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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.[1] 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.[2,3,4]Those children who have had anaphylaxis, or who are judged to be at high risk of anaphylaxis, are prescribed adrenaline (epinephrine) auto-injectors.[5] 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[1] 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.[6,7] 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.[8] There is evidence that there is often a delay in administering the prescribed medication in an emergency.[1] 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

detrimental impact both on the children themselves and also on family quality of life.[9,10] There is however as yet no clear evidence on how to improve clinical and/or psychological outcomes in this population.

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

We propose therefore to test the effectiveness of giving parents and carers of children and teenagers with known food allergy, who are medically considered to be at sufficient risk of anaphylaxis that they have been prescribed and trained in the use of adrenaline auto-injectors, 24-hour telephone access (intervention arm) or office hour access (routine care arm) to expert advice from the clinical allergy service. We will advise parents/ carers/ teen patients randomised to the intervention arm to ring this clinician-staffed advice line if they or their child has an allergic reaction and they are unsure as to how to manage it. We postulate that the availability of this service will improve disease-specific quality of life compared with families randomised to the routine care arm who do not have this 24-hour access. We also suspect that the allergic reactions that parents or families contact the allergy team about will be better managed as a result of the advice given. There is currently no service such as this available in Ireland or indeed worldwide. This is, as far as we are aware, the first ever randomised clinical trial of patient care in the field of anaphylaxis.[11]

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

Food Allergy-specific Quality of Life questionnaire (FAQL) will be completed by interested family members in relation to each child recruited.[12,13,14] This FAQL questionnaire will be sent by post to each family, with a stamp-addressed envelope.

Recruitment of families of children with food allergy who carry an adrenaline auto-injector will occur in the paediatric allergy out-patient clinics of Cork University Hospital, which is the main centre for specialist paediatric allergy service provision across Ireland. Notices with information about the study will be placed around the out-patient waiting rooms. A phone number with a 24-hour answering service will be advertised for families wishing to obtain further information about the trial. Potentially suitable patients will also be identified from the weekly clinic preview team meetings.

All potentially interested parents will be given further information about the study, and any questions they may have will be answered. Children will, where appropriate on the basis of their age and understanding, also be involved in this discussion. Written informed consent will be obtained from all parents/guardians wishing to take part in the trial. Those over the age of eight years will also be asked to sign an assent form in the presence of their parents.

Eligibility

Families of children satisfying the inclusion and exclusion criteria detailed below will be eligible to participate in the trial.

Inclusion criteria

1. <16 years of age
2. Food allergy
3. Previously prescribed an adrenaline auto-injector

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.[15] 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.[16] 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).[18]

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-β 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.[17]

'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

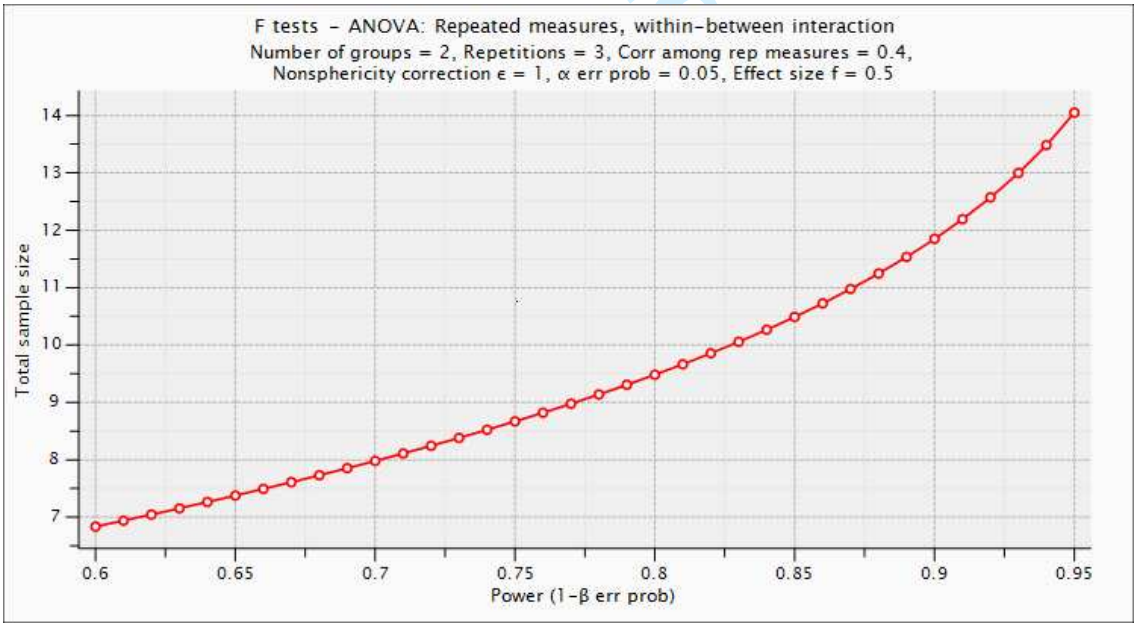
Analysis: A priori: Compute required sample size

Input: Effect size f = 0.5

α err prob = 0.05

	Power (1-β err prob)	=	0.95
	Number of groups	=	2
	Repetitions	=	3
	Corr among rep measures	=	0.4
	Nonsphericity correction ε	=	1
Output:	Noncentrality parameter λ	=	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-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 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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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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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.[2,3,4]Those children who have had anaphylaxis, or who are judged to be at high risk of anaphylaxis, are prescribed adrenaline (epinephrine) auto-injectors.[5] 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, although uncommon with an estimated incidence of one episode per 10 000 children per year,[5] most accidental exposures and subsequent reactions tend to occur in community settings[1] 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.[6,7] 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.[8] There is evidence that there is often a delay in administering the prescribed medication in an emergency.[1] This delay in administering adrenaline may lead to increased morbidity and also increases the risk of fatality.[9,10] 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 detrimental impact both on the children themselves and also on family quality of life.[11,12] There is however as yet no clear evidence on how to improve clinical and/or psychological outcomes in this population.

