Study title: E-SEE Main trial

Enhancing Social-Emotional Health and Wellbeing in the Early Years (E-SEE): A Community-based Randomised Controlled Trial and Economic Evaluation of the Incredible Years Infant and Toddler (0-2) Parenting Programmes

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List of abbreviations used

AE	Adverse Event
ASQ:SE-2	Ages and stages questionnaire: social and emotional, 2nd edition
CI	Confidence Interval
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
E-SEE	Enhancing Social and Emotional health in the Early years
FU	Follow-up
ICC	Intraclass Correlation Coefficient
IQR	Inter Quartile Range
ITT	Intention to treat
IY	The Incredible Years programme
IY-I	Incredible Years Infant programme
IY-T	Incredible Years Toddler programme
LA	Local Authority
NIHR	National Institute for Health Research
PHQ-9	Patient Health Questionnaire
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAU	Services as usual
SD	Standard Deviation
SE	Standard Error
SOP	Standard Operating Procedure
TMG	Trial management group
TSC	Trial steering committee

Summary table

Trial title	Enhancing Social-Emotional Health and Wellbeing in the Early Years (E-SEE): A Community-based Randomised Controlled Trial and Economic Evaluation of the Incredible Years Infant and Toddler (0-2) Parenting Programmes
Trial design	A parallel, two arm, individually randomised controlled trial. Participants randomly allocated to intervention or control in a 5:1 ratio. Intervention parents receive an IY-B book (universal level). Dependent on level of need at data collection points 2 and 3, intervention parents may be invited to join a IY-I programme (10 weeks; 2 hours/ week) and/or IY-T (12 weeks; 2 hours/ week). Control parents receive services as usual. IY-I and IY-T are not offered as part of SAU in participating LAs.
Trial participants	Parents of children aged 0 to 2 months at baseline, identified by children's centre staff, self-referral, Health Visitors and parent advisory committee. Level of need is assessed by completion of a self-report mental health questionnaire (parent) and a parent-report measure of child social and emotional development. Co-parents are included in measure completion (and in parent programmes if parent is allocated to intervention condition at each level of intervention dose).
Sample size	606 participants allocated in a ratio of 5:1 (intervention:control)

Follow-up	Measures are administered during home or community based visits at four intervals; baseline and three follow-ups (2, 9 and 18 months post baseline assessment).
Primary analysis	Repeated measures analysis on ASQ:SE-2 scores, comparing treatment and control groups to investigate the effectiveness of the proportionate delivery of the IY E-SEE steps/model overall on child social and emotional wellbeing.
Key Secondary analyses	Repeated measures analysis on PHQ-9 scores, comparing treatment and control groups to investigate the effectiveness of the proportionate delivery of the IY E-SEE steps/model overall on parent depression levels

1 Introduction

This document outlines the detailed statistical analysis plan (SAP) for the E-SEE main trial and is intended to be read in conjunction with the current study protocol (v10. This SAP is written in conjunction with the International Conference on Harmonisation topic E9 (ICH E9 Expert Working Group, 1999), guidance for the content of SAPs in clinical trials (Gamble *et al.*, 2017), applicable statistical standard operating procedures (SOPs) from the University of Sheffield Clinical Trials Research Unit (CTRU) and trial documents (Protocol and Data Validation Specification). The trial is conducted in accordance with Good Clinical Practice in Clinical Trials (ICH Harmonised Tripartite Guideline, 1996) and Medicine for Human Use (Clinical Trials) Regulations (UK Statutory Instruments, 2004).

This SAP will guide the Trial Statistician during the statistical analysis of all quantitative outcomes in order to answer the objectives of the study. It excludes the health economic and process evaluations (which will be described elsewhere).

All analysis will be performed in a validated statistical software package such as R (Team, 2012).

1.1 Study Outline

E-SEE is a community based randomised controlled trial (RCT) designed to assess the effectiveness of the Incredible Years (IY) parent programme when compared to service as usual (SAU). The IY intervention comprises of three levels: the Incredible Babies book, and two group-based programmes IY-Infant (IY-I) and IY-Toddler (IY-T). Detailed descriptions of these components can be found in the study protocol (v10). Control condition parents/co-parents receive SAU; IY-I and IY-T do not form part of SAU in the participating local authorities (LAs), although other parenting programmes – including IY for older children - may be available.

The E-SEE study comprises of two stages, phase 1 is an 18-month pilot study conducted in two LAs and phase 2 is a 30-month main trial conducted in four LAs. The statistical analysis of phase 1 has been outlined in a separate statistical analysis plan (see study documentation table in references section.)

1.2 Objectives

a) Main effectiveness analyses of the intervention (compared to SAU) will be established at the follow-up 18-months post-baseline to address the key research questions relating to clinical outcomes.

b) Economic evaluation: Establish cost-effectiveness using health, quality of life and service use data and IY intervention cost data, and explore the potential for long-term modelling of costs and benefits by extrapolating from trial outcomes.

c) Comparative work: (1) Match and compare intervention participant outcomes with cohort general population data (e.g. Millennium Cohort Study); and (2) Conduct international comparison of outcomes with the complementary Irish trial, with IY-I and IY-T delivered in a non-proportionate universalism model, and explore potential opportunity (pending agreement from key stakeholders) to pool data from both studies to facilitate a meta-analysis.

d) Establishing the importance of process: engagement, referral, and implementation fidelity rates will be at appropriate levels and effects of process, particularly fidelity, on outcome will be examined. Qualitative work objectives include establishing parent and co-parent perception of programmes and exploring the facilitative and inhibitive factors in service delivery.

e) Establishing for whom the programme works best and how by exploring mediators and moderators of change.

This SAP is concerned with the main effectiveness analysis (objective A). Objective B is covered by the Health Economics Analysis; objective C is covered in an ancillary sub-study (ancillary sub-study D in the protocol); objective D is covered by the process evaluation and objective E will be covered in an additional ancillary sub-study following submission of the trial manuscript. The protocol also outlines ancillary sub-studies A to C (See page 24 in Protocol V10 11.06.2019). These ancillary sub-studies are covered in the appropriate sub-study reports.

2 Outcome measures

2.1 Primary outcome measure

The following are measured at all time-points (baseline, 2, 9, and 18 months post-baseline), unless otherwise stated:

a) *Social and emotional wellbeing* – to establish effectiveness of the proportionate delivery of the IY E-SEE steps/model overall i.e. three levels of IY- the book, IY-I and IY-T, using parent report *Ages & Stages Questionnaire – Social Emotional* (ASQ:SE-2). The co-parent is not asked to complete this questionnaire.

2.2 Secondary outcome measures

2.2.1 Child secondary outcome measures[1]

The following measures are completed independently by parent and co-parent at all three timepoints unless otherwise stated.

a) *Behaviour* – measured at *18-month follow-up* using parent/co-parent report *Strengths and Difficulties Questionnaire* (SDQ).
b) *Cognitive development* – measured at *18-month follow-up* using parent/co-parent report *PedsQL Infant Scale*.
c) *Health (quality of life)* – measured at *18-month follow-up* using parent/co-parent report *PedsQL Infant Scale*.
d) *Service use* –using parent report: *Client Service Receipt Inventory (*CSRI).

2.2.2 Primary care-giver and co-parent secondary outcomes

Key Secondary Outcome[2] for primary care-giver and co-parent

a) *Depression* – to establish overall effectiveness of the IY programme, using the parent/co-parent report *Patient Health Questionnaire (PHQ-9).*

Other Secondary outcomes for primary care-giver and co-parent

b) *Carer-child attachment/interaction* – measured at *18-month follow-up* using parent/co-parent report *Maternal Postnatal Attachment Scale (MPAS) and/or Paternal Postnatal Attachment Scale (PPAS)*.
c) *Parenting skill* – using parent/co-parent report *Parent Sense of Competence (PSoC)*.
d) *Health Related Quality of Life (HRQoL)* –using parent/co-parent report *EQ5D5L*
e) *Service use* – using parent report CSRI.

2.2.3 Parent-child dyad secondary outcome measures

a) child feeding methods

[1] The original intention was to use the Eyberg child behaviour inventory. This was replaced with the SDQ in the early stages of the trial and a protocol amendment made. [See version 5 amendments in 'Protocol amendments since Version 1' in version 10 of the protocol.]
[2] In protocol v10 the PHQ-9 is described as the "parent and co-parent primary outcome". In the published protocol the PHQ-9 is described as the 'parent primary outcome'. These descriptions are technically incorrect because the trial is powered on ASQ-SE2 alone. PHQ-9 will be described as the key secondary outcome henceforth.

b) Dyadic synchrony[3] – using the CARE Index, observational report, solely conducted with the parent-child dyad.

3 Sample Size Estimation

A detailed description of the sample size for the E-SEE Main trial can be found in protocol v10.

4 Randomisation, Inclusion in the Intervention Arm & Blinding

4.1 Sequence generation

Randomisation is at the individual level using a web-based randomisation system developed by Sheffield CTRU in collaboration with a University spin-off company (epiGenesys) and using a randomisation sequence prepared by the trial statistician. E-SEE participants are randomised in a 5:1 ratio to intervention and control arms, stratified by:

- depression scores (PHQ-9 score >=5) or child social emotional wellbeing (Child ASQ:SE2 score>= Monitoring Zone);
- sex of child;
- sex of carer;
- recruitment site (see above).

Prior to recruitment starting a test system was made available for training purposes. Any user comments or suggestions on the usability of the system are fed back to the program developer before the system is made live.

Randomisation occurs after eligibility has been established, informed consent obtained, and baseline measures collected from parents to reduce initial attrition. The allocation schedule is concealed and the intervention arm is only confirmed once eligibility and consent are confirmed by researchers. A member of the University of York research team inputs participant information to the online system to enable randomisation, with allocation results returned immediately. The University of York trial coordinator informs families of allocation to condition.

4.2 Inclusion in the Intervention arm

If a participant is allocated to the intervention arm, they receive the IY-I Book. Following the first follow up (2 months post baseline), only participants with a Parent PHQ-9 score >=5 OR Child ASQ:SE2 score>= 'Monitoring' in the intervention arm are offered the IY-I programme. Following the second follow up (9 months post baseline) only participants with Parent PHQ-9

[3] In protocol v10 the CARE Index is described as a child attachment measure and listed as a child secondary outcome. Child attachment is just one part of the Index and we will use the overall dyadic synchrony score which is a parent-child dyad measure.

score >=5 OR Child ASQ:SE2 score>= ‘Monitoring’ in the intervention arm are offered the IY-T programme.

Non-research participants may be included in the IY-I and IY-T groups. Parents can be invited by service staff to join the group based on professional judgement/assessment that they meet the same eligibility criteria as research participants. We do not collect data for these participants; they attend as they would for any other parenting intervention delivered at that site. This is accepted practice in these types of research interventions when there are concerns about group size.

4.3 Blinding

The trial statistician will remain blind during the study until database freeze. At database freeze, the statistician will receive unblinded data. Full details of blinding can be found in the study protocol (v10).

5 Interim Analysis & Study Monitoring

The following committees have been established:

1. **Trial Steering Committee (TSC)** - consists of an independent chair, a member with early years expertise, an independent statistician, lay representatives (including a member of the Parent Advisory Committee) and the chief investigator. The role of the TSC is to provide supervision of the protocol and statistical analysis plan, to provide advice on and monitor progress of the study, to review information from other sources and consider recommendations from the DMEC. The TSC will meet at regular intervals as outlined in the TSC terms of reference. The TSC can prematurely close the trial following advice from the sponsor, funder, DMEC or TMG.

2. **Trial Management Group (TMG)** – The TMG consists of the chief investigator, trial managers and others as deemed necessary. The CI chairs the meetings at regular intervals as agreed by the group and oversees the day to day implementation of the trial in accordance with the terms of reference.

