

Twenty four-hour helpline access to expert management advice for food-allergy-triggered anaphylaxis in infants, children and young people: a pragmatic, randomized controlled trial

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Abstract

Background: Anaphylaxis is a life-threatening emergency. If promptly administered, adrenaline is potentially life-saving. Many food-allergic-children/carers are unsure when to use their adrenaline autoinjectors, contributing to a low quality of life and worse outcomes in the setting of an acute allergic reaction.

Objectives: The aim of this study was to assess the effectiveness of 24-hour telephone access to specialist clinical advice on disease-specific quality of life.

Methods: A pragmatic two-arm, parallel-group randomized control trial was conducted. Children/carers (<16 years) with food allergy, trained in adrenaline auto-injector use, were recruited from a hospital-based paediatric allergy clinic. Baseline disease-specific quality of life was ascertained using the validated Food-Allergy-Related Quality-of-Life Questionnaire (FAQLQ), either Parent Form, Child Form or Teenager Form depending on child's age. Participants were then centrally randomized for a 6-month period to 24-hour telephone specialist support line or to usual care. The primary outcome measure was a change in FAQL scores, at one and 6 months postrandomization, compared with baseline. The minimum clinically important difference (MCID) in score is 0.5.

Results: Fifty two children/carers were recruited. FAQL scores remained static in the control group across the three time points. Scores gradually improved in the intervention group, with a significant difference seen at 6 months (T1–T3 Mean difference = −1.5, (CI 0.87–2.25) $P < 0.005$) Follow-up questionnaires, 6 months after the intervention was removed, T4, showed sustained significant difference between the groups (control $M = 3.0$; intervention $M = 1.1$ [$t = -4.113$, $P < 0.05$]).

Conclusion: The 24-hour helpline improved food-allergy-specific quality of life in children. Six-month intervention support resulted in sustained benefits for at least a further 6 months.

Anaphylaxis is a life-threatening emergency occurring at an increasing rate (1). Food is responsible for the majority of community allergic reactions in children (2–4). There is a wide spectrum of severity of reactions to these allergens ranging from minor urticarial reactions to anaphylaxis, with the associated risk of fatality.

For food-allergic children, the risk of anaphylaxis is managed via a two-pronged approach: first lifestyle modification

to avoid the allergen and second the acute management of the anaphylactic event itself (5–7). Children who have had anaphylaxis, or who are judged to be at high risk of anaphylaxis, are prescribed adrenaline autoinjectors, which are to be carried on their person, or by their carers, at all times. Although anaphylaxis is relatively uncommon, the majority of accidental exposures and subsequent reactions occur in the community setting (8). Because of the typically rapid onset of

symptoms of anaphylaxis following the ingestion of the allergen, most young people do not have immediate access to medical support when it is most required.

Despite being prescribed an adrenaline autoinjector and being shown the correct method of administration, young people and their parents often report being unsure whether to administer the medication (9–11). Children or their carers often fail to administer the adrenaline during anaphylaxis and, even if they do it correctly, they have difficulty judging reaction severity and what medical follow-up is needed (12, 13). There is evidence of delay in administering adrenaline in an emergency setting (2), which can lead to an increased morbidity and possibly mortality (14, 15). Unsurprisingly, this can result in significant parental and child anxiety, which influences health-related quality of life (HRQL) (16, 17). Reducing uncertainty, and hence anxiety, is an important clinical target that may improve both HRQL and perception of control in managing food allergy and reduce the associated indirect costs to both the individual and the society they live in (18).

In the light of the above factors, we hypothesized that real-time expert clinical guidance and support could ameliorate this anxiety and improve food-allergy-related quality of life (FAQL). Such a service would be novel in publicly funded European healthcare systems, where allergy is managed via hospital-based ambulatory or outpatient appointments.

As a secondary outcome, we proposed that the food-allergic reactions treated according to expert advice available in real time would be more promptly and correctly treated. There is currently no such public service available in Ireland or indeed worldwide. This is, as far as we are aware, the first randomized control trial of patient care in the field of anaphylaxis.

Methods

The protocol has been described in detail elsewhere (19). We provide below a summary of the salient features of the study design.

Ethical and regulatory approval

Ethical approval was obtained by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Ireland (30 May 2011). All patients were aware of the voluntary nature of their participation and that they could withdraw from the study at any time.

