Overview

On June 30, 2015, the Addressing Disparities program at the Patient-Centered Outcomes Research Institute (PCORI) convened a multi-stakeholder workgroup in Washington, DC to solicit input on the topic of immunotherapy options for the treatment of allergic asthma, and identify and refine comparative effectiveness research questions. The workgroup included patients, researchers, clinicians, and other stakeholders and was open to the public via webinar.

Informed by the Agency for Healthcare Research and Quality's (AHRQ) review on allergen-specific immunotherapy and by recent conversations with stakeholders, PCORI is considering funding one or more trials on the comparative effectiveness of subcutaneous versus sublingual immunotherapy for the treatment of allergic asthma, with a specific interest in how these treatments could reduce disparities in asthma outcomes. The workgroup’s deliberations will be used to inform PCORI’s Board of Governors regarding a potential funding announcement.

The workgroup prioritized one topic for a potential comparative effectiveness research trial:

- What is the comparative effectiveness of guidelines-based care (i.e., inhaled corticosteroids) versus guidelines-based care + immunotherapy (subcutaneous and sublingual) on the treatment of allergic asthma among inner-city children?

At the workgroup, there was consensus that the use of immunotherapy for treating allergic asthma is an important topic for clinicians, patients, government agencies, members of Congress, and broad stakeholder groups. However, the workgroup discussed key challenges for PCORI to consider—namely, the off-label use of sublingual immunotherapy and choosing an allergen with the biggest potential for impact on inner-city children with asthma. The Addressing Disparities program will discuss the workgroup’s deliberations and present the results of the discussion to the Strategic Oversight Committee, which will inform a recommendation to PCORI’s Board of Governors regarding a future funding announcement.
**Background**

**PCORI's Investment in Asthma.** Asthma has been a priority for PCORI from the beginning. In June 2013, PCORI released its first targeted funding announcement to increase adherence to the National Asthma Education and Prevention Program guidelines among African Americans and Latinos to reduce persistent disparities in asthma care and outcomes. Through this initiative, PCORI is supporting eight comparative effectiveness trials, representing a $23 million investment—each testing multi-level, multi-component intervention strategies to improve the quality and equity of asthma care. PCORI’s interest in asthma extends beyond the Addressing Disparities program. The organization has funded an additional six studies across its other program areas, bringing PCORI’s total funding for asthma to $36M.

To complement the current cohort of asthma research, PCORI is interested in pursuing a therapeutic asthma topic that would inform patient and provider clinical decision making, and leverage future findings from the existing asthma portfolio.

**Immunotherapy Options for Treatment of Allergic Asthma: Origin of Topic.** Asthma affects 9 percent of the population, and of this group, well over half have allergic asthma. The same allergens that cause hay fever can lead to asthma exacerbations. There are three treatment options for patients with allergic asthma, including allergen avoidance, pharmacotherapy (e.g., inhaled corticosteroids), and immunotherapy. Despite available effective treatments, many patients with asthma do not have their condition under control—a problem that disproportionately affects racial and ethnic minorities. Allergen-specific immunotherapy (IT) is recommended for patients whose allergic asthma cannot be adequately controlled by allergen avoidance and medication.

There are two main forms of IT: subcutaneous IT (i.e., allergy shots) and sublingual IT (i.e., allergen placement under tongue). In 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review on subcutaneous and sublingual IT for treatment of allergic rhinoconjunctivitis and asthma. Overall, the review reports that high-quality evidence is strong that both subcutaneous and sublingual IT are effective and safe for the treatment of asthma, although there is insufficient evidence to favor one form of IT over another. There is increasing interest in sublingual forms of IT as an alternative treatment to subcutaneous IT due to more convenient administration (does not require injections or office visits), potentially improved safety (reduced risk of anaphylaxis), and shorter time to achieve effect. In addition, despite its broad use in Europe, Asia, and Latin America, sublingual IT in the United States was only recently approved by the Federal Drug Administration (FDA). In May 2014, the FDA approved the first three allergen tablets for sublingual administration (two are for grass pollens and one is for ragweed). However, even prior to the FDA approval, US physicians had been increasingly prescribing sublingual IT “off-label” (i.e., they prescribe FDA-approved allergen extracts for oral use instead of their labeled use for injections). AHRQ and the American Academy of Allergy, Asthma and Immunology (AAAAI) have both called for head-to-head trials comparing subcutaneous and sublingual IT for treatment of asthma.

