NOTTINGHAM CLINICAL TRIALS UNIT

Two-by-two factorial randomised trial to evaluate strategies to improve follow-up in a randomised prevention trial

Statistical Analysis Plan

Final version 2.0

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Table of Contents

1. INTRODUCTION & PURPOSE 5
2. SYNOPSIS OF EMBEDDED TRIAL DESIGN AND PROCEDURES 5
2.1. Embedded trial aims and objectives 5
2.2. Embedded trial design and configuration 5
2.3. The BEEP host trial 6
2.4. Participant follow-up in BEEP 6
2.5. General retention strategies used for all participants in BEEP 7
2.6. Embedded trial eligibility criteria 7
2.7. Embedded trial randomisation procedures 7
2.8. Embedded trial interventions 7
2.9. Sample size and justification 8
2.10. Blinding and breaking of blind 8
2.11. Embedded trial outcome measures 9
2.11.1. Primary outcome 9
2.11.2. Secondary outcomes 9
3. INTERIM ANALYSIS 9
3.1. Analysis strategy for interim analyses 10
3.2. Stopping rules 10
3.2.1. Interim analysis of extra prior SMS notification for questionnaires 10
3.2.2. Interim analysis of vouchers for the 24 month visit 11
3.3. Impact on final analysis 12
4. GENERAL ANALYSIS CONSIDERATIONS 13
4.1. Analysis samples 13
4.2. Derived variables 13
5. DESCRIPTION OF PARTICIPANT CHARACTERISTICS 15
5.1. Participant flow in embedded trial 15
5.2. Baseline characteristics 15
5.3. Adherence 15
6. ANALYSIS OF EFFECTIVENESS 15
6.1. Primary analysis for co-primary outcome 1 - collection of data via the chosen method of questionnaire at interim follow up times 15

6.2. Primary analysis for co-primary outcome 2 - collection of the BEEP trial primary outcome at 24 months during a home or clinic visit with a research nurse 16

6.3. Senstivity analysis for the primary outcomes 17

6.3.1. Sensitivity analyses with adjustment for other baseline covariates 17

6.3.2. Sensitivity analyses for co-primary outcome 1 - the extent of questionnaire completion 17

6.3.3. Sensitivity analyses for co-primary outcome 2 – collection of BEEP trial primary outcome data via any method 17

6.4. Secondary outcomes 17

6.4.1. Time to questionnaire completion 17

6.4.2. Number of reminders required to obtain questionnaire completion 18

7. DUMMY TABLES AND FIGURES 19

8. REFERENCES 20

9. APPENDIX 21

9.1. Analysis sample for interim analysis 1 of extra prior SMS notification that the questionnaire is ready to complete versus none on co-primary outcome 1 (collection of questionnaire data) 21

9.2. Questions from section A, part 1 of questionnaire 22

Amendments to versions

Version	Date	Change/comment	Statistician
1.0	27 Feb 2017	First final version	LB
2.0	05 Dec 2018	Updated prior to database lock for the host trial to account for changes in the trial, such as collecting primary outcome data via questionnaires and texts, and also adding details of sensitivity analyses	LB

1. INTRODUCTION & PURPOSE

This document describes the analyses that will be conducted for the two-by-two factorial randomised trial to evaluate strategies to improve follow-up in a randomised prevention trial. This includes details of two planned interim analyses.

This study has been logged on the Northern Ireland Hub for Trials Methodology Studies within a Trial (SWAT) Repository as SWAT25 [1].
http://qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/

The following terms are used throughout this document:

1. Host trial refers to the BEEP trial: A randomised controlled trial to determine whether application of emollient from birth can prevent eczema in high risk children (ISRCTN 21528841)

2. Embedded trial refers to the two-by-two factorial randomised trial to evaluate strategies to improve follow-up within the host trial

2. SYNOPSIS OF EMBEDDED TRIAL DESIGN AND PROCEDURES

2.1. Embedded trial aims and objectives

The primary aim of this embedded trial is to estimate the effectiveness of two strategies for participant retention on collection of primary outcome data in the host trial.