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

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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

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Eligibility

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2. Food allergy
3. Previously prescribed an adrenaline auto-injector

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.

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Randomisation will be undertaken only once all participants have been recruited, thereby minimising the risk of any selection biases maintaining allocation concealment. When all baseline questionnaires are collected the family will then be centrally randomised by the be independently trial statistician, centrally randomised in a 1:1 ratio, into the intervention (I) or usual (U) care arms. 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 1) to keep record of on-call encounters. It is to be filled out as soon as is practical 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. Consistency of advice given is ensured by each staff member giving out previously agreed, standardised instructions (Appendix 1) and by a teleconference to be had between all personnel, following all incidents where advice is given on the 24-Hour Helpline, to discuss the incident and ensure that the standardised advice was 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.

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

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. They will be provided with a standardised form to record this information on (See Appendix 2). 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.[18] 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. The Bonferroni correction method will be used to adjust for multiple comparisons.

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'.

Missing data will be dealt with by the Multiple Imputation (MI) method, which is suitable for ANOVA and uses an imputation method with error built in.[19]

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-β err prob), for a repeated measures within-between ANOVA analysis is 16 in each group (intervention/control) to yield a statistically significant result at >90% power with a 0.5 effect level.[20]

'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
	α err prob	=	0.05
	Power (1-β err prob)	=	0.95
	Number of groups	=	2
	Repetitions	=	3
	Corr among rep measures	=	0.4
	Nonsphericity correction ε	=	1
Output:	Noncentrality parameter λ	=	20.000000
	Critical F	=	3.340386

Numerator df	=	2.000000
Denominator df	=	28.000000
Group sample size	=	16
Actual power	=	0.973792

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.

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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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335

336

Appendix 1: 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)

Appendix 2.

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

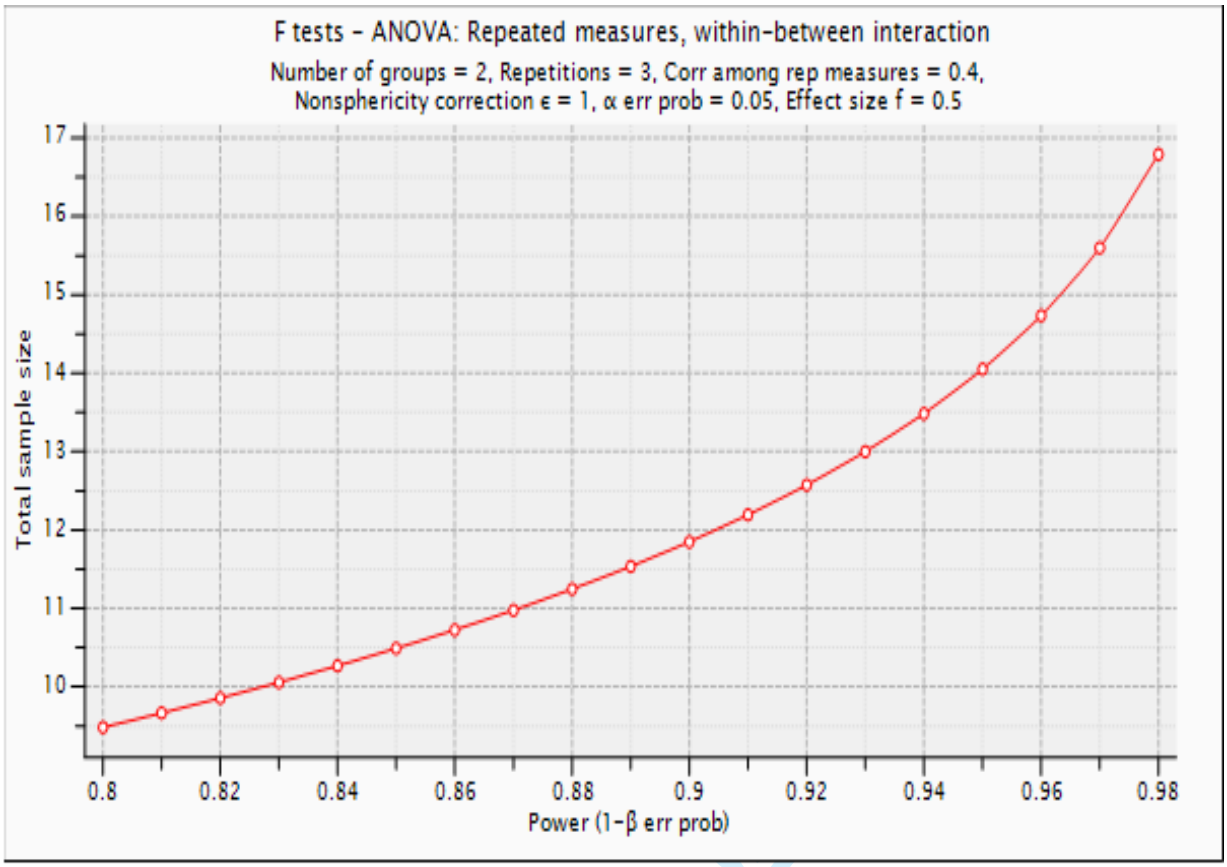
Anaphylaxis 24-hour Helpline Study

Record of any Food Allergy Reactions

Study Number __

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

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.