SUBLINGUAL IMMUNOTHERAPY

by

Melissa L. Ferrell

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As members of the DNP Project Committee, we certify that we have read the DNP Project prepared by Melissa L. Ferrell, entitled Sublingual Immunotherapy and recommend that it be accepted as fulfilling the DNP Project requirement for the Degree of Doctor of Nursing Practice.

_____ Date: May 11, 2015
Kate G. Sheppard, PhD, RN, FNP, PMHNP-BC, FAANP
Clinical Associate Professor, Nursing

_____ Date: May 11, 2015
Kathleen Piotrowski, DNP, CRNA
Clinical Assistant Professor, Nursing

_____ Date: May 11, 2105
Christy L. Pacheco, DNP, FNP-BC
Clinical Assistant Professor, Nursing

Final approval and acceptance of this DNP Project is contingent upon the candidate's submission of the final copies of the DNP Project to the Graduate College.

I hereby certify that I have read this DNP Project prepared under my direction and recommend that it be accepted as fulfilling the DNP Project requirement.

_____ Date: May 11, 2015
DNP Project Chair: Kate G. Sheppard, PhD, RN, FNP, PMHNP-BC, FAANP

STATEMENT BY AUTHOR

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SIGNED: Melissa L. Ferrell

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DEDICATION

I would like to dedicate this DNP project to my family. To my husband Roland and children, Reilly, McKenna, and Hayden for supporting me and for being so willing to take up the slack so that I could further my graduate education. I hope I have been an example to you that you can accomplish anything you set your mind to do. To my parents for instilling a love of learning through their dedication to education and for their continual support and encouragement.

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ABSTRACT

One of the most common reasons people seek primary care and emergency care is to reduce the symptoms of allergies, such as hay fever. To meet this high demand, several recent FDA-approved methods for treating seasonal and perennial allergies have been developed, including sublingual immunotherapy tablets. Furthermore, no longer must a patient endure allergy shots; this can now be delivered sublingually. Although this method has been shown to have high safety and efficacy, very few clinicians actually utilize this form of therapy. The purpose of this paper is describe the use of sublingual immunotherapy among Nurse Practitioners and discuss barriers that may prevent its use. Nurse Practitioners working in primary care settings were surveyed regarding their use of sublingual immunotherapy. Although many nurse practitioners treat patients with allergic disease, not one participant reported using sublingual immunotherapy. This discussion outlines some of the reasons NPs are not currently utilizing this method of allergy treatment and the findings are compared with the extant literature. This paper culminates in an evidence-based algorithm to outline best practices for utilizing sublingual immunotherapy to reduce allergy symptoms.

INTRODUCTION

Runny nose, itchy, watery eyes, wheezing, and episodes of sneezing are common, yet aggravating allergy symptoms most people will experience at some point in their life. Allergic rhinitis, rhinosinusitis, allergic asthma, allergic rhinoconjunctivitis, and hives (urticaria) are common diagnoses often associated with allergic disease. Allergic rhinitis is on the rise and currently affects 30-40% of adults and children and is one of the most common reasons to utilize healthcare services (Dranitsaris & Ellis, 2014; Wallace & Dykewicz, 2008). In 2012, it was estimated that more than 17 million adults in the U.S. suffered from, or sought care for allergic rhinitis (Blackwell, Lucas, & Clarke, 2014; Wise & Schlosser, 2012). Allergies are responsible for 3.5 million lost work days and two million lost school days each year (Nathan, 2007). In 2002, it was estimated that the total direct and indirect costs associated with allergic rhinitis in the U.S. were $11.58 billion (Schoenwetter, Dupclay, Appajosyula, Botteman, & Pashos, 2004). Long-term untreated allergy symptoms have the potential to aggravate asthma symptoms, increase respiratory complications, and decrease the quality of life for those suffering with allergic disease (Deliu et al., 2014).

The most practical way to relieve allergy symptoms is merely to avoid the stimulant. Unfortunately, that solution is often unrealistic or difficult, and many people may reach for medications to reduce the unpleasant symptoms. Antihistamines, nasal steroids, and nasal rinses are typically the first-line treatment for allergies. However, these interventions are less than effective, as upwards of 40% of patients who report allergy symptoms, describe their symptoms as not well controlled by traditional pharmacological treatments (Durham, Yang, Pedersen, Johansen, & Rak, 2006). If these treatments fail to provide adequate relief of allergy symptoms, allergen immunotherapy (AIT) may provide an alternative treatment. Furthermore, while

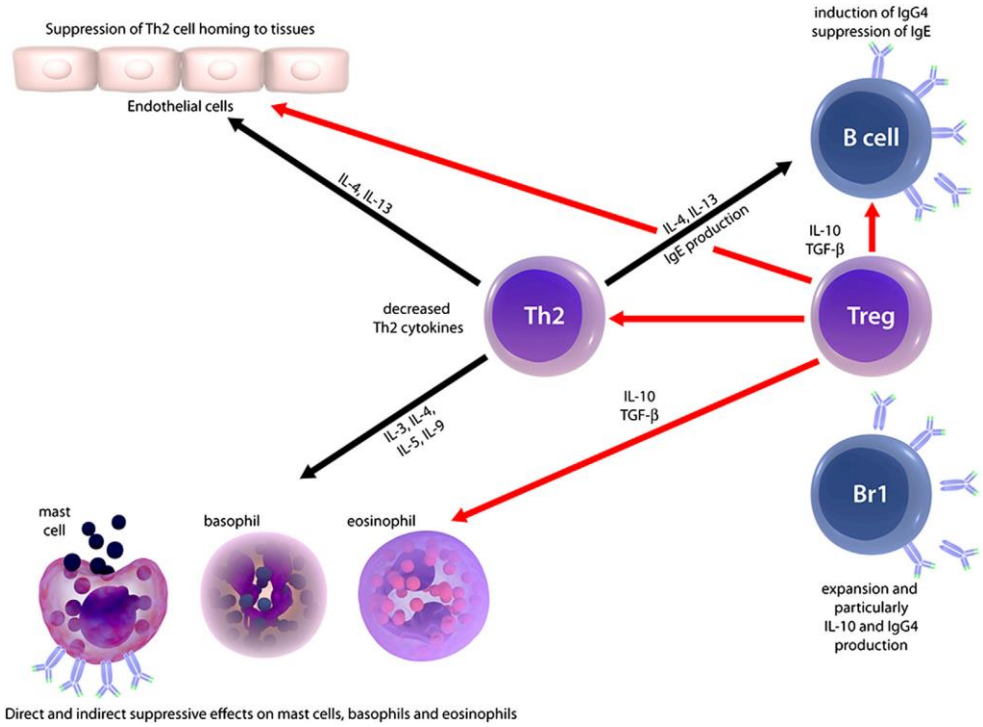
subcutaneous injection has been the predominate route to deliver AIT, sublingual immunotherapy is a painless, highly effective means to deliver the same treatment. Although three sublingual tablets were approved by the Federal Drug Administration in 2014 (Food and Drug Administration [FDA], 2014), sublingual immunotherapy may not be widely used in primary care settings by providers, such as Nurse Practitioners (NPs). The purpose of this paper is to describe the use of sublingual immunotherapy among NPs in primary care.

Background

Allergic Response

An allergic response is a cascade of events precipitated by an allergen. An allergen is a protein or glycoprotein with a defined amino acid sequence that is capable of binding Immunoglobulin E (IgE) and provoking an immediate hypersensitivity reaction (Migueres et al., 2014; Shah & Grammer, 2012). Allergic disease is thought to stem from an imbalance between regulatory T cells (T regs) and T helper (T_H) 2 cells (Ling et al., 2004). This may occur due to the inability of the T regs to suppress the allergen activation (Ling et al., 2004). Histamine is released from mast cells and basophils and also plays a key role in the production allergen-specific IgE (Akdis & Akdis, 2014). Increases in eosinophils, mast cells, and basophils are also found in conjunction with allergic disease (Akdis & Akdis, 2014). Figure 1 outlines the physiologic process in the suppression of allergic inflammation.

Figure 1. The role of T reg and B reg cells in the suppression of allergic inflammation



Note. Adapted from Akdis, M., & Akdis, C. (2014). Mechanisms of allergen-specific immunotherapy: Multiple suppressor factors at work in immune tolerance to allergens. *Journal of Allergy and Clinical Immunology*, *133*(3), 621-631. http://dx.doi.org/10.1016/j.jaci.2013.12.1088. Copyright 2014 by Elsevier.

Allergen Immunotherapy

Allergen immunotherapy (AIT) is the desensitization process used to induce tolerance to allergens. Desensitization is accomplished through repeated exposure to allergen extracts in increasing quantities (Akdis & Akdis, 2014; Marogna et al., 2009). AIT can be given by subcutaneous injection or sublingually, as a tablet or by drops placed under the tongue. Moderate-to-severe allergic rhinitis and mild-to-moderate allergic asthma are common indications for AIT (Migueres, et al., 2014). Thus far, AIT is the only treatment with the potential to promote long-term remission of allergy symptoms, possibly stop allergic disease progression, and may prevent the development of new allergies and asthma (Canonica et al., 2014; Hankin & Cox, 2014).

Significance of the Problem

Recent advances have been made in the treatment of allergies with allergen immunotherapy. Prior to the approval of the sublingual tablets, only subcutaneous injections were FDA-approved and aqueous drops continue to be an off-label route of administration. However, the drops may actually have more patient appeal as they can be self-administered at home. There is also less need for multiple medical visits and the lack of needles may be more favorable for children or those with needle phobias (Calderon, Penagos, Sheikh, Canonica, & Durham, 2011). Sublingual immunotherapy may be an attractive alternative over allergy shots as it is pain-free, easily administered, and has an excellent safety profile. However, despite the advantages, this therapy is rarely used,

The current practice of sublingual immunotherapy by Nurse Practitioners' is difficult to ascertain as minimal data can be found in the literature. Previous surveys designed to describe practice patterns for sublingual immunotherapy have specifically targeted allergist, otolaryngologist, or random health care providers and not specifically NPs (Leatherman et al., 2014; Tucker, Tankersley, & ACAAI Immunotherapy and Diagnostics Committee, 2008). As additional information regarding its safety and efficacy becomes available, primary care providers, including NPs, may increasingly be asked to prescribe sublingual immunotherapy. In rural healthcare settings, sublingual immunotherapy may be a feasible treatment option when specialty care is limited. Sublingual immunotherapy has the potential to be a mainstream, immune-modifying treatment alternative for allergic disease and as an adjunct therapy for asthma. Increasing Nurse Practitioners knowledge of sublingual immunotherapy, including when to refer for specialty care, should foster an improvement in healthcare outcomes.

