

Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Protocol

Title of project

ImmunoCAP ISAC and Microtest for multiplex allergen testing in people with difficult to manage allergic disease

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1 Plain English Summary

Allergy is a form of exaggerated sensitivity (hypersensitivity) to a substance which is either inhaled, swallowed, injected, or comes into contact with the skin. The term 'allergy' is used for situations where hypersensitivity results from an overreaction of the immune system in response to external or 'foreign' substances. Foreign substances that provoke allergies are called allergens. Examples include grass, weed and tree pollens, substances present in house dust (particularly the house dust mite), fungal spores, animal products, certain foods, and various chemical agents found in the home and at work.

Most allergic reactions happen when chemicals in the body called IgE antibodies bind to an allergen and are then taken up by specialist cells in the immune system. The body then responds by triggering allergy symptoms such as rash or skin irritation, wheezing, watering eyes, nose irritation, or stomach upset. In extreme cases, a severe allergic reaction (anaphylaxis) can result in difficulties in breathing and can even cause death.

Sometimes patients can be allergic to a number of different substances and it can be difficult to determine exactly what is causing their symptoms.

This project aims to evaluate devices which can measure levels of many different IgE antibodies in a patient's blood at the same time (multiplex allergen testing). It has been claimed that these devices may help in diagnosing the cause of symptoms in patients with an unclear cause of allergy or who are allergic to more than one substance. The project will consider both clinical effectiveness (changes in how people are treated and changes in their allergy symptoms associated with the use of multiplex allergen testing), any additional diagnostic information provided by multiplex allergen testing and cost effectiveness (cost of different assessment strategies).

2 Decision problem

2.1 Population

The indication for this assessment is to evaluate the clinical and cost effectiveness of using multiplex allergen testing (ImmunoCAP ISAC or Microtest) as an adjunct to current clinical investigations in people with allergy that is difficult to manage.

Multiplex allergen testing is likely to be used in secondary care settings or specialist tertiary care centres, as an addition to allergen challenge testing and in addition to or in place of some single specific IgE antibody testing. Multiplex allergen testing may replace some single IgE testing, but where the multiplex testing panel does not include all of the suspected allergens, additional single specific IgE tests may be needed.

Allergy is a term used to describe hypersensitivity to external stimuli (allergens). Hypersensitivity reactions are divided into two categories; IgE-mediated reactions and non-IgE-mediated reactions. IgE antibodies are normally present in very small amounts in the body, but levels are raised in allergic disease. IgE-mediated immune reactions, also called type I hypersensitivity reactions, are typically rapid in onset and can involve extreme acute symptoms as in anaphylaxis or prolonged symptoms (e.g. urticaria or eczema). In an IgE-mediated reaction IgE binds to allergen molecules, which are then taken up by receptors on the surface cells of the immune system causing the release of biologically active agents and consequent response: vasodilation (widening of blood vessels); increased capillary permeability; mucus hypersecretion; smooth muscle contraction; tissue inflammation.

Non-IgE-mediated reactions are less well understood and are mediated by other components of the immune system. They are typically delayed in onset, and occur 4 to 28 hours after exposure.

This assessment will focus on IgE-mediated hypersensitivity.

The term poly-sensitisation usually refers to sensitisation to two or more allergen sources, and the term paucisensitisation has been used to describe sensitisation to between two and four allergens. Poly sensitised patients can be particularly difficult to diagnose because of problems distinguishing between true sensitisation and cross-reactivity. Cross-reactivity occurs when an IgE antibody recognises two different antigens as the same antigen; for example, an IgE antibody that recognises and causes an allergic reaction to Bet v 1 in birch pollen can also trigger an allergic response to Cor a 1 in hazelnut. The structural similarity of Bet v 1 and Cor a 1 means that the IgE antibody cannot distinguish between them. Cross-reactive molecules can be responsible for multiple positive results from skin prick tests and specific IgE tests. These positive results may or may not correlate to clinical symptoms, depending on host factors, allergen and the nature of the exposure. It has been claimed that

multiplex allergen testing may provide improved information about the sensitisation profile in polysensitised patients. This assessment will summarise the available data on information provided by multiplex allergen testing, which is additional to that obtained from single IgE tests and/or skin prick or allergen challenge tests.

It is difficult to obtain reliable statistics on allergy prevalence in the UK. The charity Allergy UK states, on its website, that there are an estimated 21 million adults in the UK who have at least one allergy and that an estimated 10 million of these have 2 or more allergies;¹ however, these figures appear to be taken from a 2010 report on allergy and allergy remedies from the market research company Mintel. Data from the QRESEARCH project, a database containing the pseudoanonymised health records of over 13 million people, from 950 UK general practises,² can provide some information on the prevalence of allergy symptoms and diagnoses seen in primary care and on changing patterns over time. At the end of 2005, QRESEARCH data indicated that approximately one in nine people had a recorded diagnosis of “any allergic disease” (including asthma, hayfever, eczema, anaphylaxis, or peanut allergy); this figure represented a 27.7% increase over a four year period.³ Increases in the incidence of eczema and allergic rhinitis were reported for the same time period; the age and sex standardised incidence of eczema was 9.58 per 1000 patient years in 2001, rising to 13.58 per 1000 patient years in 2005,⁴ with the corresponding figures for allergic rhinitis being 5.57 per 1000 patient years and 7.41 per 1000 patient years, respectively. ⁵ QRESEARCH data also indicate that the incidence of multiple allergic disorders is increasing. The age and sex standardised incidence of multiple allergic disorders was 4.72 per 1000 patient years in 2001, rising to 6.28 per 1000 patient years in 2005. ⁶ Alongside data on increasing incidence of allergic disease, QRESEARCH reports also record increases in the number of allergy-related prescriptions and general practice consultations, which are indicative of an increasing burden upon the NHS.⁴⁻⁶ There are no QRESEARCH publications which specifically report on food allergy. NICE Clinical Guideline 116, Food allergy in children and young people, reports an estimated prevalence for self-reported food allergy of between 3 and 35% for individual foods.⁷ However, the guideline also notes that only 25 to 40% of self-reported food allergy is confirmed by oral food challenge testing⁷

