

# Pharmacokinetics of Intramuscular Adrenaline in Food-Allergic Teenagers - does dose matter?

## The PIMAT study

Version 1.2

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| Name & Role           | Date         | Signature |
|-----------------------|--------------|-----------|
| PAUL TURNER, Study CI | 29 Sept 2017 |           |

## AMENDMENT HISTORY

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made  |
|---------------|----------------------|-------------|----------------------|--|
| 1             | 1.2                  | 29/9/17     | P.TURNER (CI)        | Inclusion of pregnancy test where appropriate, requested by MHRA |
|               |                      |             |                      |  |

## PROTOCOL SYNOPSIS

|                                     |   |
|-------------------------------------|---|
| Title                               | Pharmacokinetics of Intramuscular Adrenaline in Food-Allergic Teenagers - does dose matter?   |
| Abbreviated title                   | PIMAT study   |
| Eudra CT registration no.           | 2017-003239-13  |
| IRAS Identifier                     | 232931  |
| REC Number                          | 17/LO/1568  |
| Sponsor R&D Number                  | 17SM4137  |
| Clinicaltrials.gov registration no. | NCTxxx  |
| Primary objective                   | To assess the pharmacokinetics (plasma catecholamine levels) and pharmacodynamics (cardiovascular parameters) following intramuscular self-injection of 300mcg and 500mcg adrenaline using an auto-injector device, in food-allergic teenagers over 40kg.   |
| Secondary objectives                | To assess: <ol style="list-style-type: none"><li>1. The pharmacokinetics/pharmacodynamics following intramuscular self-injection of 300mcg adrenaline using different needle lengths (15mm vs 23mm).</li><li>2. The impact of self-administration of adrenaline autoinjectors (in a non-reaction setting) on health-related quality of life (HRQL) measures in food-allergic teenagers and their parents.</li></ol>   |
| Study design                        | Open label, randomised cross-over interventional PK/PD study  |
| Patient group                       | Young people (13-18 years) of body weight over 40kg and prescribed an adrenaline autoinjector due to a diagnosis of IgE-mediated food allergy. Target recruitment: 12 subjects.   |
| Intervention                        | Intramuscular self-injection of adrenaline (using an autoinjector device) on 2 separate days, at least one month apart. The order of injections (300mcg vs 500mcg) will be randomised.  |
| Study outcomes                      | <p>Primary Outcome:</p> <ul style="list-style-type: none"><li>• Plasma catecholamine profile following intramuscular injection of 300mcg vs 500mcg adrenaline.</li></ul> <p>Secondary Outcomes:</p> <ol style="list-style-type: none"><li>1) Change in cardiovascular parameters (HR/BP/SV) and adverse events following IM injection of 300mcg vs 500mcg adrenaline.</li><li>2) Plasma catecholamine levels and change in HR/BP/SV for 3 hours following IM injection of 300mcg using 2 different autoinjector devices with different needle lengths.</li><li>3) Change in HRQL measures 1 month following self-injection.</li></ol> |
| Safety                              | Patient screening to exclude relevant co-morbidities. Study interventions will be conducted on a paediatric research unit with continuous non-invasive cardiovascular monitoring, and overseen by trained clinical staff.   |
| Sponsor                             | Imperial College London   |
| Funding                             | Medical Research Council award to Dr Paul Turner (reference MR/K010468/1)   |

## Study Management

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Imperial College London is the research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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## Funding

Funding has been obtained from a Medical Research Council grant (reference MR/K010468/1) to Dr Paul Turner.

This protocol describes the PIMAT study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary.

Problems relating to this trial should be referred, in the first instance, to the study centre.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

## GLOSSARY OF ABBREVIATIONS

| ABBREVIATION | TERM   |
|--------------|--|
| AAI          | Adrenaline Auto Injector device  |
| ADR          | Adrenaline   |
| AE           | Adverse Event  |
| AUC          | Area under the curve. Derived from the drug concentration-time curve.                  |
| BP           | Blood pressure   |
| $C_{\max}$   | The post-dosing peak plasma concentration of a drug                                    |
| FAIM         | Food Allergy Independent Measure   |
| FAQL-Q       | Food Allergy Quality of Life - Questionnaire   |
| HR           | Heart rate   |
| HRQL         | Health Related Quality of Life   |
| IM           | Intramuscular  |
| PPI          | Patient and Public Involvement   |
| SAE          | Serious adverse event  |
| SAR          | Serious adverse reaction   |
| STMD         | Skin to Muscle Depth   |
| SV           | Stroke volume  |
| $T_{\max}$   | The time (in seconds) to reach $C_{\max}$  |
| $T_{1/2}$    | The time (in seconds) for the drug plasma concentration to reach half it's peak value. |
| USS          | Ultrasound   |

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## 1. INTRODUCTION

### 1.1 BACKGROUND

Food allergy affects up to 2% of adults and 6% of children in the UK; it is the most common cause of life-threatening allergic reactions (anaphylaxis).<sup>1</sup> Food allergy is a major public health issue, with practical implications for the food industry, educational establishments and healthcare systems. The risk of fatal food-induced anaphylaxis is very low but also unpredictable;<sup>2</sup> this contributes to social restrictions and anxiety which result in the adverse impact of food allergy being comparable to that seen with other chronic illnesses, such as diabetes.<sup>3</sup> Although death from anaphylaxis is rare, the risk is greatest for those aged 10-24 years.<sup>2</sup>

A key management strategy is the provision of adrenaline autoinjector devices (AAIs) to those individuals at risk of anaphylaxis.<sup>3</sup> The prescription of AAIs in the UK has more than doubled in the last decade.<sup>2</sup> Prompt administration of intramuscular (IM) adrenaline is the recommended first-line treatment for anaphylaxis: adrenaline results in increased cardiac output, bronchodilatation and stabilization of mast cells and other effector cells, which counteract the effects of the allergic reaction.<sup>3,4</sup>

Currently, three different AAIs are marketed in the UK and EU, available in a variety of doses (table 1).<sup>5</sup> National recommendations on prescribing AAIs vary by weight and age,<sup>6</sup> resulting in significant differences in practice amongst clinicians, and leaving a grey area for dosing in adolescents/adults weighing >30kg.

