



**24-Hour Helpline for Access to Expert Management Advice  
for Food Allergy-Related Anaphylaxis in Children: Protocol  
for a Pragmatic Randomised Controlled Trial**

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## 24-Hour Helpline for Access to Expert Management Advice for Food Allergy-Related Anaphylaxis in Children: Protocol for a Pragmatic Randomised Controlled Trial

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**ABSTRACT**

**INTRODUCTION:** Anaphylaxis is an important, potentially life-threatening paediatric emergency. It is responsible for considerable morbidity and, in some cases, death. Poor outcomes may be associated with an inability to differentiate between milder and potentially more severe reactions and an associated reluctance to administer self-injectable adrenaline. This study aims to assess the effectiveness of 24-hour telephone access to specialist paediatric allergy expert advice in improving the quality of life of children and their families with potentially life-threatening food allergy (i.e. anaphylaxis) compared with usual clinical care.

**METHODS AND ANALYSIS:** Children aged less than 16 years with food allergy and who carry an adrenaline auto-injector will be recruited from the Paediatric Allergy Clinic at Cork Hospital, Ireland and baseline disease specific quality of life will be ascertained using the validated Food Allergy Quality of Life Questionnaire (FAQLQ). Participants will be randomised for a period of six months to the 24-hour telephone specialist support line or usual care. The primary outcome measure of interest is a change in FAQLQ scores, which will be assessed at 1 and 6 months post-randomisation. Analysis will be on an intention-to-treat basis using a 2x3 repeated measures within-between ANOVA. Although lacking power, we will in addition assess the impact of the intervention on a range of relevant process and clinical endpoints.

**ETHICS AND DISSEMINATION:** This trial protocol has been approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. The findings will be presented at international scientific conferences and will be reported on in the peer-reviewed literature in early 2013.

**TRIAL REGISTRATION:** Current Controlled Trials: ISRCTN29793562

## INTRODUCTION

Anaphylaxis is an important, potentially life-threatening paediatric emergency. Food is responsible for the majority of anaphylaxis cases in the paediatric population.<sup>(1)</sup> Egg, milk, peanuts and tree nuts are the most common food allergens in the preschool population; peanut and tree nuts are the most common allergen triggers in older children. There is a wide spectrum of allergic reactions to these allergens ranging from minor urticarial reactions to anaphylaxis, with the associated risk of fatality.

Anaphylaxis is managed via a two-pronged approach: firstly lifestyle modification to avoid the allergen; and secondly the acute management of the anaphylactic event itself.<sup>(2,3,4)</sup> Those children who have had anaphylaxis, or who are judged to be at high risk of anaphylaxis, are prescribed adrenaline (epinephrine) auto-injectors.<sup>(5)</sup> These are to be carried on their person, or by their carers, at all times in case of accidental exposure to the allergen(s) in question. This is important as most accidental exposures and subsequent reactions tend to occur in community settings<sup>(1)</sup> and because of the typically rapid onset and progression of reactions, most young people and their families do not have immediate access to medical support when this is most required.

Despite being prescribed an adrenaline auto-injector and being shown the correct method of administration, many young people and/or parents still often report being unsure when to administer this treatment.<sup>(6,7)</sup> They often worry whether the reaction is severe enough to warrant an injection of adrenaline or whether their child may come to harm if given unnecessary treatment.<sup>(8)</sup>

There is evidence that there is often a delay in administering the prescribed medication in an emergency.<sup>(1)</sup> This delay in administering adrenaline may lead to increased morbidity and also increases the risk of fatality. Allergy services therefore often encourage children and families/carers to use their auto-injectors if there is any doubt regarding the severity of the allergic reaction. Given the risk of further reactions and the above-described concerns about when to administer emergency treatment, it is perhaps unsurprising that studies have found that food allergy can have a

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2  
3 detrimental impact both on the children themselves and also on family quality of life.<sup>(9,10)</sup> There is  
4  
5 however as yet no clear evidence on how to improve clinical and/or psychological outcomes in this  
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7 population.  
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10  
11 In the light of the above factors, we hypothesise that: firstly, uncertainty about the likely severity of  
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13 their child's reaction (ranging from no reaction to mild to life-threatening) on accidental re-exposure  
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15 to the allergenic food in question; and secondly, what a patient or carer must do if a reaction occurs,  
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17 both contribute significantly to parental/child anxiety. We further hypothesise that this uncertainty  
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19 could be ameliorated by real-time expert clinical guidance and support.  
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21  
22 We propose therefore to test the effectiveness of giving parents and carers of children and  
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24 teenagers with known food allergy, who are medically considered to be at sufficient risk of  
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26 anaphylaxis that they have been prescribed and trained in the use of adrenaline auto-injectors, 24-  
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28 hour telephone access (intervention arm) or office hour access (routine care arm) to expert advice  
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30 from the clinical allergy service. We will advise parents/ carers/ teen patients randomised to the  
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32 intervention arm to ring this clinician-staffed advice line if they or their child has an allergic reaction  
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34 and they are unsure as to how to manage it. We postulate that the availability of this service will  
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36 improve disease-specific quality of life compared with families randomised to the routine care arm  
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38 who do not have this 24-hour access. We also suspect that the allergic reactions that parents or  
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40 families contact the allergy team about will be better managed as a result of the advice given. There  
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42 is currently no service such as this available in Ireland or indeed worldwide. This is, as far as we are  
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44 aware, the first ever randomised clinical trial of patient care in the field of anaphylaxis.<sup>(11)</sup>  
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## AIMS AND OBJECTIVES

### *Aims*

We seek to assess the effectiveness of 24-hour telephone access to specialist paediatric allergy expert advice in improving the quality of life of children and their families with potentially life-threatening food allergy (i.e. anaphylaxis) compared with usual clinical care.

### *Main objective*

1. To compare the difference in food allergy related quality of life between the 24-hour telephone access and usual care at one- and six-months post-randomisation.