Allergic disease can present as a severe, life-threatening reaction (anaphylaxis). The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network have recommended that anaphylaxis be defined as “a serious allergic reaction that is rapid in onset and may cause death” and is likely to be the diagnosis when there is involvement of skin or mucosal tissue (e.g., hives, angioedema) and airway compromise (wheezing, dyspnoea) and/or reduced blood pressure or associated symptoms (hypotonia, syncope), along with a temporal relationship (minutes to several hours) to a potential causative agent.⁸ There are limited data on the incidence of anaphylaxis in the UK. Hospital Episode Statistics record “allergy (including anaphylaxis)” as the primary diagnosis associated with

Accident and Emergency attendance for around 70,000 cases (approximately 0.4% of all reports) in both 2013 and 2014, however, no separate statistics are recorded for anaphylaxis.⁹ A 2010 study, based on the Health Improvement network database, estimated the UK incidence of anaphylaxis at 21.3 (95% CI: 17.6 to 25.4) per 100,000 patient years.¹⁰ This study included 382 cases of anaphylaxis and the causes were listed as: drug (27%); FOOD (24%); insect (12%); latex (0.8%); idiopathic (27%); no information (10%).¹⁰ NICE clinical guideline CG134, Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode, reports an estimate of 20 UK deaths per year from anaphylaxis from a study conducted in 2000,^{11, 12} but reliable up-to-date data are lacking.

Where data are available, this assessment will focus on studies conducted in the people with allergy that is difficult to manage. If data are lacking for this population, studies conducted in patients with specific allergic disease (e.g. peanut allergy) will not be excluded and all potential clinical applications of multiplex allergen testing will be considered.

2.2 Intervention technologies

The ImmunoCAP Immuno-Solid phase Allergy Chip (ISAC; Thermo Scientific) is a miniaturised immunoassay platform comprising multiple allergen components and a microarray scanner. They are intended to simultaneously measure sensitisation to multiple allergen components in a single blood test. The risk and severity of an allergic reaction to an allergen component varies from person to person. Using these technologies may provide more detailed information about individual sensitisation profiles than single IgE testing. This information may help clinicians to distinguish between genuine sensitisation to an allergen component and cross reactivity, assess the risk of a severe systemic allergic reaction and identify triggering allergen components prior to starting immunotherapy. ImmunoCAP ISAC is intended for use in more complex allergy cases such as those with inconsistent case histories, unsatisfactory response to treatment, those who are polysensitised and patients with idiopathic anaphylaxis. These are people with severe or unclear allergic disease, who test positive to a range of allergens but in whom the true cause of symptoms can be difficult to identify. It is claimed that using the ImmunoCAP ISAC test could improve health outcomes by improving allergy management, more appropriately targeting specific immunotherapy, and reducing the number of investigative diagnostic tests. These improvements could also lead to potential savings to the NHS from reducing the number of tests and avoiding the use of unnecessary immunotherapy.

ImmunoCAP ISAC 112

ImmunoCAP ISAC 112 is a molecular diagnostic test that can simultaneously test for IgE antibodies to 112 components from 51 allergen sources. The Immuno Solid-phase Allergen Chip (ISAC) is a miniaturised immunoassay platform that uses a single sample (30µl) of

serum, plasma or capillary blood to test for IgE antibodies to multiple allergens. ImmunoCAP ISAC is a two-step assay. IgE antibodies from the patient sample bind to immobilized allergen components spotted in triplets on polymer coated slides. Each slide contains 4 microarrays giving results for 4 samples per slide. The results are measured using a biochip scanner (confocal laser scanning devices, in particular the CapitalBio LuxScan 10k microarray scanner are recommended), and evaluated using proprietary software produced by the same company, Phadia Microarray Image Analysis software (MIA). ImmunoCAP ISAC is a semi-quantitative test and results are reported in ISAC standard units (ISU) giving indications of specific IgE antibody levels; the operating range is 0.3 to 100 ISU-E. This range approximately corresponds to a concentration range of 0.3 -100 kilo international units of allergen specific antibody per unit volume of sample (kUA/L) of IgE (1 kUA/L is equal to 2.4 ng/mL). The assay takes a total of four hours, including sample processing and incubation time.

MicroTest

The MicroTest Instrument is a CE-marked automated immunoassay platform which uses microarrays to simultaneously test for 26 allergen components. It is designed for processing and reading protein microarrays of allergens printed in the biochips. The MicroTest instrument can simultaneously process up to five MicroTest biochips, each containing a different serum sample, in each run. The process is fully automated. When the test is completed, the MicroTest Instrument uses a fluorimeter to read the microarrays and the results are semi-quantitative reported on an allergy risk scale of 0 to 4. The user can print or export the reports as appropriate. MicroTest is intended for use in any patient (infants, children and adults) presenting with allergy symptoms.

There is a positive correlation between levels of circulating IgE antibodies and probability of occurrence of allergic symptoms. There are a number of factors that influence whether or not clinical symptoms manifest at a certain IgE level, e.g. age, patient population, concomitant exposure to other allergens, other clinical conditions such as infections etc. Thus it is not possible to establish general cut off values valid for all patients at all times. However, when combined with clinical history, the results of multiplex allergen testing may aid the clinician in the diagnosis of allergy. Multiplex allergen testing should always be used in conjunction with allergy focused clinical history and may be used in addition to or in place of single IgE antibody tests and/or skin prick testing.

2.3 Comparator

The comparator for this assessment will be current standard care, which should always include allergy focused clinical history and can additionally involve tests of IgE antibody

status (single IgE antibody testing), tests of clinical reactivity such as skin prick testing or allergen challenge testing, or a combination of these approaches.

Single IgE testing

Allergen-specific IgE antibody assays are designed to detect and quantify circulating IgE antibodies to a given allergen. Each test is designed to detect antibodies to only one specific allergen. The choice of which antibodies to test for is based on the clinical history of the patient and multiple tests and/or a stepwise strategy which tests for the most likely causative agents first may be required.