| Device                           | Mechanism                          | Doses   | Needle length | Needle gauge | Retractable or shielded needle | Shelf life | Distributor               |
|----------------------------------|------------------------------------|---------|---------------|--------------|--------------------------------|------------|---------------------------|
| EpiPen                           | Cartridge                          | 0.3 mg  | 15 mm         | 21           | Yes (shield)                   | 18 months* | Meda Pharmaceuticals Ltd. |
| EpiPen Junior                    |                                    | 0.15 mg | 13 mm         | 21           |                                |            |                           |
| Jext (300)                       | Cartridge                          | 0.3 mg  | 15 mm         | 21           | Yes (shield)                   | 18 months* | ALK Abello                |
| Jext (150)                       |                                    | 0.15 mg | 13 mm         | 21           |                                |            |                           |
| Emerade                          | Triple Spring (pre-filled syringe) | 0.5 mg  | 25 mm         | 23           | Yes (shield)                   | 30 months* | Bausch & Lome Ltd         |
|                                  |                                    | 0.3 mg  | 25 mm         | 23           | Yes (shield)                   | 30 months* |                           |
|                                  |                                    | 0.15 mg | 16 mm         | 23           | Yes (shield)                   | 30 months* |                           |
| Minijet** (not an auto-injector) | Self-assembly                      | 1 mg    | 1.5 inch      | 21           | No                             |            | UCB Pharma                |

Data from SPC; \*from point of manufacture; \*\*no longer recommended for self-injection in the United Kingdom. Note Anapen, AAI withdrawn in United Kingdom.

**Table 1:** Available AAIs in the UK<sup>5</sup>

<sup>1</sup>Turner PJ, Campbell DE. Epidemiology of severe anaphylaxis: can we use population-based data to understand anaphylaxis? *Curr Opin Allergy Clin Immunol.* 2016;16(5):441-50.

<sup>2</sup>Turner PJ, Gowland MH, Sharma V et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol.* 2015;135(4):956-63.

<sup>3</sup>Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;69(8):1008-25.

<sup>4</sup>Simons FE, Ebisawa M, Sanchez-Borges M et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. *World Allergy Organization Journal* 2015;8(1):32.

<sup>5</sup>Ewan P, Brathwaite N, Leech S, et al. BSACI guideline: prescribing an adrenaline auto-injector. *Clin Exp Allergy* 2016;46:1258-80.

<sup>6</sup>Joint Formulary Committee. British National Formulary for children. London: BMJ Group and Pharmaceutical Press; 2016.

A single injection of adrenaline may be insufficient to counteract anaphylaxis: up to 20% of individuals experiencing anaphylaxis require a second dose of IM adrenaline to treat an accidental reaction,<sup>3</sup> and one third of food-induced fatal anaphylaxis cases occur despite timely adrenaline administration.<sup>7</sup> In an ongoing study, we have observed that teenagers may have anaphylaxis which does not respond to a 300mcg dose of self-injected adrenaline, but subsequent episodes respond well to a 500mcg dose (the BOPI study, NCT02149719, IRAS ID 158693). Given that the recommended dose of IM adrenaline for anaphylaxis is 500mcg, these observations imply that for teenagers and adults, using an AAI which only delivers 300mcg may undertreat the reaction and place such individuals at higher risk of severe anaphylaxis.

This concern was highlighted following the death of a teenager in 2010, which on the recommendation of the coroner prompted a review by the MHRA in 2014 into the clinical and quality considerations of AAIs.<sup>8</sup> One recommendation in the MHRA report was that manufacturers 'should be encouraged to develop a 0.5mg [dose] AAI.' Currently, in the UK, only Emerade produces a 500mcg device.

Both the Coroner and MHRA also raised a further concern relating to needle length. As can be seen from Table 1, the current devices have varying needle lengths. In many children, particularly older females, the skin-to-muscle depth (STMD) is greater than the needle length of the AAI, which may result in a subcutaneous rather than intramuscular injection. There are limited data relating to the pharmacokinetics of IM adrenaline in young people and adults, with interpretation of findings being hampered by limitations in study design/sample choice. Simons et al demonstrated that IM (in contrast to subcutaneous) injection of adrenaline into the thigh results in a higher and faster peak plasma adrenaline level in children (Figure 1).<sup>9</sup> Together with anecdotal data that subcutaneous adrenaline results in a slower clinical response, international guidelines for anaphylaxis management recommend the intramuscular route as the recommended route of administration.<sup>3,4</sup> Importantly, no serious adverse events were reported in this and other studies of intramuscular adrenaline injection in healthy children and adults,<sup>9</sup> although mild adverse events included tremor, palpitations and nausea.

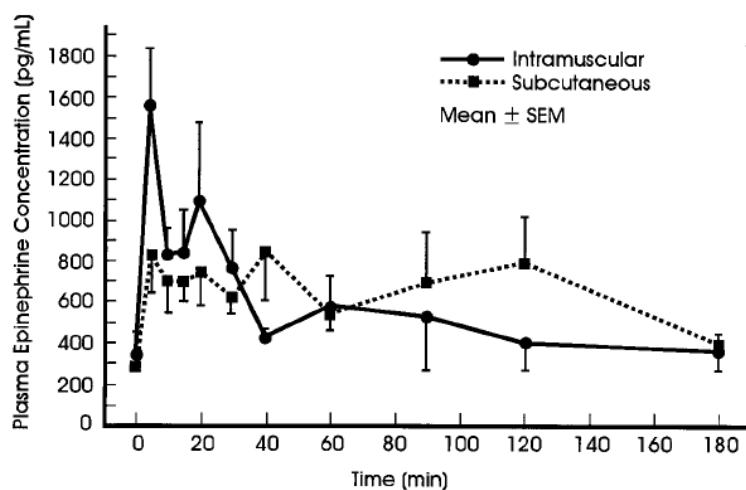


FIG. 1. Mean plasma epinephrine concentration versus time plot after injection of epinephrine subcutaneously in nine children and after injection of epinephrine intramuscularly in eight children.

<sup>7</sup>Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol*. 2007;119(4):1018-9.

<sup>8</sup>Medications and Healthcare Products Regulatory Agency. Adrenaline auto-injectors MHRA. a review of clinical and quality considerations. 04 June 2014. Available at: <http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con423091.pdf>

<sup>9</sup>Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol*. 1998;101:33-37.