The secondary aim is to estimate the effectiveness of text contact prior to sending out questionnaires on completion of questionnaires in the host trial.

2.2. Embedded trial design and configuration

The embedded trial is a two by two factorial randomised trial with the following interventions:

- Intervention 1: Compensation for parent's time in the form of £10 voucher – sent to parents either before or after the 24 month visit.
- Intervention 2: Extra prior notification that the questionnaire is ready to complete via SMS text message versus no extra notification.

2.3. The BEEP host trial

The BEEP trial is a multicentre randomised controlled trial to determine whether application of emollient from birth can prevent eczema in high risk children. Children are identified as high risk if there is a first degree relative with parental reported, doctor diagnosis of eczema, hayfever or asthma.

Families are randomised within 21 days of delivery of their baby to one of two groups in a 1:1 ratio:

- Control Group: Parents given best practice infant skin care advice only.
- Intervention Group: Parents given best practice infant skin care advice PLUS advice on how to apply emollient at least once a day for a year to their child's skin.

The planned sample size was 1282. In total, 1395 children were randomised following advice from the independent Trial Steering Committee following a planned sample size review after 20 months of recruitment.

The host trial primary outcome is a diagnosis of eczema between 12 and 24 months of age (defined as meeting the UK Working Party Diagnostic Criteria for Atopic Dermatitis).

2.4. Participant follow-up in BEEP

Approximately two weeks after randomisation the coordinating centre contacts parents to check they have received their skin care advice pack and skin care video web link and to record the date that the family started applying the emollient, where appropriate.

Parents are followed up by questionnaire at 3, 6, 12 and 18 months. These will be completed online by most parents, and an email containing a web-link will be sent to alert parents that the online questionnaire is ready to complete. Where families do not wish to do online questionnaires, paper copies of the questionnaires will be provided by post with pre-paid return envelopes. Where questionnaires are not completed or returned, a reminder will be sent by email after 2 and 3 weeks of non-completion. The link to the online questionnaire remains active for 4 weeks after the initial email invitation is sent.

Due to the lower than expected completion of questionnaires, the protocol was amended in May 2016 so that members of the BEEP trial team could ring participants where questionnaires have not yet been completed but are still active. Telephone calls began on 21 July 2016.

At 24 months, there will be a face to face visit with the researcher either in the family home or at the hospital/GP surgery (depending on parental preference). At this visit, the researcher will conduct a blinded examination of the child's skin for signs of eczema for the host trial primary outcome. If a face to face visit is not possible then the visit may be conducted remotely e.g. telephone, text, email or post.

2.5. General retention strategies used for all participants in BEEP

Small gifts are given/sent to parents at the following time points:

- Shopping trolley coin and pen given by the research nurses at the screening / consent visit
- BEEP branded muslin or bib sent by co-ordinating centre at randomisation
- Birthday card and BEEP branded plastic cutlery set or storybook sent by coordinating centre at the child's first birthday
- BEEP branded cloth shoulder bag sent by the coordinating centre at 18 months

Participant newsletters are sent every 6 months. This began in January 2016.

2.6. Embedded trial eligibility criteria

Participants in the embedded trial are parent(s) who have given consent and been randomised in the BEEP trial. There are no exclusion criteria. If a participant withdraws their consent for participation in BEEP, they will be automatically withdrawn from the embedded trial.

2.7. Embedded trial randomisation procedures

Once participants have been randomised into the main BEEP trial, they will be further randomised to each of the retention strategies (1:1), using an online system provided by the coordinating centre to ensure that allocation is concealed. Allocation will be stratified by BEEP main trial arm (advice to apply emollient or usual care).

2.8. Embedded trial interventions

Intervention 1: Compensation for parent's time in the form of £10 voucher – sent to parents either before or after the 24 month visit.

A letter will be sent to parents at around 22 months to ask them to get in touch with their BEEP study nurse for the 24 month visit.

For participants allocated to be given the voucher before the visit, the letter will include the following text:

"As a thank you for your ongoing participation with the study, we are enclosing in this letter a £10 voucher".