The single IgE test process involves incubation of a blood sample with immobilised whole allergen (or component). Allergen-specific IgE in the patient's sample bind to the allergen and unbound antibodies and excess sample are then removed by washing. Anti-IgE antibody, labelled to enable detection (e.g. fluorescently labelled anti-IgE antibody) is then added. The amount of bound allergen-specific IgE is calculated via a standard calibration curve, which is linked to the World Health Organization IgE standard and reported in arbitrary mass units (kilo international units of allergen specific antibody per unit volume of sample [kUA/L]).

Higher levels of IgE are considered to be associated with allergy, but the amount of IgE is not predictive of the severity of reaction. Not all patients with a positive specific IgE test will have clinically manifest allergic reaction when exposed to that allergen. Unlike IgE antibody testing, skin prick tests and allergen challenge tests can provide direct information about clinical reactivity to a given allergen.

Skin prick testing

Skin prick testing (SPT) is a method to diagnose IgE-mediated allergic disease in patients with rhinoconjunctivitis, asthma, urticaria, anaphylaxis, atopic eczema or gastrointestinal symptoms, which are suspected (based on clinical history) to be caused by type I (immediate) allergic reaction. It provides evidence for sensitization in the form of reaction to allergenic stimulus.

The test involves putting a drop of liquid allergen onto the skin, followed by a gentle pin prick through the drop. SPT interpretation utilises the presence and degree of skin reactivity as a marker for sensitisation. When relevant allergens are introduced into the skin, an IgE-mediated immune response occurs. This produces a 'wheal and flare' response which can be quantified. Many different allergens can be tested simultaneously because the resultant reaction to a specific allergen is localized to the immediate area of the SPT.

One potential advantage of SPT compared to *in vitro* measurement of IgE antibodies is that the test can be interpreted within 15 to 20 minutes after the reagent is applied to the skin, and therefore results can potentially be given to the patient in the same consultation. SPT

results provide evidence of clinical reactivity rather than the determining the presence of IgE antibodies which may or may not result in a clinical reaction and SPT can also be utilised to test less common allergens, (e.g. medications, and fresh fruits and vegetables) where no specific IgE antibody assays are available. As with any test, the results of SPT testing must be interpreted in the context of medical history, clinical symptoms and, where appropriate, other test results. It has been suggested that skin prick testing is an inexpensive option. However, whilst the test materials may be relatively inexpensive, any estimation of costs should consider the staff time needed to perform these tests in an appropriate and safe healthcare setting.

Skin prick testing has the following limitations:

- Skin reactivity might be affected by previous ingestion of antihistamines or other drugs
- Children often do not tolerate multiple skin needle pricks
- Prior or coexisting dermatologic conditions, such as eczema may preclude the performance of skin tests
- The potency of antigen extracts needs to be maintained
- Potential systemic reactions may occur.

Allergen challenge testing

Oral food challenges (OFCs) or inhalant challenges can be performed where there is a discrepancy between clinical history and other test results and can be useful in establishing the identity of specific triggers. The most rigorous method for allergen challenge tests is double-blinded and placebo controlled (DBPC), but single (patient) blind and open challenges also can be performed. An open challenge describes a challenge in which the patient can recognise the target trigger and there is no attempt at blinding; this is the least time intensive type of challenge test, but may produce less reliable results as there is the potential for the result to be influenced by either the patient's anxiety about a particular trigger and/or the healthcare professional's expectations. The general methodology of any challenge test is to administer the trigger in gradually increasing doses under a medical setting. Allergen challenge tests should be performed in a setting that is fully equipped for emergency treatment if an episode of anaphylaxis occurs.

2.4 Care pathway

There are a number of NICE guidelines, which consider elements of the diagnosis, management and treatment of allergy.^{7, 11, 13, 14}

Diagnosis

Clinical guidelines consistently emphasise the importance of obtaining a clinical history and asking specific, allergy focused questions.^{7, 14, 15} NICE Clinical Guideline CG116, Food allergy

in children and young people, states that this can be done by General Practitioners or other primary healthcare professionals with the appropriate competencies. According to the guidelines, the following should be included when taking a clinical history:

- Any personal history of atopic disease (asthma, eczema or allergic rhinitis)
- Any individual and family history of atopic disease (such as asthma, eczema or allergic rhinitis) or food allergy in parents or siblings
- Details of any foods that are avoided and the reasons why
- An assessment of presenting symptoms and other symptoms that may be associated with food allergy including questions about:
 - the age of the child or young person when symptoms first started
 - speed of onset of symptoms following food contact
 - duration of symptoms
 - severity of reaction
 - frequency of occurrence
 - setting of reaction (for example, at school or home)
 - reproducibility of symptoms on repeated exposure
 - what food and how much exposure to it causes a reaction
- Cultural and religious factors that affect the foods they eat
- Who has raised the concern and suspects the food allergy
- What the suspected allergen is
- The child or young person's feeding history, including the age at which they were weaned and whether they were breastfed or formula-fed – if the child is currently being breastfed, consider the mother's diet
- Details of any previous treatment, including medication, for the presenting symptoms and the response to this
- Any response to the elimination and reintroduction of foods.

NICE Clinical Guideline CG57, Atopic eczema in children, recommends that healthcare professionals should seek to identify potential trigger factors during clinical assessment including:

- Irritants
- Skin infections
- Contact allergens
- Food allergens
- Inhalant allergens

The Royal College of Paediatrics and Child Health (RCPCH) also provide advice on allergy focused questions to be used when taking a clinical history. An initial screening set of questions is recommended to identify patients, in community settings, for whom a more

detailed allergy history may need to be taken. If allergy is suspected, further questions are grouped into six areas:

- General history questions asking about general health, current medications, previous allergy testing, lifestyle and general home conditions
- General allergy history questions
- Food-related questions
- Respiratory-related questions
- Ear, Nose and Throat (ENT)-related questions
- Skin-related questions

If IgE-mediated allergy is suspected, based on the results of allergy-focused clinical history, NICE Clinical Guideline CG116 recommends that the child or young person should be offered a skin prick test and/or blood tests for specific IgE antibodies to the suspected foods and likely co-allergens. It further recommends that these tests should only be undertaken by healthcare professionals with the appropriate competencies to select, perform and interpret them and should only be undertaken where there are facilities to deal with an anaphylactic reaction.⁷ The guideline also states that information on when, where and how an oral food challenge or food reintroduction procedure may be undertaken should be given to the patient. However these tests should not be performed in primary care.⁷

Management

The management of allergy is dependent upon type and severity and many allergies can be managed and treated in primary care settings. . More severe allergies and more complex patients may require additional management and referral on to specialist services.