### *Secondary objectives*

2. To compare the number and clinical severity of incidents of suspected/confirmed allergic reaction in both groups
3. To compare clinical and health service use outcomes in both groups.

## METHODS AND ANALYSIS

### *Design*

We will undertake a pragmatic two-arm parallel group randomised controlled trial.

### *Recruitment and consent*

All families with food allergic children seen in the paediatric allergy outpatient clinics at Cork University Hospital will be informed about the study and invited to participate. A baseline validated

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3 Food Allergy-specific Quality of Life questionnaire (FAQL) will be completed by interested family  
4 members in relation to each child recruited.<sup>(12,13,14)</sup> This FAQL questionnaire will be sent by post to each  
5 family, with a stamp-addressed envelope.  
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9  
10 Recruitment of families of children with food allergy who carry an adrenaline auto-injector will occur  
11 in the paediatric allergy out-patient clinics of Cork University Hospital, which is the main centre for  
12 specialist paediatric allergy service provision across Ireland. Notices with information about the  
13 study will be placed around the out-patient waiting rooms. A phone number with a 24-hour  
14 answering service will be advertised for families wishing to obtain further information about the  
15 trial. Potentially suitable patients will also be identified from the weekly clinic preview team  
16 meetings.  
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20 All potentially interested parents will be given further information about the study, and any  
21 questions they may have will be answered. Children will, where appropriate on the basis of their age  
22 and understanding, also be involved in this discussion. Written informed consent will be obtained  
23 from all parents/guardians wishing to take part in the trial. Those over the age of eight years will also  
24 be asked to sign an assent form in the presence of their parents.  
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#### 41 **Eligibility**

42 Families of children satisfying the inclusion and exclusion criteria detailed below will be eligible to  
43 participate in the trial.  
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#### 48 Inclusion criteria

- 49 1. <16 years of age
  - 50 2. Food allergy
  - 51 3. Previously prescribed an adrenaline auto-injector
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4. Carers and, where appropriate, children trained by the clinical service how to use the prescribed adrenaline auto-injector
5. First eligible food allergic child in a family with more than one eligible child.

#### Exclusion criteria

1. Awaiting food challenge and likely to undergo this challenge during the trial period
2. Experiencing another major life stressor during timeline of trial e.g. changing school
3. Second or subsequent eligible child in families with more than one already recruited child.

#### **Baseline assessment**

All study participants will, as noted above, fill out FAQL questionnaires prior to randomisation. Parents will complete the FAQL Parent Form (FAQL-PF) as a proxy for their young children in those less than 13 years. Children age 8-13 years will complete their own validated FAQL Child Form (FAQL-CF) and teenagers will fill in the FAQL Teen form (FAQL-TF).

#### **Randomisation**

Randomisation will be undertaken only once all participants have been recruited, thereby minimising the risk of any selection biases. When all baseline questionnaires are collected the family will then be independently, centrally randomised 1:1 into the intervention (I) or usual (U) care arms. Randomisation will be on the basis of the subjects day of their date of birth being odd or even numbered.<sup>(15)</sup> The designation of odd/even date of birth to (I) or (U) arms will be determined by a coin toss by an individual who is not involved in the trial. All recruited families will thus simultaneously be allocated to the (I) or (U) arms, this marking the onset of the trial period.



### ***Intervention and control***

The (I) group will be given a direct access mobile phone number to ring in the event of a suspected serious allergic reaction. This will be given on a credit-card sized document for ease of access in the event of an emergency. The manning of this emergency 24-hour helpline will be shared between experienced members of the paediatric allergy team. In the event of a suspected serious allergic reaction, the patient or his/her parent or carer will be able to ring the on-call trial clinician for advice. Trial staff will have a standard incident report form (Appendix) to be filled out at the earliest possible time after the phone-call consultation. Their advice will be tailored according to clinical need, but will include instructions that there is either: i. No need for emergency treatment; ii. Give antihistamines by mouth and observe; or iii. Use the adrenaline auto-injector and call an ambulance. The responding staff member will keep a record of all such encounters and the advice given.

Those allocated to the U care (control) arm will receive standard care, with the option of contacting one or more of the following: the Cork University Hospital Paediatric Allergy team during working hours (Monday–Friday 8am–5pm), emergency/ambulance services, their own registered general practitioner (GP), out-of-hours primary care providers or their nearest hospital Emergency Departments .

The duration of trial period will be six months from the point of randomisation.

### ***Outcome measures***

#### Primary

All study participants will complete the age-appropriate (discussed above) validated FAQL at one- and six-months post randomisation; specifically, any change from baseline between intervention and control groups at the one- and six-month assessment points.

## Secondary

Participants in both groups will also be asked to record any possible allergic reactions that may have occurred, which were self-managed and/or required medical advice or attention other than provided through the trial helpline. We will record the clinical details of every reported event to include: incidence, severity, administration of adrenaline, hospital attendance and death.

## ***Statistical considerations***

### Analysis

We will assess the statistical significance and relative magnitude of changes over three time-points i.e. at baseline (T0), one month (T1) and six-months (T2) post-randomisation, on the FAQL scores for both the (I) and (U) care groups using a repeated measures 2x3 multivariate design.<sup>(16)</sup> That is, the same case in either experimental or control group (group factor), will complete the questionnaires at three time-points (time factor). The effect of the factors 'time' and 'group' on the total score, and the interaction of these two factors, will be analysed using a two-way within-between groups ANOVA. The interaction will address the question; 'Are the time profiles in terms of FAQL total scores of the two groups (experimental/control) significantly different'? If improvement over time is determined, a paired sample t-test will be used to ascertain at which time-point(s) the difference can be detected. Secondary outcomes will be included in univariate and multivariate models as independent and dependent variables and controls.

Independent t-tests will be used to determine if there are differences in magnitude of improvement in FAQL scores for (I) vs. (U) groups.