For participants allocated to be given the voucher after the visit, the letter will include the following text:

"As a thank you for your ongoing participation with the study, your BEEP study nurse will give you a £10 voucher at the visit."

Intervention 2: Extra prior notification that the questionnaire is ready to complete via SMS text message versus no extra notification.

For participants allocated to receive extra prior notification, a SMS text message is sent on the day prior to the email/letter with the following wording:

- For participants completing questionnaires online: "Your BEEP study questionnaire will be ready soon. Please check your email tomorrow. Contact beep@nottingham.ac.uk if you have any problems completing it.Thanks!"
- For participants completing questionnaire on paper: "Your BEEP study questionnaire is on its way to you in the post. Contact beep@nottingham.ac.uk if you have any problems completing it. Thanks!."

2.9. Sample size and justification

The target sample size for the BEEP study was just under 1300. Based on this target, if 5% of participants withdraw consent from the trial, there will be 617 per arm for analysis for each of the two factorial interventions. It is reasonable to anticipate, based on previous similar studies, collection of outcome data from around 80-85% of participants overall. With 90% power and 5% two-sided alpha, this allows an absolute between-group difference of ≥7 percentage points (equivalent odds ratio 1.7) to be detected.

The timepoint for the planned interim analyses (see section 3) was chosen so that if one or both the interventions appear effective, then the intervention can be applied for the benefit of the host trial.

2.10. Blinding and breaking of blind

The host trial statistician (LB) and host trial co-applicant (AAM) will not have access to the host or embedded trial allocation dataset until the data is ready for the main analysis of the host trial after all 24 month follow-up visits have been completed.

The planned interim analyses will be conducted by a statistician at the coordinating centre, independent of the trial.

2.11. Embedded trial outcome measures

2.11.1. Primary outcome

There are two co-primary outcomes:

1. Collection of data via the chosen method of questionnaire (postal or electronic) at interim follow up times (3, 6, 12 and 18 months).
2. Collection of the BEEP trial primary outcome at 24 months during a home or clinic visit with a research nurse.

2.11.2. Secondary outcomes

1. Time to questionnaire completion.
2. Number of reminders required to obtain questionnaire completion.

3. INTERIM ANALYSIS

The protocol for the embedded trial planned a separate interim analysis of the data for each of the two co-primary outcomes for the first 400 participants in the trial. This was to allow for the investigation and application of any strategy found to be superior while follow up is still being conducted during the trial.

The first interim analysis of the effect of the extra prior SMS notification intervention on questionnaire return rates was to be conducted after the first 400 participants in the host trial had reached the end of the completion window for the 12 month questionnaires. This was in October 2016. The analysis could not be conducted at this time and so will be completed in February/March 2017. The interim analysis will therefore use data for participants who had reached the end of the questionnaire completion window by the end of 2016. Appendix 1 gives further information on the number of participants who will be included in this interim analysis.

The second interim analysis for compensation for parent's time in the form of £10 voucher sent before or after the 24 month visit will take place once the first 400 participants in the host trial have reached the end of the completion window for the 24 month follow-up visit (at 26 months). This will be in the last quarter of 2017.

3.1. Analysis strategy for interim analyses

The interim analyses will use the analysis methods set out in Sections 6.1 and 6.2.

3.2. Stopping rules

3.2.1. Interim analysis of extra prior SMS notification for questionnaires

The interim analysis of *extra prior SMS notification that the questionnaire is ready to complete versus none* on co-primary outcome 1 (*collection of questionnaire data*) will include participants who have reached the end of the questionnaire completion window by the end of 2016. Roughly 700 participants (see Appendix 1) will have reached the end of the questionnaire window for the 12 month questionnaire at this point (roughly 50% of the 1395 participants randomised in total to BEEP).