Recent data has highlighted that a 15mm needle length may be inadequate to deliver an intramuscular injection in up to 20% of adults (majority female)<sup>10,11</sup> and up to one third of children.<sup>12</sup> The situation may be worse in adolescents: in a UK-based study, over 61% of children weighing >30 kg had a proximal thigh STMD greater than 15mm.<sup>13</sup> This was not limited to overweight/obese children: 25% of children of a healthy weight had a STMD greater than 15mm.

Although compression of the subcutaneous tissues during AAI administration might reduce the STMD, the degree of compression only results in a reduction of 0-1.2mm (interquartile range)<sup>13</sup> and a subsequent study found that unless the deep muscle fascia is breached by the needle, the fascia forms an impenetrable barrier to fluid injected subcutaneously by autoinjectors irrespective of the propulsive force behind the injection.<sup>14</sup> It is therefore not surprising that the MRHA report recommended that “the needle length for all AAIs should be reviewed by the manufacturers and increased, if necessary, to ensure that an intramuscular injection is delivered to a greater proportion of patients”. The MHRA also highlighted that further pharmacokinetic studies are needed to assess the impact of needle length on adrenaline absorption.<sup>8</sup>

In a further UK study of teenagers at risk of food-induced anaphylaxis, Noimark et al reported that over 80% of adolescents did not use their AAI when experiencing anaphylaxis.<sup>15</sup> The reasons provided included being unclear of the indications for AAI use, fear of self-administering the AAI, and fear of possible side-effects. More recently, interventions have been trialed in this age group using self-injection with either a “live” AAI or sterile needle-syringe in a supervised setting outside the context of an allergic reaction;<sup>16,17</sup> these have received positive feedback, although no formal HRQL data assessment was made. Additional support for such an intervention has come from a study assessing the treatment of anaphylaxis occurring in hospital by self-injection using an AAI: this resulted in improved HRQL measures in both the allergic individual and their parent(s), irrespective of reaction severity.<sup>18</sup>

<sup>10</sup>Tsai G, Kim L, Nevis IF et al. Auto-injector needle length may be inadequate to deliver epinephrine intramuscularly in women with confirmed food allergy. *Allergy Asthma Clin Immunol*. 2014;10(1):39

<sup>11</sup>Song TT, Nelson MR, Chang JH et al. Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. *Annals Allergy, Asthma Immunol*. 2005;94(5):539-42.

<sup>12</sup>Stecher D, Bulloch B, Sales J, Schaefer C, Keahey L. Epinephrine Auto-injectors: Is Needle Length Adequate for Delivery of Epinephrine Intramuscularly? *Pediatrics* 2009;124(1):65-70.

<sup>13</sup>Bewick DC, Wright NB, Pumphrey RS, Arkwright PD. Anatomic and anthropometric determinants of intramuscular vs subcutaneous administration in children with epinephrine autoinjectors. *J Allergy Clin Immunol Pract*. 2013;1:692-4.

<sup>14</sup>Diaco D, Pumphrey RS, Sharma V, Arkwright PD. The deep fascia of the thigh forms an impenetrable barrier to fluid injected subcutaneously by autoinjectors. *J Allergy Clin Immunol Pract*. 2015;3(2):297-9.

<sup>15</sup>Noimark L, Wales J, Du Toit G et al. The use of adrenaline autoinjectors by children and teenagers. *Clin Exp Allergy* 2012;42(2):284-92.

<sup>16</sup>Rosen JP. Empowering patients with a history of anaphylaxis to use an epinephrine autoinjector without fear. *Annals Allergy Asthma Immunol*. 2006;97(3):418.

<sup>17</sup>Shemesh E, D'Urso C, Knight C et al. Food-Allergic Adolescents at Risk for Anaphylaxis: A Randomized Controlled Study of Supervised Injection to Improve Comfort with Epinephrine Self-Injection. *J Allergy Clin Immunol Pract*. 2017;5:391-7.

<sup>18</sup>Patel, N, Vazquez-Ortiz M, Lindsley, S et al. Does anaphylaxis (with administration of adrenaline) during in-hospital food challenges impact adversely on health-related quality of life? Poster presented at EAACI 2017 (manuscript in preparation).

## 1.2 STUDY RATIONALE & JUSTIFICATION

The MHRA has highlighted the need for further in-human data relating to both dose and needle length in the AAIs prescribed to young people at risk of anaphylaxis, with a particular focus on obtaining pharmacokinetic data. Teenagers and young people are most at risk of fatal food-induced anaphylaxis, and are less likely than other ages to use their AAI.

We wish to formally assess the pharmacokinetics (PK) and pharmacodynamics (PD) of self-injection with intramuscular adrenaline in teenagers who are at risk of anaphylaxis due to food allergy, and have been prescribed AAI.

1. We will compare self-injection with 300mcg vs 500mcg in teenagers of body weight >40kg. We have chosen this weight cut-off as our local Network guidance is to consider switching teenagers over to a 500mcg device from 40-45kg. It should be noted that in a 40kg person, an adrenaline dose of 300mcg results in an effective UNDER-dosing of 30% by body weight.
2. We will also assess the impact of needle length on injection, by comparing two different devices, both of which deliver 300mcg, but one via a 15mm needle and the other with a 23mm needle.

Importantly, and in contrast to previous studies in young people, we will use a randomized-block crossover study such that each participant acts as their own control. This will increase the power of the study, controlling for differences in inter-person variation in adrenaline absorption. By undertaking the study in food-allergic teenagers, we are able to assess the PK and PD in individuals who are at greatest risk of fatal food-induced anaphylaxis, and provide training and supervision to them in the self-administration of AAI, something we have previously demonstrated increases self-efficacy and reduces the adverse impact on HRQL in such individuals.

Our study protocol and information sheets have been developed in consultation with food-allergic teenagers who have participated in previous studies on our research unit. We have specifically asked as to the perceived burden of the proposed interventions and have been reassured that the procedures proposed would not, in their opinion, be a barrier to their participation.

## 2. STUDY OBJECTIVES

### 2.1 PRIMARY OBJECTIVE

- To assess the pharmacokinetics (plasma catecholamine levels) and pharmacodynamics (cardiovascular parameters) following intramuscular self-injection of 300mcg and 500mcg adrenaline using an auto-injector device, in food-allergic teenagers over 40kg.