NICE Clinical Guideline CG 116, Food allergy in children and young people,⁷ recommends referral to secondary or specialist care when the child or young person has:

- Faltering growth in combination with one or more gastrointestinal symptoms
- Not responded to a single-allergen elimination diet
- Had one or more acute systemic reactions
- Had one or more severe delayed reactions
- Confirmed IgE-mediated food allergy and concurrent asthma
- Significant atopic eczema where multiple or cross-reactive food allergies are suspected by the parent or carer.
- There is:
 - persisting parental suspicion of food allergy (especially in
 - children or young people with difficult or perplexing
 - symptoms) despite a lack of supporting history
 - strong clinical suspicion of IgE-mediated food allergy but

- allergy test results are negative
- clinical suspicion of multiple food allergies

NICE Clinical Guideline CG57, Atopic eczema in children and NICE quality standard QS44, Atopic eczema in children, both recommend that children with a suspected food allergy should be referred for specialist investigation and management by paediatric allergist or paediatric dermatologist.^{13, 14}

With respect to management following a severe acute episode, NICE clinical guideline 134, Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode,¹¹ recommends that prior to discharge a healthcare professional with the appropriate skills and competencies should offer the following:

- Information about anaphylaxis, including the signs and symptoms of an anaphylactic reaction
- Information about the risk of a biphasic reaction
- Information on what to do if an anaphylactic reaction occurs (use the adrenaline injector and call emergency services)
- A demonstration of the correct use of the adrenaline injector and when to use it
- Advice about how to avoid the suspected trigger (if known)
- Information about the need for referral to a specialist allergy service and the referral process
- Information about patient support groups

Treatment

Mild allergies can be treated using over the counter medications such as antihistamines and simple avoidance of the identified allergen(s).

NICE Clinical Guideline CG116, Food allergy in children and young people,⁷ recommends that once an allergy is suspected based on clinical history, information should be provided to the patient about:

- Type of allergy suspected
- Risk of severe allergic reaction
- Potential impact of the suspected allergy on other healthcare issues, including vaccination.

If a food elimination diet is advised information should be provided on:

- What foods and drinks to avoid
- How to interpret food labels

- Alternative sources of nutrition to ensure adequate nutritional intake
- The safety and limitations of an elimination diet
- The proposed duration of the elimination diet
- When, where and how an oral food challenge or food reintroduction procedure may be undertaken

NICE Clinical Guideline 57, Atopic eczema in children,¹⁴ recommends that healthcare professionals should use a stepped approach for managing atopic eczema in children and should tailor the treatment step to the severity of the atopic eczema. Emollients should form the basis of atopic eczema management and should always be used, even when the atopic eczema is clear. Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other treatments such as mild potency topical corticosteroids (for mild eczema), moderate potency topical corticosteroids (for moderate eczema), tacrolimus, bandages (for moderate or severe eczema), potent topical corticosteroids, phototherapy and systemic therapy (for severe eczema only). Very potent topical corticosteroids should not be used without specialist dermatological advice.

In selected patients allergen immunotherapy may be appropriate. It involves the repeated administration, either subcutaneously or sublingually, of allergen extracts. The potential outcomes of immunotherapy are:

- Reducing allergy symptoms on subsequent allergen exposure
- Improving quality of life
- Inducing long-term tolerance

Immunotherapy is time-consuming, expensive and there is a risk of a severe allergic reaction or anaphylaxis during administration. According to the British Society for Allergy and Clinical Immunology (BSCAI) guidelines,¹⁶ the main indications for immunotherapy in the United Kingdom are:

- IgE-mediated seasonal pollen induced rhinitis, if symptoms have not responded adequately to optimal pharmacotherapy
- Systemic reactions caused by hymenoptera venom allergy
- Selected patients with animal dander or house dust mite (HDM) allergy in whom rigorous allergen avoidance and reasonable pharmacotherapy fail to control symptoms

The selection, initiation and monitoring of all patients for immunotherapy should be supervised by specialists in allergy. Immunotherapy should only be administered by physicians and nurses with specialist knowledge of allergy and specific immunotherapy. Immunotherapy is an attractive option for the treatment of food allergies, as its goal is to

induce tolerance in the person. With desensitisation, the treated person manifests a decreased response to the allergen.¹⁶

Regarding treatment following severe acute episodes, NICE clinical guideline 134: , Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode,¹¹ recommends that after emergency treatment for suspected anaphylaxis patients should be offered an appropriate adrenaline injector as an interim measure before the specialist allergy service appointment. An epinephrine autoinjector (EAI) is a medical device for injecting a measured dose or doses of epinephrine (adrenaline), by means of autoinjector technology. It is most often used for the treatment of anaphylaxis. Most individuals with a severe IgE-mediated food allergy are advised to carry an autoinjector in case of accidental exposure. There are many barriers to the successful use of an autoinjector, including the ability to recognize the symptoms of anaphylaxis, the availability and, understanding of how to use the autoinjector, and anxiety associated with its use.