Purpose Statement

The purpose of this paper is to describe the use of sublingual immunotherapy by Nurse Practitioners in primary care. The specific aims are: 1) describe current evident-based research regarding sublingual immunotherapy, 2) describe how NPs are using sublingual immunotherapy in practice, and 3) develop best practice recommendations for the use of sublingual immunotherapy in primary care. This paper will contribute to the expanding role of allergen sublingual immunotherapy as a treatment modality for allergic disease by NPs.

LITERATURE REVIEW

The purpose of this literature review was to evaluate the current research regarding the safety and efficacy of sublingual immunotherapy, discuss the gaps in knowledge, and present a summary of current evidence regarding sublingual immunotherapy. The findings of this literature review were used to develop a survey to describe prescribing practices among NPs. Survey results were used in conjunction with current evidence to develop best practice recommendations for NPs in the use of sublingual immunotherapy.

Method

A systematic search of the Cochrane Library, PubMed, and EMBASE was performed using the keyword "sublingual immunotherapy" with dates ranging from 2009 to 2014. Articles were limited to randomized controlled trials, published in English, with human subjects, and included full text. Articles were excluded if they were specific to latex, venom, food, pets, migraines, epicutaneous or intralymphatic immunotherapy, or oral desensitization. A total of 21 studies were obtained from PubMed or extrapolated from systematic reviews. These studies

were analyzed for dosing regimens, symptom and medication scoring systems, and adverse events.

Dosing

The allergen extracts used in sublingual immunotherapy are typically the same aqueous solutions FDA-approved for subcutaneous immunotherapy. Currently, there is not an international standardized expression or measurement for allergen extracts. Concentrations have been found to vary between manufacturers. This has posed substantial challenges in comparing randomized controlled studies to evaluate effective dosing parameters. Each lab varies in how it labels the allergen extracts. Extracts are measured in bioequivalent allergy units (BAU/mL), allergen units (AU/mL), protein nitrogen units (PNU), and by weight/volume (w/v) of the extract. The quality of the allergen extract greatly influences the efficacy; allergen extracts from one manufacturer cannot be compared with another until standardization and controlled trials are performed (Ridolo et al., 2014).

One challenge that has proven to be a barrier in determining the efficacy of sublingual immunotherapy is the variety of dosing regimens used in studies. Studies reveal quite different build-up or up-dosing administration schedules. Maintenance dosing regimens and dosing units also varied between studies. Allergen dosing units were frequently reported as: IR (Index of Reactivity), RU/mL (Rast Units per milliliter), IR/mL, drops, puffs, and µg. These differences further compound the confusion in establishing recommended dosing guidelines. Treatment lengths also ranged significantly with some studies as short as eight months and others as long as five years. Dosing schedules for allergies can be year round (perennial), seasonal, or precoseasonal (prior to and through the end of the peak allergy season) (Ahmadiafshar,

Maarefvand, Taymourzade, Mazloomzadeh, & Torabi, 2012; Makino et al., 2010; Wang et al., 2013).

Symptom Scoring

Variations in symptom and medication scoring tools contribute to the heterogeneity in reporting clinical outcomes. A commonly used method to evaluate symptoms is a four-point scale. The points are often applied as follows: 0 points: no symptoms; 1 point: mild symptoms; 2 points: moderate symptoms; and 3 points: severe symptoms (Aydogan et al., 2013; Bush et al., 2011). Commonly measured symptoms include; rhinorrhea (nose blowing/runny nose), sneezing, itchy nose, nasal congestion (blocked nose), postnasal drip, red itchy eyes, watery (tearing/tear flow), gritty eyes, cough, wheeze, dyspnea, chest tightness, breathlessness or shortness of breath. Other symptoms used to evaluate the efficacy of study outcomes include throat symptoms, ear symptoms, headache, dry cough, ocular swelling, and chest congestion (Bozek, Ignasiak, Filipowska, & Jarzab, 2013).

The inclusion of a visual analogue scale and/or a Quality of Life questionnaire, in addition to a point-value scoring system, further contributed to variations in study outcomes. The visual analogue scale is a measurement tool used to grade symptoms by choosing a point along a scale (Eifan et al., 2010; O'Hehir et al., 2009). Quality of Life questionnaires include the Allergy Control SCORE (ACS), Control of Allergic Rhinitis and Asthma Test (CARAT), Rhinitis Control Assessment Test (RCAT), Allergic Rhinitis Control Test (ARCT), and Pediatric and Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ and AdolRQLQ, respectively) (De Bot et al., 2012). These questionnaires are used to gauge the severity and control of the allergic disease (Demoly et al., 2013). Rarely, were studies replicated that employed similar dosing, symptom scoring, and medication scoring systems.

Medication Scoring

In addition to symptom scoring, medication scoring is often used to quantify the amount and frequency of allergy-related medication used in conjunction with allergen immunotherapy. Medication selection and the point-valuation applied for similar medications often differed between studies. For example, some studies applied one point for each dose of oral antihistamine while others applied two, three or four points (Aydogan et al., 2013; Ott et al., 2009; Skoner et al., 2010). Most studies either allowed the patient to continue taking antihistamines and/or rescue asthma medications as needed, or only allowed certain medications to be taken while participating in the study.

Studies were found to either report symptom and medication scores individually or as a combined score. These results were then used to measure the efficacy of sublingual immunotherapy. A review of the literature revealed that the frequency in which study participants were asked to record symptoms and medication use varied. Scores were reported typically once or twice a day, at follow-up visits, daily during peak season, annually, or only after treatment cessation. The World Allergy Organization (WAO) proposes that the ideal study should provide a balanced evaluation of the symptom and medication scores (Canonica et al., 2009).

Adverse Events

The safety profile of subcutaneous immunotherapy is often a deterrent for many clinicians and patients. Non-fatal reactions from subcutaneous immunotherapy has a prevalence rate as low as 0.13% and up to 34% in rush immunotherapy studies (Cox, Larenas-Linnemann, et al., 2010). In 2004, Berstein and colleagues reported that 41 fatalities occurred over a 12 year period (Berstein, Wanner, & Borish, 2004). This equated to an estimated one fatality per 2.5

million injections or 3.4 deaths per year (Bernstein et al., 2004). The cause of death was often attributed to delayed treatment of anaphylaxis. In contrast, there have been no reported deaths from sublingual immunotherapy.

Side effects are also common for both subcutaneous and sublingual routes of administration, however, inconsistency exists in defining and differentiating between local and systemic reactions. Local reactions for subcutaneous immunotherapy include redness and/or swelling at the injection site and generalized pruritus (Cox, Larenas-Linnemann, et al., 2010). Sublingual immunotherapy side effects are typically oral in nature, but can include generalized itching, soreness, oropharynx swelling, and facial flushing (Ahmadiafshar et al., 2012; Bozek et al., 2013). Oral side effects are usually self-limiting and resolve shortly after administration. Antihistamines can be prescribed for prevention and/or treatment of local side effects.

Key elements that should be included when reporting systemic adverse reactions are: 1) patient characteristics (severity of allergic disease, co-morbidities, risk factors), 2) the type of allergen extract used, 3) the route of administration, 4) the dose of the antigen given during the up-dosing and maintenance phases, 5) the dosing schedule (conventional, cluster or rush), and 6) the experience of the treating physician in the early identification and treatment of the systemic reaction (Calderon et al., 2014).

Current Practice Guidelines

The current practice of sublingual immunotherapy is varied as demonstrated by the number of dosing regimens, symptom and medication scoring tools, and methods for identifying and recording adverse events. In the U.S., only about 11.4% of allergists prescribe sublingual immunotherapy and multi-allergen, aqueous or glycerinated formulations, prepared in the physician's office are typically used (Cox, 2014). In comparison, sublingual immunotherapy is

prescribed by about 45% of European clinicians and they tend to prescribe single-allergen, depot extracts prepared by allergen extract manufacturers (Cox, 2014). Sublingual immunotherapy is an approved treatment for allergies by the European Medicinal Agency (EMEA) (Cox, 2014). However, in the U.S., FDA-approval necessitates additional randomized controlled trials (RCTs) to determine effective administration regimens, appropriate patient selection, and standardization of allergen extracts (Compalati, Braido, & Canonica, 2013).

Although sublingual immunotherapy is supported by the World Allergy Organization (WAO) and the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, it is only recently being recognized as a treatment option in the U.S. (Brozek et al., 2010; Canonica et al., 2009). The *Otolaryngology – Head and Neck Surgery* recently published new guidelines for the treatment of allergic rhinitis and recommended sublingual or subcutaneous immunotherapy for patients that are not responding to pharmacological measures (Seidman et al., 2015). In February 2015, experts at the American Academy of Allergy, Asthma, and Immunology (AAAAI) began drafting additions to the Joint Task Force Practice Parameter specifically for sublingual immunotherapy (Cox, 2015; Cox, Nelson & Lockey, 2010).

Gaps in the Literature

In reviewing the literature, several key findings were lacking. There is very little consensus as to the ideal dosing frequency, allergen concentration, and length of treatment for sublingual immunotherapy. Patient selection criteria and primary endpoints are also quite varied. Although, all the studies reviewed were randomized controlled trials, they often had small sample sizes and the potential for publication bias. Additional randomized, placebo-controlled, double-blind trials with similar dosing protocols are needed for individual and multi-allergen mixtures. This will help to determine the most efficacious and cost-effective dosing regimen

with the fewest adverse events. Studies are also needed to confirm the indications for alternative allergic diagnoses, such as eosinophilic esophagitis, allergy-induced urticaria, angioedema, food allergies, atopic dermatitis, and moderate to severe asthma. Long-term studies will help to confirm immunologic changes and reaffirm the mechanism of action for sublingual immunotherapy.