We will calculate the responsiveness index (mean change score/SD of change score), using Cohen's change index benchmarks; 0.2–0.4 (small); 0.5–0.7 (moderate); and 0.81 (large).

We will assess the reliability of the change score by computing the intra-class coefficients of change in the FAQLQ. The minimal important difference (MID) will also be calculated. Because the validity of a retrospective assessment of change has been questioned, we will determine the MID by computing the standard error of measurement (SEM ( $sp(1-r)$ )), using baseline FAQLQ scores as an 'anchor'.

The Last Observation Carried Forward (LOCF) imputation method will be used to deal with missing data, since this is an appropriate method for longitudinal studies (i.e. repeated measures have been taken per subject by time point).<sup>(18)</sup>

Analysis will be on an intention-to-treat basis by the trial statistician who will be blinded to allocation. There are no interim analyses planned.

#### Power

We will utilise a within/between repeated measures analysis of variance. An a priori total sample size required x power ( $1-\beta$  err prob), for a repeated measures within-between ANOVA analysis is 16 in each age group to yield a statistically significant result at >90% power with a 0.5 effect level.<sup>(17)</sup>

'Within' refers to expected differences between three time periods (T0, T1 and T2) and 'between' refers to expected differences between the intervention and control groups.

**F tests** - ANOVA: Repeated measures, within-between interaction

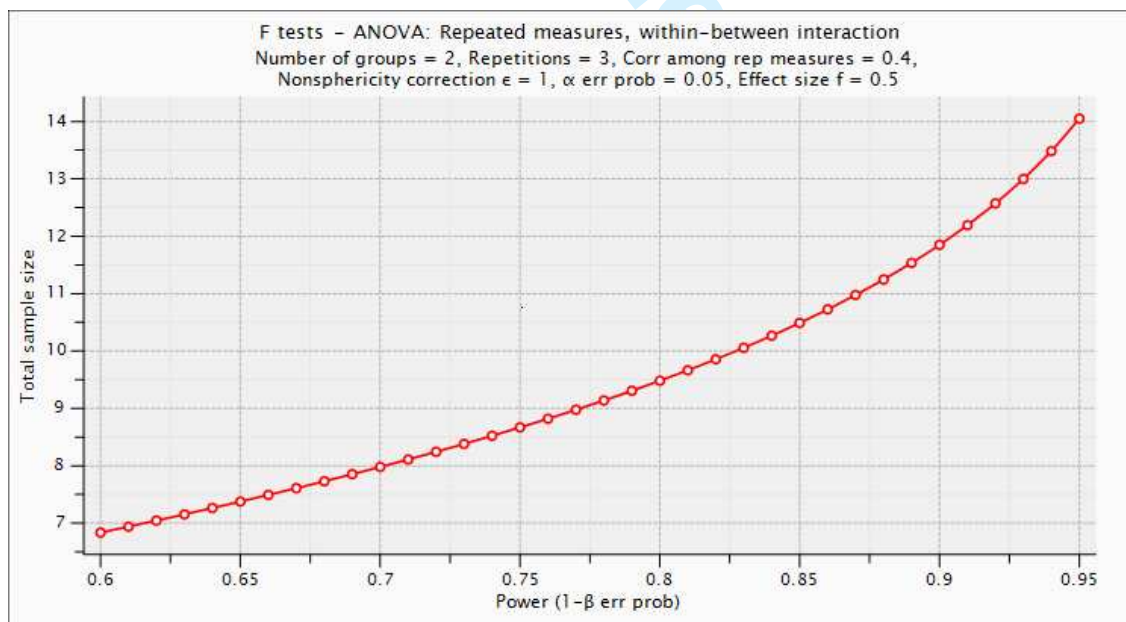
**Analysis:** A priori: Compute required sample size

**Input:** Effect size  $f$  = 0.5

$\alpha$  err prob = 0.05

Power (1- $\beta$ err prob)	=	0.95
Number of groups	=	2
Repetitions	=	3
Corr among rep measures	=	0.4
Nonsphericity correction $\epsilon$	=	1
<b>Output:</b> Noncentrality parameter $\lambda$	=	20.000000
Critical F	=	3.340386
Numerator df	=	2.000000
Denominator df	=	28.000000
Total sample size	=	16
Actual power	=	0.973792

**Figure 1: A – priori total sample size required x power (1- $\beta$  err prob), for a repeated measures within-between ANOVA analysis**



With an anticipated drop-out rate of 20%, we therefore plan to recruit a total of 50 families.

## ETHICS AND DISSEMINATION

Ethical approval has been obtained by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (30.05.2011). All patients are aware that their participation is voluntary and they may withdraw from study at any time.

The PI for the trial is Jonathan Hourihane and he will lead the Trial Management Group and he is responsible for the overall governance and running of this trial. Other members of the Trial Management Group are: Maeve Kelleher, John Fitzsimons, Audrey DunnGalvin, Claire Cullinane and Aziz Sheikh, and they will support the PI in delivering this trial. Audrey DunnGalvin is the trial statistician.

We plan to report our findings at major national and international scientific conferences. We also plan to publish our findings in the peer-reviewed literature. We anticipate being in a position to report on findings in early 2013.

**ACKNOWLEDGEMENTS:** We are very grateful to the children and their families who have agreed to participate in this trial.

**CONFLICT OF INTERESTS:** None known.

**AUTHORS' CONTRIBUTIONS:** JOH and AS conceived the idea for this trial, and this was then further developed in association with MH and ADG. MH led the drafting of this manuscript, which was critically commented on by all co-authors.