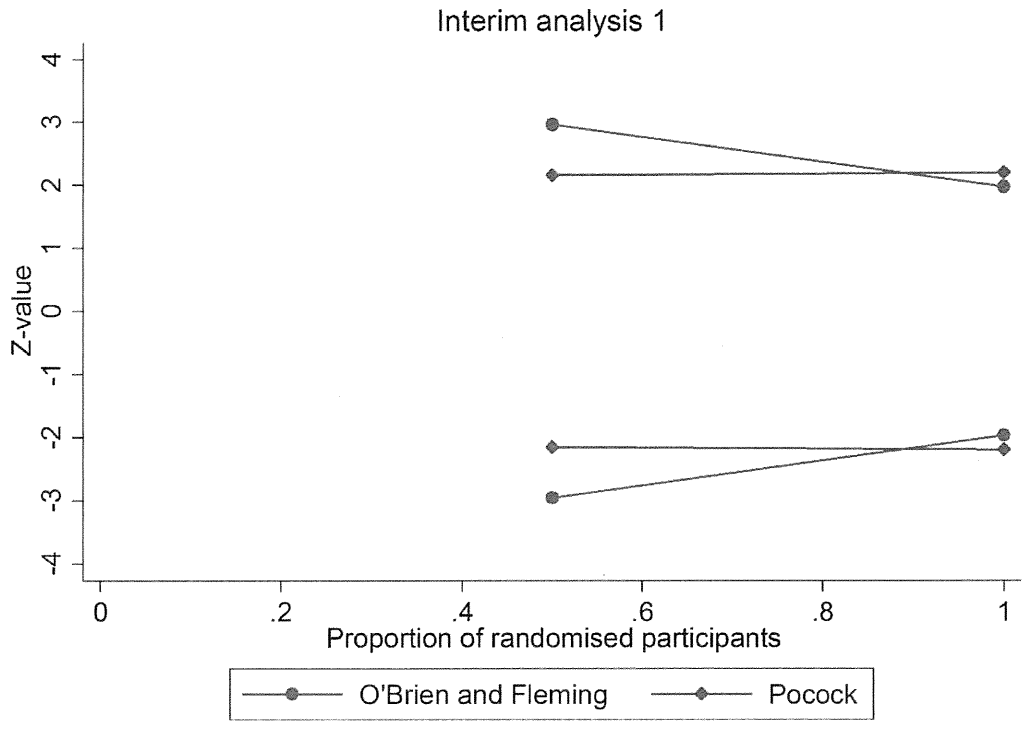
The table below shows the stopping boundaries using the O'Brien and Fleming or Pocock alpha spending function for a total type 1 error (α) of 0.05 with one interim analysis after 700 participants. A trial would be stopped at the interim analysis point if the absolute value of the test statistic is greater than the stopping boundary.

Analysis number	O'Brien and Fleming		Pocock	
	Stopping boundary (B)	α	Stopping boundary (B)	α
1 (n = 700)	2.9626	0.003051	2.157	0.03101
2 (n = 1400)	1.9686	0.04695	2.201	0.01899

Stopping boundaries calculated using landemets add on package in Stata

These stopping boundaries are also shown in the plot below.

The embedded trial should only be stopped at the interim analysis if there is strong evidence of an effect, the O'Brien and Fleming stopping boundaries will therefore be used. The embedded trial of extra prior SMS notification for questionnaires will stop at the interim analysis if the absolute value of the test statistic is greater than 2.9626.