3. **Data Monitoring and Ethics Committee (DMEC)**- includes an independent chair and two independent members. The DMEC works in accordance with an agreed Charter, reviewing reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required.

These committees function in accordance with Sheffield CTRU standard operating procedures. Membership details of these committees are provided in the protocol (v10).

6 Data Collection

6.1 Data Sources

The randomisation list is held on the CTRU's randomisation system. Trial data are extracted from source documents and entered onto the CTRU's in house data management system (PROSPECT). University of York staff conduct a data entry check on a 10% sample of CRFs. The data management team in the Sheffield CTRU validate and query electronic data for inconsistencies during the course of the trial (as stipulated in SOP DM005), The trial statistician will conduct any additional validation checks where appropriate before database lock (as guided by ST003, DM005 and DM012). Details of data collected at each time point are given in Table 1.

Table 1: List of outcome measures and timing of data collection

Outcome measures	Baseline	2 month follow up (FU1)	9 month follow up (FU2)	18 month follow up (FU3)
Primary care-giver				
PHQ-9	X	X	X	X
PSoC	X	X	X	X
EQ5D-5L	X	X	X	X
MPAS/PPAS				X
CSRI	X	X	X	X
Child				
ASQ:SE-2	X	X	X	X
PEDSQL				X
SDQ				X
CSRI	X	X	X	X
Co-parent				
PHQ-9	X	X	X	X
PSoC	X	X	X	X
EQ5D-5L	X	X	X	X
CSRI	X	X	X	X
Parent-child dyads				
CARE Index	X	X	X	X

7 Statistical Analysis

7.1 General Considerations

Data will be reported according to the Consolidated Standards Of Reporting Trials (CONSORT) statement for individually randomised parallel group trials (Schulz, Altman and Moher, 2010) and extension (Juszczak *et al.*, 2019).

Summaries of continuous variables will comprise the number of observations used, mean, median, standard deviation (SD), inter-quartile range (IQR), minimum and maximum as appropriate for the distribution of the data.

Summaries of categorical variables will comprise the number of observations used, and the number and percentage of observations in each category. Tables containing the results of the statistical modelling will present the overall difference between treatment groups with two-sided 95% confidence intervals (CI) and p-values. Hypothesis tests will use a two-sided 5% significance level.

Complete details of data derivations and methods for handling missing data is covered in sections 8.1 and 9.

All analyses are based on the overall score only unless otherwise stated.

7.2 Participant flow

A CONSORT style flow diagram will show the flow of participants through the trial (Figure 1). In addition to the flow diagram, tables showing more detailed summaries of the reasons for refused consent and reasons for withdrawal will be presented.

7.2.1 Attrition

There are several reasons that a participant may not complete outcome data collection. These include withdrawal of consent and loss to follow up. The number and proportion in each category will be presented by intervention arm.

The number of each type of discontinuation will be presented as part of the CONSORT flow diagram and will be summarised in more detail in a separate table which will include the timing of discontinuation (between randomisation & FU1, between FU1 & FU2, between FU2 & FU3) where possible (Appendix, Table 4). Where given, the reasons for withdrawal of consent will be presented.

7.3 Baseline Characteristics

The baseline demographics and clinical characteristics of the participants will be reported. For the continuous variables (e.g. age) mean and SD, median and IQR and minimum and maximum values will be presented. The number of observations used in each calculation will be presented alongside the summaries. For the categorical variables, (e.g. ethnicity), the number and percentage of participants in each of the categories and the total number of observations will be presented.

All baseline summaries will be presented and reported for each treatment group and in total. No statistical significance testing will be done to test baseline imbalances between the intervention arms but any noteworthy differences will be descriptively reported.

The following summaries will be presented:

Demographics

- Child: Age (weeks), Sex, Ethnicity
- Primary caregiver: Age, Sex, Ethnicity, Religion, Income, Marital Status, Highest qualification previously achieved
- Co-parent: Age, Sex, Ethnicity, Religion, Income, Marital Status, Highest qualification previously achieved

Outcome measures

- Child: ASQ:SE-2,
- Primary caregiver: PHQ-9, PSoC, EQ5D-5L
- Co-parent: PHQ-9, PSoC, EQ5D-5L
- Parent-child dyad – CARE Index

Other measures

- Child: Premature, Difficulties at birth, Received immunisation
- Parent-child dyad – details of child feeding methods

Baseline summaries will be presented separately by child, primary caregiver and co-parent (Appendix Table 4, Table 5).

7.4 Intervention Adherence & Fidelity

The number and proportion of participants who received the book will be presented. For the IY-I and IY-T stages, the following intervention attendance summaries (Appendix Table 11) will be presented:

- Number offered/eligible for IY-I or IY-T at each site
- Number of groups at each site
- Session size for each group by week
- Session size (median, IQR, minimum, maximum)
- Number of sessions attended per participant (median, IQR, minimum, maximum)
- The proportion of participants attending at least 1/2/3/5/10/12 sessions (denominator to be all those who attended at least 1 session)

Methods for the assessment of fidelity will be part of the Process Evaluation component of the study which is described in further detail in the study protocol v10.

7.5 Analysis Populations

7.5.1 Intention to treat (ITT)

To avoid any potential bias in the analysis, the primary outcome analysis will be conducted on the ITT population unless otherwise stated. Participants will be analysed according to the treatment arm they were randomised to and analysis will include all participants with outcome data.

7.5.2 Per protocol

The per-protocol analysis will be descriptive because there is no satisfactory way to define a per-protocol population for those in receipt of IY-B only. If the per-protocol population definition were based on IY-I and IY-T only we would only be removing people with higher scores at follow up 2 and 3 which would reduce the effects size compared to the ITT analysis and bias upwards the estimated impact on compliers because efficacy is demonstrated by a reduction in primary outcome.

Instead we will undertake a descriptive analysis comparing the characteristics of compliers compared to non-compliers. For example did compliers tend to be people with the greatest need (scores just over the eligibility threshold) or those with the higher scores. The characteristics investigated in this descriptive analysis will be the same as those used for the subgroups. This descriptive analysis will be an important input to the process evaluation.

7.6 Analysis of the primary outcome

7.6.1 Primary Analysis of the primary outcome

The ASQ:SE-2 is a set of questionnaires with different versions for different age groups. Consequently, different versions will be completed at each time point. The primary analysis will use raw ASQ:SE-2 scores as the scoring is the same across treatment arms and estimates will be easier to interpret. For ASQ:SE-2 either the 2 month or the 6 month questionnaire is administered at Follow-up 1 dependent upon the developmental age of the baby. If we observe an imbalance between arms in the number receiving the 2 months and 6 months versions we will adjust the score for those receiving the 2 months version by multiplying by 1.24. We have based the adjustment on the monitoring thresholds (25 and 30 for the 2 and 6 months surveys) and referral thresholds (35 and 45 for the 2 and 6 months surveys). The adjustment is midway between those required to preserve the monitoring threshold (30/25) and the referral threshold (45/35). If participants have completed both questionnaires, we will use the 6 months version and exclude them from the potential adjustment procedure.

The overall treatment effect will be estimated using a marginal model fitted using general estimating equations to account for the repeated measures with a Gaussian family, identity link, robust standard errors and an autoregressive covariance structure of order 1 AR(1). If the model does not converge using AR (1) we will use an unstructured correlation structure. The fixed effects will be stratifying variables (baseline ASQ:SE-2 score, baseline PHQ-9 score,

site[4] and sex of child); potential confounders (ethnicity of the primary caregiver, marital status and highest level of education and follow up time (using an indicator variable for each time point).

- The therapist induced clustering effect will not be fitted because the offer of IY-I and IY-T is conditional on outcome at FU1 and FU2 so clustering is confounded with treatment effect leading to biased estimation of the latter.
- The repeated measurements will be accounted for using a marginal model fitted using GEE because accounting for repeated measures using a mixed model inflates the type 1 error (random intercept only model) or gives a biased estimate of the treatment effect (random intercept and slope model).

These analysis decisions above were based on previous research (Candlish 2019) and simulation work undertaken during SAP development included in appendix B.
Descriptive statistics will be presented for ASQ:SE-2 and PHQ-9 at each time point (Appendix Table 6). Mean ASQ:SE-2 and PHQ-9 scores and 95% CIs by treatment arm will be presented in line plots. Spaghetti plots will also be used to visualise individual changes over time.

The following categories of the categorical variables will be used:

- Ethnicity of the primary caregiver: English/Welsh/Scottish/Northern Irish/British/Irish; Any other White background, Indian, Pakistani and Any Other ethnic group.
- Marital status: Married and living together; Cohabiting/living together; Other type of relationship and Not in a relationship or separated
- Highest level of education: Higher Education and Other (see Section 10.1 for details of how this will be defined).

7.6.2 Sensitivity Analysis of the primary outcome

Further sensitivity analyses will be carried out to assess the impact of not standardising the raw scores by applying standardisation methods described in detail in section 9.1.1. A missing data sensitivity analysis will also be conducted and is described in more detail in section 8.1.1.

A per protocol analysis was considered but deemed not to be appropriate as outlined in section 7.5.2. Similarly, complier average causal effect (CACE) analysis was deemed not to be appropriate.

[4] Blackburn with Darwen, North Yorkshire, Portsmouth and Suffolk

7.7 Analysis of key secondary outcomes

The impact of the intervention on PHQ scores will be investigated using the same approach as the primary analysis of the primary outcome. Descriptive statistics will be presented for PHQ-9 at each time point (Appendix Table 6). Mean PHQ-9 scores and 95% CIs by treatment arm will be presented in line plots. Spaghetti plots will also be used to visualise individual changes over time.

The IY intervention in this trial comprises three main components – the IY-I book, IY-I and IY-T programmes. All participants who meet the eligibility requirement for being stepped up to IY-I and/or IY-T are given the opportunity to do so and there is no randomisation element in the step up. As such the following secondary analysis provides a non-randomised indicative analysis of the possible impact of individual components. The impact of individual components will be investigated using ASQ:SE-2 and PHQ-9 at the relevant follow up point with those participants in the control arm who would have been eligible for IY-I or IY-T in each case used as the control group comparator.

- Comparison between intervention and control groups at FU1 will provide an indicative analysis of IY-B;
- Comparison between intervention and control for the subgroup of parents with PHQ-9 score >=5 OR Child ASQ:SE-2 score>= Monitoring Zone at FU2 will provide an indicative analysis of IY-I;
- Comparison between intervention and control in the subgroup of parents with PHQ-9 score >=5 OR Child ASQ:SE-2 score>= Monitoring Zone at FU3 will provide an indicative analysis of IY-T.

These analyses will be conducted using multiple linear regression models including the same stratification variables (baseline ASQ:SE-2 score, baseline PHQ-9 score, sex of child and recruitment site) and potential confounders (ethnicity of the primary caregiver, marital status and highest level of education) as covariates. The mean difference, 95% confidence interval and associated p-values will be presented (Appendix Table 7).

7.8 Analysis of other secondary outcomes

Not all secondary outcomes will be collected at all four time points. For those outcomes that have been collected at all four time points (PSoC, EQ5D-5L, CARE Index), mean scores by treatment arm will be presented in line plots (Figure 4) and the impact of the intervention on these outcomes will be investigated using the same approach as the primary analysis of the primary outcome.

For those outcomes only collected at FU3 (MPAS/PPAS, PEDSQL, SDQ), descriptive statistics will be presented by treatment arm. A multiple linear regression model will be used to estimate the adjusted mean difference between treatment arms. Stratification variables (baseline PHQ-9 score, baseline ASQ:SE-2 score, sex of child and site) will be included in the model as covariates.