Conclusion

Numerous observational and retrospective studies, without randomization, blinding or placebo groups, have been published that provide descriptive information for sublingual immunotherapy. These studies are important as they provide suggested dosing regimens and the length of treatment potentially required for sustained desensitization. Many of the randomized controlled trials are considered to be suggestive, rather than demonstrative because they lack sufficient high quality evidence (Canonica et al., 2009). As additional large scale randomized, double-blind, placebo-controlled trials are completed using similar primary endpoints and dosing regimens, the statistical significance and generalization of results should improve.

METHODS

Conceptual Framework

The Plan-Do-Study-Act (PDSA) model for quality improvement was the framework used to describe how NPs are using sublingual immunotherapy. Sublingual immunotherapy may be a safe and effective alternative when standard drug therapy is ineffective, yet it is unknown how many NPs are currently prescribing this in practice. The PLAN stage was to query NPs to see if and how sublingual immunotherapy is being prescribed in practice. In the DO stage, an 8-question survey was developed and administered to NPs throughout the U.S. In the STUDY stage, survey results were analyzed, variances and similarities were documented and unexpected

outcomes were identified. The knowledge gained in this study leads to the ACT stage in the PSDA cycle. Evidence-based findings from the literature and survey results were used to develop an algorithm for NPs to improve best practice when treating patients with sublingual immunotherapy. The PDSA cycle can then be repeated to future research, if additional changes are needed to further improve outcomes.

Protection of Human Subjects

Prior to data collection, grant exemption from the Institutional Review Board at the University of Arizona was obtained. Each recipient received the following: (1) a cover letter introducing the principle investigator (PI) and the purpose of the survey, (2) a disclosure form explaining the anticipated time commitment, voluntary nature of the survey, how responses will be used in this DNP project, and how participants will be protected in the study, (3) an 8-question survey, and (4) a stamped return envelope addressed to the PI. No identifiable information was requested in the survey. It was anticipated that only respondents who could read and write English would participate and no expected vulnerable populations were included.

Study Design

A stratified, randomized sampling of 500 actively practicing NPs from the American Association of Nurse Practitioners (AANP) membership database was obtained. Surveys were then mailed to each potential participant. Participants were asked to return the survey within 14 days.

Setting and Sample

NPs self-reporting family practice, pediatrics, and/or allergy/immunology as their specialty were included in the study. Participants were excluded if they are not actively practicing or were not active members of the AANP.

Survey

This survey specifically targeted NPs actively practicing in the U.S. The aims of this survey were: 1) discover the number of NPs prescribing sublingual immunotherapy and to which patient population, 2) discover what types of allergy testing are being performed, 3) discover treatment preferences (single versus multi-allergen), and 4) determine what barriers may exist that prevent NPs from employing this therapy.

Analysis

Quantitative results were counted and expressed as a percentage of respondents. Qualitative responses were analyzed and reported according to common themes and trends.

RESULTS

Description of the Sample

A total of 157 surveys were returned, two of which were excluded, as the respondents stated that they were retired and did not complete the survey (N=155). The majority of respondents in this sample were Family Nurse Practitioners. Additional areas of NP specialization included Adult Gerontology Acute Care, Adult Gerontology Primary Care, emergency department, neurology, lipidology, addiction, HIV/AIDS, internal medicine in the Veteran's Administration, and orthopedics. Several participants reported more than one area of specialization.

Table 1

Demographics by specialty

Nurse Practitioner Specialty	**Response**	**Percentage**
Family Nurse Practitioner	152	98.06%
Adult-Gerontology Primary Care	1	0.65%
Pediatric Nurse Practitioner	0	0.00%
Neonatal Nurse Practitioner	0	0.00%
Woman's Health Nurse Practitioner	0	0.00%
Certified Nurse Midwife	0	0.00%
Certified Registered Nurse Anesthetist	0	0.00%
Other	9	5.81%
Adult-Gerontology Acute Care	1	0.65%
Emergency Department	1	0.65%
FNP - Neurology	2	1.29%
Lipidologist, Anti-Coagulation Mgmt	1	0.65%
Addiction	1	0.65%
HIV/AIDS	1	0.65%
VA-Internal Medicine	1	0.65%
Orthopedics	1	0.65%

The sample represented NPs from 45 of the 50 states. All states of licensure reported by participants were counted, including those reporting licensure in multiple states. Texas and Florida were most widely represented by the sample, followed by California, Indiana, and Virginia. Three NPs did not disclose the state in which they were licensed.

Table 2

State distribution of licensure by respondents.

	States by Scope of Practice		
No. of participants	Restricted	Reduced	Full
> 6 Participants	Florida Texas California Virginia	Indiana	
5-6 Participants	N. Carolina Oklahoma Michigan	Mississippi Pennsylvania Ohio	Washington Maine
3-4 Participants	Tennessee Georgia S. Carolina Massachusetts	Louisiana Kentucky Illinois	N. Mexico Minnesota Iowa Colorado Alaska N. Dakota Nebraska
1-2 Participants	Missouri	Wisconsin W. Virginia New York New Jersey Maryland Kansas Delaware Alabama	Montana Arkansas Vermont Oregon N. Hampshire Nevada Idaho Connecticut Arizona

Results

Interestingly, no NPs in this sample currently prescribe sublingual immunotherapy in their practice. Allergy testing performed or ordered by NPs was infrequently done. Over 80% (N=126) of the sample did not perform any type of allergy testing, but rather referred patients to an allergist. A small percentage of NPs ordered serum IgE blood testing, RAST testing, serum food allergy testing or performed intradermal or scratch/puncture skin tests.

In this sample, 39% (N=60) of NPs responded that they would consider prescribing sublingual immunotherapy, but limited or no knowledge about how to manage this therapy was a barrier. Sixty percent (N=94) responded that they would not consider prescribing sublingual immunotherapy. Of the 94 who would not consider prescribing this treatment, one-third (N=30) reported working in a subspecialty that does not treat allergies and one-third (N=31) would rather refer to an allergist. Overwhelmingly, the most common barrier to prescribing sublingual immunotherapy was limited or no knowledge of how to prescribe or initiate (N=92). The second most common reason cited as a barrier to prescribing was the NPs preference to refer patients to an allergist for allergy shots. The off-label designation was a barrier for a small percentage of NPs and lack of insurance reimbursement was problematic for about 10% (N=16) of those surveyed. Additional barriers included a concern for malpractice, the need for physician over-site, prescribing limited by individual practice protocols, lack of knowledge regarding the applicability in geriatric or pregnant populations, and lack of staffing for patient monitoring.

Table 3

Results

Currently Prescribing SLIT?	**Response**	**Percentage**
Yes	0	0.00%
No	155	100%
SLIT Patient Population	**Response**	**Percentage**
< 5 years old	0	0.00%
5-18 years old	0	0.00%
19-65 years old	0	0.00%
> 65 years old	0	0.00%
I do not prescribe	137	88.39%
N/A or Did not respond	18	11.61%
Allergy Testing	**Response**	**Percentage**
Puncture/scratch skin test	1	0.65%
Intradermal skin test	1	0.65%
Serum IgE blood test	20	12.90%
None-referral to specialist	126	81.29%
Other - none	1	0.65%
Other - Adult food allergy test	1	0.65%
Other - RAST	1	0.65%
Did not respond	5	3.23%
SLIT Formulation	**Response**	**Percentage**
Single-allergen	0	0.00%
Allergen-specific	0	0.00%
Multi-allergen	0	0.00%
Sublingual tablets	0	0.00%
Other	0	0.00%
Do not prescribe	142	91.61%
SLIT tablets if appropriate	1	0.65%
Did not respond	11	7.10%
Would you consider prescribing SLIT?	**Response**	**Percentage**
Yes	60	38.71%
No	94	60.65%
I currently prescribe	0	0.00%
Maybe	1	0.65%
Barriers preventing SLIT prescribing	**Response**	**Percentage**
"Off-label"	5	3.23%
Minimal or no insurance reimbursement	16	10.32%
Limited/no knowledge of SLIT	92	59.35%
Prefer to refer for allergy shots	42	27.10%
None, I currently prescribe	0	0.00%
Other	41	26.45%

DISCUSSION

This study was aimed at describing NPs practice of using sublingual immunotherapy for allergies. It was anticipated that the number of NPs prescribing this therapy would be small, however, it was surprising that among the sample (N=155) no participants reported using sublingual immunotherapy. The following discussion relates the results from this project to the current literature and helps to outline the factors that may limit the use of sublingual immunotherapy.

Scope of Practice

Currently, the scope of practice and prescribing regulations for Nurse Practitioners differ among the 50 states. More than half of the states have either restricted or limited scope of practice. Respondents with NP licensure in Florida (N=11), Texas (N=10), California (N=8), and Virginia (N=7) had the highest rates of survey responses and those states have some of the most restrictive practice regulations ("AANP," n.d.). Forty-one percent (N=68) of the respondents reported licensure in a state with restricted scope of practice, 30% (N=50) reported licensure in a reduced scope of practice state, while only 28% (N=47) practice in a state allowing full scope of practice. NPs practicing in states with restricted practice require supervision, delegation, or team-management in order to provide care ("AANP," n.d.).