3.2.2. Interim analysis of vouchers for the 24 month visit

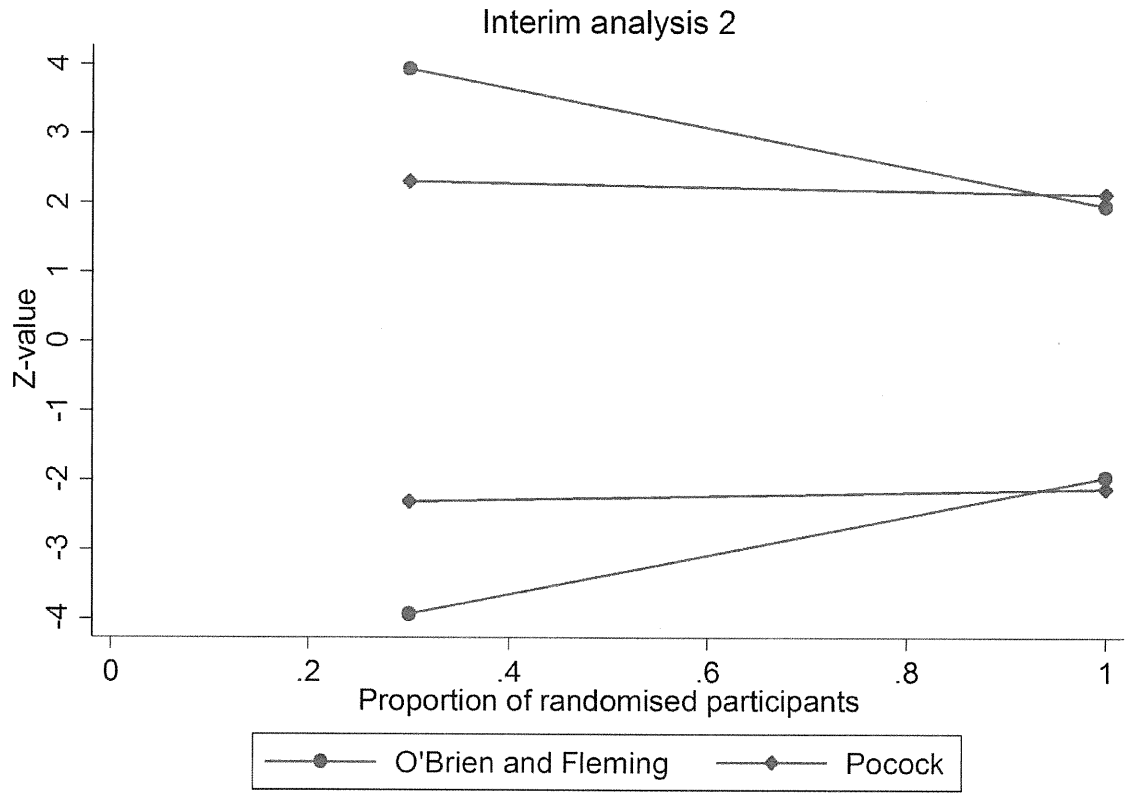
The interim analysis of *timing of compensation for parent's time for the 24 month visit in the form of £10 voucher* on co-primary outcome 2 (*collection of host trial primary outcome data*) will be performed for the first 400 participants in the trial, roughly 30% of the 1395 participants randomised in total to BEEP.

The table below shows the stopping boundaries using the O'Brien and Fleming or Pocock alpha spending function for a total type 1 error (α) of 0.05 with one interim analysis after 400 participants. A trial would be stopped at the interim analysis point if the absolute value of the test statistic is greater than the stopping boundary.

Analysis number	O'Brien and Fleming		Pocock	
	Stopping boundary (B)	α	Stopping boundary (B)	α
1 (n = 400)	3.9286	0.000085	2.3118	0.021
2 (n = 1400)	1.9602	0.04991	2.1237	0.029

Stopping boundaries calculated using landemets add on package in Stata

These stopping boundaries are also shown in the plot below.



The embedded trial should only be stopped at the interim analysis if there is strong evidence of an effect, the O'Brien and Fleming stopping boundaries will therefore be used. The embedded trial of vouchers for the 24 month visit will stop at the interim analysis if the absolute value of the test statistic is greater than 3.9286.

3.3. Impact on final analysis

If the embedded trial of extra prior SMS notification for questionnaires is stopped at the interim analysis, this strategy will be implemented for the remainder of the trial and the interim analysis will be reported as the final analysis. If the embedded trial of extra prior notification continues, the final analysis of this strategy on questionnaire return rates will be after the data is frozen for the main analysis of the host trial.

If the embedded trial of vouchers for the 24 month visit is stopped at the interim analysis, this strategy will be implemented for the remainder of the trial and the interim analysis will be reported as the final analysis. If the embedded trial of vouchers for the 24 month visit continues, the final analysis of this strategy will be after the data is frozen for the main analysis of the host trial.