7.9 Safety

Safety will be assessed by recording adverse events (AEs) and serious adverse events (SAEs). Details of definitions of AEs and SAEs are outlined in the study protocol. Descriptive statistics of AEs and SAEs will be presented by treatment arm on the ITT population. The following figures will be included overall; separately for child, primary carer and co-parent and by type (Appendix Table 10):

- The total number of AEs;
- The number and percentage of participants reporting at least 1 AE;
- The number and percentage of participants reporting a treatment related AE;
- The total number of SAEs;
- The number and percentage of participants reporting at least 1 SAE;
- The number and percentage of participants reporting a treatment related SAE;
- The number and percentage of participants reporting each severity and frequency of SAE.

7.10 Changes from analysis specified in the Protocol

Section 10 of protocol version 10 says “Evaluating the overall effectiveness of the proportionate delivery of IY will be assessed using a multilevel mixed model to allow for a treatment and time effect whilst allowing for the clustering by participant and group treatments and confounding and stratifying variables”. As discussed in section 7.6.1 we will no longer account for treatment level clustering and will account for repeated measurements using a marginal model fitted using GEE.

Section 10 of protocol version 10 says “ITT analysis will be conducted at the cluster level using summary measures” as well as “the individual level with test statistics adjusted for intra-cluster correlation”. Because participants can get IY-I alone, IY-T alone or both, there is no way of grouping participants into clusters that remain stable throughout the intervention.

Sex of primary caregiver will no longer be used as a covariate due to the finding from the pilot that there were too few male primary caregivers for the associated model parameter to be estimated.

Section 10 of protocol version 10 says the ITT analysis will include “predictors of missing values”. This has been operationalised in this SAP by undertaking sensitivity analysis of the primary ITT using multiple imputation as described in section 8.1.1.

8 Detailed Statistical Methods and Calculations

8.1 Missing Spurious & Unused Data

8.1.1 Missing data

The primary outcome will be analysed using observed data with imputation for item non-response (see Table 2 in Section 9.2) but no imputation for missing survey data, and we will assess the amount and patterns of missing data and test the sensitivity of estimates of treatment effects using the multiple imputation by chained equation (MICE) technique (Buuren and Groothuis-Oudshoorn, 2011) implemented in STATA for those variables where a logistic regression model shows them to be significant predictors of missing-ness. In addition to all variables in the primary analysis including treatment group, which will all be included the MI, we will consider the following variables:

- Age of primary caregiver;
- Eligibility for IY-I
- Eligibility for IY-T

Treatment effects and their 95% CIs will be presented in a forest plot alongside those produced using the primary analysis methods (section 7.6).

8.1.2 Missing items within questionnaires

The scoring of questionnaires with missing items is described in table 2 for the primary outcome (ASQ:SE-2), key secondary outcome (PHQ-9) and SDQ. Justification for the approach taken is also provided in the table.

For other secondary outcomes appropriate guidance does not exist so we will impute up to 25% missing values using the average score of completed items for surveys / time-points where more than 5% of responses have item non-response. Where questions are subdivided into groups this rule will be applied at the group level. Where there are no groupings of survey questions this rule will be applied at the whole survey level.

9 Data manipulations and definitions

9.1 Primary outcome

9.1.1 Combining ASQ:SE-2 scores

The ASQ:SE-2 is a set of questionnaires with different versions for different age groups. Consequently, different versions are completed at each time point and so scores may be standardised as part of sensitivity analyses. Four version are used in the study:

- ASQ:SE-2 2 month version – used at baseline and FU1 for some participants
- ASQ:SE-2 6 month version – used at FU1
- ASQ:SE-2 12 month version – used at FU2

- ASQ:SE-2 18 month version – used at FU3

To standardise the scores, two methods will be applied.

9.1.1.1 Z scores

For each of the four versions, Z scores will be calculated as follows:

Z score= (raw score- mean)/ standard deviation

Control participants will be used to calculate the control population mean and standard deviation.

9.1.1.2 Percentages

For each of the four versions, percentage scores will be calculated as follows:

Percentage = (raw score-minimum possible score) / maximum possible score

9.2 Patient reported outcomes

Table 2: Summary questionnaires and how the scores are calculated

Name	Score range	Description	Interpretation of score
Primary caregiver and co-parent			
PHQ-9	0-27	Measure of depression. 9 item questionnaire, 0-3 for each item	- Score 1-04 = minimal depression - Score 5-09 = mild depression - Score 10-14 = moderate depression - Score 15-19 = moderately severe depression - Score 20-27 = severe depression **Desired direction of effect**: *decrease* *Imputation: up to 2 missing values will be imputed using the average score for completed items based on NHS guidance* (NHS, no date)
PSoC	0-100	The PSoC contains 17 items developed to assess parenting self-esteem. The measure has two subscales, related to parent satisfaction (e.g., *A difficult problem in being a parent is not knowing whether you're doing a good job or a bad one)*, and	Scores 70 to 96 = high parental confidence Scores 51 to 69 = moderate parental confidence

		parent self-efficacy (e.g., *Being a parent is manageable, and any problems are easily solved)*. Items are rated on a 6-point scale ranging from *strongly agree* (1) to *strongly disagree* (6	Scores 16 to 50 = low parental confidence **Desired direction of effect**: *increase*
EQ-5D-5L	*This section of the questionnaire yields a total of 243 theoretically possible health states.*	The measure comprises 6 questions. The main EQ-5D-5L health utility is based on questions 1-5 (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which are scored on a five point scale (1: best response, 5: worst). The final question is a stand-alone item, a 0-10 self-assessed thermometer scale scored in units of 0.1 (0=worst, 10=best).	0 = equivalent to death 1 = full health negative score = state worse than death **Desired direction of effect**: *increase*
MPAS	*Quality of attachment: Minimum score = 9, Maximum score = 45.* *Absence of Hostility: Minimum score = 5, Maximum score = 25. Pleasure in interaction: Minimum*	The MPAS contains 19 items developed to assess a mother's attachment to their infant during the first year of life. Each item is scored on a 2, 3, 4, or 5 point scale. Items are scored on different scales: - Items 8 and 12 are scored on a 2-point scale - Item 14 is scored on a 3-point scale - Items 4, 5, 6, 7, 10, 15, 16, 17, 18 and 19 are scored on a 4-point scale - Items 1, 2, 3, 9, 11 and 13 are scored on a 5-point scale. To ensure equal weighting of all questions it is recommended that responses should be recoded to represent a score of 1 (low attachment) to 5 (high attachment) for every question: - Item 1 would be scored as 1; 2; 3; 4; 5 - Item 2 would be scored as 1; 2; 3; 4; 5	- Quality of attachment: Low scores indicate poor quality of attachment - Absence of Hostility: Low scores indicate high levels of hostility. - Pleasure in interaction: Low scores indicate a lack of pleasure in interaction. **Desired direction of effect**: *increase*

	score = 5, Maximum score = 25.	- Item 3 would be scored as 1; 2; 3; 4; 5 - Item 4 would be scored as: 1; 2.3; 3.6; 5 - Item 5 would be scored as 1; 2.3; 3.6; 5 - Item 6 would be scored as 1; 2.3; 3.6; 5 - Item 7 would be (reverse) scored as: 5; 3.6; 2.3; 1 - Item 8 would be (reverse) scored as: 5; 1 - Item 9 would be (reverse) scored as: 5; 4; 3; 2; 1 - Item 10 would be (reverse) scored as: 5; 3.6; 2.3; 1 - Item 11 would be (reverse) scored as: 5; 4; 3; 2; 1 - Item 12 would be (reverse) scored as: 5; 1 - Item 13 would be (reverse) scored as: 5; 4; 3; 2; 1 - Item 14 would be (reverse) scored as: 5; 3; 1 - Item 15 would be scored as 1; 2.3; 3.6; 5 - Item 16 would be scored as 1; 2.3; 3.6; 5 - Item 17 would be scored as 1; 2.3; 3.6; 5 - Item 18 would be scored as 1; 2.3; 3.6; 5 - Item 19 would be scored as 1; 2.3; 3.6; 5 The 19 items can be pooled together to create three factors for analysis (with items in brackets reverse scored): - Quality of attachment: items 3 4 5 6 (7) (10) (14) 18 19 - Absence of hostility: items 1 2 15 16 17 - Pleasure in interaction: all items reversed (8 9 11 12 13)	
PPAS	*Patience and Tolerance: Minimum = 8, Maximum = 40.* *Pleasure in Interaction:*	The PPAS contains 19 items developed to assess a father's attachment to their infant during the first year of life. Each item is scored on a 2, 3, 4, or 5 point scale. Items are scored on different scales: - Item 8 is scored on a 2 point scale - Items 13 and 16 are scored on a 3 point scale	- Patience and Tolerance: Low scores are indicative of low levels of patience and tolerance. - Pleasure in Interaction: Low scores are indicative of low levels of pleasure in interaction with the child. - Affection and Pride: Low scores are indicative of low levels of affection and pride towards the child.

	Minimum = 7, Maximum = 35 *Affection and Pride: Minimum = 4, Maximum = 20*	- Items 6, 7, 9, 11, 15, 17, 18 and 19 are scored on a 4 point scale - Items 1, 2, 3, 4, 5, 10, 12, and 14 are scored on a 5 point scale. Items should be coded in the following manner: - Item 1 would be scored as 1; 2; 3; 4; 5 - Item 2 would be scored as 1; 2; 3; 4; 5 - Item 3 would be scored as 1; 2; 3; 4; 5 - Item 4 would be (reverse) scored as: 5; 4; 3; 2; 1 - Item 5 would be (reverse) scored as 5; 4; 3; 2; 1 - Item 6 would be scored as 1; 2.3; 3.6; 5 - Item 7 would be (reverse) scored as: 5; 3.6; 2.3; 1 - Item 8 would be (reverse) scored as: 5; 1 - Item 9 would be (reverse) scored as: 5; 3.6; 2.3; 1 - Item 10 would be (reverse) scored as: 5; 4; 3; 2; 1 - Item 11 would be (reverse) scored as: 5; 3.6; 2.3; 1 - Item 12 would be (reverse) scored as: 5; 4; 3; 2; 1 - Item 13 would be (reverse) scored as: 5; 3; 1 - Item 14 would be (reverse) scored as: 5; 4; 3; 2; 1 - Item 15 would be (reverse) scored as 5; 3.6; 2.3; 1 - Item 16 would be (reverse) scored as 5; 3; 1 - Item 17 would be scored as 1; 2.3; 3.6; 5 - Item 18 would be scored as 1; 2.3; 3.6; 5 - Item 19 would be scored as 1; 2.3; 3.6; 5 The 19 items can be pooled together to create three factors for analysis: - Patience and tolerance = items 2, 1, 6, 19, 11, 17, 13, and 18 - Pleasure in interaction = items 5, 15, 9, 12, 4, 8, and 10 - Affection and pride = items 3, 7, 14, and 16	**Desired direction of effect**: *increase*

<table>
<tr><td colspan="4">Child</td></tr>
<tr><td>ASQ-SE-2 2 month

ASQ-SE-2 6 month

ASQ-SE-2 9 month

ASQ-SE-2 18 month</td><td>Varies depending on time-point and measure</td><td>The ASQ:SE-2 is a 36-item parent-report based tool for screening children’s social and emotional development during the first five years of life. The master set comprises 9 questionnaires, ranging from 1-72 months covering 9 specific developmental ages; 2, 6, 12, 18, 24, 30, 36, 48, and 60 months. Each questionnaire covers 6 key social and emotional development areas: self-regulation, compliance, adaptive functioning, autonomy, affect, social-communication, and interaction with people

The parent answers the questions by responding on a three-point scale (Most of the time / Sometimes / Rarely or Never). Parents are also provided with the option to highlight any questions where they feel there is a concern.