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## REFERENCES

1. De Silva SL, Mehr S, Tey D, Tang MLK. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy* 2008; 63: 1071–107.
2. Walker S, Sheikh A. Managing anaphylaxis: effective emergency and long-term care are necessary. *Clin Exp Allergy* 2003; 33: 1015-18.
3. Soar J, Pumphrey R, Cant A, Clarke S, Corbett A, Dawson P et al. Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. Working Group of the Resuscitation Council (UK). *Resuscitation* 2008; 77: 157-69
4. Simons FE, Arduoso LR, Bilò MB, El-Gamal YM, Ledford DK, Ring J et al. World Allergy Organization anaphylaxis guidelines: Summary. *J Allergy Clin Immunol* 2011; 127: 587-93.e1-22.
5. Muraro A, Roberts G, Clark A et al The management of anaphylaxis in childhood: position paper of the EAACI. *Allergy* 2007; 62: 857–71.
6. Gold MS, Sainsbury R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol* 2000; 106: 171-76.
7. Arkwright P, Farragher AJ. Factors determining the ability of parents to effectively administer intramuscular adrenaline to food allergic children. *Pediatr Allergy Immunol* 2006; 17: 227–29.
8. Kim S, Sincacore J, Pongracic J. Parental use of EpiPen for children with food allergies. *J Allergy Clin Immunol* 2005; 116: 164-68.
9. Sicherer S, Noone S, Munoz-Furlong. The impact of childhood food allergy on quality of life. *Ann Asthma, Allergy Immunol* 2001; 87: 461-464.
10. Avery N, King RM, Knight S, Hourihane JO'B. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol* 2003; 14: 378–82.
11. Simons FE, Sheikh A. Evidence-based management of anaphylaxis. *Allergy* 2007; 62: 827-29.
12. DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. *Clin Exp Allergy* 2008; 38: 977-86.
13. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for Adolescents. *J Allergy Clin Immunol* 2008; 122: 139-144.e2

14. de BlokFlokstra, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. *Clin Exp Allergy* 2009; 39: 127–37.
15. Routsis C, Gerovasili V, Vasileiadis I, Karatzanos E, Pitsolis T, Tripodaki E et al. Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial. *Crit Care* 2010; 14: R74.
16. Hinkelmann, Klaus & Kempthorne, Oscar. *Design and Analysis of Experiments*. 2008;I and II (Second ed.). Wiley.
17. Cohen J. A power primer. *Psychol Bull* 1992; 112: 155–59.
18. Hamer RM, Simpson PM. Last observation carried forward versus mixed models in the analysis of psychiatric clinical trials. *Am J Psychiatry* 2009; 166: 639-41.

**Appendix**

Incident Report Form

Patient Name \_\_\_\_\_

Staff member Name \_\_\_\_\_

Caller Mother/father/ patient/ other \_\_\_\_\_

(Please specify)

Time of call (24h) \_\_: \_\_ h

Patient location \_\_\_\_\_

Food suspected \_\_\_\_\_

How much eaten? \_\_\_\_\_

Time since ingestion \_\_\_\_\_

Asthma y/n \_\_\_\_\_

**Current condition**

**Advice to be given**

Rash only Give antihistamine, Do not Use Anapen yet

Rash and swelling Give antihistamine, Do Not Use Anapen yet

Cough/hoarseness Use Anapen, call ambulance, go to hospital

Wheeze Use Anapen, call ambulance, go to hospital

Dizzy/collapse Use Anapen, call ambulance, go to hospital

Outcome (to be completed by study team in Cork, ASAP next working day)

\_\_\_\_\_

\_\_\_\_\_





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27 13 2 Paediatrics, Our Lady of Lourdes Hospital, Drogheda, Co Louth, Ireland

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30 Edinburgh, Scotland  
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34 17 Correspondence to: Professor Aziz Sheikh, Professor of Primary Care Research & Development,  
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36 Teviot Place, Edinburgh EH8 9AG, Scotland. Tel: +44 (0)131 651 4151; Fax: +44 (0)131 650 9119;  
37 Email: [aziz.sheikh@ed.ac.uk](mailto:aziz.sheikh@ed.ac.uk)  
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3 **23 ABSTRACT**  
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## 45 INTRODUCTION

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47 for the majority of anaphylaxis cases in the paediatric population.<sup>(1)</sup> Egg, milk, peanuts and tree nuts  
48 are the most common food allergens in the preschool population; peanut and tree nuts are the most  
49 common allergen triggers in older children. There is a wide spectrum of allergic reactions to these  
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51 Anaphylaxis is managed via a two-pronged approach: firstly lifestyle modification to avoid the  
52 allergen; and secondly the acute management of the anaphylactic event itself.<sup>(2,3,4)</sup> Those children who  
53 have had anaphylaxis, or who are judged to be at high risk of anaphylaxis, are prescribed adrenaline  
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55 in case of accidental exposure to the allergen(s) in question. This is important as, although  
56 uncommon with an estimated incidence of one episode per 10 000 children per year,<sup>(5)</sup> most  
57 accidental exposures and subsequent reactions tend to occur in community settings<sup>(1)</sup> and because  
58 of the typically rapid onset and progression of reactions, most young people and their families do  
59 not have immediate access to medical support when this is most required.

60 Despite being prescribed an adrenaline auto-injector and being shown the correct method of  
61 administration, many young people and/or parents still often report being unsure when to  
62 administer this treatment.<sup>(6,7)</sup> They often worry whether the reaction is severe enough to warrant an  
63 injection of adrenaline or whether their child may come to harm if given unnecessary treatment.<sup>(8)</sup>

64 There is evidence that there is often a delay in administering the prescribed medication in an  
65 emergency.<sup>(1)</sup> This delay in administering adrenaline may lead to increased morbidity and also  
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67 families/carers to use their auto-injectors if there is any doubt regarding the severity of the allergic  
68 reaction. Given the risk of further reactions and the above-described concerns about when to

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2  
3 69 administer emergency treatment, it is perhaps unsurprising that studies have found that food allergy  
4  
5 70 can have a detrimental impact both on the children themselves and also on family quality of life.<sup>(11,12)</sup>  
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7 71 There is however as yet no clear evidence on how to improve clinical and/or psychological outcomes  
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10 72 in this population.