Design

This study was designed as a pragmatic two-arm, parallel-group, randomized control group. (See Appendix S2 in the Supporting Information for the CONSORT checklist.) The intervention group was given a direct access helpline number to ring in the event of a suspected serious allergic reaction, and the control group was given routine care. The 24-hour helpline was active for 6 months from December 2011 through to June 2012.

This helpline number was given in the form of a credit-card-sized document with both the helpline phone number and emergency advice written clearly. Parents were advised to ring the helpline only in the event of a suspected allergic reaction. The number could be shared with anyone acting in *loco parentis* (e.g. teacher, family member, babysitter, etc.). Older children could use the helpline number themselves if desired.

Intervention group parents were advised that contacting the helpline should not delay any urgent treatment that their child required, and if they deemed it necessary, treatment was to be delivered first and then the helpline should be contacted.

The helpline was manned 24 hours a day by an experienced member of the paediatric allergy team, namely one of a paediatric allergist, a paediatrician, a clinical research fellow and a clinical nurse specialist. Protocols were implemented to guide team members on the advice they should give, if called (see Appendix S1 in the Supporting Information). The responding staff member kept a record of all incidents and what advice was given. A teleconference was held by the whole clinical study team as soon as was practicable after the incident, to review the incident, to ensure that the standard advice was offered and adhered to and that the allergic event was managed appropriately. A phone interview was also conducted with the contacting parent after the incident, to assess the parents' understanding of incident, to assess their experience with the helpline and to gauge what their actions would have been had they not had access to the 24-hour helpline.

Those allocated to the control arm received routine clinical care, offered to all patients of the Allergy Clinic, in Cork University Hospital. In the event of an emergency, they had the option of contacting one of the following: the study centre's paediatric allergy team during working hours (Monday–Friday 8:00–17:00), emergency/ambulance services, their own registered general practitioner, out-of-hours primary care providers or their nearest hospital emergency department.

The duration of trial was 6 months from randomization, December 2011–June 2012. At the end of the trial, parents in the intervention group were given adequate and clear notice that the helpline was to be discontinued and they could no longer contact the clinical team via that helpline for emergency guidance. The helpline phone card was destroyed.

Inclusion/exclusion criteria

Inclusion criteria for the study were as follows:

Attending the paediatric allergy clinic in Cork University Hospital (the study centre), with

Clinician-diagnosed IgE-mediated food allergy

- aged under 16 years
- prescribed adrenaline autoinjectors (2 or 4 units)
- carers and, where appropriate, children trained by our clinical service on the use of adrenaline autoinjectors.

Exclusion criteria were as follows:

- likely to undergo an oral food challenge over timeline of the study

- undergoing any other major life stressors during the study time period
- second or subsequent eligible child in families with one child already recruited.

Sample size and power

We utilized a within/between repeated-measures analysis of variance. An a priori total sample size required $\times$ power (1- β err prob) for a within/between repeated-measures ANOVA was 16 in each group (intervention/control) to yield a statistically significant result at >90% power with a 0.5 effect level. 'Within' refers to expected differences between four time periods (T1, T2, T3 and T4), and 'between' refers to expected differences between the intervention and control groups (20). We recruited 52 patients, of whom 51 were retained to time point three.

Randomization

Randomization took place after the recruitment was completed. This was to ensure minimization of risk of selection bias, by maintaining allocation concealment. Also, it limited the effect on baseline FAQLQ, which may have been influenced if families knew which group they were about to be enrolled on. When all baseline questionnaires were collected, the families were centrally randomized independently by the trial statistician in a 1 : 1 ratio, into the intervention or control (usual care) arms. All recruited families were thus simultaneously allocated to the intervention or control arms, marking the onset of the trial period.

Baseline assessment of FAQL (Food-Allergy-Related Quality of Life)

Validated tools were used: the Food-Allergy-Related Quality-of-Life Questionnaires. These are age-appropriate parent-administered (FAQLQ-PF), child self-administered (FAQLQ-CF) and teen self-administered (FAQLQ-TF) questionnaires that measure the impact of food allergy on health-related quality of life (HRQL) of children aged 0–18 years (21–23). For children aged <8 years, the parent completed the FAQLQ-PF form. For children aged 8 to 12 years, the parent completed FAQLQ-PF and the child also completed FAQLQ-CF. Teenagers aged 13 years and more completed their own FAQLQ-TF only. The questionnaire items are scored on a seven-point Likert scale ranging from 0 (no impact on HRQL) to 6 (extreme impact on HRQL). A change of 0.5 is considered a clinically meaningful change in FAQLQ score (24). These questionnaires have previously demonstrated good cross-sectional and longitudinal reliability and validity (24, 25).