Using the questionnaire Z’s are scored 0, V’s are scored 5, X’s are scored 10 and any box checked for concern is scored as a 5. Total scores for each page are then calculated and summed to provide an overall score for the 36 items.</td><td>Total scores are transferred onto a simple score-grid, which include cut off scores indicating possible problems. If the child score falls within the clinical range (see table) we will inform the health visitor at the final data collection time-point.

<table><tr><td></td><td colspan="5">Version</td></tr><tr><td></td><td>2 month</td><td>6 month</td><td>12 month</td><td>18 month</td><td>24 month</td></tr><tr><td>Low or no risk: It is below the cut-off. Social-emotional development appears to be on schedule.</td><td>0-24</td><td>0-29</td><td>0-39</td><td>0-49</td><td>0-49</td></tr><tr><td>Monitor: It is close to the cut-off. Review behaviours of concern and monitor.</td><td>25-34</td><td>30-44</td><td>40-49</td><td>50-64</td><td>50-64</td></tr><tr><td>Refer: It is above the cut-off. Further assessment with a professional may be needed</td><td>35+</td><td>45+</td><td>50+</td><td>65+</td><td>65+</td></tr></table></td></tr>
</table>

			Desired direction of effect: *decrease* *Imputation: scores will be calculated for up to 3 missing items using the average score of completed items. In the context of using the measure as a screening tool, the ASQ:SE-2 user guide recommends this method of imputation for 3 missing items, but recommends no imputation for 1 or 2 missing items because it would not take somebody over one of the screening thresholds.* (Jane Squires Ph.D., Diane Bricker Ph.D., 2015). *Because we are using the measure for a trial of efficacy we will also impute for 1 or 2 missing items.*
Peds-QL	Subscale scores range from 0-100	The PedsQL Infant is a 45-item questionnaire designed for parents with infants aged 13-24 months. The items represent 5 dimensions; physical functioning, physical symptoms, emotional functioning, social functioning and cognitive functioning. Psychosocial Health Summary Score = the sum of the items over the number of items answered in the emotional social and cognitive functioning subscales.	High scores indicate better health related quality of life. **Desired direction of effect**: *increase*

<table>
<tr>
<td></td>
<td></td>
<td>- Physical Health Summary Score = the sum of items over the number of items answered in the physical functioning and physical symptoms scales.

- Total score = sum of all the items over the number of items answered on all the scales.</td>
<td></td>
</tr>
<tr>
<td>SDQ</td>
<td>Subscale scores range from 0-10 and total difficulties score ranges from 0-40</td>
<td>The SDQ is a 25-item questionnaire, with an additional impact supplement, developed to assess children’s behaviour and social and emotional functioning. Our analysis will use `Total difficulty’ score comprising 4 of the 5 subscales

• Emotional problems
• Conduct problems
• Hyperactivity
• Peer problems</td>
<td>
<table>
<tr><th>Subscale</th><th>Range of possible scores</th><th>Close to average</th><th>Slightly raised (slightly lowered)</th><th>High (low)</th><th>Very high (very low)</th></tr>
<tr><td>Emotional problems</td><td>0-10</td><td>0-2</td><td>3</td><td>4</td><td>5-10</td></tr>
<tr><td>Conduct problems</td><td>0-10</td><td>0-3</td><td>4</td><td>5</td><td>6-10</td></tr>
<tr><td>Hyperactivity</td><td>0-10</td><td>0-5</td><td>6</td><td>7</td><td>8-10</td></tr>
<tr><td>Peer problems</td><td>0-10</td><td>0-2</td><td>3</td><td>4</td><td>5-10</td></tr>
<tr><td>Total difficulties</td><td>0-40</td><td>0-12</td><td>13-15</td><td>16-18</td><td>19-40</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td>
</tr>
</table>

			Desired direction of effect: *varies depending on subscale. An increase is desired for prosocial behaviour. For other measures a decrease is desired - see table above* *Imputation: up to 2 missing values will be imputed for each of the 4 subscales based on guidance from the developers website* (Youth in Mind, 2016). *In addition, up to one missing subscale score will be imputed using the average score of the 3 completed subscales, based on guidance from the Department of Health and Ageing, Canberra, Australia* (Department of Health and Ageing, Canberra, 2006).

9.3 CARE Index

The CARE-Index is an independent observational assessment of parent-child interaction. The CARE-index assesses interaction over the first four years (infant index = birth to 15 months and toddler index = 16 to 48 months) based on a short, videotaped play interaction of 3-5 minutes. Once the coder is trained, coding of an interaction takes about 15-20 minutes. The coding initially focuses on item-by-item scoring of seven aspects of adult and child behaviour, four affective aspects (facial expression, vocal expression, position and body contact, expression of affection) and three cognition aspects (the response of one party to the behavioural signals of the other, turn-taking and control of the activity, developmental appropriateness of the activity). Each aspect of behaviour is scored separately for the adult and the child and the scores combined to generate seven scale scores (Farnfield and Holmes, 2016) . The coder then takes a holistic view of the observations and item by item scores and assigns an overall dyadic synchrony score (0-14). The scoring manual explains that "neither approach is more accurate than the other" and that dyadic synchrony score "prevent[s] misalignment of ordinary dyads to the high and low extremes of the scale" but [on its own] "there is too little detail to permit disagreements between coders to be resolved (Crittenden, 2010). As such, the item-by-item coding and "dyadic synchrony" score will be recorded but analysis will be based on the overall dyadic synchrony scale alone (range: 0-14) as a continuous variable.

10 Additional Analyses

10.1 Subgroup analyses

As suggested by the literature, the subgroup analysis will be restricted to the primary analysis and subgroups will be defined by baseline data i.e. data that is not dependent on the intervention. The subgroup analysis will be performed using the primary analysis of the primary outcome model (ASQ:SE-2). An interaction statistical test between the randomised treatment group and subgroup will be used to directly examine the strength of evidence for the difference between treatment arms varying between subgroups. Subgroup analysis will be performed regardless of the results of the primary analysis. The mean difference and 95% CI will be computed for each subgroup category and visually displayed using a forest plot. The regression coefficient for the interaction between treatment group and subgroup will be presented with the associated confidence interval and P-value. We will not calculate separate p-values within each subgroup category (Wang et al. 2007). Results will be presented as shown in Appendix Table 9. The subgroups of interest are described below.

- **Social and economic background** using a binary variable for whether or not the primary caregiver was educated to degree level as a proxy. In a previous US study

(Lavigne *et al.*, 2008) mothers educated to high school level or below (typically left education aged 17 or 18) responded better to parent training than better educated mothers. Participants with overseas and vocational qualifications will be allocated to the higher education group if they left full time education aged 19 or above.

- **First child (Yes or No).** A Netherlands study found that intervention mothers of first-born children displayed an increase in their use of positive discipline strategies as compared to first-time mothers in the control group. (Stolk *et al.*, 2008)
- **Sex of index child (Male or Female)** child gender has been found to differentiate response in previous trials of parenting interventions (Lavigne *et al.*, 2008); (Gardner *et al.*, 2010).
- **Site**

10.2 Breastfeeding

At FU0, FU1 and FU2, participants are asked several questions on feeding their child. For the categorical variables, (e.g. Ever breastfed), the number and percentage of participants in each of the categories and the total number of observations will be presented. For the continuous variables (e.g. child's age when stopped breastfeeding) either mean and SD will be presented or median and IQR depending on the distribution of the data. The number of observations used in each calculation will be presented alongside the summaries.

11 Implementation of the Analysis Plan

This SAP will be used as a work description for the statistician involved in the trial. All analyses should ideally be performed by the same statistician (under the supervision of senior trial statistician) and consequently none of the investigators involved in the trial will perform any of the statistical analyses.

Initially, the data manager will provide blinded data for preliminary checks by the statistician. Following database freeze, unblinded data will be delivered to the statistician to define analysis sets and test statistical programs. Any queries will be communicated to the data manager prior to database lock, and any changes to the database during this time will be documented. The database will be locked after agreement between the statistician, data manager and study manager. It is expected that no data amendments should be required following database lock. However, if an amendment is required, the process is documented in CTRU SOP DM012.

12 References

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Trial Documents

Title	Version	Date	Location
Study Protocol	10	11/06/2019	X:\ScHARR\PR_ESEE\General\PROJECT DOCUMENTATION\Protocol Development\Final Protocol versions\Version 10
Data Management Plan	2	15/08/2016	X:\ScHARR\PR_ESEE\General\Data Management\Study Documentation\Data management plan
External pilot Statistical Analysis Plan	1	05/11/2018	X:\ScHARR\PR_ESEE\General\Statistics\Revised Pilot Report\Documents\SAP

CTRU Standard Operating Procedures

Title	Version	Date	Location
ST001 The Statistical Analysis Plan	5	9 Jan 2018	X:\ScHARR\WG_CTRU_SOPs
ST003 Data Evaluation	5		
ST006 Undertaking a Statistical Analysis	2	11 May 2017	
ST007 Randomisation			
DM005 Central Data Validation	5	21 Jun 2018	
DM012 Study database lock and retention	4	28 Mar 2017	

13 Appendix

A. Appendix A Dummy Tables

i. Participant flow

Figure 1: CONSORT flow diagram showing the participant flow through the study

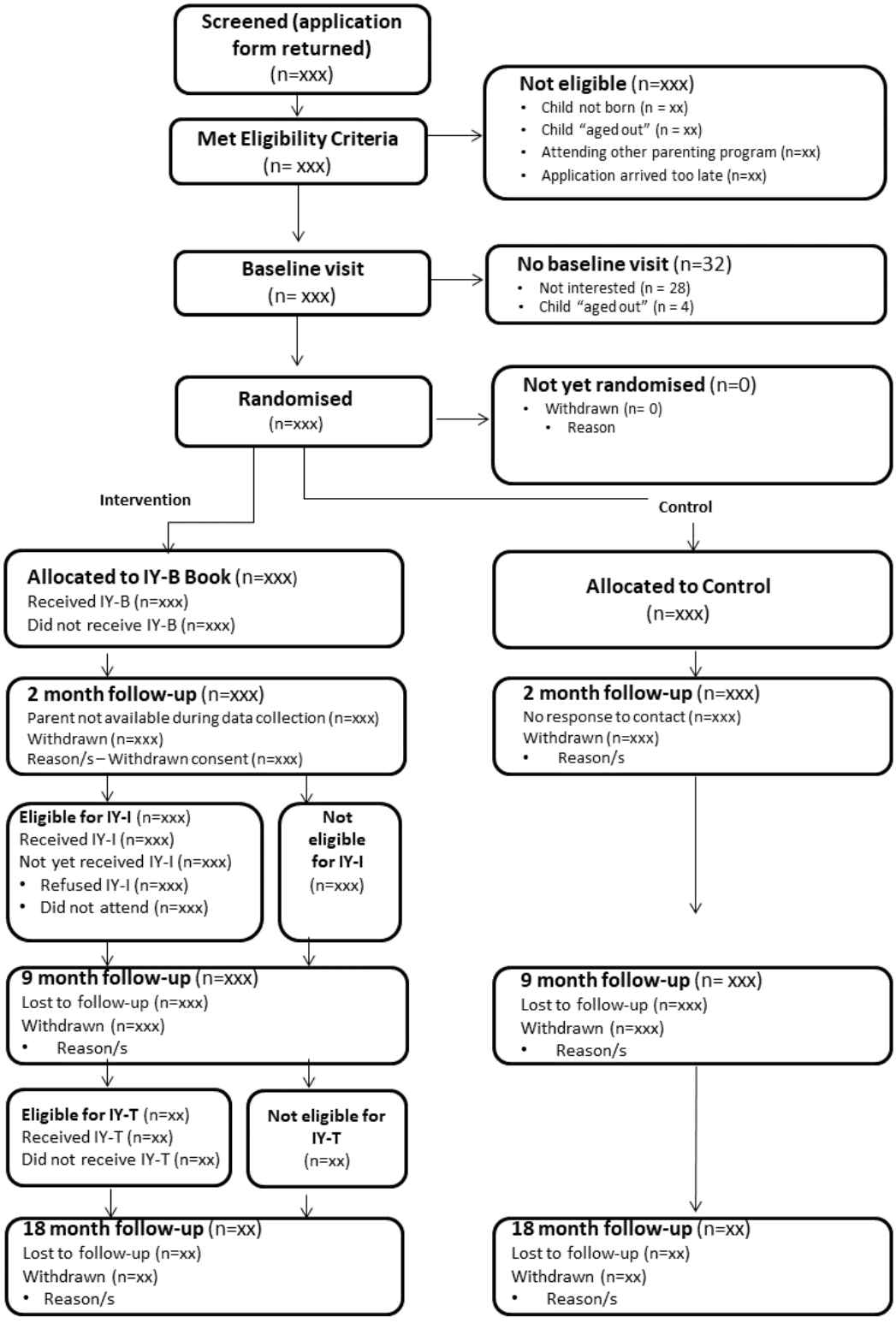


Table 3: Summary of study discontinuation during the 18 month follow up period

	Between baseline and FU1		Between FU1 and FU2		Between FU2 and FU3		Overall	
Type of discontinuation	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Withdrew from the intervention	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Withdrew from study	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Lost to follow up*	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)