4. GENERAL ANALYSIS CONSIDERATIONS

4.1. Analysis samples

Analysis will be conducted according to allocation:

- Extra prior notification that the questionnaire is ready to complete via SMS text message versus no extra notification regardless of whether the SMS was sent out or received
- Compensation for parent's time in the form of £10 voucher – sent to parents either before or after the 24 month visit regardless of whether the voucher was actually received

All randomised participants will be included in the embedded trial analysis.

One participant randomised in error at 62 days after birth will not be included in the numbers randomised or any analyses for the host trial. The family were not informed of the randomisation and were not contacted for follow-up between birth and 24 months. Therefore this participant will also not be included in the embedded trial analyses.

4.2. Derived variables

Questionnaire data collection

Questionnaire data collection at 3, 6, 12 and 18 months will be derived from the dataset containing data from section A, part 1 of the questionnaire (q_a1.csv, see Appendix 9.2). If any of the questions are completed (completion date, who the questionnaire was completed by, details of any skin problems that the baby has had) the questionnaire will be derived as being completed at that timepoint. If no information is in the dataset for the particular timepoint, the questionnaire will be derived as not being completed. A secondary analysis will investigate the effect of SMS notification on questionnaire completion coded as either: completed all key sections, did not complete all key sections or not completed. Key sections on each questionnaire are shown in the table below.

3 month	6 month	12 month	18 month
Diagnosis with eczema by a doctor or a nurse	Diagnosis with eczema by a doctor or a nurse	Diagnosis with eczema by a doctor or a nurse	Diagnosis with eczema by a doctor or a nurse
Skin infections	Skin infections	Skin infections	
Emollient/moisturiser use	Emollient/moisturiser use	Emollient/moisturiser use	
Slippages	Slippages	Slippages	
		UK Working party criteria questions	

Time to questionnaire completion

The number of days to questionnaire completion will be derived as the difference between the date the questionnaire was completed and the date the questionnaire was sent out.

Number of reminders required to obtain questionnaire completion

Number of reminders and questionnaire completion will be categorised as:

- Questionnaire completed with no reminder
- Questionnaire completed after first reminder
- Questionnaire completed after second reminder
- Questionnaire completed after additional manual reminder by NCTU
- Questionnaire not completed

Collection of BEEP trial primary outcome data

The BEEP trial primary outcome is a diagnosis of eczema between 12 and 24 months of age, defined as meeting the UK Working Party Diagnostic Criteria for Atopic Dermatitis:

- An itchy skin condition in the last 12 months
- **Plus three or more of:**
    - i. Onset below age 2*
    - ii. History of flexural involvement
    - iii. History of a generally dry skin
    - iv. Personal history of other atopic disease**
    - v. visible flexural dermatitis as per photographic protocol

    * not used in children under 4 years

    ** in children aged under 4 years, history of atopic disease in a first degree relative may be included

Information to derive the primary outcome will be collected at the 24 month visit and entered onto the eCRF by the research nurse. Full details are given in Section 2.3.1 of the Statistical Analayis Plan for the BEEP trial.

The embedded trial primary outcome at 24 months (collection of the BEEP trial primary outcome at 24 months during a home or clinic visit with a research nurse) will be derived as:

- Yes if a face to face visit was conducted at 24 months and the BEEP trial primary outcome was collected
- No otherwise (i.e. BEEP trial outcome data collected via remote methods or the participant was not able to be followed up at 24 months)

5. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

5.1. Participant flow in embedded trial

Participant flow through the embedded trial will be presented in a Consort flow diagram showing number randomised to the host trial, numbers randomised to each group of the embedded trial, numbers receiving the embedded trial intervention(s) (see section 5.3) and numbers analysed.

5.2. Baseline characteristics

Baseline characteristics of families and babies that may be associated with retention and host trial allocation will be summarised by embedded trial intervention.

5.3. Adherence

The number of participants who do/do not supply a mobile phone number will be summarised. Participants who did not supply a mobile phone number could not receive the extra prior SMS notification intervention.

For each questionnaire time point whether the SMS notification was sent will be summarised by allocated group for the extra prior SMS notification. Information about whether the SMS notifications were received by the participant, where sent, is not known.