### 2.2 SECONDARY OBJECTIVES

To assess:

- 1) The pharmacokinetics/pharmacodynamics following intramuscular self-injection of 300mcg using different needle lengths (15mm vs 23mm).
- 2) The impact of in-hospital self-administration of adrenaline autoinjectors, in a non-reaction setting, on health-related quality of life (HRQL) measures in food-allergic teenagers and their parents.

### 2.3 STUDY HYPOTHESES

- 1) In young people over 40kg, intramuscular self-injection of 500mcg adrenaline results in a greater peak plasma adrenaline level compared to 300mcg injection, without causing a significant increase in adverse events.
- 2) In young people over 40kg, self-injection using an AAI with a 23mm needle will result in a more-favourable PK profile than an alternative device with a 15mm needle, without causing a significant increase in adverse events.
- 3) Self-administration of AAI as a method to provide training in the use of AAI is associated with a positive impact of HRQL measures in food-allergic teenagers.

### 3. STUDY DESIGN

**Type of Study:** Open label, randomised cross-over study at a single centre.

**Number of Subjects:** 12 children will be recruited from the Adolescent Allergy Service at St Mary's Hospital, Paddington.

**Expected Duration:** Recruitment to commence 1<sup>st</sup> September 2017

Two clinical visits (full day) one month apart, with a follow-up questionnaire one month after the second visit.

Expected completion: 31 July 2018.

### 3.1 STUDY OUTCOMES MEASURES

#### 3.1.1 PRIMARY STUDY OUTCOME

- Plasma catecholamine profile – determined through  $C_{max}$ ,  $T_{max}$ , AUC – following self-injection of adrenaline (300mcg, 500mcg) on separate occasions.

#### 3.1.2. SECONDARY STUDY OUTCOMES

1. Cardiovascular parameters [HR, BP, SV] following self-injection of adrenaline (300mcg, 500mcg) on separate occasions.
2. Plasma catecholamine levels [ $C_{max}$ ,  $T_{max}$ , AUC] and cardiovascular parameters [HR, BP, SV] following self-injection of 300mcg adrenaline using 2 devices with different needle lengths (15mm, EpiPen 0.3mg; 23mm, Emerade 300mcg).
3. Adverse events following AAI administration.
4. Change in HRQL measures (FAQLQ, FAIM, self-efficacy) 1 month following each study visit.

## 4. STUDY POPULATION

This is an open label, randomised-block crossover study to assess the pharmacokinetics/pharmacodynamics of 2 different doses of adrenaline following self-injection with an auto-injector. Laboratory and cardiovascular assessments will be analysed by personnel blinded as to the intervention received.

### 4.1 RECRUITMENT

Subjects will be recruited from the Adolescent Allergy Service at St Mary's Hospital, Paddington. Potential participants will receive the study information leaflets either in person (during a routine clinic appointment) or via email. Interested participants may be screened by telephone to determine suitability for this study.

### 4.2 ELIGIBILITY CRITERIA:

#### 4.2.1 INCLUSION CRITERIA

1. Age 13 – 18 years inclusive
2. Body mass >40kg
3. Prescription of AAI due to physician diagnosis of IgE-mediated food allergy.
4. Written informed consent from parent/guardian together with patient assent, for participants under 16 years of age. For young people age 16+ years, consent will be obtained from the participant themselves.

#### 4.2.2 EXCLUSION CRITERIA

1. Known cardiac comorbidity (including hypertension, structural or electrophysiological diagnoses) or prescribed a medicine to control cardiovascular disease/hypertension.
2. Known endocrine or renal disease
3. Poorly controlled asthma requiring daily rescue treatment with a bronchodilator.
4. Pregnancy
5. Unwilling or unable to comply with study requirements

All participants must be well on the study day, with:

- No fever ( $\geq 38.0^{\circ}\text{C}$ ) in the preceding 48 hours
- No additional  $\beta$ -agonist containing medication (e.g. Salbutamol) or antihypertensive (e.g.  $\beta$ -blocker) in the 72 hours prior to study visit
- No intramuscular adrenaline given in the preceding week

### 4.3 SUBJECT WITHDRAWAL

Parents/guardians may withdraw their child at any time without giving a reason. In accordance with the current revision of the Declaration of Helsinki and any other applicable regulations, the parents or legal representatives of the child have the right to withdraw the participant from the study at any time and for any reason, without prejudice to his or her future medical care, and are not obliged to give his or her reasons for doing so.

The investigator may withdraw a participant from the study at any time if, in the investigator's clinical judgment, it is in the best interests of the participant's health and well-being. In addition the participant may be withdrawn for any of the following reasons:

- Decision by the Investigator
- Ineligibility (either newly arising during the study, or retrospective having been overlooked at screening)
- Significant protocol deviation where this will impact irreversibly on data integrity  
e.g. failure to administer adrenaline autoinjector correctly
- Participant non-compliance with study requirements
- An adverse event which requires discontinuation of the study treatment, or results in inability to continue to comply with study procedures.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for appropriate follow-up through telephone calls (and/or visits if necessary) until the adverse event has resolved or stabilised.

Any data generated from monitoring or samples already taken from a withdrawn participant will be included in the data analyses, unless specific instruction for their destruction is received from the participant or their parent/guardian. Withdrawn participants will be replaced, where feasible.

## 5. STUDY TREATMENT

### 5.1 DESCRIPTION

- 1) Emerade 500 micrograms solution for injection in pre-filled pen. Emerade 500 micrograms delivers a single dose of 0.5 ml containing 500 micrograms of adrenaline (as tartrate).
- 2) Emerade 300 micrograms solution for injection in pre-filled pen. Emerade 300 micrograms delivers a single dose of 0.3 ml containing 300 micrograms of adrenaline (as tartrate).
- 3) EpiPen® Adrenaline (Epinephrine) Auto Injector 0.3 mg.

### 5.2 DOSAGE AND ROUTE OF ADMINISTRATION

0.3-0.5ml intramuscular injection, to be administered according to the SmPC provided.

### 5.3 DOSE MODIFICATION

No dose modification proposed.