Practice Patterns and Beliefs

Although descriptions of practice patterns using allergen immunotherapy can be found in the literature, elucidating concrete numbers of prescribers is challenging. The Allergies, Immunotherapy, RhinoconjunctivitiS (AIRS) survey sought to describe practice patterns, attitudes, and beliefs from healthcare providers treating allergic rhinoconjunctivitis (ARC) with AIT (Leatherman et al., 2014). This study surveyed 500 healthcare providers, including 50 NPs,

who provided care at least once a week to at least one patient with (ARC) (Leatherman et al., 2014). Total responses from NPs and Physician Assistants (PAs) were combined and 10% reported using sublingual immunotherapy (Leatherman et al, 2014). However, raw data from this study is unpublished. Additionally, Cox (2014) reports that since 2000, it is estimated that over one billion doses of sublingual immunotherapy have been administered in the U.S. by physicians, physician assistants, and NPs, but does not further quantify how many doses have been prescribed by NPs alone. These studies provide supplementary information to this study and confirm that there is a small number of NPs prescribing sublingual immunotherapy. Further studies would be warranted to evaluate if targeted education influences prescribing practices.

Barriers

Barriers to diagnosing allergies and treating with sublingual immunotherapy differ between healthcare specialties. In a survey of U.S. allergists (N=520), the most common reasons for not prescribing sublingual immunotherapy included lack of FDA-approval, lack of established practice parameters, unknown effective dose, and inadequate training (Sikora et al., 2012). While the lack of FDA-approval is a significant prescribing barrier for allergist, it was not a significant barrier for a majority of NPs in this study. In comparison, this survey demonstrated that a lack of general prescribing knowledge is more of a significant barrier for NPs. Lack of training was also cited as the primary barrier preventing otolaryngologist and other physicians from prescribing AIT in the AIRS study (Leatherman et al., 2014). This difference in perceived barriers between allergists, NPs, and other healthcare providers, is an expected outcome as allergists are trained specifically to treat and manage allergic disease. It was anticipated that limited or no knowledge of treating allergic disease with allergen immunotherapy would be common among NPs. The findings in the AIRS study also illustrates

that the variability in training influences practices and beliefs between specialties (Leatherman et al., 2014). As additional sublingual immunotherapy tablets and potentially aqueous solutions, gain FDA-approval, it is likely that awareness of AIT and prescribing knowledge will increase. Targeted education and collaboration between specialties will serve to improve the diagnosis and treatment of allergic disease, including the evidence-based use of AIT (Leatherman et al., 2014).

Skin Testing

Evidence-based treatment guidelines for diagnosing allergic disease recommend the skin prick test (SPT) as the first-line diagnostic tool, in conjunction with the patient history and physical assessment. In this study, serum IgE testing was used more frequently than SPT to diagnose allergies (12.9% and 0.65%, respectively). However, the majority of NPs did not perform any allergy testing (81.29%) and referred patients to a specialist for further management. These results are similar to the AIRS study as 24.7% of NPs and PAs combined, used blood tests to diagnose ARC, while only 1.1% performed skin testing, and 71.9% did neither (Blaiss et al., 2014). The "Joint Force Practice Parameter" recommends initial allergy testing by SPT as it is safe, less expensive and more sensitive that serum IgE testing, and results are immediate (Cox, Nelson, & Lockey, 2010). Serum IgE testing should be reserved for those that are unable to have skin testing or if further diagnostic information is needed.

Study Limitations

Due to the homogeneity of survey responses, it is unknown if a larger sample size would yield significantly different results. The lack of NPs prescribing sublingual immunotherapy in this study could also be attributed to the fact that none of the respondents reported allergy and immunology as a subspecialty. Study results may be generalizable to Family Nurse Practitioners, but may not be applicable to other specialties. The following section discusses

how the findings in this study may be applied to DNP practice to improve best practice when prescribing sublingual immunotherapy.

Implications in DNP Practice

The results of this study indicate the need for NP education in treating allergic disease. This includes NPs practicing in rural areas, who may confronted with limited referral options due to geographic and financial limitations. The World Allergy Organization recommends collaboration between primary care providers and allergist in treating patients with allergen immunotherapy (Canonica et al., 2014). Improving education for providers on diagnosing and treating allergies as well as improving community awareness are also sanctioned by the World Allergy Organization (Canonica et al., 2014). Current evidence supports the use of allergen immunotherapy as a treatment modality when other therapies have failed, but this therapy is not frequently employed in practice. Clinical guidelines and consensus statements from experts in allergen immunotherapy were used to develop an algorithm to guide NPs when treating allergic disease with sublingual immunotherapy (Canonica et al., 2009; Canonica et al, 2014; Cox et al., 2010; Wise & Schlosser, 2012). Figure 2 outlines the algorithm.

The first step in treating allergic disease begins with a patient evaluation. The patient history and physical assessment must be consistent with allergic disease and other potential causes of symptoms should be ruled out. Once the diagnosis of allergic disease has been made, the next step is to structure a management plan.

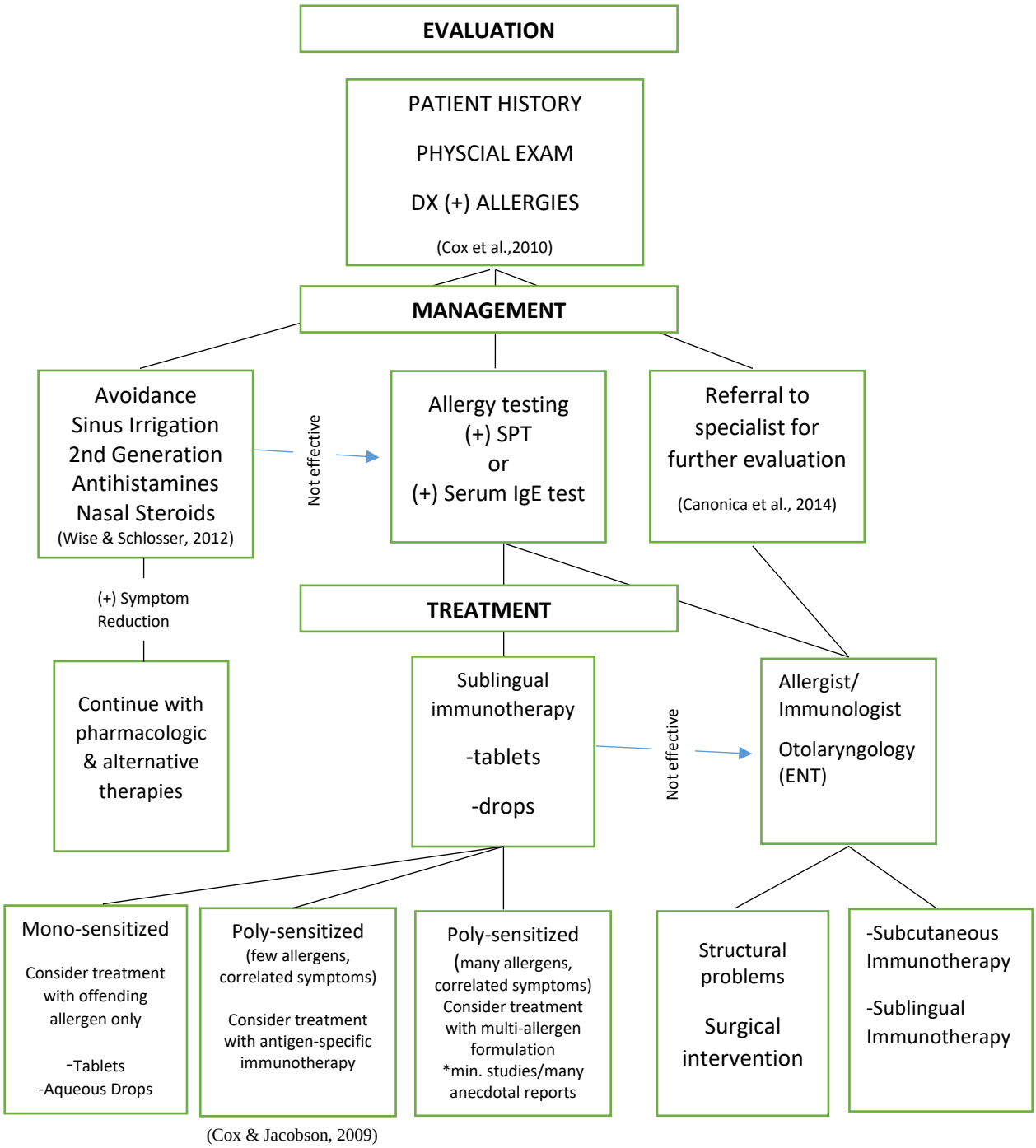
Management options include symptom control therapies, allergy testing, or referral to a specialist, such as an otolaryngologist or allergist for further evaluation. If the patient is well-controlled using non-pharmacological treatments, antihistamines and/or nasal steroids, then allergen immunotherapy is usually not indicated. If the patient continues to be symptomatic,

then allergy testing and further management is necessary. Positive allergy testing may indicate the need for allergen immunotherapy.

The final stage is to develop a treatment plan. If sublingual immunotherapy is an appropriate treatment option, a NP must then decide to either refer to a specialist or follow safe and efficacious recommendations. An evaluation of different sublingual treatment options is important in determining the safest, most efficacious, and cost effective treatment for the patient. Patients not improving with sublingual immunotherapy or have a history of increased risk for anaphylaxis, or potential structural abnormalities should be referred to a specialist.

Figure 2

Algorithm for Evaluation and Management of Allergies with Allergen Immunotherapy



(Cox & Jacobson, 2009)

Dissemination of Results

NPs would benefit from additional education regarding sublingual immunotherapy. The results of this study will be submitted to the *Journal of Nurse Practitioners (JNP)* for potential publication. Study results may be submitted to future NP conferences for further dissemination of recommendations for best practice when prescribing sublingual immunotherapy.

Conclusion

The media and market availability of medications often influence treatment and prescribing practices among NPs and other clinicians. With the recent over-the-counter availability of commonly prescribed nasal steroids and the FDA-approval of three sublingual tablets, allergy treatment is a predominant topic of interest. This study demonstrated the need for additional education for NPs in the area of allergen immunotherapy. Increased knowledge of the most recent indications and treatment options, as well as testing and referral knowledge, may potentially alleviate many of the barriers associated with sublingual immunotherapy. This will improve best-practice and expand treatment options for patients.