*date of last contact will be used

ii. Baseline characteristics

Table 4: Summary of baseline characteristics by treatment arm

		Intervention (n=xxx)	Control (n=xxx)	All (n=xxx)
Primary caregiver variables				
Ethnicity	White: English / Welsh / Scottish / Northern Irish / British	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
		xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Qualification	Higher Education	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	A, AS or S Levels	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	O levels or GCSE: 5 or more	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Vocational or Overseas qualifications	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	None or Low Level Qualifications	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Religion	None	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Christian	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Other Religions	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Relationship status	Married and living together	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)

	Cohabiting/living together	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Other	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Age (years)	N (%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Mean (SD)	xx.x(xx.x)	xx(xx.x)	xx.x(xx.x)
	Median (IQR)	xx.x(xx.x-xx.x)	xx.x(xx.x-xx.x)	xx.x(xx.x-xx.x)
	Min., Max.	xx,xx	xx,xx	xx,xx
Index Child variables				
Born premature	No	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Yes	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
First Child	No	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Yes	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Ever Breastfed	No	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Yes	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Currently breastfeeding	No	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Yes	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)

Baseline characteristics tables will be presented separately for primary caregivers, child and co-parents

Table 5: Summary of questionnaire scores for parents at baseline by treatment arm

Variable		Control (n=xx)	Intervention (n=xx)	All (n=xx)
PHQ-9	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx

PSoC	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx
EQ5D-5L	N	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx

The table will be repeated for child outcomes (ASQ:SE-2 and CARE Index) and co-parent outcomes (PHQ-9, PSoC, EQ5D-5L)

iii. Analysis of primary outcomes results

Table 6: Summary statistics for the primary outcome at each time point

ASQ:SE-2 scores		Intervention	Control	Overall
FU0	N (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min, Max.	xx,xx	xx,xx	xx,xx
FU1	N (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min, Max.	xx,xx	xx,xx	xx,xx
FU2	N (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min, Max.	xx,xx	xx,xx	xx,xx
FU3	N (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min, Max.	xx,xx	xx,xx	xx,xx

This table will be repeated for Primary caregiver and co-parent PHQ-9 scores

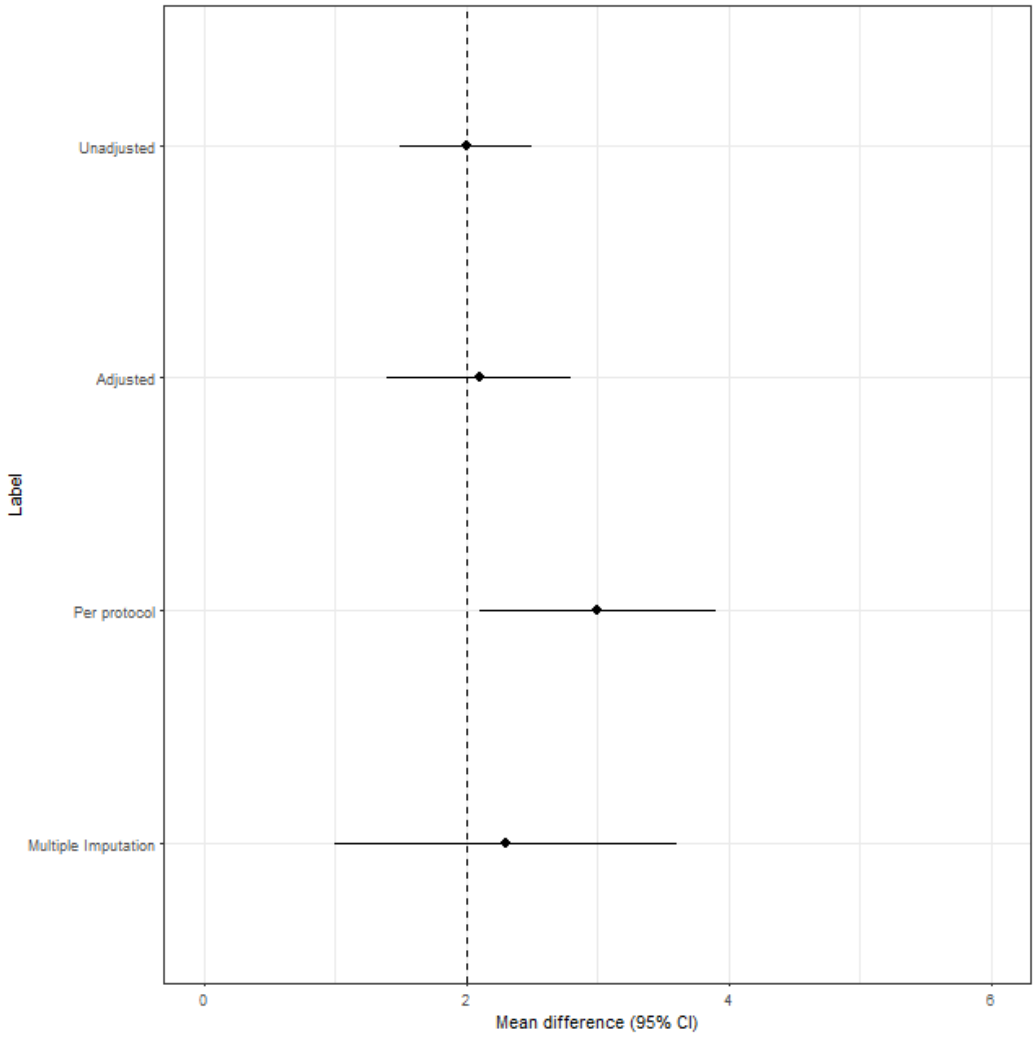


Figure 2: Forest plot showing results from the primary analysis

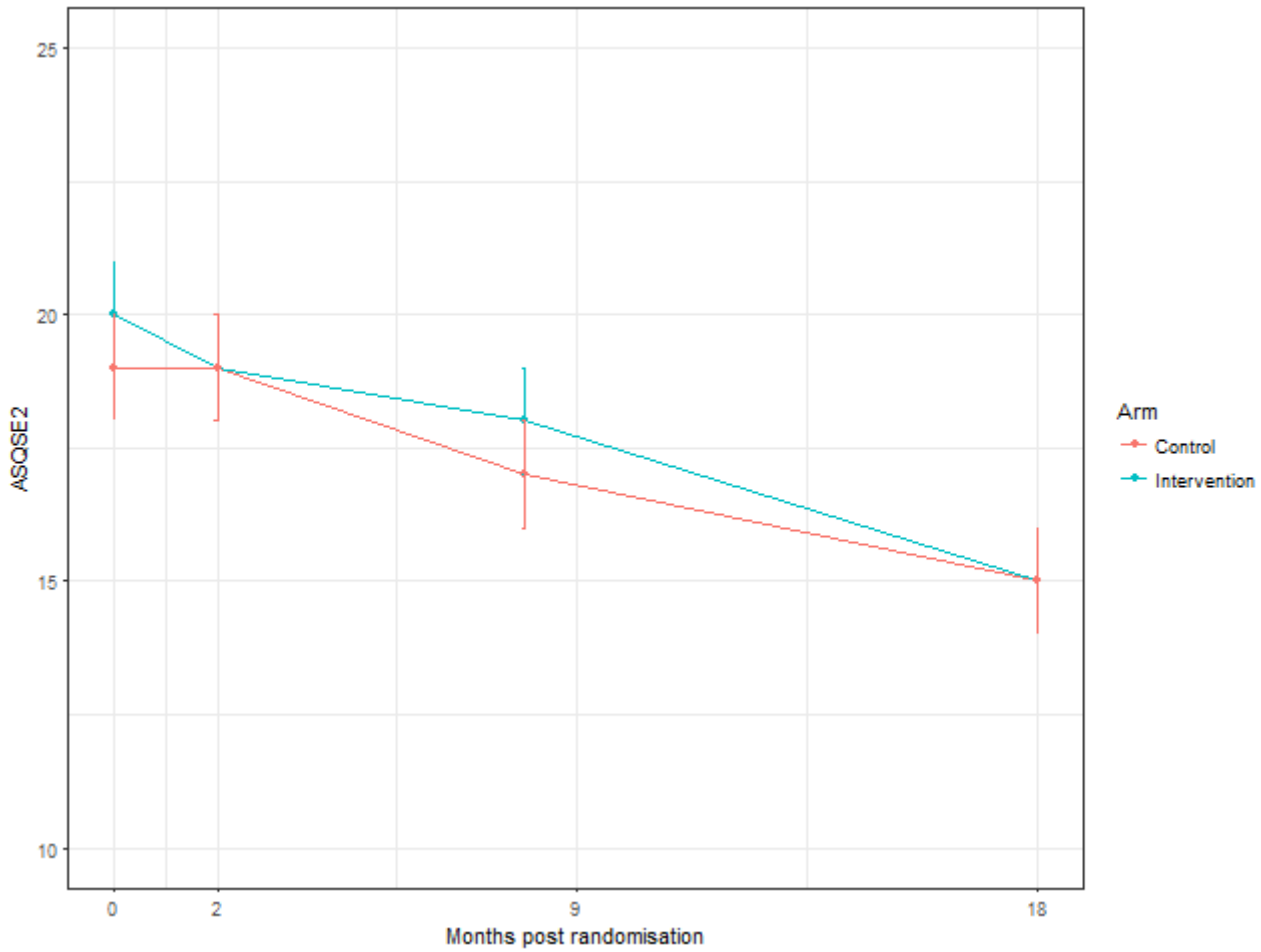


Figure 3: Line plot of mean ASQ:SE-2 at each time point
This figure will be repeated for PHQ-9

Table 7: Results of the analysis of key secondary outcome 2

Outcome measure	n	Mean (SD) Intervention	n	Mean (SD) Control	n	Mean difference (95%CI)	Adjusted Mean difference (95%CI)*	p-value
ASQ:SE-2 at FU1	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	xx.x(xx.x-xx.x)	0.xxxx
ASQ:SE-2 at FU2 in the subgroup of parents with PHQ-9 score >=5 OR Child ASQ:SE2 score>= Monitoring Zone	Xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	xx.x(xx.x-xx.x)	0.xxxx
ASQ:SE-2 at FU3 in the subgroup of parents with PHQ-9 score >=5 OR Child ASQ:SE2 score>= Monitoring Zone	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	xx.x(xx.x-xx.x)	0.xxxx