### 5.4 PREPARATION AND ADMINISTRATION OF STUDY DRUG

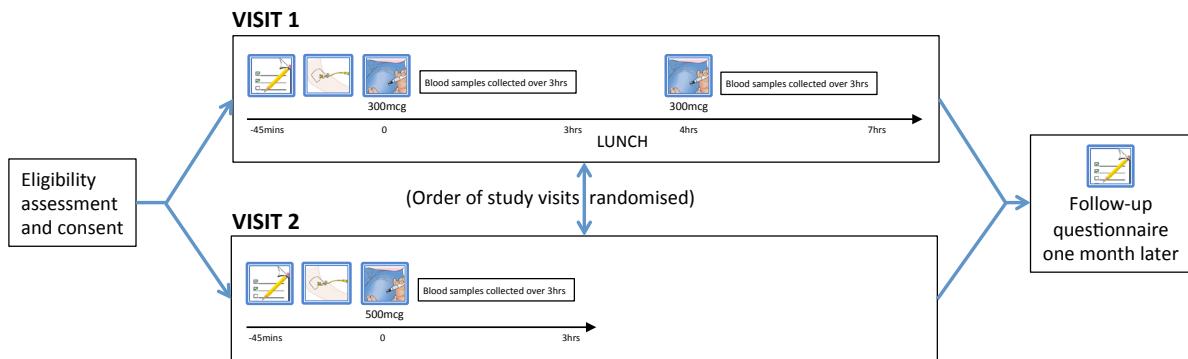
This is a Phase IV study. AAIs will be stored in a locked cupboard on our research unit, and in accordance with SmPC recommendations (room temperature, out of direct sunlight etc). AAI will be administered according to the respective SmPC, following which devices will be disposed of in accordance with local requirements for medical waste.

### 5.5 DISPENSING AND PRODUCT ACCOUNTABILITY

All AAIs will be prescribed on local drug charts prior to study interventions, and released according to local procedure, using existing hospital pharmacy systems and logging (rather than CTIMP-specific documentation). The application for a clinical trials authority will include an exemption for study specific labelling.

**6. STUDY VISITS, PROCEDURES SCHEDULE and PATIENT FLOW DIAGRAM**

The study is summarised in Figure 2:



**Figure 2:** Study Flowchart

Following eligibility assessment (which can be done via telephone or in clinic), participants will be randomised to attend for either:

- 2 x self-administered doses of 300mcg adrenaline (given 4 hours apart), or
- 1 x self-administered dose of 500mcg adrenaline (given using an Emerade 500 device).

These study visits will happen one month apart. On the day when 2 doses of 300mcg adrenaline are administered, the order of devices used (Epipen 0.3mg, Emerade 300mcg) will also be randomised. The randomisation will follow a balanced, randomized-block crossover design, as follows:

| Study visit 1 |                | Study visit 2  |                |                |
|---------------|----------------|----------------|----------------|----------------|
|               | Morning        | Afternoon      | Morning        |                |
| 1             | Emerade 300mcg | Epipen 0.3mg   | Emerade 500mcg | -              |
| 2             | Epipen 0.3mg   | Emerade 300mcg | -              | Emerade 500mcg |
| 3             | Emerade 500mcg | -              | Emerade 300mcg | Epipen 0.3mg   |
| 4             | -              | Emerade 500mcg | Epipen 0.3mg   | Emerade 300mcg |

**Figure 3:** Randomisation table

This randomisation process is designed to reduce the influence of circadian variations on endogenous adrenaline levels and assess any impact of the order of administration of the 300mcg devices. The randomisation list will be generated using an online randomisation tool (<http://www.randomization.com>).

To reduce participant inconvenience, where eligibility has been confirmed, randomisation may occur prior to consent in order to arrange study visits to suit the participant and their family. In such an event, consent will be obtained prior to any intervention at the first study visit.

## 6.1 STUDY PROCEDURES

|   | Visit 1 | Visit 2 | Follow-up one month later   |
|---|---------|---------|---|
| Written Informed Consent (parent/ guardian)<br>Written Assent (young person)  | X<br>X  |         |   |
| Confirm eligibility   | X       |         |   |
| Medical assessment including: <ul style="list-style-type: none"><li>Physical examination</li><li>Height/weight</li><li>Assessment of vital signs</li><li>Peak expiratory flow</li></ul> | X       | X       |   |
| Urine pregnancy test in female participants of child-bearing potential  | X       | X       |   |
| Ultrasound assessment of surface-muscle depth (blinded)   | X       |         |   |
| HRQL assessments<br>(in both young person and parent/guardian): <ul style="list-style-type: none"><li>FAQLQ</li><li>FAIM</li><li>Self-efficacy</li></ul>                                | X       | X       | X<br>Questionnaires done at home and then returned to research team by post or email scan |
| Venous cannulation (with prior use of local anaesthetic cream to minimise discomfort)   | X       | X       |   |
| Non-invasive cardiac monitoring   | X       | X       |   |
| Education of AAI technique, followed by self-administration of AAI and collection of blood samples thereafter.  | X       | X       |   |
| Follow-up telephone call next day   | X       | X       |   |

## 6.2 PRE-INTERVENTION ASSESSMENTS AND PROCEDURES

### 6.2.1 PRE-STUDY PRECAUTIONS

Participants will be asked to avoid tea/coffee/cocoa/cola in the 24 hours prior to a study visit, in order to minimise intake of caffeine or methyloxanthines which may affect plasma catecholamine levels.

### 6.2.2 MEDICAL ASSESSMENT

- 1) Consent and medical eligibility will be confirmed.
- 2) Physical examination and vital signs (HR, BP, Temperature, Respiratory rate and oxygen saturations) with specific assessment for evidence cardiovascular abnormalities.
- 3) Height/weight will be measured according to local protocol.
- 4) Peak expiratory flow rate will be measured using a Wright Peak Flow meter, according to local protocol.
- 5) Urine pregnancy test in female participants of child-bearing potential.

- 6) On the first visit, the surface skin-to-muscle depth (STMD) will be measured by a blinded individual on both legs, at the mid-point of the antero-lateral thigh, by ultrasound. The measurement will be withheld from both the participant/family and the study team until the end of the study for the participant.
- 7) Venous cannulation will be performed to secure venous access, from which blood samples can be taken during the study day without requiring a further needle-stick procedure. Local anaesthetic cream will be applied first for 30mins, to minimise discomfort due to cannulation. The first blood sample will be taken at least 30mins after cannulation, to limit the impact of the cannulation procedure on baseline catecholamine levels.