2.5 Patient issues and preferences

Allergic reactions can have a daily impact on the quality of life of the individual, and can affect their ability to participate in everyday and social activities, perform work related duties, undertake examinations and pursue their career of choice. The effect of allergies is described in two reports produced by Allergy UK. The 'Stolen lives' survey found that for 28.4% of respondents allergies had a serious effect on how they planned important life events, and for 26% their allergy severely affected their everyday life.¹⁷ The 'Impact of skin allergy and sensitivity in the UK' report states that 78% of respondents suffered from reactions to their skin allergy all year round, and for 62% their condition had stopped them from going out socially and carrying out day to day activities.¹⁸

Where food allergy is diagnosed, implementing special diets for children can also be difficult for families to manage, particularly where there are multiple dietary requirements in one family. A 2010 review on the psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families reported that non allergic siblings often adopted the restricted diet that the allergic child followed.¹⁹ The same review highlighted the effect of allergy on the quality of life of patients and care givers. It reported that allergy heightened patients' and care givers' anxiety because of the need for constant vigilance, particularly in new situations. It also showed that parents tended to be overprotective of children with allergy, particularly those who have had anaphylaxis. There can also be anxiety for a parent or care giver associated with administering an epinephrine injection.¹⁹

2.6 Summary of decision problem

Full assessment of the clinical and cost-effectiveness of multiplex allergen testing requires studies which measure the effects of using these upon clinical outcomes or, as a minimum, upon further testing and/or treatment pathways. Ideally, such studies would compare these outcomes in patients whose diagnostic work-up included multiplex allergen testing to patients who received standard diagnostic work-up (i.e. with single IgE testing and without multiplex allergen testing).

If no studies of multiplex allergen testing which report clinical outcomes or change to treatment are identified, this assessment will summarise data from studies of any design that report diagnostic information provided by multiplex allergen testing additional to that provided by clinical history and skin prick tests, allergen challenge testing, single IgE tests or combinations of these techniques (i.e. standard care). Similarly, any studies that assess clinical outcomes, treatment changes, or additional diagnostic information associated with multiplex allergen testing will be included, whether or not they report a comparison with single IgE testing. Studies that assess the accuracy of multiplex allergen testing for the predicting clinical reactivity (response to allergen challenge testing), or response to immunotherapy will also be included. This inclusive approach will be taken in order to provide some information on the possible potential role(s) of multiplex allergen testing in the diagnosis of allergic disease. It should, however, be noted that, whilst such studies may be seen as indicative of the potential utility of multiplex allergen testing, they do not constitute evidence of clinical effectiveness for the specified populations and applications.

3 Objectives

The overall aim of this project is to summarise the evidence available to inform estimates of the clinical and cost effectiveness of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease, in secondary or tertiary care settings. Multiplex allergen testing may replace some single IgE testing, but where the multiplex testing panel does not include all of the suspected allergens, additional single specific IgE tests may be needed.

We defined the following research objectives to address this aim:

- To assess the effects on clinical outcomes (e.g. allergy symptoms, incidence of acute exacerbations, mortality, adverse events of testing and treatment, healthcare presentations or admissions, Health-Related Quality of Life (HRQoL)) of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease.

- To assess the effects on treatment (e.g. restriction diets, immunotherapy, use of other medications such as corticosteroids, number of allergen challenge tests required) of adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease.
- To assess the accuracy of multiplex allergen testing in predicting clinical reactivity (response to allergen challenge testing or response to immunotherapy) and to investigate whether multiplex allergen testing can provide diagnostic information additional to that provided by clinical history and skin prick tests, single IgE testing or a combination of these approaches.
- To assess the cost-effectiveness of adding multiplex allergen testing to the investigation of people difficult to manage allergic disease in secondary or tertiary care settings.

4 Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care²⁰ and NICE Diagnostic Assessment Programme manual.²¹

4.1 Inclusion and exclusion criteria

Population

Adults and children with difficult to manage allergic disease who are being assessed in secondary or tertiary care settings. If studies are lacking for this population, studies conducted in people with a single allergy diagnosis (e.g. peanut allergy, latex allergy), which do not specify a reason for further investigation, will also be included. All presentations of allergic disease (respiratory, skin, gastrointestinal, anaphylaxis) will be included.

Intervention/Index test

Multiplex allergen testing:

ImmunoCAP ISAC 112 and previous generations of ImmunoCAP ISAC (ImmunoCAP ISAC 103)

MicroTest

Comparator

The comparator for this assessment will be current standard care, which should always include allergy focused clinical history and can additionally involve tests of IgE antibody status (single IgE antibody testing), tests of clinical reactivity such as skin prick testing or allergen challenge testing, or a combination of these approaches.

Outcomes

Clinical outcomes (e.g. allergy symptoms, incidence of acute exacerbations, mortality, adverse events of testing and treatment, healthcare presentations or admissions, HRQoL, patient anxiety/preferences)

Change to treatment or treatment plan (e.g. restriction diets, immunotherapies, use of other medications such as corticosteroids, number of allergen challenge test required)

Additional diagnostic information – accuracy (sensitivity and specificity) for the prediction of clinical reactivity, as defined by skin prick tests, allergen challenge tests or response to immunotherapy, plus numbers of participants for whom multiplex allergen testing provided additional information (e.g. allergens component-specific information, cross-reactivities, information on multiple sensitisation), diagnostic yield (number of participants with a definitive diagnosis).

Study design

There will be no restrictions on study design. Randomised controlled trials (RCTs), controlled clinical trials (CCTs), diagnostic test accuracy studies (DTAs) and other observational study designs will be eligible for inclusion. Diagnostic accuracy studies will be included only where such studies report the accuracy (sensitivity and specificity) of multiplex allergen testing for the prediction of clinical reactivity, as defined by skin prick tests, allergen challenge tests, or response to immunotherapy; numbers of participants for whom multiplex allergen testing provided additional information will also be recorded. Similarly other observational study designs will only be included if they report measures of additional diagnostic information provided by multiplex allergen testing; studies which only assess concordance between multiplex allergen testing and single IgE antibody testing or other tests, without exploring the possible reasons for any discordance, will not be included.

If any studies are identified that provide direct information on the clinical-effectiveness using multiplex allergen testing in the diagnosis of allergic disease (i.e. trials comparing clinical outcomes or treatment decisions made with multiplex allergen testing to standard diagnostic work-up including single IgE testing), DTAs and other observational studies will be excluded.

4.2 Search strategy

Development of search strategies will follow the recommendations of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,²⁰ Strategies will be based on the technologies of interest.

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase Emtree), any existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches will be used to

generate test sets of target references, which will inform text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies will be developed specifically for each database.