This table will be repeated for primary care givers and co-parents (PHQ-9 scores)

iv. Analysis of secondary outcomes results

Table 8 : EQ5D-5L for primary care-givers

	n	Mean (SD) Intervention	n	Mean (SD) Control	n	Mean difference (95%CI)	Adjusted Mean difference (95%CI)*	p-value
Primary carer EQ5D-5L								
Baseline	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)		
FU1	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	xx.x(xx.x-xx.x)	0.xxxx
FU2	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	xx.x(xx.x-xx.x)	0.xxxx
FU3	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	xx.x(xx.x-xx.x)	0.xxxx

*adjusted for baseline ASQ:SE-2 score, baseline PHQ-9 score, sex of child and recruitment site and baseline measure
This table will be repeated for secondary outcome data collected at FU2 and FU2

Each Secondary outcomes will be reported in separate table showing outcome by time-point in a similar manner to table

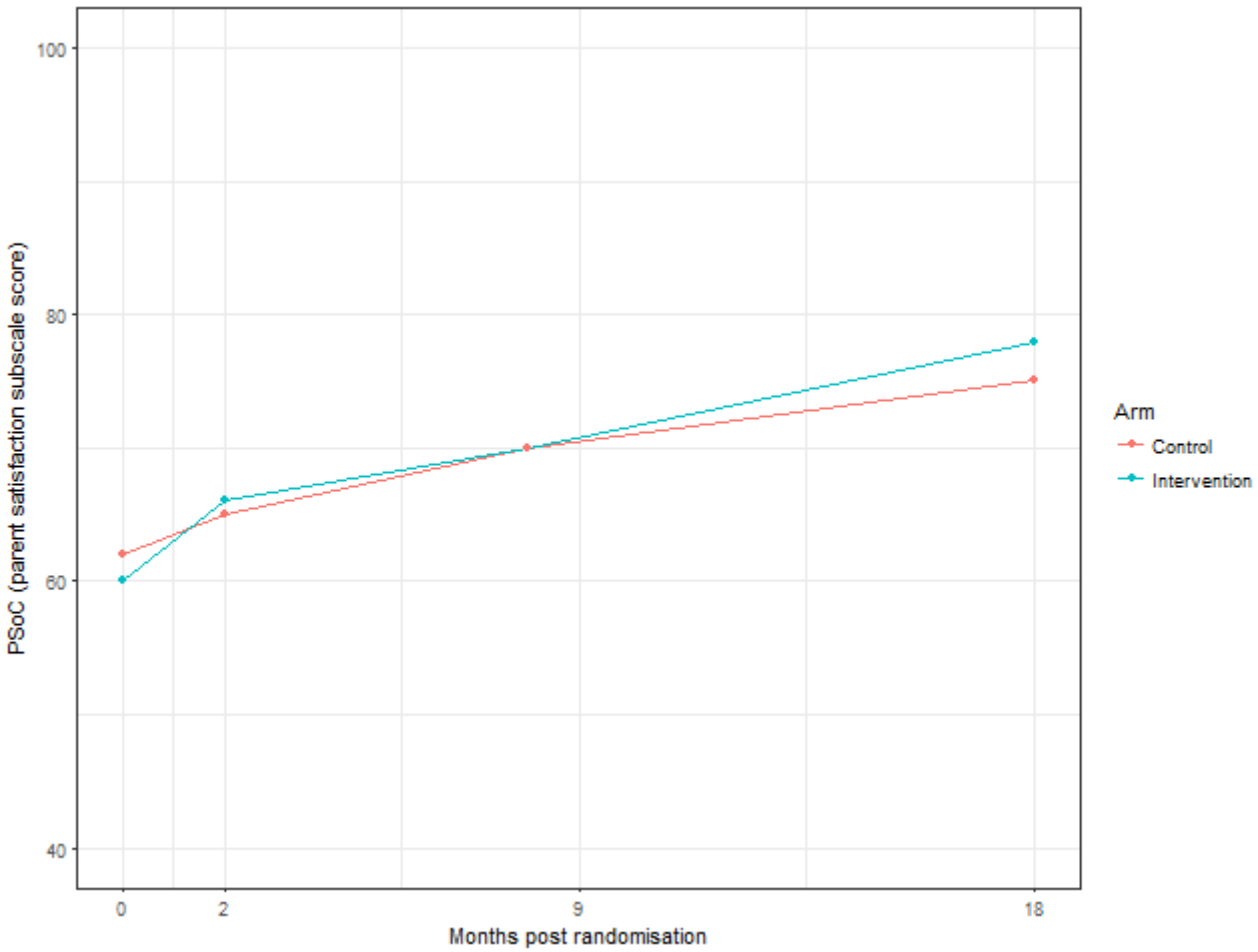


Figure 4: Line plot showing mean secondary outcome scores

v. Subgroup analysis results

Table 9: Results of subgroup analysis

Subgroup	n	Mean (SD) Intervention	n	Mean (SD) Control	n	Mean difference (95%CI)*	p-value*
TBC	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx
	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	
	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	
	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx
	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	
	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx
	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	
	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	
	xx	xx.x(xx.x)	xx	xx.x(xx.x)	xx	xx.x(xx.x-xx.x)	0.xxxx

* p-value from interaction test

vi. Safety analysis results

Table 10: Summary of safety data

	Intervention	Control	All
Number (%) of participants who experienced >=1 AE	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Number of all AEs (including repeated events)	xx	xx	xx
AE related to intervention			
Unlikely	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Unrelated	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)

	Intervention	Control	All
Number (%) of participants who experienced >=1 SAE	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Number of all SAEs (including repeated events)	xx	xx	xx
SAE related to intervention			
Unrelated	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Intensity of SAE			
Mild	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Moderate	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Severe	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Frequency of SAE			
Isolated	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Intermittent	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Unknown	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)

vii. Adherence to intervention

Table 11: Summary of the number of sessions received by participants

Programme	Consent			Number of sessions						
				1	2	3	5	8**	10	12
IY-I	Xx	Attended at least this many sessions	n	xx	xx	xx	xx	xx	xx	xx
			(%)	xx%	xx%	xx%	xx%	xx%	xx%	xx%
IY-T	xx	Attended at least this many sessions	n	xx	xx	xx	xx	xx	xx	xx
			(%)	xx%	xx%	xx%	xx%	xx%	xx%	xx%

Table 12: Summary of IY-I and IY-T groups

	Number assigned to a group	Number who attended one or more sessions	Median sessions attended (IQR)	Min, Max.
IY-I	xx	xx(xx%)	xx(xx,xx)	x,xx
IY-T	xx	xx(xx%)	xx(xx,xx)	x,xx

Table 13: Summary of all intervention sessions

	Number of Sessions that occurred	Median (IQR)	Min, Max.
IY-I	xx	xx(xx,xx)	x,xx
IY-T	xx	xx(xx,xx)	x,xx

Table 14: Summary of breastfeeding at baseline

Variable		Intervention (n=xxx)	Control (n=xxx)	All (n=xxx)
Breastfeeding History	Never breastfed	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Previously breastfed, now stopped	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Currently breastfeeding -	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Not Known[1]	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Of those currently breastfeeding	Does not use bottle	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Also uses bottle	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
Childs age when stopped breastfeeding (weeks)	N (%)	xx(xx.x%)	xx(xx.x%)	xx(xx.x%)
	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Median (IQR)	xx.x(xx,xx)	xx.x(xx,xx)	xx.x(xx,xx)
	Min., Max.	xx,xx	xx,xx	xx,xx

This table will be repeated for FU1 and FU2

Appendix B: E-SEE Primary Outcome – methods comparison

Proposed Primary Analysis

For our primary analysis, we propose to ignore the clustering by treatment group, as it is not possible to account for it appropriately in the methods we have explored. This is also current practice in the wider community.

Background

The E-SEE intervention has three distinct phases. In stage 1, all participants in the treatment arm get a self-help intervention book and in stages 2 and 3, participants with interim outcomes above a threshold are eligible for a group therapy.

The objective of the primary analysis is to estimate the impact of the intervention as a whole rather than the specific stages. In many ways, E-SEE is similar to stepped care treatments where higher intensity treatments are available to those unresponsive to a lower intensity treatment. The difference here is that the higher intensity E-SEE interventions is group based, which may induce clustering ("within-arm partial nesting" in the literature). The recent systematic review arising from the E-SEE sub-study (Candlish et al, 2019) found it is common practice to ignore such treatment induced clustering in the statistical analysis. This seems to contrast with the recommendation that trials with single arm treatment induced clustering should account for clustering in the analysis (Candlish et al. 2018). In Chapter 5 of her PhD thesis Candlish explored a number of approaches to analyse a simple within-arm partially nested trial. The thesis demonstrated that random assignment of a treatment group subset to a stepped up group based treatment then adjusting for clustering was appropriate. However, with targeted allocation (as in a proportionate intervention such as ESEE) adjusting for clustering gave biased estimates of the treatment effect even under the null. The thesis also explored linear regression with fixed effects only with and without cluster robust standard errors.

The thesis showed that naïve linear regression not accounting for clustering gives the best coverage and control of type 1 error rate provided the ICC is below 0.1. Using cluster robust standard errors always over controlled the type 1 error rate (and hence 95%CI coverage was too high), whereas cluster bootstrap robust standard errors poorly controlled the type 1 error rate and hence the coverage of 95%Cis was too low. The reason behind these possibly counterintuitive results is because the within therapy group and within person correlations are confounded with the correlation caused by selection. Candlish recommended that provided the treatment induced ICC is below 0.05 then ignoring

the clustering is the most cautious approach. However, estimating the ICC in proportionate intervention designs is not generally possible because of the confounding induced by selection.

Approach to justifying our proposal

As we cannot know the true ICC and the E-SEE design is more complex than scenarios simulated by Candlish, we have used simulations to explore the robustness of four naïve models that do not account for clustering for a scenario similar to E-SEE. As a simplifying assumption, we simulated data for two follow up measurements with equal correlation between each time point and a single high intensity treatment delivered between FU1 and FU2 for those with the highest outcome score at FU1. We then estimate the impact of treatment using the outcome at FU1 and FU2 using the two models and compared the approaches by looking at their estimates for treatments effect, treatment effect standard error and type I and type II error rates. We considered the following models:

1. Mixed effects model with time and clusters as random components.
2. Mixed effect models with time as a random component (random intercept only)
3. Mixed effect models with time as a random component (random intercept and slope) with an exchangeable correlation structure and Satterthwaite adjusted standard errors.
4. Marginal model estimated using GEE with a Gaussian family, identity link and an exchangeable correlation structure.
5. Marginal model estimated using GEE with a Gaussian family, identity link, an exchangeable correlation structure and robust standard errors.

Detailed Method

For various value of intra cluster correlation (ρ) between 0 and 0.2, we simulated between 100 and 500 samples under both the null and the alternative hypothesis using the following assumptions:

- The outcomes under the null at FU1 and FU2 vary according to a normal distribution with mean 26 and 36 respectively and standard deviation (s) of 10 (before clustering) for each time point;
- An overall effect size of 3.46 (2.5 at FU1 and 15 for those stepped up at FU2);
- A correlation (τ) of 0.4 between time points;
- 13 clusters sized between 2 and 12[5] as in ESEE (see appendix C);

The number of samples and values of ICC considered was lower for the more complex models because the time taken to estimate the model for each sample was prohibitively high.

[5] Actual cluster sizes were: 2, 2, 2, 3, 6, 6, 6, 6, 7, 7, 8, 9 and 12

Outcomes for the three time points are generated using two stages. First by simulating values from a normal distribution with fixed mean and standard deviation reduced to account for time correlation [$s\sqrt{(1-\tau)}$] and second, by adding an individual component common to each of the individual's three time points with mean 0 and standard deviation [$s\sqrt{\tau}$].