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### 6.2.2 HRQL ASSESSMENTS

The impact of AAI self-administration (in a non-reaction, supervised setting) on HRQL measures will be assessed both from the participant's and their parent/guardian's perspective using:

- 1) abbreviated versions of disease-specific validated "food-allergy quality of life questionnaire" (FAQL-Q) in its parental,<sup>19</sup> and teenage<sup>20</sup> forms;
- 2) Food allergy independent measure (FAIM)
- 3) Food allergy self-efficacy questionnaire

These will be completed prior to the first intervention on the first study day, approximately 1 month later (which should coincide with the second study visit), and one month later.

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### 6.2.3 STUDY INTERVENTION

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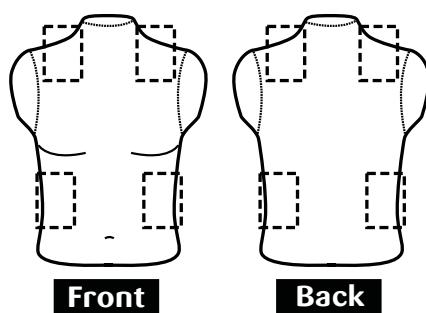
#### 6.2.3.1 PATIENT MONITORING

Participants will be monitored throughout using **non-invasive hemodynamic monitoring** (Cheetah NICOM monitor). The NICOM monitor has been extensively validated, has FDA approval and is CE marked. Data is collected through 4 ECG-type sensors (size 108 x 20 mm) placed on the front or back of the thorax, as shown in Figure 4. Measurements are not prone to movement artefact. The monitor allows for continuous cardiovascular monitoring (including cardiac output and peripheral resistance), and will allow us to monitor the effects of intramuscular adrenaline on the cardiovascular system.

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<sup>19</sup>DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire - Parent Form in children 0-12 years following positive and negative food challenges. *Clin Exp Allergy*. 2010;40:476-85.

<sup>20</sup>Flokstra-de Blok B, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. *J Allergy Clin Immunol*. 2008;122:139-44, 144.e1-2.



**Figure 4: NICOM Sensor placement**

Respiratory monitoring (respiratory rate, oxygen saturations and peak flow) will be performed at regular intervals (prior to, and 10min, 25min, 65min, 125min, 185min after AAI administration).

#### 6.2.3.2 SELF-ADMINISTRATION OF AAI

Participants will be randomised (see Figure 3) as to the order of AAIs administered. In addition, participants will be randomised separately to receive their Emerade dose on the left or right thigh in a 1:1 ratio (with the Epipen dose given on the opposite side at the appropriate time). Each participant will have a printed randomisation log confirming the order of the AAI administrations and the side used for Emerade injection.

Prior to self-administration of the AAI, the participant will receive a demonstration of AAI administration technique and location using a trainer pen, and be asked to demonstrate this on themselves with a trainer pen, prior to actual administration. Administration will be supervised by a trained clinician.

Following administration, the participant will be asked to remain semi-recumbent on a bed for 3 hours. Participants may drink clear fluids but should avoid food for 2 hours, in order to avoid post-prandial effects on endogenous adrenaline levels.

Any AEs reported by the participant will be recorded on a dedicated Case Report Form.

#### 6.2.3.3 BLOOD SAMPLING AND PROCESSING

4ml blood samples (plasma) will be obtained from the venous cannula at the following timepoints AFTER self-injection: 5, 10, 15, 20, 30, 45, 60, 80, 100, 120 and 180 minutes. A maximum of 2.5ml/kg blood will be withdrawn during each study visit. Oral fluid intake will be encouraged and intake volumes monitored.

Blood samples will be taken into sealed Lithium Heparin tubes and immediately put on ice. They will then be transferred at the earliest opportunity to an on-site sample processing laboratory and centrifuged at 2500g, 4°C for 15 mins, then aliquoted and snap frozen at -80°C. Samples will be batched and then transferred on dry ice to the Department of Clinical Biochemistry at the Royal Brompton Hospital for catecholamine measurement.

## 7 ADVERSE EVENT REPORTING

### 7.1 DEFINITIONS

**Adverse Event (AE):** any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

An adverse event will be followed until it resolves or until 30 days after a participant terminates from the study, whichever comes first.

**Adverse Reaction (AR):** all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

**Unexpected Adverse Reaction:** an AR, the nature or severity of which is not consistent with the applicable product information (eg investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). *When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*

**Serious Adverse Event (SAE) or Serious Adverse Reaction:** any untoward medical occurrence or effect that at any dose

- **Results in death**
- **Is life-threatening** – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations.

Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

**Suspected Unexpected Serious Adverse Reaction (SUSAR):** any suspected adverse reaction related to an IMP that is both unexpected and serious.

**Any symptoms requiring treatment for anaphylaxis** (adrenaline, steroids, salbutamol) **will be classified as a SERIOUS ADVERSE REACTION** and must be documented on both the CRF as well as through completion of a SAE form. The investigator should also make a notification to the MHRA through the yellow card scheme (<https://yellowcard.mhra.gov.uk/>).

For the purpose of this study, SARs and SAEs will only be collected where onset is within 24 hours of AAI administration.

### 7.1.1 DOCUMENTATION OF ADVERSE EVENTS

Safety data will be recorded on a specifically designed case report form (CRF). All serious adverse events (SAEs) or reactions (SARs) will be reported on a SAE report form in addition to CRFs. Throughout the study, the investigator will record all adverse events on the appropriate CRF regardless of their severity or relation to study medication or study procedure. The investigator will treat participants experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

SAEs will be reported within 24 hours of the Site Study Team becoming aware of the event. All SUSARs will be reported by the CI to the relevant Competent Authority, Sponsor, REC and other parties, as applicable. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days. All SAE information must be recorded on an SAE form and emailed to the JRCo ([jrco.ctimp.team@imperial.ac.uk](mailto:jrco.ctimp.team@imperial.ac.uk)).

SARs will also be reported to MHRA through the yellow card system.

### 7.2 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

The study site will grade the severity of adverse events experienced by study participants according to the criteria set forth in the NCI-CTCAE Version 3.0

([http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcaev3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf)).