Appendix A

LITERATURE REVIEW TABLE

Randomized controlled trials (RCTs) – Databases: EMBASE, PubMed, Cochrane Library
Key words: sublingual immunotherapy

Author/ Title	**Study Design/ Methods**	**Purpose**	**Sample Size**	**Results**	**Conclusions**	**Limitations**
Ahmadiafshar, A., Maarefvand, M., Taymourzade, B., Mazloomzadeh, S., & Torabi, Z. (2012). Efficacy of sublingual swallow immunotherapy in children with rye grass pollen allergic rhinitis: a double-blind placebo-controlled study	Randomized, DBPC study of 5-18 year olds with rye grass pollen allergy rhinitis or rhinoconjunctivitis for > 2 years & positive SPT to rye grass Rye grass spray extracts 10, 100, 300 IR	The effects of SLIT on symptoms and medication score and skin prick test (SPT) evaluation of patients with allergic rhinitis	N=24 (5-18 years) N=12 treatment group N=12 placebo	Significant reduction in symptom score at 21 weeks for treatment group Significant reduction in medication scores at 15 weeks for treatment group Adverse effects increased in placebo group from 19th-22nd week. Significant reduction in wheal diameter from baseline to 6 months for rye	Study showed that SLIT is safe and effective for treatment of allergic rhinitis in 5-18 years and high doses of allergen may be safely administered at home.	Small sample size Short duration of treatment Statistical significance only calculated for SPT

				grass and grass in treatment group		
Amar, S. M., Harbeck, R. J., Sills, M., Silveira, L. J., O'Brien, H., & Nelson, H. S. (2009). Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in multiallergen extract	Single-center, randomized, double-blind, placebo-controlled trial with SLIT Treated for 10 months	To examine whether the efficacy of SLIT w/timothy extract was reduced when combined with other allergen extracts	N=54 N=17 MAT Timothy 1mL 100,000 BAU/mL 680 µg/mL Phl p 5 & 9 mL 50% gly. Soln (19 µg Phl p 5) plus 1 mL 1:20 w/v in 50% glycerin, maple, ash, juniper, American Elm, cottonwood, Kochia, ragweed, sagebrush, Russian Thistle N=19 TM Timothy 1mL 100,000 BAU/mL 680 µg/mL Phl p 5 & 9 mL 50% gly. Soln (19 µg Phl p 5) N=17 Placebo	No significant differences in pre-post symptom scores (P=0.96) or medication scores (p=0.7) in all 3 groups. Nasal challenge improved w/TM vs. placebo (p=0.03), no diff. MAT vs. placebo (P=0.11) tSPT TM (P=0.001) improvement vs. placebo, MAT (P=0.04) vs. placebo Timothy-specific IgG4 increased in TM only (P-0.005); Decrease IFN-γ in TM only (-	Clinically relevant responses achieved with monotherapy; MAT showed limited response	Low grass pollen count during observational season, all 3 groups had improved medication & symptoms scores Small sample size Low risk bias

				0.62; P=0.09)		
Aydogan, M., Eifan, A. O., Keles, S., Akkoc, T., Nursoy, M. A., Bahcecil er, N. N., & Barlan, I. B. (2013). Sublingu al immunot herapy in children with allergic rhinoconj unctivitis mono-sensitize d to house-dust-mites: a double-blind-placebo-controlle d randomis ed trial	Randomized to active or placebo by double-blind method for 12 months. DSS, medication scores, baseline lung functions, bronchial hyper reactivity, nasal provocation & skin prick tests	Asses the clinical efficacy and safety of house dust mite (HDM) SLIT for children with AR mono-sensitized to HDM without asthma	N=18 N=8 Active group; cum dose 11.7 mg Der p1 & 28.2 mg Der f1 N=10 Placebo	No significant differences detected between groups based on total rhinitis symptoms/ medication scores (P>0.05). Decrease in total conjunctivi tis symptoms for both groups, but no statistical difference (p>0.05). No difference in cough, wheezing or asthma symptoms	Small sample size	
Bozek, A., Ignasiak, B., Filipows ka, B., & Jarzab, J.	Randomized DBPC trial 60-75 year olds for 3 years Staloral 300 SR Der p &	Assess nasal symptom s during HDM season, reduce	N=111 60-75 years w/AR & HDM allergy N=51 SLIT	Total nasal symptom score reduced 44% (P<0.05) in HDM	Significant clinical improvement in active group w/SLIT & well tolerated.	7-point visual analogue scale used to pick up small

(2013). House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis	Der f 50/50% extract Average cumulative dose 421 200 IR of allergens for all 3 years	medication use & monitor adverse advents during immunotherapy	N=57 placebo	SLIT; 6% in placebo after 3 yrs. Total medication score decreased in HDM group 35% (P<0.05); no change in placebo group (P=0.56) No systemic adverse reactions	Aging immune system does not appear to influence the effectiveness of immunotherapy.	differences in nasal reaction and diaries filled weekly to simplify the procedure for older adults, but could reduce the reliability of the results.
Bush, R. K., Swenson, C., Fahlberg, B., Evans, M. D., Esch, R., Morris, M., & Busse, W. W. (2011). House dust mite sublingual immunotherapy: results of a US trial	Randomized, double-blind, placebo-controlled feasibility SLIT study over 12-18 months *D farinae* sensitive adults with allergic rhinitis with or without mild intermittent asthma	Compare the safety and physiologic effects of high vs. low-dose *Dermatophagoides farinae* vaccine (HDM) in adults 18-50 with ≥ 2 yr. hx of allergic rhinitis, positive SPT to D. *Farinae,* and *in vitro* D	N=31 N=10 High-dose (4200 allergen units 70 µg of Der f 1/d) N=10 Low-dose (60 allergen units 1 µg Der f 1/d) N=11 Placebo	AE': All subjects tolerated the highest targeted daily dose of treatment. 55.6% high-dose 57.1 low-dose 60% placebo Symptoms and medication use: No significant differences between treatment group &	SLIT with high-dose D *farinae* appears to be safe and tolerable in adults. No significant differences were found in symptom scoring or medication use between the 3 groups.	Dust samples were low and self-collected by study participants. Small sample size All participants were poly-sensitized to other aeroallergens

		farinae-specific serum IgE > 2x that of non-allergenic control		placebo after 12 months. IgE serum slight, but statistically non-significant increase in high-dose group at 6 mo. & end of study. IgG4 levels in high-dose significantly increased at 6 mo (P=.03) & end of study (P=.02) Bronchoprovocation: significant increase in high dose group only (P=.04 vs placebo)		
Cortellini, G., Spadolini, I., Patella, V., Fabbri, E., Santucci, A., Severino, M., ... Passalacqua, G.	Randomized, prospective, double-blind, placebo-controlled, 2 parallel groups trial Patients with rhinitis with or without intermittent asthma and ascertained	To assess the efficacy of standardized SLIT in patient sensitized to *Alternaria*	N=27 (14-42 years) N= 15 SLIT (cum dose 60 µg of Alt a 1) N=12 placebo	Mean (SD) symptom scores reduced in active group (182 [67] vs 315 [115], P=.02) Medication scores significant reduction in active	Results favored SLIT for symptom reduction and medication scores only in active group. Cum 60 µg Alt a 1 = 6 µg per month – considered low dose	Small sample size Short length of study Difficulty in recruitment due to strict inclusion criteria

(2010). Sublingual immunotherapy for Alternaria-induced allergic rhinitis: a randomized placebo-controlled trial	allergy to *Alternaria* 10 months of SLIT or placebo			group (P=.02) Mean (SD) diameter of wheal decreased vs baseline (10.9 [3.4] vs 8.7 [3] mm) 1 patient has oral itching and conjunctivitis in active group with spontaneous resolution		Only 1 maintenance dose was used. A dose-ranging study would be necessary to see if efficacy could be improved.
Creticos, P. S., Esch, R. E., Couroux, P., Gentile, D., D'Angelo, P., Whitlow, B., ... Coyne, T. C. (2014). Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingu	Phase 3 RCT DBPC in North America (US & Canada) parallel group (26 centers) for 18-55 year olds with or without asthma Treatment or placebo 8-16 weeks before & through the end of ragweed pollen season. (MTD approx.. 50 µg Amb a 1)	To determine the efficacy and tolerability of standardized glycerinated short ragweed sublingual allergen immunotherapy liquid (RW-SAIL) extract in subjects with ragweed-related allgeric rhinoconj	N=218 RW-SAIL N=211 placebo	43% decrease in TCS in RW-SAIL compared with placebo The change from baseline in active treatment and placebo TCS was 0.82 versus 1.44, respectively Median change was 0.45	Potential bias. Several authors have potential conflicts of interests with allergen extract manufacturer (Greer) and Drug Manufacturers (Merck, TEVA, GlaxoSmithKline, & Sunovian). Scores were adjusted from baseline to account for polysensitization. Could be seen as enhanced treatment effect of	

al-liquid immunotherapy for allergic conjunctivitis	The primary end point was subject-assessed total combined daily rhinoconjunctivitis symptom and medication scores (TCS)	unctivitis (ARC)		versus 0.92 (difference in LS means, 20.83 [95% CI, 21.30 to 20.37]; P <.001) Significantly greater increase in ragweed-specific IgG4 antibody with RW-SAIL than with placebo [0.99 (60.13) versus 20.01 (60.01) mg/L]	primary end point	
De Bot, C. A., Moed, H., Berger, M. Y., Roder, E., Hop, W. C., De Groot, H., ... Van der Wouden, J. C. (2012). Sublingual	Randomized DBPC trial SLIT in children 6-18 yrs. old with HDM allergic rhinitis for 2 years Maintenance dosing after escalation 20 drops twice weekly (1 mL or 700 BU) Der p 1, Der f 1	Investigate if SLIT for dust-mite allergic children is safe and effective in primary care	N=257 N=251 safety population N=226 ITT population N=185 PP (per protocol) population	Mean nose symptoms score reduced 37% in placebo, 26% in active group No significant differences between placebo and active study drug for well	No significant effects of SLIT when compared with placebo Low dose SLIT not effective for HDM in children with allergic rhinitis	Lower than normal cum dose (435 mcg of Der p 1) for most studies could account for low efficacy. Twice-weekly dosing

