

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	24-Hour Helpline for Access to Expert Management Advice for Food Allergy-Related Anaphylaxis in Children: Protocol for a Pragmatic Randomised Controlled Trial
<b>AUTHORS</b>	Sheikh, Aziz ; Kelleher, Maeve; Hourihane, Jonathan; DunnGalvin, Audrey; Cullinane, Claire; Fitzsimons, John

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Dr David Noble Consultant in Intensive Care Medicine Aberdeen Royal Infirmary Foresterhill Aberdeen UK  I have no conflict of interest with regards to assessing this manuscript.
<b>REVIEW RETURNED</b>	18-May-2012

<b>THE STUDY</b>	<p>P3. The hypothesis that early intervention is better should be supported by references. Unecessary adrenaline can be detrimental too. eg Takotsubo cardiomyopathy-like syndrome The prevalence of the disorder would be useful information for readers. Is 6 months follow-up sufficient or will that overestimate the (potential) usefulness of the intervention?</p> <p>p7. I am unsure why a more standard method of randomisation is not possible rather than pseudo-randomisation based on date of birth? Will assessors be blind to group allocation at assessment?</p> <p>p8. Who will provide the advice - one single person or multiple persons? How will consistency of advice be ensured if multiple persons will be involved?</p> <p>p9. I have not used RM ANOVA. I note that there will be multiple comparisons and in other ANOVA designs there can be methods to adjust for multiple comparisons. Is that relevant for this study? Is the "responsiveness index" a validated tool? If so a reference might be considered.</p> <p>P10. Imputation is used more commonly these days. Are there limits to imputation with respect to missing data. If so how will they be applied?</p> <p>P10-11. Is a study effect of 0.5 realistic to calculate trial size? If not why cannot a larger study be constructed, incorporating other allergy centres - if required? If the study is too small then perhaps the word "pilot" should be incorporated into the title.</p>
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<b>REPORTING &amp; ETHICS</b>	more attention to sections 7-10 of the CONSORT 2010 statement would further enhance the proposed RCT.
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<b>REVIEWER</b>	Dr. David Hailey, Professorial Fellow, University of Wollongong, Australia.  I have no competing interests related to the article or the proposed study
<b>REVIEW RETURNED</b>	22-Apr-2012

<b>THE STUDY</b>	Methods: 1) Randomisation is to be on the basis of the subjects' day of their date of birth. Allocation methods such as date of birth are generally not considered acceptable for RCTs. Use of an approach such as a random-number table or a computerised random number generator is recommended. 2) The LOCF imputation method, which is to be used to deal with missing data, is known to give biased estimates. The editorial cited in support as reference 18 is itself critical of the LOCF method. The low number of repeated measures in the proposed study is also a consideration. An alternative approach may be appropriate. 3) Clarification is needed on the material dealing with power of the study. A sample size of 16 for each age group is calculated but the following Figure 1 relates to a sample size of 14, which appears to have been used to arrive at a planned recruitment of 50 families (rather than 60).
<b>GENERAL COMMENTS</b>	Under Intervention and Control, is the incident report form to be used by responding staff members for keeping a record of on-call encounters? Under secondary outcome measures, how are participants to record occurrence of possible allergic reactions? For example, will diaries be provided for this?

<b>REVIEWER</b>	Suneeta Monga, MD, FRCPC Psychiatrist, Anxiety Disorders Clinic Hospital for Sick Children Assistant Professor of Psychiatry, University of Toronto Canada
<b>REVIEW RETURNED</b>	25-Apr-2012

<b>THE STUDY</b>	This is a novel study proposal, which will be an interesting research paper upon completion of the study. It is important to note that the investigators do not clarify in their inclusion/exclusion criteria as to whether subjects will be newly identified cases of allergy diagnosis or any child who has had a diagnosis of potentially life threatening allergies – leading to potential bias as newly diagnosed subjects may have more difficulties adjusting to the diagnosis and be more anxious and have greater impairment on a questionnaire such as the FAQLQ than subjects who have managed their allergies for a longer time period. Furthermore, not everyone is familiar with the FAQLQ (the main outcome measures) and therefore in the final research paper as well as in the proposal further detail about this questionnaire should be included.
<b>RESULTS &amp; CONCLUSIONS</b>	The study methodology and plan for analyses are generally well thought out although waiting for all subjects to be recruited prior to randomization may be difficult as subjects would be at different stages in their awareness and understanding of their allergy

	symptoms at time of randomization which potentially could bias results.
<b>REPORTING &amp; ETHICS</b>	No concerns with the ethics or reporting of the proposal.

### VERSION 1 – AUTHOR RESPONSE

Reviewer: Dr David Hailey

1. Randomisation: We have explained that randomisation is centrally undertaken by the trial statistician only one all individuals have been recruited and this approach will minimise the risk of breaches to allocation concealment.
2. Dealing with missing data: We accept the concerns around LOCF and the potential risk of bias and we now plan to use multiple imputation to deal with missing data, which should reduce the risk of bias.
3. Sample size calculations: Figure 1 shows a power of 0.95 for 14 subjects per group, however, we used an actual power of 0.97, with 2 groups (experimental/control) of 16 = 32. With 20% drop out, this should be 40. The number 50 is a 'typo', which has now been corrected both in the text and figure.
4. Incident report form: Yes this Incident Report form is used by staff members for keeping a record of on-call encounters. It is to be filled out as soon as is practical after the incident.
5. Recording of secondary outcome measures: A standardised form is given to participants in both groups to record occurrence of possible allergic reaction.