This document provides a common language to describe levels of severity, to analyse and interpret data, and to articulate the clinical significance of all adverse events.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

All adverse events will be recorded and graded whether they are or are not related to disease progression or treatment. The NCI-CTCAE grades will be the primary source for scoring.

The relation, or attribution, of an adverse event to study participation will be determined by the investigator and recorded on CRF and/or SAE reporting form. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below (Table 2). In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made relating to a SUSAR, the MHRA will be informed of both points of view.

| Relationship          | Description   |
|-----------------------|---|
| <b>Unrelated</b>      | There is no evidence of any causal relationship   |
| <b>Unlikely</b>       | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).            |
| <b>Possible</b>       | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments). |
| <b>Probable</b>       | There is evidence to suggest a causal relationship and the influence of other factors is unlikely.  |
| <b>Definitely</b>     | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.  |
| <b>Not assessable</b> | There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.   |

**Table 2: Assignment of causality for adverse events**

### 7.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

#### 7.3.1 NON SERIOUS AR/AES

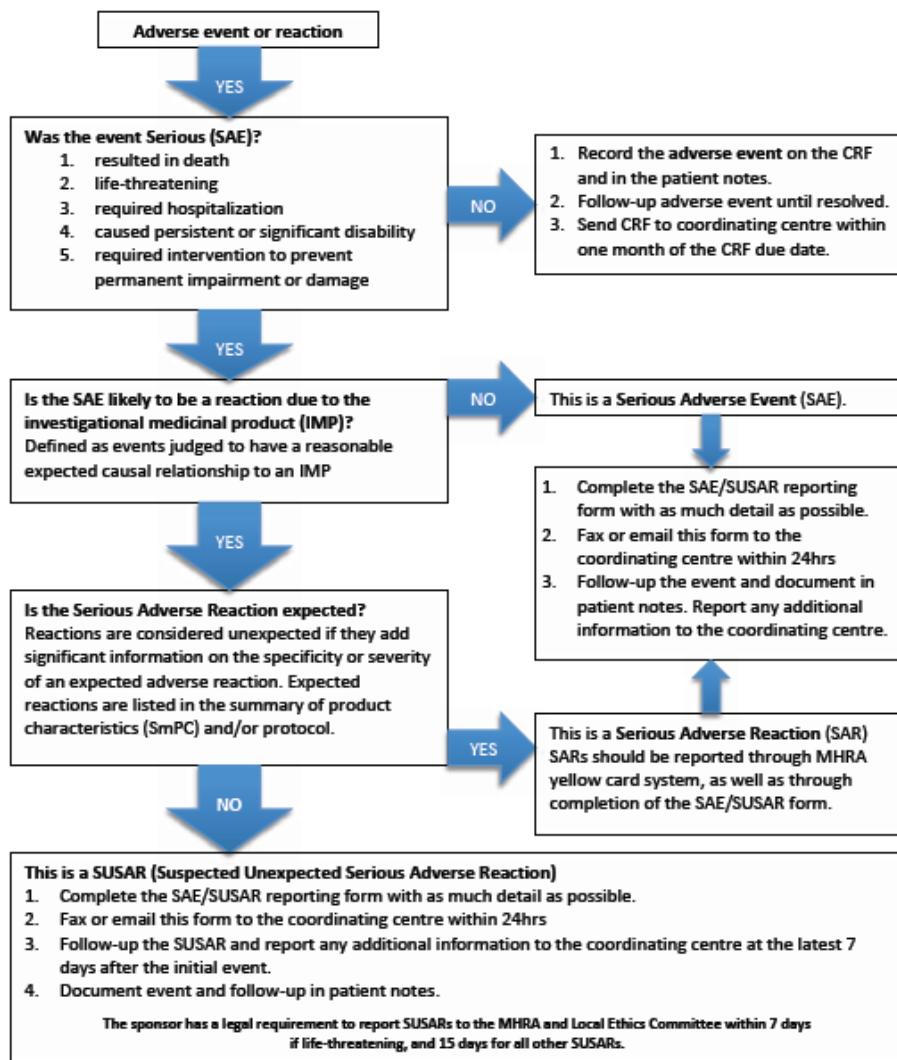
All such events, whether expected or not, should be recorded in the adverse event section of the relevant case report form and reported to the study CI within one month of the form being due.

### 7.3.2 SERIOUS AR/AES

Fatal or life threatening SAEs and SUSARs should be reported on the day of occurrence. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be sent to the CI within 5 days if the reaction has not resolved at the time of reporting. Any expected SAR will also be reported via the MHRA yellow card system.

**SAEs:** An SAE/SUSAR form should be completed and emailed to the study CI immediately, who will in turn inform the JRCO (email to [jrco.ctimp.team@imperial.ac.uk](mailto:jrco.ctimp.team@imperial.ac.uk)) within 24 hours.

**SUSARs:** All SUSARs will be reported by the CI to the relevant Competent Authority (MHRA) and to the REC and other parties as applicable. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.



Contact details for reporting SAEs and SUSARs:

Email: [jrco.ctimp.team@imperial.ac.uk](mailto:jrco.ctimp.team@imperial.ac.uk)

#### 7.4 TRIAL CLOSURE

The expected study duration is ~2 months for any individual participant.

The study will be considered complete following enrolment of the last patient, completion of all study procedures and determination of plasma catecholamine levels in that patient.

No interim analyses are planned.

The study will be placed on hold and, following discussion with the JRCO, may be terminated early if any of the following occur:

- An SAR (whether expected or not) occurring following AAI administration
- Death of a participant during the study period, from any cause

#### 8. DATA MANAGEMENT

Paper records will be maintained at St Mary's Hospital (Imperial College Healthcare NHS Trust) of all participants enrolled in the study. Data will be collected by paper CRF and then transferred to a password-protected electronic record with participants identified by study number. Cardiovascular data from monitoring equipment will be downloaded straight into the electronic record.

Study data will be kept for 10 years following the child's 18<sup>th</sup> birthday, and then disposed of securely. Local paperwork will be kept as part of the patient notes/CRF as per local policy.