The following databases will be searched for relevant studies from 2005 to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- Pubmed (NLM) (Companion search)*
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley Online Library)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library)
- Database of Abstracts of Reviews of Effects (DARE) (Wiley Online Library)
- Health Technology Assessment Database (HTA) (Wiley Online Library)
- Science Citation Index (SCI) (Web of Science)
- Conference Proceedings Citation Index – Science (CPCI-S) (Web of Science)
- Biosis Previews (Web of Science)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet) <http://lilacs.bvsalud.org/en/>
- NIHR Health Technology Assessment Programme (Internet) <http://www.hta.ac.uk/>
- US Food and Drug Administration (FDA) (www.fda.gov)

*An additional companion PubMed search will be undertaken in tandem with Medline via OvidSP, this approach aims to detect the latest ‘ahead of print’ and ‘Online first’ electronic content promoted by many leading journals.

A supplementary search will be undertaken on the following resource to identify grey literature:

- OpenGrey (Internet) <http://www.opengrey.eu>

Completed and ongoing trials will be identified by searches of the following resources:

- NIH ClinicalTrials.gov (<http://www.clinicaltrials.gov/>)
- WHO International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictrp/en/>)
- ISRCTN Registry (<http://www.isrctn.com>)

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. References in retrieved articles and any relevant systematic reviews will be checked.

No restrictions on language or publication status will be applied. Searches will take into account generic and other product names for the intervention. An example of the initial search strategies to be used is presented in Appendix 1; these will be adapted as necessary following consultation with clinical experts. The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist, using the CADTH Peer Review checklist.²² Identified references will be downloaded in Endnote X7 software for further assessment and handling. References in retrieved articles will be checked for additional studies.

4.3 Review strategy

Two reviewers will independently screen titles and abstracts of all reports identified by searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details; participants characteristics (e.g. age, gender, presenting symptoms, primary allergy diagnosis and method of diagnosis (e.g. skin prick test), duration of disease; details of multiplex allergen testing test (e.g. ImmunoCAP ISAC 112 or 103, MicroTest, full panel or specific components assessed); details of standard diagnostic work-up (e.g. single IgE testing); clinical outcomes (e.g. allergy symptoms, incidence of acute exacerbations, mortality, adverse events of testing and treatment, healthcare presentations or admissions); number of participants in whom treatment or treatment plan is changed and details of changes; accuracy (sensitivity and specificity) for the prediction of clinical reactivity, as defined by skin prick test, allergen challenge test or response to immunotherapy plus numbers of participants for whom multiplex allergen testing provided additional information (e.g. allergens component-specific information, cross-reactivities, information on multiple sensitisation). Data will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

4.4 Quality assessment strategy

The methodological quality of any included RCTs will be assessed using the Cochrane Risk of Bias Tool.²³ Any included DTAs will be assessed using QUADAS-2.²⁴ A narrative description of the potential limitations of any other included studies will be provided. The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by

consensus or discussion with a third reviewer. Applicability of studies to current UK practice will also be considered.

4.5 Methods of analysis/synthesis

We will provide a narrative synthesis involving the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by application of multiplex allergen testing (investigation of known or strongly suspected allergic disease where the cause of symptoms is unclear, risk assessment, or initial diagnosis), the presenting characteristics of participants (e.g. atopic eczema, asthma, idiopathic anaphylaxis), type of multiplex allergen testing, age (adults and children), outcome measure and study design. A detailed commentary on the major methodological problems or biases will also be included, together with a description of how these may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological limitations of the existing evidence base.

If more than one sufficiently similar study is identified that report the same clinical effectiveness or treatment change outcome, meta-analyses will be used to calculate summary effect estimates (e.g. hazard ratios, odds ratio, relative risks, weighted mean differences) together with 95% CIs, using DerSimonian and Laird random effects models.²⁵ Forest plots will be used to display results from individual studies and summary estimates to allow visual assessment of heterogeneity. Heterogeneity will be assessed statistically using the τ^2 and I^2 statistics.

If diagnostic accuracy studies are included and where available data allow, summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions will be calculated for each multiplex allergen testing method compared to diagnosis based on skin prick test or allergen challenge test. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an HSROC curve.²⁶⁻²⁸

5 Methods for synthesising evidence of cost-effectiveness

5.1 Identifying and reviewing published cost-effectiveness studies

Exploration of the literature regarding published economic evaluations, utility studies and cost studies will be performed. A review of published economic evaluations will be undertaken on the following databases, utilising a methodological study design filter where appropriate:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- NHS Economic Evaluation Database (NHS EED)(Wiley Online Library): Please note that records will no longer be added to this resource from 31st March 2015, we will continue to search NHS EED for archival material only.
- EconLit (EBSCO)
- Research Papers in Economics (REPEC) (Internet) (<http://repec.org/>)
- CEA Registry (www.cearegistry.org)

Supplementary searches may be undertaken to focus on original papers that report on cost, cost-effectiveness, or cost-utility analyses that study multiplex allergen testing in people with difficult to manage allergic disease. For our assessment cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model and estimation of model input parameters that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.²⁹ Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

5.2 Evaluation of costs, quality of life and cost-effectiveness

Decision analytic modelling will be undertaken to determine the cost-effectiveness of multiplex allergen testing compared to current clinical assessment in patients referred for specialist allergy investigation in secondary or tertiary care settings. More specifically, the following research question will be addressed:

- What is the cost-effectiveness adding multiplex allergen testing to the investigation of people with difficult to manage allergic disease in secondary or tertiary care settings?

Diagnosis and treatment strategies

The economic analyses will consider multiplex allergen testing compared to current clinical assessment (consisting of clinical history, skin prick testing and/or singleplex specific IgE). Here multiplex allergen testing might be used to inform clinical decisions (i.e. to perform a food challenge and/or to initiate Immunotherapy) through aiding allergy diagnosis, predicting the grade of allergic reaction and/or predicting response to immunotherapy.

Whenever possible, test specific costs and effects will be considered. However, if this is not feasible, the multiplex allergen tests will be assessed as a group (comparing multiplex allergen testing versus current clinical assessment), assuming equal costs and effects of all multiplex tests.