**Workgroup Objective.** The AD program convened a multi-stakeholder workgroup with diverse perspectives to solicit input on a potential trial examining the comparativeness effectiveness of sublingual versus subcutaneous IT for the treatment of allergic asthma. The goal of the workgroup was to identify and refine specific comparative effectiveness research questions and get feedback on topics such as cost and feasibility of a trial, as well as patient, health system, and community considerations.

**Discussion**

Before identifying and refining specific research questions, each workgroup participant offered general insight on how evidence in this clinical area would inform decision making for their own asthma care, a family member’s, and/or their constituents, and discussed high-priority considerations for PCORI to optimize access and sustainability. There was strong consensus that immunotherapy carries enormous potential for treating allergic asthma and reducing disparities. Some say immunotherapy is currently the only hope for a “cure.” However, a potential trial must be pragmatic and employ delivery methods that are realistic for the targeted populations and sustainable for practices and health systems long-term. Two key themes emerged from this discussion:
Access. Workgroup participants discussed the potential for innovation in treatments, such as immunotherapy, to reduce disparities as well as the potential for such innovations to widen existing disparities due to structural barriers to care. There was strong consensus that a potential trial must anticipate and mitigate these barriers, and go where the patients are—that is, extend the practice of immunotherapy beyond the specialty setting and into primary care. Currently, immunotherapy is largely administered by immunologists—specialists who rarely care for populations most likely to experience asthma disparities. The workgroup agreed that a trial comparing immunotherapy treatment options should be closely linked to primary care and/or take place in primary care in order to reach underserved populations, including low-income, inner-city, and rural communities. Beyond the context of a trial, the workgroup also discussed the likelihood of uptake of immunotherapy in the real world. To this end, participants discussed the need for primary care provider training and buy-in from public and private payers.

Patient preferences and adherence. Access to immunotherapy is a fundamental consideration, and patient adherence to immunotherapy is a challenge that follows. Sublingual and subcutaneous IT require different administration and resources (in-office injections by providers versus patient-administered oral tablets), carrying implications for patient-centered care and outcomes. The workgroup discussed several strategies for tailoring the interventions to patient preferences to promote adherence. Participants discussed the importance of effective communication between providers and patients and use of health information technology to accommodate varying levels of health literacy and numeracy. Participants also discussed the possibility of differential responses to treatment, and capturing this data to shed light on which treatment may be better for certain populations. It will also be important to design a trial that fosters a reciprocal relationship between patients and providers, and supports caregivers and families to promote retention in the study.

The workgroup’s discussion made it clear that the foremost consideration for a trial comparing immunotherapy options is choice of allergen (e.g., pollen, ragweed, cockroach). Because specific allergens affect different populations in different environments and, for seasonal allergens, at different times of year, the choice of allergen will dictate the target population (e.g., children versus adults) and setting (e.g., rural versus urban). The workgroup agreed that the trial should be designed to maximize impact on disparities, and this is driven by the choice of allergen. For instance, a trial looking at cockroach immunotherapy is more relevant for inner-city populations than rural populations. Similarly, since allergies to grass and pollen accumulate over time, a trial examining grass or pollen immunotherapy is more relevant to adults than pediatric populations. A complicating factor is that while subcutaneous immunotherapy is approved by the FDA and has been in use for decades, the FDA only recently approved three oral tablets for sublingual administration. Therefore, a trial involving sublingual immunotherapy using an allergen extract that has not been approved by the FDA is considered “off-label” use and would require investigational new drug approval—a process that presents administrative hurdles for investigators.