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12 73 In the light of the above factors, we hypothesise that: firstly, uncertainty about the likely severity of  
13  
14 74 their child's reaction (ranging from no reaction to mild to life-threatening) on accidental re-exposure  
15  
16 75 to the allergenic food in question; and secondly, what a patient or carer must do if a reaction occurs,  
17  
18 76 both contribute significantly to parental/child anxiety. We further hypothesise that this uncertainty  
19  
20 77 could be ameliorated by real-time expert clinical guidance and support.

21  
22  
23  
24 78 We propose therefore to test the effectiveness of giving parents and carers of children and  
25  
26 79 teenagers with known food allergy, who are medically considered to be at sufficient risk of  
27  
28 80 anaphylaxis that they have been prescribed and trained in the use of adrenaline auto-injectors, 24-  
29  
30 81 hour telephone access (intervention arm) or office hour access (routine care arm) to expert advice  
31  
32 82 from the clinical allergy service. We will advise parents/ carers/ teen patients randomised to the  
33  
34 83 intervention arm to ring this clinician-staffed advice line if they or their child has an allergic reaction  
35  
36 84 and they are unsure as to how to manage it. We postulate that the availability of this service will  
37  
38 85 improve disease-specific quality of life compared with families randomised to the routine care arm  
39  
40 86 who do not have this 24-hour access. We also suspect that the allergic reactions that parents or  
41  
42 87 families contact the allergy team about will be better managed as a result of the advice given. There  
43  
44 88 is currently no service such as this available in Ireland or indeed worldwide. This is, as far as we are  
45  
46 89 aware, the first ever randomised clinical trial of patient care in the field of anaphylaxis.<sup>(13)</sup>

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3 93 **AIMS AND OBJECTIVES**  
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5

6 94 ***Aims***  
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8

9 95 We seek to assess the effectiveness of 24-hour telephone access to specialist paediatric allergy  
10  
11 96 expert advice in improving the quality of life of children and their families with potentially life-  
12  
13 97 threatening food allergy (i.e. anaphylaxis) compared with usual clinical care.  
14

15  
16 98 ***Main objective***  
17  
18

- 19 99 1. To compare the difference in food allergy related quality of life between the 24-hour  
20  
21 100 telephone access and usual care at one- and six-months post-randomisation.  
22  
23 101

24  
25 102 ***Secondary objectives***  
26  
27

- 28 103 2. To compare the number and clinical severity of incidents of suspected/confirmed allergic  
29  
30 104 reaction in both groups  
31  
32 105 3. To compare clinical and health service use outcomes in both groups.  
33  
34  
35 106

36  
37  
38 107 **METHODS AND ANALYSIS**  
39  
40

41 108 ***Design***  
42  
43

44 109 We will undertake a pragmatic two-arm parallel group randomised controlled trial.  
45  
46  
47 110

48  
49 111 ***Recruitment and consent***  
50  
51

52  
53 112 All families with food allergic children seen in the paediatric allergy outpatient clinics at Cork  
54  
55 113 University Hospital will be informed about the study and invited to participate. A baseline validated  
56  
57  
58  
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60

1  
2  
3 114 Food Allergy-specific Quality of Life questionnaire (FAQL) will be completed by interested family  
4  
5 115 members in relation to each child recruited.<sup>(14,15,16)</sup> This FAQL questionnaire will be sent by post to each  
6  
7 116 family, with a stamp-addressed envelope.  
8  
9

10 117 Recruitment of families of children with food allergy who carry an adrenaline auto-injector will occur  
11  
12 118 in the paediatric allergy out-patient clinics of Cork University Hospital, which is the main centre for  
13  
14 119 specialist paediatric allergy service provision across Ireland. Notices with information about the  
15  
16 120 study will be placed around the out-patient waiting rooms. A phone number with a 24-hour  
17  
18 121 answering service will be advertised for families wishing to obtain further information about the  
19  
20 122 trial. Potentially suitable patients will also be identified from the weekly clinic preview team  
21  
22 123 meetings.  
23  
24

25  
26 124 All potentially interested parents will be given further information about the study, and any  
27  
28 125 questions they may have will be answered. Children will, where appropriate on the basis of their age  
29  
30 126 and understanding, also be involved in this discussion. Written informed consent will be obtained  
31  
32 127 from all parents/guardians wishing to take part in the trial. Those over the age of eight years will also  
33  
34 128 be asked to sign an assent form in the presence of their parents.  
35  
36

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### 39 40 130 **Eligibility**

41  
42  
43 131 Families of children satisfying the inclusion and exclusion criteria detailed below will be eligible to  
44  
45 132 participate in the trial.  
46  
47

### 48 49 133 Inclusion criteria

- 50  
51 134 1. <16 years of age  
52  
53 135 2. Food allergy  
54  
55 136 3. Previously prescribed an adrenaline auto-injector  
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- 1  
2  
3 137 4. Carers and, where appropriate, children trained by the clinical service how to use the  
4  
5 138 prescribed adrenaline auto-injector  
6  
7 139 5. First eligible food allergic child in a family with more than one eligible child.  
8  
9

10 140 Exclusion criteria  
11

- 12  
13 141 1. Awaiting food challenge and likely to undergo this challenge during the trial period  
14  
15 142 2. Experiencing another major life stressor during timeline of trial e.g. changing school  
16  
17 143 3. Second or subsequent eligible child in families with more than one already recruited child.  
18  
19

20 144  
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22  
23 145 **Baseline assessment**  
24

25  
26 146 All study participants will, as noted above, fill out FAQL questionnaires prior to randomisation.  
27  
28 147 Parents will complete the FAQL Parent Form (FAQL-PF) as a proxy for their young children in those  
29  
30 148 less than 13 years. Children age 8-13 years will complete their own validated FAQL Child Form  
31  
32 149 (FAQL-CF) and teenagers will fill in the FAQL Teen form (FAQL-TF).  
33  
34

35 150  
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38  
39 151 **Randomisation**  
40