Similarly, the number of participants who were sent/given the voucher and the timing of the voucher compensation will be summarised. The number of vouchers returned after being sent/given (i.e. due to being refused by the family) will also be summarised.

6. ANALYSIS OF EFFECTIVENESS

6.1. Primary analysis for co-primary outcome 1 - collection of data via the chosen method of questionnaire at interim follow up times

The number and percentage of participants completing the questionnaire at 3, 6, 12 and 18 months will be presented by allocated group for the extra prior SMS notification.

The model for the between-group comparison for extra prior SMS notification will use data from all questionnaire timepoints (4 per participant). Generalized estimating equations with the Binomial family and logit link with an exchangeable correlation matrix to account for multiple observations per participant will be used including a term for allocated group in the host trial and questionnaire timepoint as covariates. The odds ratio for the extra prior SMS

notification intervention will be presented with a 95% confidence interval. The difference in the percentage of participants completing the questionnaire will also be presented with a 95% confidence interval using similar methods.

If there appears to be evidence of an interaction between the intervention and questionnaire timepoint, odds ratios for each timepoint will be presented rather than a single odds ratio averaging over all timepoints.

6.2. Primary analysis for co-primary outcome 2 - collection of the BEEP trial primary outcome at 24 months during a home or clinic visit with a research nurse

The number and percentage of participants with host trial primary outcome data collection at 24 months during a face to face visit will be presented by allocated group(s) for the embedded trial.

The between group comparisons for the embedded trial interventions will be conducted using a multivariable logistic regression model. An interaction between embedded trial interventions will be investigated by inclusion of an interaction term in the model.

In the absence of any evidence for an interaction, the odds ratio for vouchers for the 24 month visit and the odds ratio for extra prior SMS notification will be presented from a model including allocated group for the host trial as a covariate with 95% confidence intervals. The difference in the percentage of participants with primary outcome data collection for each intervention will also be presented with a 95% confidence interval using similar methods.

Note if the embedded trial of extra prior SMS notification intervention for questionnaires is stopped after the interim analysis, the effect of extra prior SMS notification on collection of the host trial primary outcome data will not be investigated and will be used as a covariate only in the model. In this case, the term for extra prior notification used for adjustment will be:

- According to allocated group for the extra prior SMS notification intervention for participants that had reached the 18 month timepoint in the study prior to the extra SMS notification being implemented for all remaining questionnaires in the host trial
- Derived as if allocated to extra prior notification for all other participants since extra notification will have been used for at least one questionnaire timepoint

6.3. Senstivity analysis for the primary outcomes

6.3.1. Sensitivity analyses with adjustment for other baseline covariates

Baseline variables will be examined for imbalances between the groups. Any characteristics where an imbalance is observed (based on comparison of summary statistics only, not statistical testing) will additionally be included as covariates in the models specified in Section 6.1 and 6.2.

6.3.2. Sensitivity analyses for co-primary outcome 1 - the extent of questionnaire completion

The extent of questionnaire completion, as described in Section 4.2, at each timepoint will be tabulated by allocated group for the extra prior SMS notification.

6.3.3. Sensitivity analyses for co-primary outcome 2 – collection of BEEP trial primary outcome data via any method

The number and percentage of participants with host trial primary outcome data collection at 24 months via any method (i.e. including data collected remotely) will be presented by allocated group(s) for the embedded trial, along with the method of collection. The number of months from birth to host trial primary outcome collection (24 month visit) will also be summarised using the median, lower & upper quartiles, minimum and maximum and in categories (prior to 23 months, between 23 and 26 months and after 26 months). Data collected outside of the preferred window of 21 to 30 months after birth will also be tabulated. Reasons that primary outcome data was not collected (e.g.no response, withdrew consent etc) will also be summarised.

6.4. Secondary outcomes

6.4.1. Time to questionnaire completion

Time to questionnaire completion will be presented in Kaplan-Meier curves according to allocated group for the extra prior SMS notification intervention for each questionnaire timepoint. We will use the Kaplan-Meier curves to explore descriptively whether the effect of extra prior SMS notification on time to questionnaire completion varies according to questionnaire timepoint.