On enrolment, all the study participants completed the age-appropriate FAQLQs prior to randomization to assess baseline food-allergy-related quality of life. The same questionnaires were then repeated at 1 month (T2), 6 months (T3, i.e. end of intervention) and 12 months postrandomization (T4).

Analysis of these results was carried out blind to group allocation, helpline use and other healthcare use.

Statistics

Statistical analysis was carried out (by AD) blind to group allocation. Other members of the team were not blinded to group allocation for clinical and operational purposes. SPSS, version 18.0, was utilized. A between-groups multivariate repeated-measures ANOVA was used to investigate whether change over time occurred for intervention compared with control participants across four time points and whether this change was significant ($P < 0.05$).

Preliminary assumption testing was conducted to check for normality, linearity, univariate and multivariate outliers, homogeneity of variance-covariance matrices, and multicollinearity, with no violations noted.

We assessed the statistical significance and relative magnitude of changes over 3 or 4 time points (T1 – baseline, T2, T3, T4) on the summed scores of FAQLQ-PF, FAQLQ-CF and FAQLQ-TF for both control and intervention groups, using a repeated-measures 2×4 multivariate design; that is, the same parent of a child in either the control or intervention group (group factor) completed the questionnaires at four time points (time factor). Paired *t*-tests were used to determine any change in FAQL scores for the intervention and control groups at T2, T3, T4, relative to the baseline. The effect of the factors 'time' and 'group' on the total score and the interaction of these two factors were analysed using a two-way within- and between-groups ANCOVA, which also controls for possible confounding variables. The interaction addressed the question, 'Are the time profiles of the total score and subscales of the two groups (positive/negative) significantly different?' Independent *t*-tests were used to determine whether there were differences in magnitude of improvement in total score for intervention vs. control groups.

Results

Fifty four parents were approached; all 54 consented to recruitment onto the study. Prior to randomization, all participants were given a FAQLQ to complete. Two participants withdrew consent at this stage. 52 participants completed baseline FAQLQ and were therefore eligible for randomization (Table 1). Postrandomization, one participant withdrew from the study as at a subsequent clinic visit, their risk of anaphylaxis was deemed so low and they were advised they could cease carrying adrenaline autoinjectors. Analysis was based therefore on 51 participants. See Fig. 1 for CONSORT recruitment flow.

Primary outcome: impact on FAQLQ

We examined the difference in FAQL total scores from baseline to T4 separately for both the intervention and the control groups, using a series of paired sample *t*-tests (see Fig. 2). We found that the FAQL score decreased from baseline to T3 and remained improved for 6 months poststudy

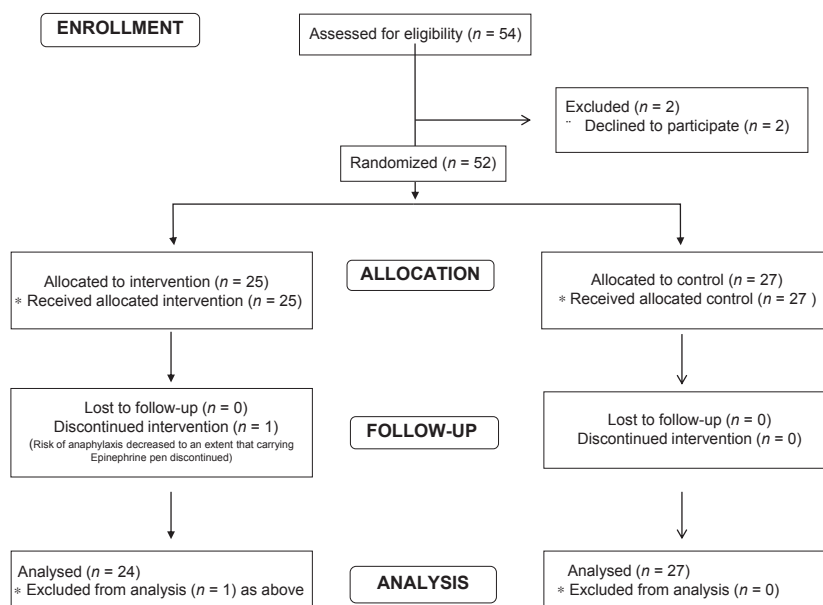


Figure 1 CONSORT recruitment flow diagram.