41  
42 152 Randomisation will be undertaken only once all participants have been recruited, thereby  
43  
44 153 minimising the risk of any selection biases maintaining allocation concealment. When all baseline  
45  
46 154 questionnaires are collected the family will then be centrally randomised by the be independently  
47  
48 155 trial statistician, centrally randomised in a 1:1 ratio, into the intervention (I) or usual (U) care arms.  
49  
50 156 All recruited families will thus simultaneously be allocated to the (I) or (U) arms, this marking the  
51  
52 157 onset of the trial period.  
53  
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55 158  
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159 ***Intervention and control***

160 The (I) group will be given a direct access mobile phone number to ring in the event of a suspected  
161 serious allergic reaction. This will be given on a credit-card sized document for ease of access in the  
162 event of an emergency. The manning of this emergency 24-hour helpline will be shared between  
163 experienced members of the paediatric allergy team. In the event of a suspected serious allergic  
164 reaction, the patient or his/her parent or carer will be able to ring the on-call trial clinician for  
165 advice. Trial staff will have a standard incident report form (Appendix 1) to keep record of on-call  
166 encounters. It is to be filled out as soon as is practical after the phone-call consultation. Their  
167 advice will be tailored according to clinical need, but will include instructions that there is either: i.  
168 no need for emergency treatment; ii. give antihistamines by mouth and observe; or iii. use the  
169 adrenaline auto-injector and call an ambulance. The responding staff member will keep a record of  
170 all such encounters and the advice given. Consistency of advice given is ensured by each staff  
171 member giving out previously agreed, standardised instructions (Appendix 1) and by a  
172 teleconference to be had between all personnel, following all incidents where advice is given on the  
173 24-Hour Helpline, to discuss the incident and ensure that the standardised advice was given.

174 Those allocated to the U care (control) arm will receive standard care, with the option of contacting  
175 one or more of the following: the Cork University Hospital Paediatric Allergy team during working  
176 hours (Monday–Friday 8am–5pm), emergency/ambulance services, their own registered general  
177 practitioner (GP), out-of-hours primary care providers or their nearest hospital Emergency  
178 Departments .

179 The duration of trial period will be six months from the point of randomisation.

180

181 ***Outcome measures***

182 Primary

183 All study participants will complete the age-appropriate (discussed above) validated FAQL at one-  
184 and six-months post randomisation; specifically, any change from baseline between intervention and  
185 control groups at the one- and six-month assessment points.

186 The Food Allergy Quality of Life Questionnaire - Parent Form, Child Form, and Teen (FAQLQ-PF, -CF,  
187 -TF) are age appropriate parent-administered, child self administered, and teen self administered  
188 questionnaires that measure the impact of food allergy on HRQL of children age 0-18 years. They  
189 were developed and validated under the auspices of EuroPrevall, a European Commission funded  
190 project with over 60 partners ([www.europrevall.org](http://www.europrevall.org)). We have previously demonstrated good cross-  
191 sectional and longitudinal reliability and validity in European and US samples. The questionnaire  
192 items are scored on a 7-point likert scale ranging from 0 (no impact on HRQL) to 6 (extreme impact  
193 on HRQL). The measures have three subscales assessing general emotional impact; food anxiety;  
194 social and dietary limitations. The total score is calculated as the mean of these three subscales.<sup>(14-17)</sup>

195 Secondary

196 Participants in both groups will also be asked to record any possible allergic reactions that may have  
197 occurred, which were self-managed and/or required medical advice or attention other than  
198 provided through the trial helpline. They will be provided with a standardised form to record this  
199 information on (See Appendix 2). We will record the clinical details of every reported event to  
200 include: incidence, severity, administration of adrenaline, hospital attendance and death

201

202 ***Statistical considerations***203 Analysis

1  
2  
3 204 We will assess the statistical significance and relative magnitude of changes over three time-points  
4  
5 205 i.e. at baseline (T0), one month (T1) and six-months (T2) post-randomisation, on the FAQL scores for  
6  
7 206 both the (I) and (U) care groups using a repeated measures 2x3 multivariate design.<sup>(18)</sup> That is, the  
8  
9 207 same case in either experimental or control group (group factor), will complete the questionnaires  
10  
11 208 at three time-points (time factor). The effect of the factors 'time' and 'group' on the total score, and  
12  
13 209 the interaction of these two factors, will be analysed using a two-way within-between groups  
14  
15 210 ANOVA. The interaction will address the question; 'Are the time profiles in terms  
16  
17 211 of FAQL total scores of the two groups (experimental/control) significantly different'? If  
18  
19 212 improvement over time is determined, a paired sample t-test will be used to ascertain at which  
20  
21 213 time-point(s) the difference can be detected. Secondary outcomes will be included in univariate and  
22  
23 214 multivariate models as independent and dependent variables and controls.

24  
25  
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27  
28 215 Independent t-tests will be used to determine if there are differences in magnitude of improvement  
29  
30 216 in FAQL scores for (I) vs. (U) groups. The Bonferroni correction method will be used to adjust for  
31  
32 217 multiple comparisons.

33  
34  
35 218 We will calculate the responsiveness index (mean change score/SD of change score), using Cohen's  
36  
37 219 change index benchmarks; 0.2–0.4 (small); 0.5–0.7 (moderate); and 0.81 (large).

38  
39  
40 220 We will assess the reliability of the change score by computing the intra-class coefficients of change  
41  
42 221 in the FAQLQ. The minimal important difference (MID) will also be calculated. Because the validity  
43  
44 222 of a retrospective assessment of change has been questioned, we will determine the MID by  
45  
46 223 computing the standard error of measurement (SEM ( $sp(1-r)$ )), using baseline FAQLQ scores as an  
47  
48 224 'anchor'.

49  
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226 Missing data will be dealt with by the Multiple Imputation (MI) method, which is suitable for ANOVA  
 227 and uses an imputation method with error built in.<sup>(19)</sup>

228

229 Analysis will be on an intention-to-treat basis by the trial statistician who will be blinded to  
 230 allocation. There are no interim analyses planned.