immunotherapy not effective in house dust mite-allergic children in primary care				days, use of rescue meds, eye symptoms, asthma symptoms.		regimen may contribute to low efficacy
Eifan, A. O., Akkoc, T., Yildiz, A., Keles, S., Ozdemir, C., Bahcecil er, N. N., & Barlan, I. B. (2010). Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic /rhinitis children sensitized to house	Single center, prospective, randomized, controlled, open labelled, 3 parallel group trial Symptom, medication, & VAS evaluated for 12 months	Compare SLIT, SCIT & pharmacology in relation to clinical efficacy & immunological mechanisms in asthmatic /rhinitis children sensitized to house dust mite (HDM)	N=48 children (5-10 years old) N=16 SLIT (total 295.5 µg Der P 1 295.5 µg Der f 1 N=16 SCIT 111µg Der P 1 156 µg Der f 1 N=16 Pharm	SLIT & SCIT demonstrated significant reduction in total rhinitis & asthma symptoms score, total medication score, VAS & skin reactivity to HDM ($P<0.05$) compared to pharmacotherapy No AE's with SLIT. 2 AE's with SCIT	SCIT & SLIT demonstrated clinical improvement over pharmacotherapy in asthma/rhinitis children with HDM No difference in SCIT & SLIT – equally effective in controlling severity of disease SCIT 2 AE's SLIT had greater reduction in medication usage than SCIT	Small sample size increased risk of statistical error II & raised ethical issues without using a placebo

dust mite: an open randomized controlled trial						
Fujimura, T., Yonekura, S., Horiguchi, S., Taniguchi, Y., Saito, A., Yasueda, H., ... Okamoto, Y. (2011). Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in 2-year sublingual immunotherapy (SLIT)	Randomized, DBPC clinical trial Japanese Cedar in Japan (Cry j 1) 2000 JAU extract contains 1.5-4.2 µg of Cry j 1 (monthly cum. Dose 8000 JAC/10 µg) Primary endpoints: safety & clinical effects of SLIT & upregulation of iTregs as a response monitoring biomarker Secondary: Carry-over effects, immunological changes, and biomarkers for positive clinical	Examine the therapeutic effects of SLIT to identify potential biomarkers that would predict therapeutic response over 2 pollen seasons	N=130 N=58 SLIT N=43 placebo	Mild symptoms (SMS≤4) SLIT 55% Placebo 28% Increase in IL2 ($p<0.05$), IL3 (p=N.S.) in mild subgroup significantly less than placebo– tendency to be attenuated compared with severe subgroup (P=0.053) SMS correlated with sIgE/tIgE ratio in SLIT group (Rs=0.39, $P<0.01$) but not in placebo (Rs=0.008, P=n.s.)	SMS significantly ameliorated in SLIT group when compared with placebo. Treatment with SLIT may be more effective in those with low sIgE/tIgI ratio than with high ratio. iTregs may downregulate effector cells at local sites of inflammation to suppress clinical symptoms. A change in the immunoglobulin profile (IgG4) may require higher doses or longer duration of exposure.	Sample size too small to generalize findings in clinical management.

for Japanese cedar pollinosis	effects induced by SLIT			Increased iTreg group had increased QOL symptom & QOL total when compared with placebo		
Makino, Y., Noguchi, E., Takahashi, N., Natsyniti, Y., Kubo, S., Yamada, T., ... Fujieda, S. (2010). Apolipoprotein A-IV is a candidate target molecule for the treatment of seasonal allergic rhinitis	25 patients randomly categorized into placebo-treated and an active treated group with Japanese Cedar pollen extract (2000 JAU/mL maintenance – 15 µg Cry j 1 and 2 to 5 µg Cry j 2)	Precise mechanism of AIT is not well understood. Aim is to identify protein expression signatures reflective of AIT First **Proteomic** study for inhalant allergen immunotherapy	N=25 N=15 actively treated N=9 placebo treated	SMS during peak pollination lower in SLIT group, but not significant (p=.36). No difference in medication scores. QOL SLIT superior to placebo (9.5 ± 8.3 vs 15.9 ± 19.6; P=0.48) Levels of apoA-IV significant reverse correlation with SMS and JRQLQ in active group	Levels of apoA-IV, complement C4A & transthyretin increased in SLIT group, trend not observed in placebo group. Identified proteins associated with SKIT by 2-DE analysis	Small sample size. 37% of population were polysensitized to other allergens

Marogna, M., Colombo, F., Spadolini, J., Massolo, A., Berra, D., Zanon, P., ... Passalacqua, G. (2010). Randomized open comparison of montelukast and sublingual immunotherapy as add-on treatment in moderate persistent asthma due to birch pollen	Open randomized controlled, 2 parallel groups trial (ethics committee denied permission to blind the treatments and use a placebo arm) Endpoints: Seasonal symptoms plus drug intake score, pulmonary function, brochial hyperresponsiveness, nasal eosinophils	Compare the effects of montelukast & SLIT added to standard therapy in moderate asthma over 5 years	N=33 adults N=16 SLIT with birch pollen and fluticasone /salmeterol (500/50 mcg BID) N=17 MK 10 mg/day with fluticasone /salmeterol (500/50 mcg BID)	Upper airway scores (UAS) & Lower airway scores (LAS) improved sign only in SLIT group at 3 & 5 yrs ß2 agonist use and methacholine reactivity were lower in SLIT group at 3 years & both groups at 5 years FEV_1 with constant increase with SLIT group only Nasal eosinophils were reduced at 3 & 5 years only in SLIT group	SLIT as an add-on to treatment for moderate persistent asthma provided greater clinical benefit than montelukast for birch pollen-induced asthma	Absence of placebo control & double dummy design
Marogna, M., Spadolini, I.,	Open, 2-parallel groups, Randomized	Compare effects of inhaled budesoni	N=51 N=25 SLIT	All compariso ns detected a	The magnitude of benefit was greater for the SLIT patients.	Long duration required to

Massolo, A., Berra, D., Zanon, P., Chiodini, E., ... Passalacqua, G. (2009). Long-term comparison of sublingual immunotherapy vs inhaled budesonide in patients with mild persistent asthma due to grass pollen	controlled trial of patients with rhinitis and mild asthma due to grass pollen (Ethics committee denied permission to blind and use a placebo group due to length of study) Build up to 10,000 RU/mL grass pollen Cum. Annual dose 70 µg Phl p 1	de and SLIT for up to 5 years	N=26 Budesonide 800 µg	statistically significant improvement in the SLIT group compared with budesonide group	Improved nasal symptoms not appreciated by inhaled budesonide SLIT produces greater benefit over solely inhaled budesonide in patients with asthma & rhinitis due to grass pollen	appreciate effects of immunotherapy No double blind Parameters evaluated at 3 & 5 years—missing information
O'Hehir, R. E., Gardner, L. M., De Leon, M. P., Hales, B. J., Biondo, M., Douglass, J. A., ... Sandrini, A. (2009).	Randomized DBPC study of adults with moderate to severe perennial rhinitis to HDM for 12 months.	Perform detailed immunological investigation of SLIT-HDM	N=30 N=15 HDM SLIT N=15 placebo	HDM SLIT reduced symptom score ($P<0.05$) and total asthma score ($P< 0.01$) Decrease in CD4+ T cells @ 6 & 9 mo. in	SLIT clinical efficacy supported by longitudinal (within groups) improvement in clinical outcomes & decreases in allergen-specific CD4+ T cell proliferation, transient increase in	Some authors have financial relationships or board membership with pharmaceutical co.

House dust mite sublingual immunotherapy: The role for transforming growth factor-b and functional regulatory T cells				active group ($p<0.05$) Der p 2 (but not Der p 1) – specific IgG4 increased in SLIT ($p<0.05$), but not placebo & maintained at 24 mo.	CD4+CD25+Foxp3+/CD127^{lo} Possible difference between perennial & seasonal allergens	
Ott, H., Sieber, J., Brehler, R., Folster-Hoist, R., Kapp, A., Klimek, L., ... Merk, H. (2009). Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the	Randomized DBPC study (2:1 randomization) 7.9-64.7 years old with grass pollen allergy, ultra-rush titration	Evaluate the efficacy, carry-over effect and safety of grass pollen SLIT using co-seasonal treatment **E**fficacy, safety, & tolerability of **C**oseasonal ultra-**R**ush sublingual **I**mmuno **T**herapy **(ECRIT)**	N=213 (7.9-64.7 years) randomized, but data obtained for 183 patients & diaries for 145 patients – ITT population. N=99 SLIT w/21 µg Phl p 5 (mix cocksfoot or orchard, meadow, perennial rye, sweet vernal & timothy grasses) N=46 placebo	Combined symptom & medication score decreased significantly w/SLIT (P=0.043); magnitude of efficacy 33.9% for symptom with SLIT (P=0.0366); Medication decrease not statistically significant	Efficacy of co-seasonal treatment was demonstrated over 3 years and may be beneficial for those presenting late for treatment	Study applicable to adults and need confirmation before generalization to pediatric population Study sponsored by allergen extract manufacturer

ECRIT study						
Pajno, G. B., Caminiti, L., Crisafulli, G., Vita, D., Valenzise, M., De Luca, R., & Passalacqua, G. (2011). Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy: A randomized controlled study	Randomized, open, with two parallel groups (inclusion of placebo group denied by ethics committee due to length of study)	Phase IV open study to compare the clinical efficacy of a continuous and a coseasonal SLIT for grass allergy for 3 years in 8-16 year olds with hx of rhinoconjunctivitis / asthma only during grass pollen season in the last 2 years	N=80 N= 40 CON-SLIT w/ 300 IR/ml (14 mcg/ml Phl p 5) w/6 day build up then maint of 6 gtts 5 days/wk N=40 COS-SLIT (same dose started on the first days of pollen season (March) until the end of June)	Year 1: Symptom scores, medication scores, & chest symptoms significantly lower in CON-SLIT than baseline (p=0.001, 0.007, 0.02 respectively) COS-SLIT only medication scores was reduced (p=0.05) SMS reduced CON-SLIT 44% COS-SLIT 20% (p=0.04) Symptom scores fell 39% CON-SLIT; 15% COS-SLIT (p=0.02) Medication scores fell 60% CON-SLIT and 18% COS-SLIT (p=0.03)	Continuous treatment with grass pollen SLIT in children with seasonal respiratory allergies was more effective than co-seasonal treatment in the 1st year. Co-seasonal reached similar efficacy in year 2 and equal in 3rd year.	No blinding or placebo group