The effect of the extra prior SMS notification intervention on time to questionnaire completion will be estimated using a Cox proportional hazards model including a term for

allocated group in the host trial and using a shared frailty to account for inclusion of four questionnaire timepoints for each participant. The hazard ratio with 95% confidence interval will be given. Questionnaires that are not completed will be censored at 28 days (i.e 4 weeks after questionnaire sent).

6.4.2. Number of reminders required to obtain questionnaire completion

The number of reminders required to obtain questionnaire completion (see section 4.2) at each questionnaire timepoint will be presented by allocated group for the extra prior SMS notification intervention. Reasons that questionnaires were not completed (e.g. withdrew consent, no response, etc..) will also be tabulated.

7. DUMMY TABLES AND FIGURES

The dummy table for interim analysis 1 of extra prior SMS notification that the questionnaire is ready to complete versus none on co-primary outcome 1 (collection of questionnaire data) is shown below. See 0935 BEEP retention SWAT dummy tables final version 1.0 20181204 for full dummy table document for the final analysis.

Table 1: Questionnaire completion at 3, 6 and 12 months by extra prior SMS notification that the questionnaire is ready to complete versus none

(a) All participants who have reached each follow-up timepoint

	No SMS contact prior to sending questionnaire	SMS contact prior to sending questionnaire	Difference in % completion (95% CI)	Odds ratio (95% CI)
3 months	n = xx	n = xx		
Completed				
Not completed				
6 months	n = xx	n = xx		
Completed				
Not completed				
12 months	n = xx	n = xx		
Completed				
Not completed				

Data shown are n (%).
xxx timepoints from xxx participants included in model.
Test statistic for extra prior SMS intervention from model (using logit link):
The embedded trial of extra prior SMS notification for questionnaires will stop at the interim analysis if the absolute value of the test statistic is greater than 2.9626.

(b) Participants who have reached the 12 month follow-up timepoint

Repeat Table 1 only including the participants who have reached the 12 month follow-up timepoint. This is for descriptive purposes only.

8. REFERENCES

[1] A Montgomery, H Williams, L Bradshaw, J Chalmers. SWAT 25: Two-by-two factorial randomised trial to evaluate strategies to improve follow-up in a randomised prevention trial.
https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/FileStore/Filetoupload,545015,en.pdf (Accessed 27th February 2017)

9. APPENDIX

9.1. Analysis sample for interim analysis 1 of extra prior SMS notification that the questionnaire is ready to complete versus none on co-primary outcome 1 (collection of questionnaire data)

The interim analysis will use data for participants who had reached the end of the questionnaire completion window by the end of 2016 (e.g. reached questionnaire timepoint by end of November 2016).

A greater number of participants had reached the 3 and 6 month follow-up timepoints by the 30th November 2016. The following data will also be used:

- All participants randomised up to and including the 31st August 2016 for the 3 month follow-up timepoint.
- All participants randomised up to and including the 31st May 2016 for the 6 month follow-up timepoint.

The number and percentage of participants completing the questionnaire at 3, 6 and 12 months will be presented by allocated group for the extra prior SMS notification intervention. This will be done for the participants who have reached the 12 month timepoint and for all participants who have reached the 3 and 6 month timepoints.

The model for the between-group comparison for the extra prior SMS notification intervention will use data for all questionnaire timepoints reached for the participants randomised up to and including the 31st August 2016 (between 1 and 3 timepoints per participant).

Note if there is an interaction between the intervention and questionnaire timepoint, the test statistic for the effect of the intervention at the 12 month timepoint will be used for evaluation of the stopping rule.

9.2. Questions from section A, part 1 of questionnaire

Please tell us who is completing this questionnaire	Mother	☐	Father	☐
	Other (please state relationship to baby):	☐	_____	

In the last 3 months, has your baby suffered from any of the following skin problems?	Impetigo	☐	Eczema	☐
	Chicken pox	☐	Facial spots	☐
	Cradle cap	☐	None of these	☐