### 231 Power

232 We will utilise a within/between repeated measures analysis of variance. An a priori total sample  
 233 size required x power (1- $\beta$  err prob), for a repeated measures within-between ANOVA analysis is 16  
 234 in each group (intervention/control) to yield a statistically significant result at >90% power with a  
 235 0.5 effect level.<sup>(20)</sup>

236 'Within' refers to expected differences between three time periods (T0, T1 and T2) and 'between'  
 237 refers to expected differences between the intervention and control groups.

238

### 239 **F tests** - ANOVA: Repeated measures, within-between interaction

240 **Analysis:** A priori: Compute required sample size

241 **Input:** Effect size f = 0.5

242  $\alpha$  err prob = 0.05

243 Power (1- $\beta$  err prob) = 0.95

244 Number of groups = 2

245 Repetitions = 3

246 Corr among rep measures = 0.4

247 Nonsphericity correction  $\epsilon$  = 1

248 **Output:** Noncentrality parameter  $\lambda$  = 20.000000

249 Critical F = 3.340386

250	Numerator df	=	2.000000
251	Denominator df	=	28.000000
252	Group sample size	=	16
253	Actual power	=	0.973792

## 254 ETHICS AND DISSEMINATION

255 Ethical approval has been obtained by the Clinical Research Ethics Committee of the Cork Teaching  
256 Hospitals (30.05.2011). All patients are aware that their participation is voluntary and they may  
257 withdraw from study at any time.

258

259 The PI for the trial is Jonathan Hourihane and he will lead the Trial Management Group and he is  
260 responsible for the overall governance and running of this trial. Other members of the Trial  
261 Management Group are: Maeve Kelleher, John Fitzsimons, Audrey DunnGalvin, Claire Cullinane and  
262 Aziz Sheikh, and they will support the PI in delivering this trial. Audrey DunnGalvin is the trial  
263 statistician.

264 We plan to report our findings at major national and international scientific conferences. We also  
265 plan to publish our findings in the peer-reviewed literature. We anticipate being in a position to  
266 report on findings in early 2013.

267

268 **ACKNOWLEDGEMENTS:** We are very grateful to the children and their families who have agreed to participate in this trial.

269 **CONFLICT OF INTERESTS:** None known.

270 **AUTHORS' CONTRIBUTIONS:** JOH and AS conceived the idea for this trial, and this was then further developed in  
271 association with MH and ADG. MH led the drafting of this manuscript, which was critically commented on by all co-authors.

1  
2  
3 272 **FUNDING STATEMENT:** 'This research received no specific grant from any funding agency in the public, commercial or not-  
4  
5 273 for-profit sectors.  
6

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15 278 **REFERENCES**

16  
17 279 1. De Silva SL, Mehr S, Tey D, et al. Paediatric anaphylaxis: a 5 year retrospective review.  
18 280 *Allergy* 2008; 63: 1071–107.

21 281 2. Walker S, Sheikh A. Managing anaphylaxis: effective emergency and long-term care are  
22 282 necessary. *Clin Exp Allergy* 2003; 33: 1015-18.

24 283 3. Soar J, Pumphrey R, Cant A, et al. Emergency treatment of anaphylactic reactions--guidelines  
25 284 for healthcare providers. Working Group of the Resuscitation Council (UK). *Resuscitation*  
26 285 2008; 77: 157-69

28 286 4. Simons FE, Arduzzo LR, Bilò MB, et al. World Allergy Organization anaphylaxis guidelines:  
29 287 Summary. *J Allergy Clin Immunol* 2011; 127: 587-93.e1-22.

31  
32 288 5. Muraro A, Roberts G, Clark A et al The management of anaphylaxis in childhood: position  
33 289 paper of the EAACI. *Allergy* 2007; 62: 857–71.

35 290 6. Gold MS, Sainsbury R. First aid anaphylaxis management in children who were prescribed an  
36 291 epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol* 2000; 106: 171-76.

38 292 7. Arkwright P, Farragher AJ. Factors determining the ability of parents to effectively  
39 293 administer intramuscular adrenaline to food allergic children. *Pediatr Allergy Immunol* 2006;  
40 294 17: 227–29.

43 295 8. Kim S, Sincacore J, Pongracic J. Parental use of EpiPen for children with food allergies. *J*  
44 296 *Allergy Clin Immunol* 2005; 116: 164-68.

46 297

48 298 9. Sampson HA, Mendelson L, Rosen JP(1992) Fatal and near-fatal anaphylactic reactions to  
49 299 food in children and adolescents. *N Engl J Med.* 327:380–384.

51 300 10. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin*  
52 301 *Exp Allergy.* 2000 30(8):1144–1150.

54  
55 302

- 1  
2  
3 303 11. Sicherer S, Noone S, Munoz-Furlong. The impact of childhood food allergy on quality of life.  
4 304 *Ann Asthma, Allergy Immunol* 2001; 87: 461-464.
- 5  
6 305 12. Avery N, King RM, Knight S, et al. Assessment of quality of life in children with peanut  
7 306 allergy. *Pediatr Allergy Immunol* 2003; 14: 378–82.
- 8  
9 307 13. Simons FE, Sheikh A. Evidence-based management of anaphylaxis. *Allergy* 2007; 62: 827-29.
- 10  
11 308 14. DunnGalvin A, de BlokFlokstra BM, Burks AW, et al. Food allergy QoL questionnaire for  
12 309 children aged 0-12 years: content, construct, and cross-cultural validity. *Clin Exp Allergy*  
13 310 2008; 38: 977-86.
- 14  
15 311 15. Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of  
16 312 the self-administered Food Allergy Quality of Life Questionnaire for Adolescents. *J Allergy*  
17 313 *Clin Immunol* 2008; 122: 139-144.e2
- 18  
19 314 16. de BlokFlokstra, DunnGalvin A, Vlieg-Boerstra BJ, et al. Development and validation of a self-  
20 315 administered Food Allergy Quality of Life Questionnaire for children. *Clin Exp Allergy* 2009;  
21 316 39: 127–37.
- 22  
23 317 17. Hourihane J.O’B., Chiang, WC, et al. Psychometric validation of the FAQLQ-PF in a US sample  
24 318 of children with food allergy. *J Aller Clin Immunol* 2008; 121-2:1: S106-S107.
- 25  
26 319 18. Hinkelmann, Klaus & Kempthorne, Oscar. *Design and analysis of experiments*. 2008; I and II  
27 320 (Second ed.). Wiley
- 28  
29 321 19. Graham JW. Missing data analysis: making it work in the real world. *Ann Rev Psychol* 2009;  
30 322 60: 549-76.
- 31  
32 323 20. Cohen J. A power primer. *Psychol Bull* 1992; 112: 155–59.
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For peer review only