				Chest symptoms reduced in CON-SLIT 72% and 11% in COS-SLIT (p<0.01) Year 2: No significant difference between groups SMS, Medication scores. Symptoms CON-SLIT fell 51%, COS-SLIT 34% (p=0.04) Chest symptoms CON-SLIT 88% & 53% COS-SLIT (p=0.05) Year 3. No sign diff		
Pozzan, M., & Milani, M. (2010). Efficacy of sublingual specific immunotherapy in patients	Randomized, assessor-blinded, parallel group, placebo-controlled 3 year study	Evaluate the efficacy of SLIT treatment – clinical improvement and rescue medication usage in patients	N=52 N=34 SLITI with AA one vial/day w/o up-dosing for 3 years (Alt a 1 cum monthly dose 3.6 µg/month)	VAS score 4.7±0.8 SLIT; 2±1.5 placebo (P=0.0002) 97% clinical improvement in SLIT group;	SLIT with *Alternaria alternata* efficacious and well tolerated over 3 year course for patients with AA respiratory allergy	The study was not double-blind Efficacy was not assessed with validated

with respiratory allergy to Alternaria alternata: a randomised assessor-blinded, patient-reported outcome, controlled 3-year trial		with *Alternaria alternata* allergy	N=18 control group treated with symptomatic drugs only.	27% in placebo (p=0.0001) MS significantly decreased 4.3 to 1.7 (p=0.0001) in SLIT group; Increased in control from 3.4 to 4.		sympto m score MM employee of ALK (SLIT manufacturer)
Skoner, D., Gentile, D., Bush, R., Fasano, M., McLaughlin, A., & Esch, R. E. (2010). Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed pollen.	Randomized, double-blind, placebo-controlled trial. 1-day (rush) dose-escalation regimen until max tolerable or scheduled dose reached. Maintained thru ragweed season	Identify a safe and effective maintenance dose range of sublingual standardized glycerinated short ragweed pollen extracts in adults w/ragweed-induced rhinoconjunctivitis	N=115 N=40 placebo (glycerin soln) N=39 med dose (4.8µg Amb a 1/d) N=36 high dose (48 µg Amb a 1/d)	15% reduction in rhinosinusitis symptom scores (not stat. sign p>.10) Analysis of covariance; symptom scores & medication scores significantly reduced in high-dose group (p≤.05) Ragweed-specific IgG, IgG_4, IgA increased in med &	Maintenance dosed of 4.8 µg-48 µg Amb a 1/d safe & induce favorable clinical & immunologic changes in ragweed-sensitive subjects. Additional trials are needed to establish efficacy	90% of study participants had multiple perennial &/or seasonal allergies – symptoms could be caused by other allergens. Well controlled multi-allergen studies in poly-sensitized subjects

				high dose groups		are needed. Use of subjective endpoint measures based on symptom scores; variability of the magnitude of natural pollen exposure; variability in pt sensitivity. (same limitations in most immunotherapy studies).
Stelmach, I., Kaluzinska-Parzyszek, I., Jerynska, J., Stelmach, P., Stelmach, W., & Majak, P. (2011). Compara	Randomized DBPC 2 year prospective trial of 6-18 year olds with grass pollen rhinitis	Compare the efficacy & safety of SLIT given pre-coseasonally and continuously in children allergic to grass pollen	N=60 (6-18 years old) sensitive to grass pollen with rhinitis N=20 Pre-coseasonal SLIT (Staloral 300 IR 5-grass pollen extract, 3.6	TSS & medication scores, no difference between active groups, both better than placebo ($p<0.05$). Both active significantly reduced nasal,	Both active arms showed reductions in combined symptom and medication scores when compared with placebo, no change between the active groups, Continuous, pre-seasonal therapy was more effective	Small sample size Does not address immune modifying effects due to duration of treatment

tive effect of pre-coseasonal and continuous grass sublingual immunotherapy in children			mg) given 8 weeks before pollen season and through pollen season (6 months of treatment, 6 months of placebo). N=20 continuous SLIT with Staloral 300 IR 5-grass pollen extract for 12 months (7.3 mg) N=20 Placebo given for 12 months	asthma, & ocular symptoms within the groups.	in reducing nasal symptoms, but no difference in asthma or ocular scores.	
Voltolini, S., Troise, C., Incorvaia, C., Bignardi, D., Di Cara, G., Marcucci, F., ... Frati, F. (2010). Effectiveness of high dose sublingual	Randomized DBPC single center trial with birch pollen allergy for 2 years	Evaluated the effects of high dose birch SLIT on birch induced rhinitis and asthma	N=24 N=14 SLIT co-seasonal protocol (cum. 6.9 mcg Bet v 1) N=10 placebo	Significant decrease ($p<0.05$) in rhinorrhea and nasal obstruction Median asthma days 3rd visit: SLIT 10, Placebo 13; 6th visit: SLIT 2, placebo 7;	Birch pollen asthma may be able to step down after prolonged treatment with SLIT birch extract	Small sample size (difficulty finding mono-sensitized adults) Possible non-normal distribution of data due to small sample size

immunotherapy to induce a stepdown of season asthma: a pilot study				Asthma stepdown 77% in SLIT, 0 in placebo (p=0.05) No severe AE's		dictated nonparametric tests, thus the pilot study status. Study funded by extract manufacturer Authors with financialties to extract manufacturer and drug companies
Wahn, U., Klimek, L., Ploszczuk, A., Adelt, T., Sandner, B., Trebas-Pietras, E., ... SLIT Study Group (2012). High-dose sublingual	Randomized DBPC study in children 4-12 years with grass pollen-allergic rhinitis/rhinoconjunctivitis with or w/o bronchial asthma. (Germany & Poland)	Efficacy and safety of high-dose SLIT in children allergic to grass pollen	N=207 (4-12 years old) N=158 Active group (3600-4800 µg of grass group 5) N=49 placebo	Primary outcome: Mean AUC (change of the area under the curve of the symptom-medication score (SMS) from baseline to post 1 pre-/co-seasonal treatment period)	Daily single-dose aqueous grass pollen SLIT is efficacious and safe in children 4-12 years with allergic rhinitis/rhinoconjunctivitis.	Unable to compare results with other SLIT tablet trials due to the inclusion of a baseline season patient symptom diary.

immunotherapy with single-dose aqueous grass pollen extract in children is effective and safe: a double-blind, placebo-controlled study				Active - 212.5 Placebo - 97.8 (P=.0040).		Comparative studies show treatment for >12 months demonstrate greater clinical improvement and should be considered in future guidelines and recommendations
Wang, D. H., Chen, L., Li, K. N., Yuan, H., Lu, J. H., & Li, H. (2013). Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a	Multicenter, randomized DBPC trial with house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farina*) treated for 6 months Symptoms, medication, visual analog scale score were recorded	Investigate how quickly AR symptoms will improve with SLIT, potential side effects, common reason for dropout,	N=120 patients w/AR symptoms screened(4-60 years) N=60 HDM N=60 placebo	Significant decrease in symptoms between HDM group & placebo was week 14 ($p<0.05$) No difference in daily medication scores at each visit; HDM meds lower at weeks 7, 9, 10 than	SLIT w/HDM showed a significant improvement in AR symptoms w/onset at 14 weeks & acceptable safety profiles	20% dropout rate for treatment group; 38% dropout rate for placebo group. SLIT new to China, additional patient education may decrease dropout rates in

multicenter, randomized, double-blind, placebo-controlled trial.				baseline (P<0.05); no change in placebo group VAS reduction week 14 (P<0.05) & more pronounced at end of trial		future studies.

Appendix B

THE UNIVERSITY OF ARIZONA

Human Subjects
Protection Program

1618 E. Helen St.
P.O.Box 245137
Tucson, AZ 85724-5137
Tel: (520) 626-6721
http://orcr.arizona.edu/hspp

Date:	March 06, 2015
Principal Investigator:	Melissa Leann Ferrell
Protocol Number:	1503719837
Protocol Title:	Sublingual Immunotherapy
Level of Review:	Exempt
Determination:	Approved
Documents Reviewed Concurrently:	**HSPP Forms/Correspondence:** *F107 v2014-01_02262015.doc* **HSPP Forms/Correspondence:** *IRB F200_Ferrell_SLIT_02262015_revised IRB.doc* **HSPP Forms/Correspondence:** *Signature page.pdf* **Informed Consent/PHI Forms:** *Document 2_Disclosure.pdf* **Participant Material:** *Document 1.docx* **Participant Material:** *Document 3_Survey Questions.docx*

This submission meets the criteria for exemption under 45 CFR 46.101(b).

- The University of Arizona maintains a Federalwide Assurance with the Office for Human Research Protections (FWA #00004218).
- All research procedures should be conducted in full accordance with all applicable sections of the Investigator Manual.
- Exempt projects do not have a continuing review requirement.
- Amendments to exempt projects that change the nature of the project should be submitted to the Human Subjects Protection Program (HSPP) for a new determination. See the Investigator Manual, 'Appendix C Exemptions,' for more information on changes that affect the determination of exemption. Please contact the HSPP to consult on whether the proposed changes need further review.
- All documents referenced in this submission have been reviewed and approved. Documents are filed with the HSPP Office. If subjects will be consented the approved consent(s) are attached to the approval notification from the HSPP Office.