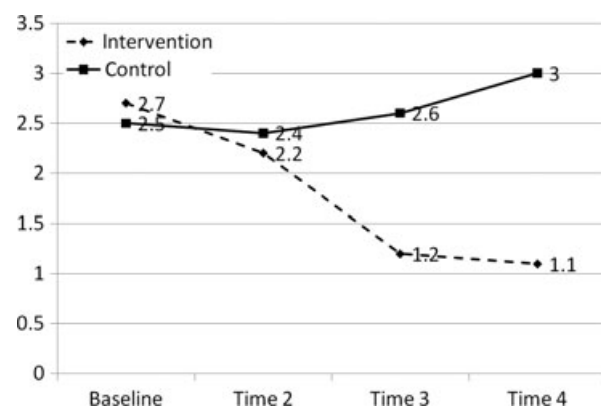


Figure 2 Significant difference found between control and intervention groups after randomization at T3 and T4 ($P < 0.05$) for all age groups. *T*-test analysis showed that the *magnitude of improvement* between T1 (baseline) and T4 for the intervention group was 2 points on the FAQLQ 7-point scale ($P < 0.05$) (MID is 0.5).

for the intervention group (T1–T2 Mean difference -0.5 ; CI -0.04 – 1.05 , $P = 0.07$]; T1–T3 Mean difference -1.5 , (CI 0.87 – 2.25) $P < 0.005$] and; T1–T4 Mean difference -1.6 (CI 0.89 – 2.36), $P < 0.001$, whereas scores remained static for the control group (T1–T2 Mean difference -0.1 (CI, -0.49 – 1.05) $P > 0.05$; T1–T3 Mean difference $+0.1$ (CI -0.36 – 0.16) $P > 0.05$ and; T1–T4 Mean difference $+0.5$ (CI -0.71 – 0.05) $P > 0.05$. We next used ANOVA to investigate the impact of ‘time’ (baseline, T2, T3, T4) and group (intervention vs control) on HRQL. Statistically, the interaction between ‘time’ and ‘group’ for FAQL total score was significant [$F = 3.236$, $P = 0.019$] with a large effect size (partial eta-squared = 0.4) (20).

Table 1 Participant demographics

	Intervention	Control	<i>P</i> value
Total number	<i>n</i> = 24	<i>n</i> = 27	
Sex M:F%	45.8: 54.2	51.9: 48.1	$P = 0.78$
Age: mean (years)	6.08 (± 3.74)	6.44 (± 3.34)	$P = 0.72$
Age			
0–7	17	20	
8–12	5	6	
13 +	2	1	
Time since first clinic visit (months [SD])	23.21 (± 20.47)	31.93 (± 21.76)	$P = 0.15$

Analysis using *t*-tests demonstrated a significant difference between groups at T4 (control $M = 3.0$; intervention $M = 1.1$ [$t = -4.113$, $P < 0.05$]). The magnitude of the difference between groups from T1 to T4 on the FAQLQ was -1.6 (-2.4 ; -0.8 , 95% CI). Having only a difference of 0.2 points on the FAQLQ at baseline, the magnitude of the difference between groups at T4 was 1.9 points on the FAQLQ.

Events reported

There were three events that resulted in contact to the helpline (see Table 2). Events one and two involved the same child, 10 days apart.

Secondary outcomes

(1) Comparing food-allergic incidents in intervention and control groups. Participants in both groups kept records of any suspected food-allergic reactions during the course of

Table 2 Events reported to helpline

	Event 1	Event 2	Event 3
Caller	Mother	Mother	Mother
Known food allergies	Peanut	Peanut	Peanut, tree nut, milk, egg
Food implicated	Danish pastry	Kiwi (first time ingested)	Kiwi (first time ingested)
Symptoms	Lip swelling Nausea	Itchy mouth Lip swelling	Itchy mouth Lip swelling Urticaria
Treatment advised	Antihistamine	Antihistamine	Antihistamine
Outcome	Resolved	Resolved	Resolved

the study. In the intervention group, five other children reported incidents of allergic reactions where the parents did not feel the need to use the helpline. All of these events were minor allergic reactions that were treated successfully with H1-antihistamines and no child was brought to medical attention.