We simulate the assumed intra-cluster correlation (ρ) by adding a mean cluster effect to each member of the cluster at FU2 with mean 0 and variance ${\sigma_u}^2$ such that:

$\frac{{\sigma_u}^2}{{\sigma_u}^2+{\sigma_e}^2}$ =ρ, i.e. $\sigma_u = s\sqrt{\rho}\sqrt{(1-\tau)}$

The simulations used STATA.

Results

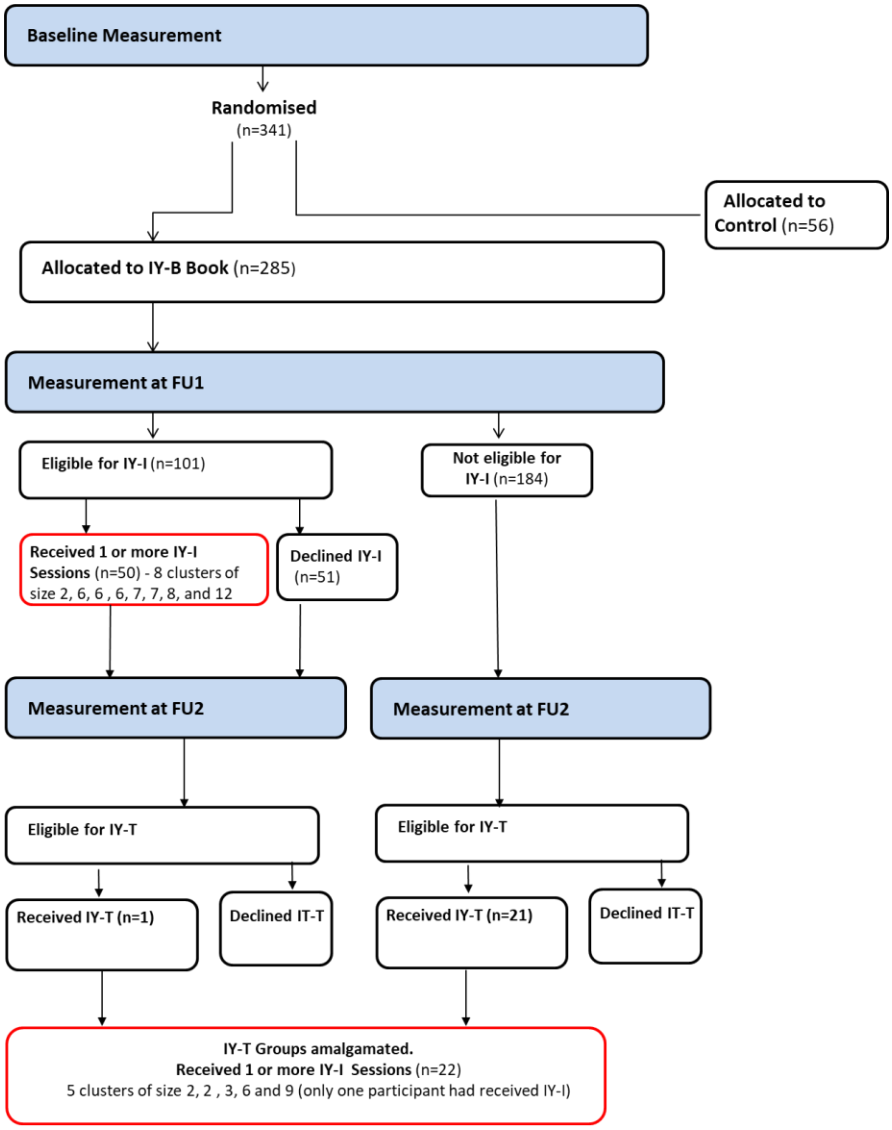
Charts are in appendix D and results are summarised in Table A1. Table A1 shows that selecting the most appropriate model will require a trade-off between bias and precision. Model 1 gives highly biased estimates and can be discounted immediately. Model 3 (random intercept and slope with adjustment for unequal variance) best controls for precision with type I error appropriately controlled (5%) and type II error increasing as ICC and total variance increases; but gives biased estimates of the treatment effect. Unbiased estimates are given by models 2, 4 and 5 and while they all exhibit similar levels of type II error, model 5 gives the best control for type I error and is our preferred model for the primary analysis because we believe that an unbiased estimate is more important that precision.

Table A1: Results of methods comparison

		Effect	Type 1	Power	Runs
Full mixed model	1 Random effects for time and clusters[6]; exchangeable correlation, Satterthwaite SE	2.5 (biased)	0.05	0.83	100
Naïve Mixed model	2 Random intercept	3.46	0.08	0.99	500
	3 Random intercept and slope; exchangeable correlation, Satterthwaite SE	3.2 (biased)	0.04?	Decreases as ICC increases	200
Naïve GEE	4 Exchangeable correlation	3.46	Increases as ICC increases	0.98	200
	5 Exchangeable correlation, robust SE	3.46	0.05	0.988	500

Appendix C – reduced consort

[6] Random intercept and slope for time. Random intercept and random slope to restrict to stepped up participants for clusters.

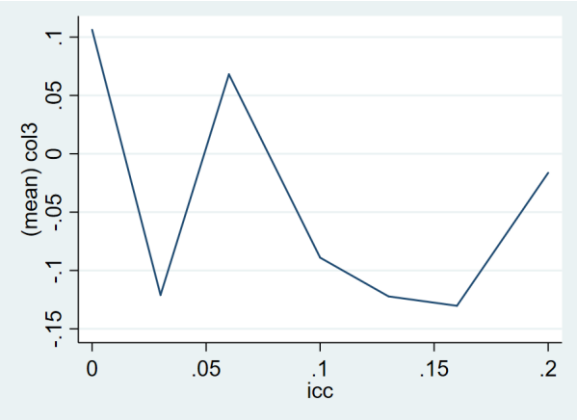

Baseline Measurement
Randomised
(n=341)
Allocated to Control (n=56)
Allocated to IY-B Book (n=285)
Measurement at FU1
Eligible for IY-I (n=101)
Not eligible for IY-I (n=184)
Received 1 or more IY-I Sessions (n=50) - 8 clusters of size 2, 6, 6 , 6, 7, 7, 8, and 12
Declined IY-I (n=51)
Measurement at FU2
Measurement at FU2
Eligible for IY-T
Eligible for IY-T
Received IY-T (n=1)
Declined IT-T
Received IY-T (n=21)
Declined IT-T
IY-T Groups amalgamated.
Received 1 or more IY-I Sessions (n=22)
5 clusters of size 2, 2 , 3, 6 and 9 (only one participant had received IY-I)

Appendix D – Results of Primary Analysis Model Comparison

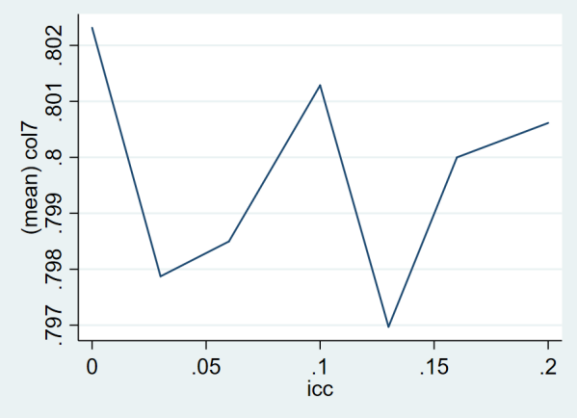
1 Time and cluster random effects: exchangeable correlation, Satterthwaite