Your proposal is in compliance with Federalwide Assurance 00004218. This project should be conducted in full accordance with all applicable sections of the IRB Investigators Manual and you should notify the IRB immediately of any proposed changes that affect the protocol. You should report any unanticipated problems involving risks to the participants or others to the IRB.

This project has been reviewed and approved by an IRB Chair or designee.

APPENDIX C

AANP | American Association of NURSE PRACTITIONERS™

The Voice of the Nurse Practitioner

Faculty Advisor Approval of Data Collection Program Proposal

Instructions: Print this form and fill in your name and the title of your research project. Discuss your project with your faculty advisor and obtain his or her signature indicating that they have reviewed and support your research proposal before submitting it to AANP.

Student Researcher: Melissa Ferrell

Project Title: Sublingual Immunotherapy

I, Kate G Sheppard (printed name of faculty advisor), have met with the student listed above and reviewed this research proposal with respect to the proposed participants, methods, instruments, and informed consent requirements.

I hereby support this proposal and student seeking approval to purchase a mailing list from AANP.

Faculty Advisor Signature

3.2.2015
Date

AANP | American Association of NURSE PRACTITIONERS™

The Voice of the Nurse Practitioner®

AGREEMENT FOR USE OF AANP MAILING LIST

The American Association of Nurse Practitioners (AANP) agrees to grant Melissa Ferrell a non-exclusive and non-transferable license to use a mailing list provided by the American Association of Nurse Practitioners consisting of 500 nurse practitioner members with family, pediatric and or allergy/immunology as main specialty (the "Mailing List") subject to the following terms and conditions:

Melissa Ferrell agrees:

- Neither the Mailing List nor the information contained on the Mailing List will be reproduced or used for any purpose other than the single and exclusive purpose of providing a mailing piece approved in advance by AANP concerning *Sublingual Immunotherapy*.
- The Mailing List may not be reproduced, sold, reused, or disseminated for or to third parties.
- The Mailing List may be used only 1 for the purpose indicated above, and will be protected from further use by any other group or individual working on Melissa Ferrell's behalf.
- All copies of the Mailing List will be destroyed within 5 days after the mailing is completed.
- The Mailing List may not be used in connection with any communication which, in the sole opinion of AANP, appears to be deceptive or misleading or which may be unacceptable in content or presentation.
- A hard copy summary of completed research will be submitted to AANP.

To accommodate this arrangement, AANP agrees to supply the Mailing List on a 7-Zip password protected file which will be emailed to Melissa Ferrell.

Melissa Ferrell agrees to remit payment to AANP in the amount of $125.00 representing $0.25/name for each name included on the Mailing List. A check, money order or Visa/MasterCard/AMEX payment in the amount of $125.00 must be received and processed by AANP before AANP will release the Mailing List to Melissa Ferrell.

The parties acknowledge that remedies at law may not be adequate to protect AANP's rights in the event that Melissa Ferrell or his or her employees or vendors breach any duty or provision contained in this agreement. Therefore, the parties agree that in addition to any other remedies at law, AANP shall have the right to injunctive relief in order to enforce its rights under this agreement.

Having read and understood the above items and conditions of this agreement, Melissa Ferrell agrees to assume full responsibility for compliance with this agreement. Any breach of this agreement will subject the undersigned to any or all legal and equitable remedies available to AANP. Noncompliance will disqualify the undersigned from receiving future goods or services from AANP.

If paying with credit card please complete the following and return by fax, or call 512-442-4262 with payment information:

9/17 — Expiration Date
Melissa L Ferrell — Name as it appears on Card
Signature of Card Holder

(Name): Melissa Ferrell, FNP-BC

FNP-BC — Requester Signature / Title
3/11/15 — Date

Email Address for receipt of attached file: melissaferrell7@email.arizona.edu

Please return the executed agreement to:
American Association of Nurse Practitioners Administrative Office
ATTN: Research
P.O. Box 12846
Austin, TX 78711

Or return this agreement by fax: **512-442-5221.**

Appendix D

March 10, 2015

Dear Fellow Nurse Practitioner,

I am a Doctor of Nursing Practice (DNP) student at the University of Arizona. For my DNP project, I am looking at the number of nurse practitioners prescribing allergen sublingual immunotherapy and what barriers exist that prevent the use of sublingual immunotherapy as a treatment for allergies and asthma. Because you are nurse practitioner specializing in the area of Family Practice, Pediatrics and/or Allergy/Immunology, I am inviting you to participate in this study by completing the enclosed survey.

The survey should take approximately five minutes to complete and there is no compensation for participation and no known risks. Participation is voluntary and to maintain confidentiality, please keep your survey responses anonymous and answer the questions as honestly as possible. Feel free to skip any questions that you are not comfortable answering and return the completed survey in the provided stamped envelope by March 24, 2015.

Thank you for taking the time to participate in my study. The data collected will provide useful information about number of nurse practitioners prescribing sublingual immunotherapy and what barriers may exist that prevent the use of allergen sublingual immunotherapy in clinical practice. This information will be used to improve the quality and safety of prescribing practices for nurse practitioners using or interested in using sublingual immunotherapy to treat allergies and asthma. This information will be presented as part of my DNP defense, may be submitted to a nursing or allergy/immunology journal or used as part of an educational presentation for nurse practitioners.

Completion of the questionnaire will indicate your willingness to participate in this study. If you desire additional information or have questions, please contact me at (480) 272-0733.

Thanks again for your participation.

Melissa Ferrell, MSN FNP-BC
DNP student
College of Nursing
University of Arizona
melissaferrell7@email.arizona.edu

Please return surveys to: PO BOX 20695
Mesa, AZ 85277

Project Title: Sublingual Immunotherapy

DISCLOSURE FORM

You are being invited to participate in a research study being conducted by the University of Arizona and asked to read this form prior to your participation so that you are aware of potential risks and how the information you may provide will be used. If you decide to take part in the study, your responses will be anonymous. If you decide you do not want to participate, there is no penalty to you, and you will not lose any benefit you normally would have.

WHY IS THIS STUDY BEING DONE?

The purpose of the study is to ascertain how many Nurse Practitioners are utilizing sublingual immunotherapy for allergy treatment in their practice.

WHAT WILL YOU BE ASKED TO DO IN THIS STUDY?

You will be asked to complete a survey of 8 questions, taking approximately 5 minutes of your time.

ARE THERE ANY BENEFITS, COSTS, OR RISKS TO ME?

There may be no direct benefit to you by participating in the study. What researchers find out from this survey may help other healthcare providers learn how many nurse practitioners are utilizing sublingual immunotherapy as a treatment for allergies in their practice. Aside from your time, there are no costs for taking part in the study. Although the researchers have tried to avoid risks, you may feel that some questions are uncomfortable. You do not have to answer any questions that you do not want to answer.

WILL INFORMATION FROM THIS STUDY BE KEPT CONFIDENTIAL?

Information about you will be kept confidential to the extent permitted or required by law. People who have access to your information include the Principal Investigator and advisement committee. Representatives of regulatory agencies such as the Office of Human Research Protections (OHRP) and entities such as the University of Arizona Human Subjects Protection Program may access your records to make sure the study is being run correctly and that information is collected properly. If there are any professional presentations or publications about this study or survey responses, your name, practice name, e-mail address, or postal address will not be in them.

HOW THE FINDING WILL BE USED?

The results of the study will be used for scholarly purposes only. The results from the study will be presented in educational settings and potentially at professional conferences. The results might be published in a professional journal in the field of nursing and/or allergy and immunotherapy.

WHOM CAN I CONTACT FOR MORE INFORMATION?

The Principal Investigator, Melissa L. Ferrell, FNP-BC, can be reached at (480)272-0733 if you have a concern or complaint about this research study. You may also contact the Principal Investigator's advisor, Kate G. Sheppard, PhD, RN, FNP, PMHNP-BC, FAANP at kbs1@email.arizona.edu. If you want to talk to someone other than the Investigator or advisor, your may call the University of Arizona Human Subjects Protection Program office.

- Local phone number (520) 626-6721
- Website (this can be anonymous: http:///www.orcr.arizona.edu)

By returning the survey in the addressed stamped envelope, you acknowledge that you have read this information and agree to participate in this research survey.

Survey Questionnaire

1. In what state do you hold licensure as a nurse practitioner?

2. What is your healthcare specialty?
   a. Family Nurse Practitioner
   b. Adult-Gerontology Primary Care
   c. Pediatric Nurse Practitioner
   d. Neonatal Nurse Practitioner
   e. Women's Health Nurse Practitioner
   f. Certified Nurse Midwife
   g. Certified Registered Nurse Anesthetist
   h. Other _____

3. Do you currently prescribe sublingual immunotherapy for allergic disease in your practice?
   a. Yes
   b. No

4. For which patient population do you currently prescribe sublingual immunotherapy? (Circle all that apply)
   a. Patients < 5 years old
   b. Patients 5 – 18 years old
   c. Patients 19 – 65 years old
   d. Patients > 65 years old
   h. I do not prescribe sublingual immunotherapy

5. What type of allergy testing do you offer in your practice?
   a. Puncture/scratch skin test
   b. Intradermal skin test
   c. Serum IgE blood test
   d. None – referral to specialist
   e. Other _____

6. What type of sublingual immunotherapy preparation do you use?
   a. Single-allergen (monotherapy)
   b. Allergen-specific formulation based off of allergy test results
   c. Multi-allergen formulation (> 15 allergens)
   d. Sublingual tablets
   e. Other _____
   f. I do not prescribe sublingual immunotherapy

7. Would you consider prescribing sublingual immunotherapy in your practice?
   a. Yes
   b. No
   c. I currently prescribe sublingual immunotherapy

8. What are barriers preventing you from prescribing sublingual immunotherapy in your practice?
   a. Sublingual immunotherapy is an "off-label" route of administration
   b. Minimal or no insurance reimbursement
   c. Limited or no knowledge of how to prescribe or initiate sublingual immunotherapy

d. I prefer to refer patients to an allergist for allergy shots
e. None, I currently prescribe sublingual immunotherapy in my practice
f. Other_____

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