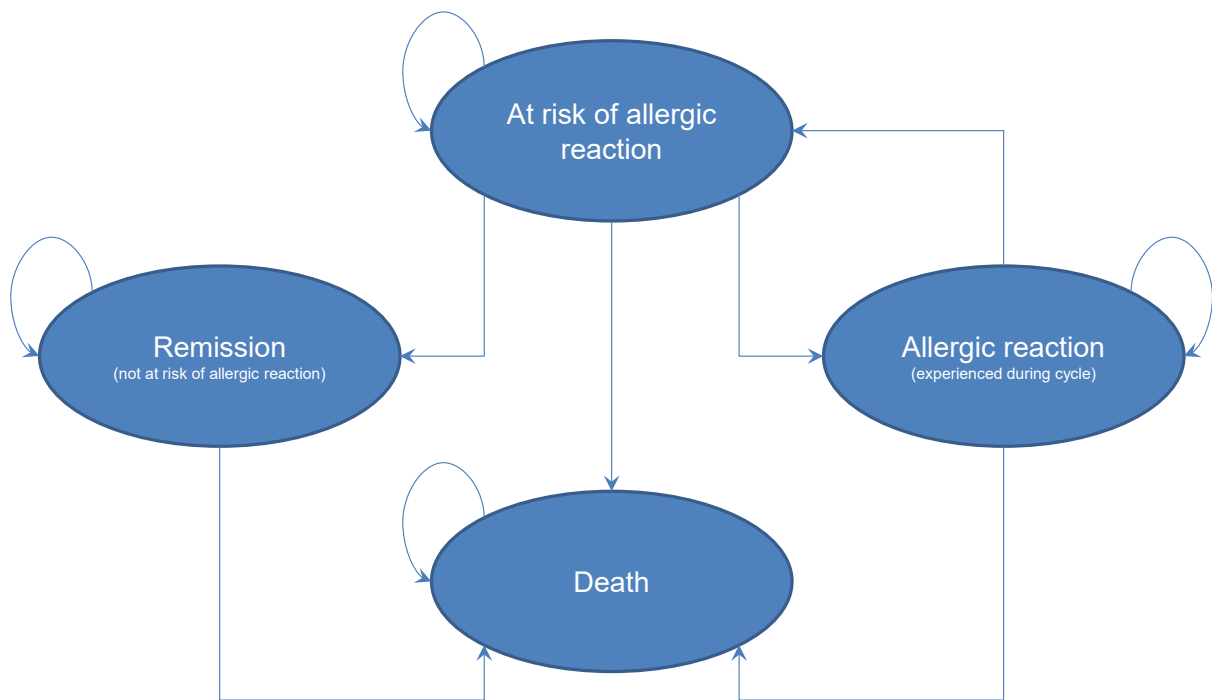
Model structure

The model structure will be developed to take into account the following:

- The patient benefit and costs of current clinical assessment as opposed to multiplex allergen testing.
- The potential health and monetary consequences of (treatments for) allergic reactions and adverse events of testing.

The model is likely to start with a short-term decision tree to model the diagnostic strategy. If the evidence suggests that mortality, allergic reactions or adverse events of testing and treatment differ between the technologies being compared, and these differences impact the cost-effectiveness results, the long term consequences of these differences will be explored by extrapolating the short-term results to a long-term time horizon using a state-transition model (i.e. a Markov model; see Figure 1 for a concept model structure). However, necessary choices and definitions regarding the final structure of the model will depend on the findings from the literature review and consultation with clinical experts. Hence, the concept model structure, presented below, may be adjusted. Moreover, if evidence is lacking, no health economic model or a restricted model will be developed (e.g. restricted to a short-term decision tree (independently on the expected long term consequences), or restricted to exclude some of the costs and consequences listed above).

Figure 1: State-transition model (concept)*



*Potential adverse events of testing will be considered in the short-term decision tree

Health outcomes

Utility values, based on literature or other sources, will be incorporated in the economic model. QALYs will be calculated from the economic modelling.

Costs

Resource utilisation will be estimated for multiplex allergen testing. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), test manufacturers and discussions with physicians.

Issues relevant to analyses

- If possible, given the availability of data, scenario analyses will be performed to examine the impact of the number of specific IgE tests used on the cost-effectiveness.
- Longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the model which are based on expert opinion.
- Probabilistic sensitivity analyses will be performed.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

6 Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 13/07/2015. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

7 Competing interests of authors

None

8 Timetable/milestones

Milestones	Completion data
Draft protocol	16/03/2015
Final protocol	13/04/2015
Progress report	13/07/2015
Draft assessment report	08/09/2015
Final assessment report	06/10/2015
Final executable economic model	08/10/2015

9 References

- [1] Allergy UK. *Allergy Statistics [Internet]*. Sidcup: Allergy UK, 2014 [accessed 10.3.15] Available from: <http://www.allergyuk.org/allergy-statistics/allergy-statistics>
- [2] Hippisley-Cox J. *A description of the 4th version of the QRESEARCH Database: an analysis using QRESEARCH for the Department of Health [Internet]*. Nottingham: Department of Health, 2007 [accessed 5.3.15] Available from: http://www.qresearch.org/Public_Documents/DataValidation/A%20description%20of%20the%204th%20version%20of%20the%20QRESEARCH%20database.pdf
- [3] Hippisley-Cox J, Jumbu G, Fenty J, Holland R, Porter A, Heaps M. *Primary care epidemiology of allergic disorders: analysis using QRESEARCH database 2001-2006: final report to the Information Centre and Department of Health [Internet]*. Nottingham: Department of Health, 2007 [accessed 5.3.15] Available from: http://www.qresearch.org/Public_Documents/HSCIC%20allergies%20report%20from%20QRESEARCH%20.pdf
- [4] Simpson CR, Newton J, Hippisley-Cox J, Sheikh A. Trends in the epidemiology and prescribing of medication for eczema in England. *J R Soc Med* 2009;102(3):108-17.
- [5] Ghouri N, Hippisley-Cox J, Newton J, Sheikh A. Trends in the epidemiology and prescribing of medication for allergic rhinitis in England. *J R Soc Med* 2008;101(9):466-72.
- [6] Simpson CR, Newton J, Hippisley-Cox J, Sheikh A. Incidence and prevalence of multiple allergic disorders recorded in a national primary care database. *J R Soc Med* 2008;101(11):558-63.
- [7] National Institute for Health and Clinical Excellence. *Food allergy in children and young people: diagnosis and assessment of food allergy in children and young people in primary care and community settings NICE clinical guideline 116 [Internet]*. London: NICE, 2011 [accessed 5.3.15] Available from: <http://www.nice.org.uk/guidance/cg116/resources/guidance-food-allergy-in-children-and-young-people-pdf>
- [8] Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report. Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117(2):391-7.
- [9] Health and Social Care information Centre. NHS accident and emergency attendances in England 2013-14: Tables [Excel Spreadsheet]. Leeds: HSCIC, 2015 [accessed 5.3.15]. Available from: <http://www.hscic.gov.uk/searchcatalogue?productid=17200&q=title%3a%22accident+and+emergency+attendances%22&topics=0%2fHospital+care&sort=Relevance&size=10&page=1#top>