In the control group, five children reported allergic reactions during the course of the study; four of these were minor and treated successfully with H1-antihistamines. During one event, adrenaline was administered. This involved a child with nut allergy who experienced an episode of pallor, throat tightening and feeling of doom when in the vicinity of a nut allergen in a cafe. A general practitioner attended the child and advised not to administer adrenaline as only subjective symptoms were present. The child's mother, however, deemed it necessary to administer the adrenaline.

(2) Comparing clinical and health-service-use outcomes. In the intervention group, five minor allergic events occurred that were treated at home with antihistamine without the need for further medical attention. When subsequently asked about the three events reported to the helpline, parents stated they would have contacted an out-of-hours GP service if the 24-hour helpline had been unavailable.

In the control group, four minor allergic reactions did not lead to healthcare service use. In the single event where adrenaline was administered by mother, an ambulance was called and the child was brought to the local emergency department to be monitored, as remains our standard clinical advice if adrenaline is ever administered. The child was discharged later that day.

Discussion

Food allergy is a disease of paradox, where the affected child remains completely well while the food allergen in question is avoided, yet the daily potential for anaphylaxis and even death on accidental exposure to the food is real. As there is no cure for food allergy yet, allergen avoidance is the mainstay of treatment. The constant vigilance for food avoidance impacts on all aspects of daily life and causes anxiety and reduced quality of life in affected children and their families. This study has demonstrated that 24-hour access to expert paediatric allergist advice improves FAQL.

Over the course of the study, those in the intervention arm, who had the reassurance of 24-hour expert guidance, developed and then sustained improved food-associated quality-of-life scores, even from as early as 1 month posttran-

domization. These improved scores at 6 months were both clinically and statistically significant. The persistence of improved FAQL up to 6 months after the intervention was withdrawn is also an important finding, implying simple, time-limited interventions can have long-lasting effects even in those who have great fear for their children's health and well-being.

Of 24 children in the intervention group, events were only reported to the helpline for two children. However, the improvement in FAQL scores was seen across the whole group, which demonstrated that the apparent security provided by 24-hour access to expert guidance, and not just the actual contact and guidance given, was sufficient to have a significant impact on FAQL. We have previously demonstrated that a food challenge may be valuable, not only as an essential diagnostic tool, but as a therapeutic one. In effect, by providing a sense of certainty, a food challenge (overseen by an allergist) has a positive impact on FAQL, irrespective of the outcome (24). Similar psychological mechanisms may underlie our findings in this study.

In each of the three helpline uses, the allergic reaction was mild and successfully treated with antihistamine only. No adrenaline use was advised, and no child in the intervention group was administered adrenaline over the course of the study. From the finding that five other children in the intervention group had minor allergic reactions, which were treated successfully at home with antihistamine without parent contacting the helpline, we infer that parents attending our paediatric allergy clinic are competent in managing minor reactions independently. Most children with food allergies and their parents already have or are taught the knowledge and skills of avoidance and emergency management, so possibly it is a lack of confidence in these abilities, related to risk perception, that contribute to poor FAQLQ scores. Interventions to improve patient and parental empowerment and subsequently improve self-confidence in food allergy management would be welcome.

The persistence of improved scores in the intervention group was an interesting finding. Over the course of the 6-month study period, the majority of parents on the study did not need to avail of the expert assistance provided. The food-allergic reactions that occurred were minor, both those notified to the helpline and those not notified. Having access to a 'safety net', yet not needing to avail of this 'net', may have provided parents and children with sufficient increased confidence in their own ability to manage their food allergy, and hence, even when the intervention was withdrawn, the self-confidence remained, leading to persistent improved FAQL scores.