337 **Appendix 1: Incident Report Form**

338 Patient Name \_\_\_\_\_

339 Staff member Name \_\_\_\_\_

340 Caller Mother/father/ patient/ other \_\_\_\_\_

341 (Please specify)

342 Time of call (24h) \_\_: \_\_ h

343

344 Patient location \_\_\_\_\_

345 Food suspected \_\_\_\_\_

346 How much eaten? \_\_\_\_\_

347 Time since ingestion \_\_\_\_\_

348 Asthma y/n \_\_\_\_\_

349

350

351 **Current condition**

**Advice to be given**

352 Rash only Give antihistamine, Do not Use Anapen yet

353 Rash and swelling Give antihistamine, Do Not Use Anapen yet

354 Cough/hoarseness Use Anapen, call ambulance, go to hospital

355 Wheeze Use Anapen, call ambulance, go to hospital

356 Dizzy/collapse Use Anapen, call ambulance, go to hospital

357

358

359 Outcome (to be completed by study team in Cork, ASAP next working day)

360

361

362

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364

365

366 **Appendix 2.**



**UCC**  
Coláiste na hOllscoile Corcaigh, Éire  
University College Cork, Ireland

367

368

# Anaphylaxis 24-hour Helpline Study

369

Record of any Food Allergy Reactions

370

Study Number \_\_

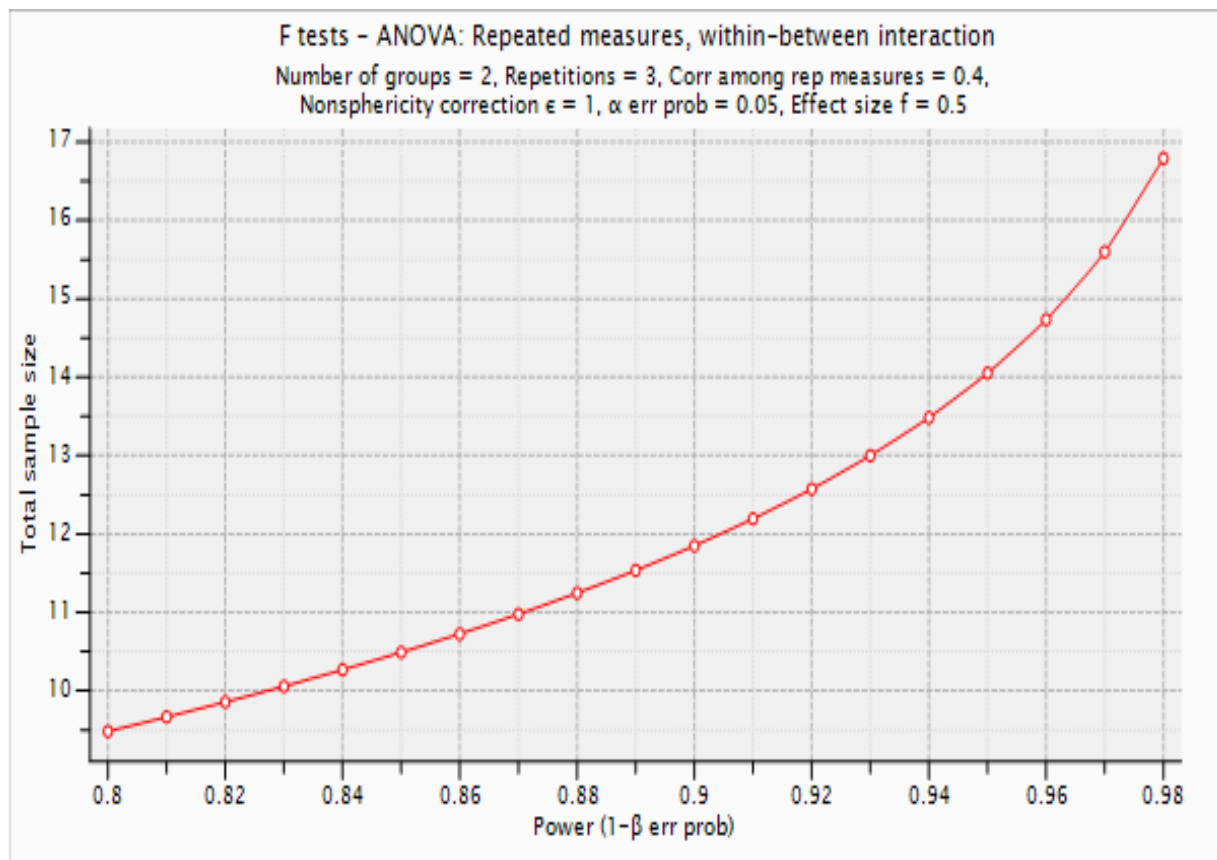
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Food	Symptoms	How long after eating?	What Treatment Given?	Did you attend doctor?	Outcome

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Figure 1: A – priori total sample size required x power (1-β err prob), for a repeated measures within-between ANOVA analysis



With an anticipated drop-out rate of 20%, we therefore plan to recruit a total of 40 families.