Professor Suneeta Monga

6. Clarification of inclusion/exclusion criteria and recruitment: It is worth noting that longitudinal studies of outpatient attenders' quality of life have not yet been performed, so the potential bias mentioned about new cases cannot be conclusively confirmed or denied. There is a range of clinic attendance duration in this study; they are not all newly diagnosed. No patient is recruited at their first visit, and for the newest patients the earliest time of recruitment would be 3 months after the first appointment. Recruiting only newly diagnosed patients may also adversely increase initial anxiety levels across both groups(control/intervention) and perhaps the changes in anxiety scores seen after the 6month trial period would reflect the natural adjustment to the diagnosis and cause intrinsic bias towards the effect of the intervention. The study has been powered to examine any main or interaction effects with regard to the relative scores versus the length of time in contact with the clinic but this feasibility/pilot study is not designed or powered to conclusively address this interesting issue.
7. Description of the FAQLQ: This instrument is now described more fully and further supporting references in relation to its validation are now also provided.
8. Rolling vs. fixed start: It was a pragmatic decision to not use a rolling start. While it would not lengthen the duration of the study overall, the actual "time on call commitment" of the study staff would be much longer. Our primary intention is to explore if patients find this access useful/helpful, but we are also pragmatically exploring if staff can provide this 24/7 access without too much inhibition of their own out of hours time. Rolling randomisation would also involve asking the subjects who were early recruits to desist from calling the helpline number if they had an allergic reaction after 6months, even though that phonenumber would still be active for later recruitee's. This potential bias will be controlled for in the analyses. The power calculation was devised to allow us to investigate any interactions between factors.

Dr David Noble

9. Need for further supporting references to support the hypothesis: These have now been added.
10. Unecessary adrenaline can be detrimental too. eg Takotsubo cardiomyopathy-like syndrome: UK Resuscitation Council <http://www.resus.org.uk/pages/reaction.pdf> guidelines state that adverse effects from intramuscular adrenaline injected correctly are extremely rare and adrenaline should be given to all patients with life threatening features. Children are remarkably resistant to the physiological effects of adrenaline (often incorrectly called side effects)and we are not aware of any allergic child in the world literature who has suffered harm from adrenaline given correctly intramuscularly. Intravenous

adrenaline is for experts only under ICU or similar monitoring conditions. With proper training as in this protocol, incorrect use of adrenaline injectors is very unlikely.

11. The prevalence of the disorder would be useful information for readers:

It is estimated that anaphylaxis occurs at a rate of 1 episode per 10 000 children per year and 82% of such episodes occur in school-age children and this has now been provided

12. Is 6 months follow-up sufficient or will that overestimate the (potential) usefulness of the intervention? We have found in previous research that 6 months is a critical period when confidence and reassurance provided by the autoinjector begins to fall. From a food allergy specific perspective, 6 months is therefore we believe an appropriate follow-up point. (A. DunnGalvin, A. E. J. Dubois, B.M.J Flokstra- de Blok, J.O'B.Hourihane. Impact of Food Challenge Tests on Children's and Parent's Health Related Quality of Life: A Time Series Case-Control Study. Revision submitted to Clinical Experimental Allergy, June 2012)

13. Randomisation: See above response (Point #1)

14. Blinding of assessors: The analysis of the results will be performed by the trial statistician (ADG) who will be blind to group allocation and is not involved in the emergency contact aspect of the study. The staff member contacted by phone will of course know the allocation as only one group has the phone number.

15. Who will provide the advice - one single person or multiple persons?

Four clinical personnel will provide the advice. They will be involved in a rota system for manning of the helpline. Three of the personnel work in the same clinic, which is the primary paediatric allergy clinic for the whole of the Republic of Ireland. The fourth person is the only other Paediatric Allergist in Ireland. The advice to be given has been agreed and is provided in Appendix 1

16. How will consistency of advice be ensured if multiple persons will be involved? Consistency of advice is ensured in two ways: i. Discussion between all members will take place prior to commencement of the study and standardised advice agreed upon (see Appendix 1); and ii. There will be a teleconference 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

17. Adjustment for multiple comparisons: The Bonferroni correction will be used to adjust for multiple comparisons.

18. Is the "responsiveness index" a validated tool? If so a reference might be considered. Yes, and a supporting reference has now been provided: Cohen J. A power primer. Psychol Bull 1992; 112:155–159.

19. Missing data: As noted above, we will now use multiple imputation techniques to minimise the risk of bias.

20. Likely effect size: Cohen (1992) defines a moderate to large effect size to be  $r \geq 0.5$ . We have also calculated power at 97% when 80% is considered acceptable. Previous research using the FAQLQ has defined the minimal important difference for clinical significance following intervention at 0.45 (Cohen J. A power primer. Psychol Bull 1992; 112:155–159 and DunnGalvin et al. 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(3):476-85).

We trust that these revisions are to your satisfaction and we look forward to your decision in due course.

With kind regards

Aziz Sheikh, on behalf of the co-authors