In two of the events reported, the food allergen implicated was ingested for the first time. Neither of the children had previously been screened for the allergen (kiwi in both cases), nor had parents sought testing. Reasons given for first ingestion were 'they were in season' and 'good source of vitamin C' when child had a minor intercurrent illness. Although both were reasonable reasons to ingest kiwi, we had to be suspicious that the easy access to expert allergy care could have been a contributory factor in why both noninfant children ingested kiwi for the first time while enrolled in the study. This is particularly the case in Event 2 where the family had already received successful guidance from the helpline in relation to a previous food-allergic incident (Event 1). Increased risk-taking behaviour in the setting of perceived safety is seen in other areas of medicine, particularly sports medicine (26, 27). This is an aspect to the study that should be considered carefully if this helpline facility is to be expanded.

Strengths and limitations

This study was a formal RCT involving children at risk of food-triggered anaphylaxis and their carers. We used a widely validated measurement of disease-specific quality of life as the outcome measure. This study was adequately powered to assess the primary outcome. The primary outcome of the study was achieved with an additional sustained effect on the intervention group, as shown by continued improved disease-specific QOL scores 6 months postremoval of the intervention. We are aware that in other healthcare settings such as the United States, such 24-hour access to allergy specialists is commonly provided by doctors in private practice, but it is not common in the public health systems in Ireland or Europe, and to our knowledge, this is the first time its impact has ever been systematically measured in the field of anaphylaxis.

This was a single-centre study, in what is the *de facto* national referral centre for paediatric allergy in Ireland. Therefore, there were standardized protocols in place for prescription of adrenaline and parental education in its use. In Ireland, one brand of adrenaline autoinjector had a near monopoly of the market at the time of the study, but there is no reason to suspect that if this study was employed in other settings that different findings would be seen with a different autoinjector.

Our secondary objective to compare clinical and health-service-use outcomes in both groups was difficult due to small numbers of reported allergic reactions; therefore, it was not possible to measure a definite decrease in access to health care using our findings. This may be possible in a larger study.

This intervention was provided free of charge as the publicly employed study staff volunteered to be on a 24-hour on-call rota. This may lead to funding issues if this intervention

were to be implemented widely as part of routine clinical practice. Finally, this study involved paediatric patients only, and while we would expect it could be generalizable to an adult population, this remains to be demonstrated.

Conclusions

The 24-hour availability of expert guidance to children with food allergy and their families resulted in significantly improved food-associated quality-of-life scores during and after a 6-month pilot period in what is the first randomized control trial of a support intervention in the acute setting of potential anaphylaxis. This simple intervention rapidly delivered significant and sustained changes in food-allergy-related quality of life. We intend to embark on an implementation phase to roll this practice out initially on a national basis.

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Author contributions

JH, ADG and AS conceived and designed the study. ADG provided statistical input and advice. MK, CC, JF and JH provided the helpline clinical support. MK supervised the clinical aspects of the trial and wrote the drafts of the paper. JH is the guarantor of the study.

Conflicts of interest

The authors declare they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Incident report form.

Appendix S2. CONSORT checklist.

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Appendix S1: 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 autoinjector yet
Rash and swelling	Give antihistamine, do not use autoinjector yet
Cough/hoarseness	Use autoinjector, call ambulance, go to hospital
Wheeze	Use autoinjector, call ambulance, go to hospital
Dizzy/collapse	Use autoinjector, call ambulance, go to hospital

Appendix S2: CONSORT checklist

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract	1a	Identification as a randomized trial in the title	1598
	1b	Structured summary of trial design, methods, results and conclusions (for specific guidance see CONSORT for abstracts)	1598
Introduction	2a	Scientific background and explanation of rationale	1599
	2b	Specific objectives or hypotheses	1599
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	1599
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	1599
	4b	Settings and locations where the data were collected	1599, 1600

Section/Topic	Item No	Checklist item	Reported on page No
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	1599
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	1599
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	1600
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomization			
Sequence generation	8a	Method used to generate the random allocation sequence	1600
	8b	Type of randomization; details of any restriction (such as blocking and block size)	1600
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants and who assigned participants to interventions	1600
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	1600
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	1600
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	1600
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomization, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	1599
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	1601
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	1601, 1602
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses Harms	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	N/A
	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	1603
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	1603

Section/Topic	Item No	Checklist item	Reported on page No
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	1602, 1603
Other information			
Registration	23	Registration number and name of trial registry	1598
Protocol	24	Where the full trial protocol can be accessed, if available	1599
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1603