## 9. STATISTICS AND DATA ANALYSIS

### 9.1 SAMPLE SIZE ESTIMATION

This is an exploratory analysis to assess the pharmacokinetics/pharmacodynamics of self-injection of adrenaline in young people with IgE-mediated food allergy. Existing PK/PD studies have not, in general, used a crossover design, but a parallel design with sample size from 5-9 participants per study arm.

In this study, with a cross-over design and a sample size of 12, we expect to detect, with 80% power, a treatment difference of 0.35pg/ml at a two-sided 0.05 significance level (this is based on pilot data (n=55) where the standard deviation of the difference between baseline plasma adrenaline levels on 2 separate occasions in the same individuals was 0.39 pg/ml).<sup>21</sup> In a previous parallel-design study comparing EpiPen 0.15mg to 0.3mg, the latter dose was associated with plasma levels of, on average, >500pg/ml.<sup>22</sup> We therefore expect a sample size of 12 should provide sufficient power to detect any difference in plasma catecholamine levels following AAI administration due to differences in dose or needle length.

### 9.2 DATA ANALYSIS

Data analysis will be undertaken by members of the Research Study Team.

#### 9.2.1 ANALYSIS SET

Children aged 13-18 years (inclusive) self-administering AAI according to the study protocol. Analysis will be as treated.

#### 9.2.2 DEALING WITH MISSING VALUES

The reason for missing data will be indicated but missing data will not be imputed.

#### 9.2.3 SUPPLY OF DATA AND LOCKING OF THE DATABASE

Data will be entered into an excel database at Imperial College London. Data will be imported into Prism for analysis. Checks will be performed to ensure correct transfer. Once satisfactory the database will be locked.

#### 9.2.4 INTERIM ANALYSIS

No interim analyses are planned.

<sup>21</sup> [http://hedwig.mgh.harvard.edu/sample\\_size/js/js\\_crossover\\_quant.html](http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html)

<sup>22</sup> Simons FE, Gu X, Silver NA, Simons KJ. EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. J Allergy Clin Immunol. 2002;109(1):171-5.

## 9.3 STATISTICAL ANALYSIS PLAN

### 9.3.1 STATISTICAL PACKAGE

Prism (GraphPad Software Inc) version 7 or higher will be used.

### 9.2 SIGNIFICANCE LEVEL AND CONFIDENCE INTERVALS

95% confidence intervals will be reported. Where comparisons are made between sub-groups a 5% significance level will be used.

### 9.3 ANALYSES

Descriptive tables of numbers by age, gender, baseline variables and adverse events following AAI administration will be produced.

Paired data will be analysed, according to the paired difference between outcomes within the same individual between the different interventions, with all comparisons to data arising from Emerade 300mcg intervention. The planned analyses will therefore be:

- 1) Difference in peak plasma epinephrine ( $C_{max}$ ), time to  $C_{max}$  ( $T_{max}$ ), area under the plasma epinephrine versus time curve (AUC) between Emerade 300mcg and Emerade 500mcg.
- 2) Difference in peak plasma epinephrine ( $C_{max}$ ), time to  $C_{max}$  ( $T_{max}$ ), area under the plasma epinephrine versus time curve (AUC) between Emerade 300mcg (23mm needle) and Epipen 0.3mg (15mm needle).
- 3) Blood pressure, heart rate, stroke volume and change in PEFR versus plasma epinephrine concentrations over time after AAI administration (compared to both baseline and to Emerade 300mcg) will be explored using analysis of variance, analysis of covariance, and linear regression analyses.
- 4) Change in HRQL measures (FAQLQ, FAIM, self-efficacy) 1 month following each study visit, compared to baseline.

Other exploratory analyses:

- 1) Pharmacokinetic parameters of IM adrenaline injection ( $T_{1/2}$ , terminal elimination half-life;  $Cl$ , total body clearance;  $Vdss$ , volume of distribution at steady state) will be calculated from plasma epinephrine concentration versus time plots using Prism.
- 2) For the comparison between Emerade 300mcg (23mm needle) and Epipen 0.3mg (15mm needle), a sub-analysis of the difference in  $C_{max}$ ,  $T_{max}$  and AUC will be undertaken with reference to body weight, BMI and STMD.

Statistical differences will be determined using paired T-test for parametric data, or Wilcoxon signed-rank test for non-parametric data.

## 10. ADMINISTRATIVE AND REGULATORY ISSUES

### 10.1 CLINICAL TRIALS AUTHORISATION

This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA.

Reference: 19174/0381/001-0001.

### 10.2 ETHICS APPROVAL

The Chief Investigator has obtained the required approvals from the London - Hampstead Research Ethics Committee (reference 17/LO/1568). The study will be submitted for Management approval (confirmation of capacity and capability) at the participating NHS Trust. The Chief Investigator will require a copy of the Trust Confirmation of Capacity and Capability before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

### 10.3 INFORMED CONSENT AND PARTICIPANT ASSENT

Consent to enter the study must be sought for each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed consent from the parent/legal guardian should be obtained, along with participant assent will also be sought. The right of the parent/guardian and/or young person to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. In these cases any data or samples already collected will be included within the study for the purposes of follow-up and data analysis.

### 10.4 CONFIDENTIALITY

Participants' identification data will be required for the registration process. Imperial College Healthcare NHS Trust / Imperial College London is registered under the Data Protection Act. The Chief Investigator will preserve the confidentiality of participants taking part in the study under the Data Protection Act. Contact details will be destroyed at the termination of the study.

### 10.5 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

### 10.6 SPONSOR

Imperial College London will act as the main Sponsor for this study.

### 10.7 FUNDING

Funding has been secured through a Medical Research Council award to Dr Paul Turner (grant reference MR/K010468/1).

**10.8 AUDITS**

The study may be subject to inspection and audit by Imperial College Healthcare NHS Trust / Imperial College London JRCO under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

**10.9 MONITORING**

The JRCO Clinical Trial Monitor will be responsible for monitoring this study throughout its duration, including site initiation visit and close out visit. The monitor will conduct a risk assessment and compile a monitoring plan accordingly. After each monitoring visit the monitoring report will be sent to the chief investigator and any action point that needs to be completed will be done so by the study team.

**12 STUDY MANAGEMENT**

The day-to-day management of the study will be co-ordinated through Dr Paul Turner (CI).

**13 PUBLICATION POLICY**

Results of this study will be published in scientific peer-reviewed literature.