- [10] Gonzalez-Perez A, Aponte Z, Vidaurre CF, Rodriguez LA. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol* 2010;125(5):1098-1104 e1.
- [11] National Institute for Health and Clinical Excellence. *Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode: NICE clinical guideline 134 [Internet]*. London: NICE, 2011 [accessed 5.3.15] Available from: <http://www.nice.org.uk/guidance/CG134>
- [12] Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;30(8):1144-50.
- [13] National Institute for Health and Care Excellence. *Atopic eczema in children: NICE quality standard 44 [Internet]*. London: NICE, 2013 [accessed 5.3.15] Available from: <http://www.nice.org.uk/Guidance/QS44>
- [14] National Institute for Health and Care Excellence. *Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years: NICE clinical guideline 57 [Internet]*. London: NICE, 2007 [accessed 5.3.15] Available from: <http://www.nice.org.uk/guidance/cg57/resources/guidance-atopic-eczema-in-children-pdf>
- [15] Royal College of Physicians. *Allergy: the unmet need: a blueprint for better patient care (A report of the Royal College of Physicians Working Party on the provision of allergy services in the UK) [Internet]*. London: RCP, 2003 [accessed 5.3.15] Available from: http://www.bsaci.org/pdf/allergy_the_unmet_need.pdf
- [16] Walker SM, Durham SR, Till SJ, Roberts G, Corrigan CJ, Leech SC, et al. Immunotherapy for allergic rhinitis. *Clin Exp Allergy* 2011;41(9):1177-200.
- [17] Allergy UK. *Stolen lives the allergy report: the impacted allergies on people's lives in the UK today [Internet]*. Sidcup: Allergy UK, 2003 [accessed 5.3.15] Available from: <https://www.allergyuk.org/downloads/resources/reports/stolenlives.pdf>
- [18] Allergy UK. *The disturbing impact of skin allergy and sensitivity in the UK [Internet]*. Sidcup: Allergy UK, 2013 [accessed 5.3.15] Available from: <http://www.allergyuk.org/skinallergyreport>
- [19] Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. *Allergy* 2010;65(8):933-45.
- [20] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 23.3.11] Available from: <http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm>

- [21] National Institute for Health and Clinical Excellence. *Diagnostics Assessment Programme manual [Internet]*. Manchester: NICE, 2011 [accessed 28.8.13]. 130p. Available from: <http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf>
- [22] Canadian Agency for Drugs and Technologies in Health. *CADTH peer review checklist for search strategies [Internet]*. Ottawa: CADTH, 2013 [accessed 17.7.13]. 3p. Available from: <http://www.cadth.ca/en/resources/finding-evidence-is>
- [23] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- [24] Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155(8):529-36.
- [25] Der Simonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7(3):177-88.
- [26] Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PMM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;58(10):982-90.
- [27] Harbord RM, Whiting P, Sterne JA, Egger M, Deeks JJ, Shang A, et al. An empirical comparison of methods for meta-analysis of diagnostic accuracy showed hierarchical models are necessary. *J Clin Epidemiol* 2008;61(11):1095-103.
- [28] Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2007;8(2):239-51.
- [29] National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013 [Internet]*. London: NICE, 2013 [accessed 11.3.15]. 93p. Available from: <http://publications.nice.org.uk/pmg9>

Appendix 1

Clinical effectiveness search – example search strategy

Embase (OvidSP): 1974-2015/03/11

Search Strategy: CN_ImmunoCAP_Emb3

Searched 12.3.15

ImmunoCAP + 2005-Current Date Limit (No animal limit due to topic)

- 1 allergy rapid test/ (312)
- 2 (ImmunoCAP or Immuno-CAP or Thermo Scientific).af. (2098)
- 3 ISAC.ti,ab,ot. (489)
- 4 (Immuno\$ adj3 solid\$ adj3 phase\$ adj3 allerg\$ adj3 chip\$).af. (48)
- 5 (compon\$ adj3 resolv\$ adj3 diagnos\$).af. (531)
- 6 (multi adj3 compon\$ adj3 assay\$).af. (14)
- 7 23\$ allerg\$.ti,ab,ot,hw. (52)
- 8 26\$ allerg\$.ti,ab,ot,hw. (50)
- 9 103\$ allerg\$.ti,ab,ot,hw. (35)
- 10 112\$ allerg\$.ti,ab,ot,hw. (20)
- 11 (Allerwatch or ComforTen or "MultiTest" or "true test" or "Microtest DX" or "Micro Test DX").af. (803)
- 12 or/1-11 (3687)
- 13 exp microarray analysis/ or (microarray\$ or micro array\$ or nanoarray\$).ti,ab,ot,hw. (135882)
- 14 (multiplex adj3 (test\$ or assay\$)).ti,ab,ot,hw. (5843)
- 15 or/13-14 (141421)
- 16 exp hypersensitivity/ or (allerg\$ or anaphyla\$ or hypersensiti\$ or hyper-sensiti\$ or poly-sensiti\$ or polysensiti\$ or paucisensiti\$).ti,ab,ot,hw. (567877)
- 17 15 and 16 (2706)
- 18 12 or 17 (6041)
- 19 limit 18 to yr="2005 -Current" (5154)