
<td>A bit worse</td>
<td>0.8 %</td>
<td>0.2 %</td>
</tr>
<tr>
<td>No change</td>
<td>4 %</td>
<td>3.8 %</td>
</tr>
<tr>
<td>A bit better</td>
<td>17.6 %</td>
<td>20.4 %</td>
</tr>
<tr>
<td>Better</td>
<td>42%</td>
<td>57.9 %</td>
</tr>
<tr>
<td>Much better</td>
<td>33 %</td>
<td>17.3 %</td>
</tr>
</tbody>
</table>
Figure 1. Correlation between patients’ and physicians’ satisfaction level (VAS score) on subcutaneous (A; r=0.612, p<0.001) and sublingual (B; r=0.608, p<0.001) SIT.
Appendix

A. Patient questionnaire

**SIT SURVEY DATA**
Patient’s code

<table>
<thead>
<tr>
<th>Male □</th>
<th>Female □</th>
<th>Age .............</th>
</tr>
</thead>
</table>

**Education:**

- Primary school □
- Secondary school □
- High school □
- Academic degree □
- Postgraduate □

When did you start SIT? .................................................................

For which allergen/s do you take the SIT?
........................................................................................................
........................................................................................................
The following questions are aimed at evaluating your point of view on vaccination (specific immunotherapy - SIT) that you are taking. There are no right or wrong answers. For each question, please tick choose one answer that best describes your experience and what you think.

1) Who did first tell you of SIT for allergies?
   - Friends
   - TV, newspapers, Internet
   - My general practitioner
   - The specialist
   - I do not remember

2) Which result do you expect from SIT?
   - Recover from allergy
   - Improve the quality of life
   - Have fewer allergic symptoms
   - Use less medication for allergy
   - Do not get worse
   - I do not know

3) How soon do you expect that SIT begins to have an effect?
   - From the beginning
   - After a few months
   - After one year
   - After 2 years
   - I do not know

4) How long do you think that SIT should be continued?
   - For a few months
   - For a year
   - For 2 years
   - For more than 2 years
   - I do not know
5) What percentage of success do you expect from SIT?

6) According to you, can SIT give side effects?
   - Yes
   - No
   - I do not know

7) In your opinion, does SIT prevent the development of new allergies?
   - Yes
   - No
   - I do not know

8) In your opinion, when taking SIT, any other medications for allergies must be suspended?
   - Yes
   - No
   - I do not know

9) Your knowledge about SIT is based on:
   - The information provided by the specialist
   - The information provided by the general practitioner
   - The information you got from newspapers, television, internet
   - The information you got from friends

10) When you decided to start SIT, what did influenced your choice?
    - The possibility of reducing the drugs for allergy treatment
    - The ability to act on the disease rather than on symptoms
    - The ability to prevent the development of new allergies
    - Dissatisfaction with the drugs I had used
11) How much did the physician’s opinion influenced your choice to start SIT?


not at all  | very much

Indicate the answer that best describes how TRUE or FALSE are the following statements as regards SIT?
(Answer scale: completely true - partly true - I do not know - partly false - completely false)

12) SIT is safe
   completely true  partly true  partly false  completely false  I do not know

13) SIT is easy to take
   completely true  partly true  partly false  completely false  I do not know

14) SIT is handy to use in daily routine
   completely true  partly true  partly false  completely false  I do not know

15) It is easy to remember to take SIT
   completely true  partly true  partly false  completely false  I do not know

16) SIT allows to better control your allergy
   completely true  partly true  partly false  completely false  I do not know

17) Has SIT caused to you severe side effects?
   No  Yes (please indicate which side effects)

_________________________________________________________________________________________

_________________________________________________________________________________________

_________________________________________________________________________________________

_________________________________________________________________________________________

_________________________________________________________________________________________
18) Has SIT caused to you not severe but annoying side effects?
   No   Yes (please indicate which side effects)

19) Since you started being treated with SIT, have you used less drugs for allergy?
   No   Yes (please indicate which drugs)

20) Since you started treatment with SIT, how much has your allergy improved?
    not at all    very much

21) How much are you satisfied with the effect of SIT on symptoms?
    not at all    very much

22) Has SIT improved your quality of life?
    not at all    very much

23) Do you trust that SIT can be effective in your case?
    not at all    very much
24) Considering your experience, if you decided now to start a therapy with SIT, what would you do?
   I would surely not start
   I would probably not start
   I do not know
   I would probably start
   I would definitely start

25) Considering your experience, would you be willing to continue the treatment with a vaccine given by injection instead of by mouth (for SCIT patients)/ would you be willing to continue the treatment with a vaccine given by mouth instead of by injection (for SLIT patients)?
   Yes
   No
   I do not know

26) Do you think the benefits of SIT are greater than costs?
   Yes
   No
   I do not know

27) How much are you overall satisfied with the treatment with SIT?

   not at all                                very much

28) Compared to when you started SIT, how is your allergy now?

   -3  -2  -1  0  +1  +2  +3
   much worse  a little worse  no change  a little worse  better  much better
### B. Physician questionnaire

#### SIT SURVEY DATA

**ALLERGY**

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Intermittent</th>
<th>Mild</th>
<th>Persistent</th>
<th>Moderate - severe</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Asthma</th>
<th>GINA</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Mono-sensitized</th>
<th>Poly-sensitized</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>SCIT</th>
<th>SLIT</th>
</tr>
</thead>
</table>

1) How much are you overall satisfied with the treatment with SIT that your patient is taking?

Not at all | very much

2) Compared to when your patient started SIT, was there a change in his clinical condition (as regards allergy)? (Global Rating Scale)

<table>
<thead>
<tr>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
<th>+3</th>
</tr>
</thead>
<tbody>
<tr>
<td>much worse</td>
<td>worse</td>
<td>a little worse</td>
<td>no change</td>
<td>a little better</td>
<td>better</td>
<td>much better</td>
</tr>
</tbody>
</table>
3) Taking into account the clinical results obtained, the levels of adherence to the treatment, any potential difficulties emerged, and patient's characteristics, in this specific case would you prescribe the same type of SIT or would you change it?

Surely yes  Probably yes  I do not know  Probably no  Surely no