With these considerations in mind, workgroup participants considered specific research questions for a comparative effectiveness research trial.

Action
There was early consensus among the workgroup participants that the population with the most potential to benefit from immunotherapy are low-income, inner-city children with mild to moderate allergic asthma. Given the context of the discussion and agreement to target children, the workgroup considered three comparative effectiveness research questions. Below is each research question, followed by a summary of considerations and challenges raised by the workgroup.

1. What is the comparative effectiveness of sublingual versus subcutaneous immunotherapy using a mix of standardized seasonal and perennial allergens (timothy grass + ragweed + house dust mite + cat) on the treatment of allergic asthma?
While the subcutaneous administration of a mixture of allergens is approved by the FDA and a practical comparator arm (most allergists in the United States administer multi-allergen immunotherapy), the preparation of multi-allergen extracts for sublingual administration is “off-label” use of the extracts. While this type of off-label use of immunotherapy is common practice among specialists (an estimated 15–30 percent use extracts off-label), there remain the challenges with obtaining investigational new drug approval from the FDA and legal and ethical considerations for PCORI. Off-label use also poses challenges with reimbursement, and therefore has implications for sustainability and access post-trial, particularly for disparities populations.

The workgroup also discussed the choice of allergens and potential for impact. Workgroup participants noted there are other allergens, such as cockroach and mouse, that have a bigger impact on allergic asthma, particularly for children. However, there are ongoing studies at the NIH looking at cockroach immunotherapy among children that would make a trial in this area duplicative and premature. Given these concerns about feasibility and potential for impact, the workgroup recommended not to pursue this research question at this time.

2. What is the comparative effectiveness of a placebo versus sublingual immunotherapy versus subcutaneous immunotherapy on the prevention of asthma among inner-city children?

The workgroup agreed that examining the impact of immunotherapy as a primary prevention strategy of allergic asthma is a very appealing research topic and one that should offer great value to the field. However, there are challenges with this study design. The trial would require a placebo-control group, and a subcutaneous placebo arm entails giving injections to small children with a placebo. While there is clinical equipoise to justify the trial, the subcutaneous placebo arm poses patient considerations, particularly since the participants are children. In addition, the trial requires a 7+ year timeline, which is typically too long for PCORI. Given these factors, the workgroup agreed that this research question is not poised for a trial sponsored by PCORI.

3. What is the comparative effectiveness of guidelines-based care (i.e., inhaled corticosteroids) versus guidelines-based care + immunotherapy (sublingual AND subcutaneous) on the treatment of allergic asthma among inner-city children?

The workgroup agreed that this research question is the most promising question for PCORI. This trial represents a highly individualized, real-world study that would demonstrate if immunotherapy improves asthma outcomes for children whose asthma remains uncontrolled by guidelines-based care. However, the use of immunotherapy, including subcutaneous and sublingual administration, would be at the physician’s discretion. Therefore, this trial also entails off-label use of sublingual immunotherapy. In addition, the workgroup expressed the same concern about choice of allergen and potential for impact. In the context of looking at inner-city children, cockroach would be important to include in the study and there are ongoing studies to establish efficacy for this particular allergen.

Next Steps
The use of immunotherapy for treating allergic asthma is an important topic for clinicians, patients, government agencies, members of Congress, and other broad stakeholder groups. However, the workgroup discussed key challenges with pursuing a trial at this time—namely, the off-label use of sublingual immunotherapy and choosing an allergen with the biggest potential for impact on inner-city children with asthma. The Addressing Disparities program will discuss the workgroup’s deliberations and present the results of the discussion to the Strategic Oversight Committee of PCORI’s Board of Governors (note: this took place in early July 2015).