Null: 100 runs

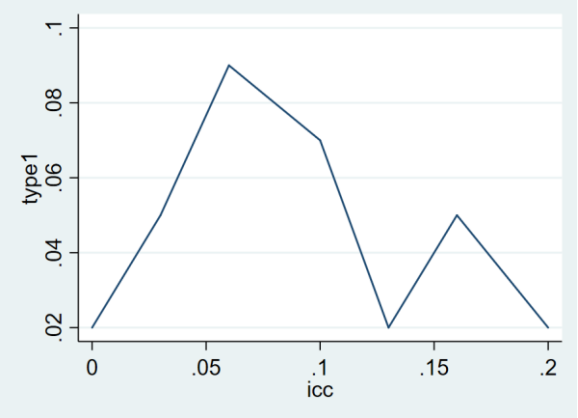
Effect Estimate



Effect SE

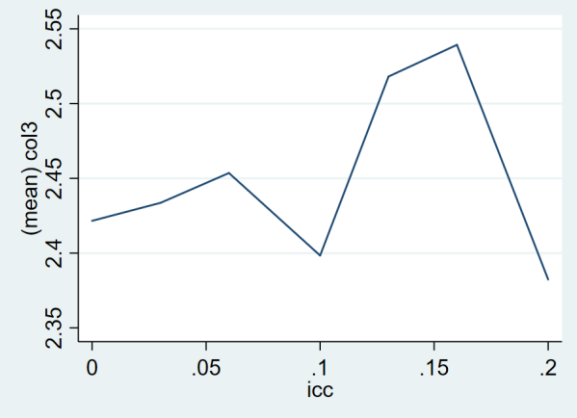


Type 1

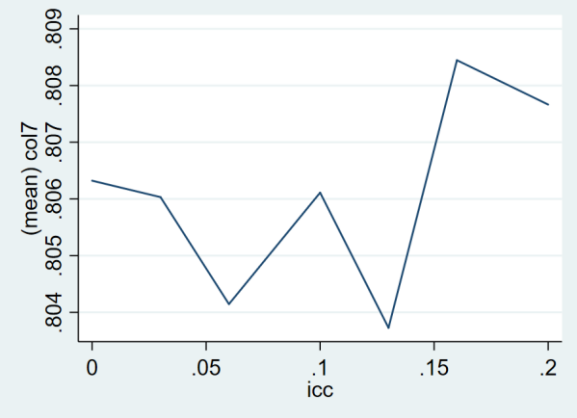


H1: 100 runs

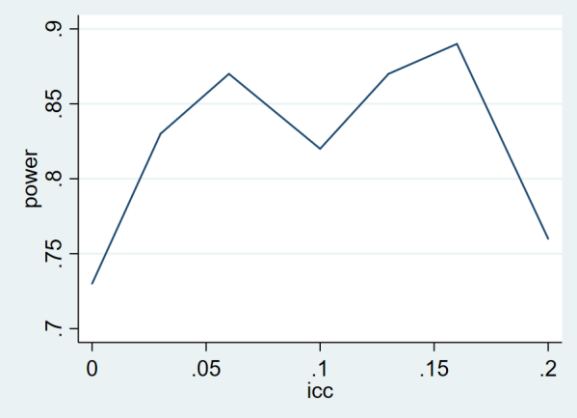
Effect Estimate



Effect SE



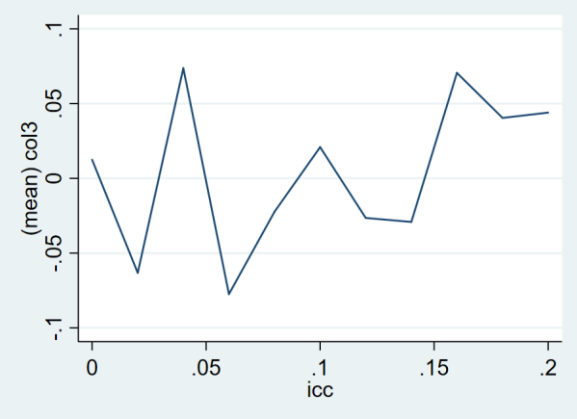
Power



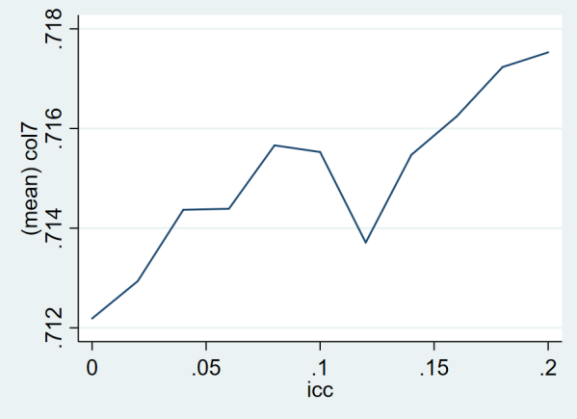
2 Random intercept, ML

Null: 500 runs

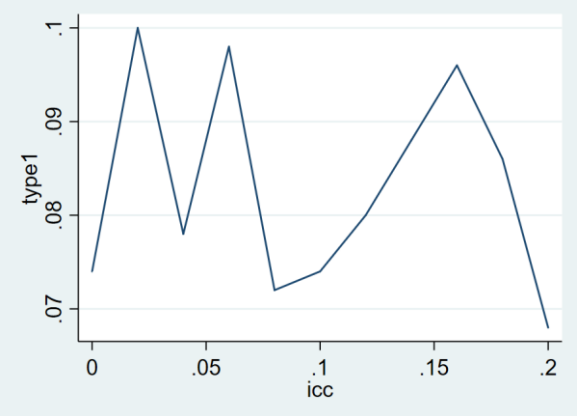
Effect Estimate



Effect SE

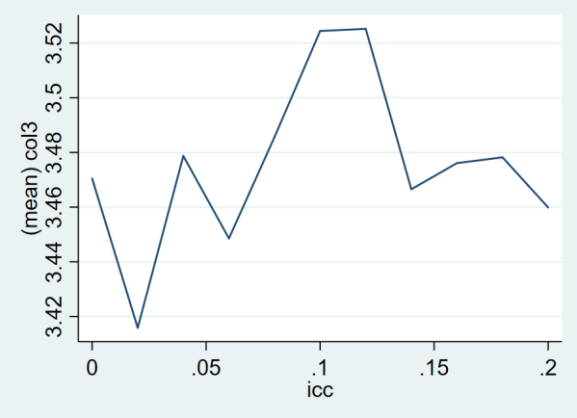


Type 1

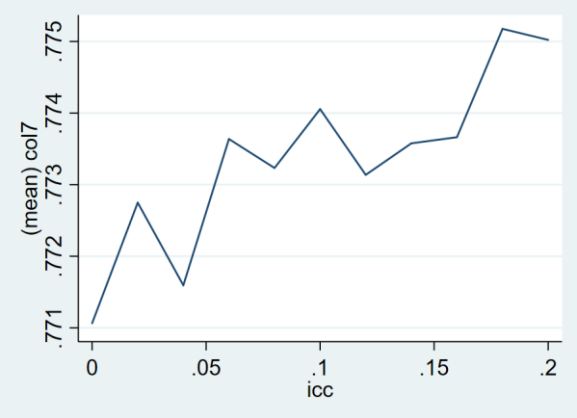


H1: 500 runs

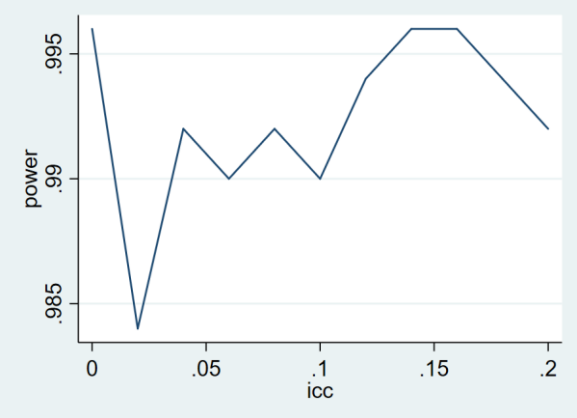
Effect Estimate



Effect SE



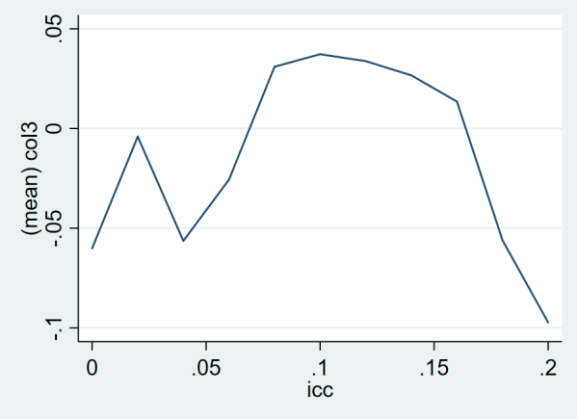
Power



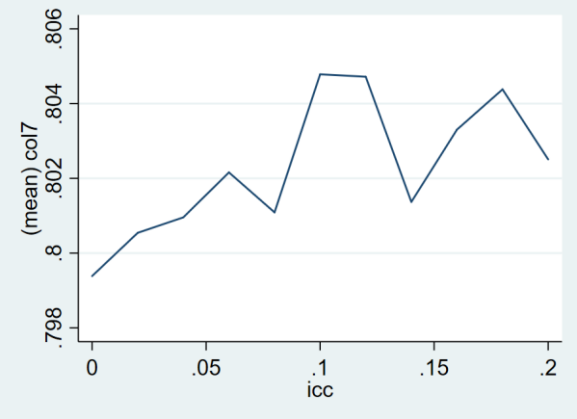
3 Random intercept and slope: exchangeable correlation, Satterthwaite

Null: 200 runs

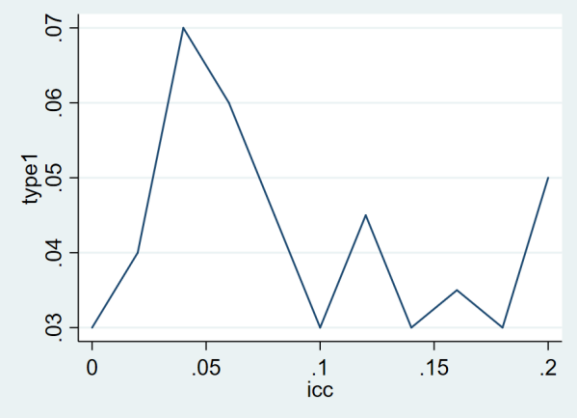
Effect Estimate



Effect SE

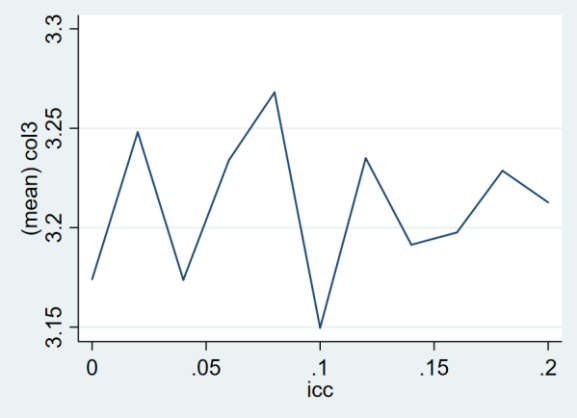


Type 1

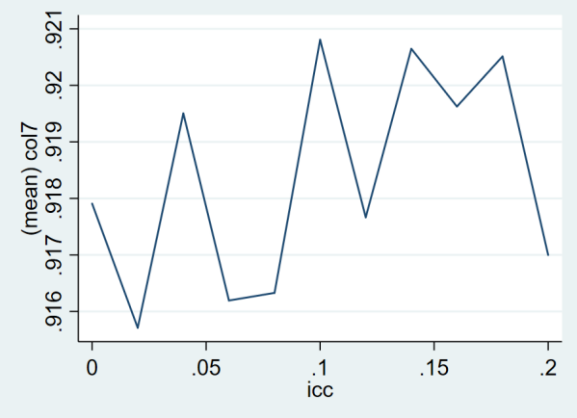


H1: 200 runs

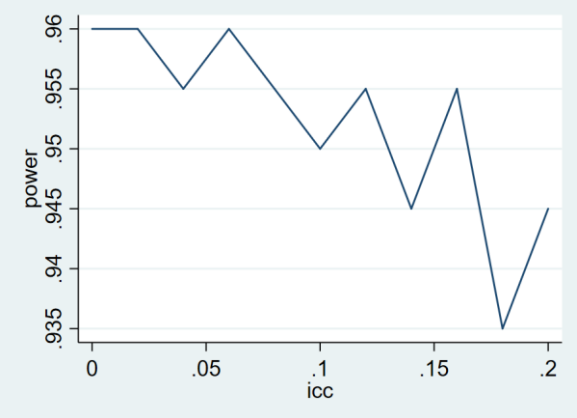
Effect Estimate



Effect SE



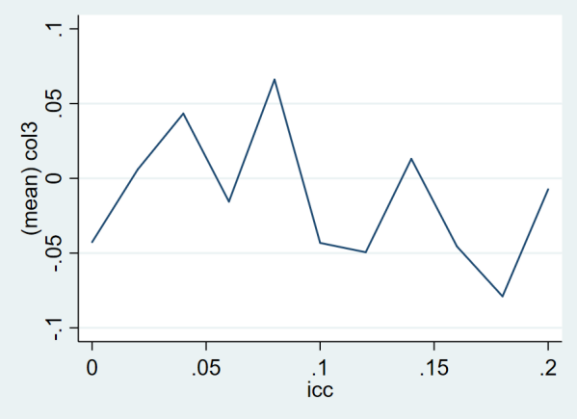
Power



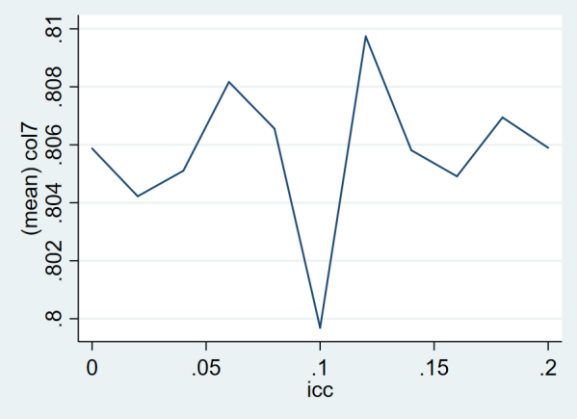
4 GEE, exchangeable correlation

Null: 200 runs

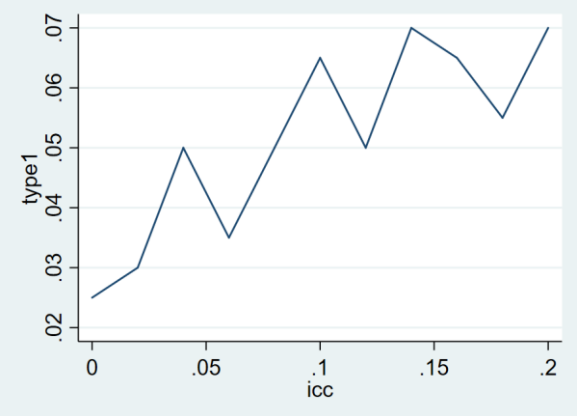
Effect Estimate



Effect SE

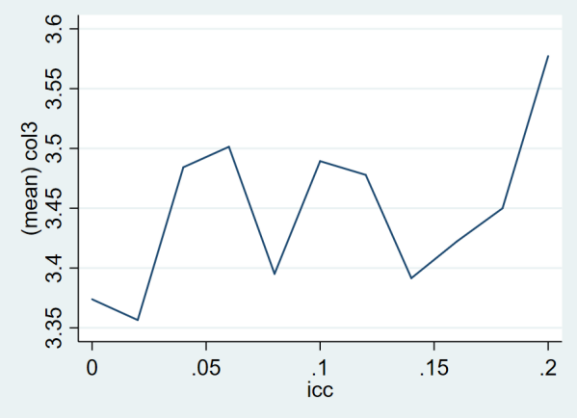


Type 1

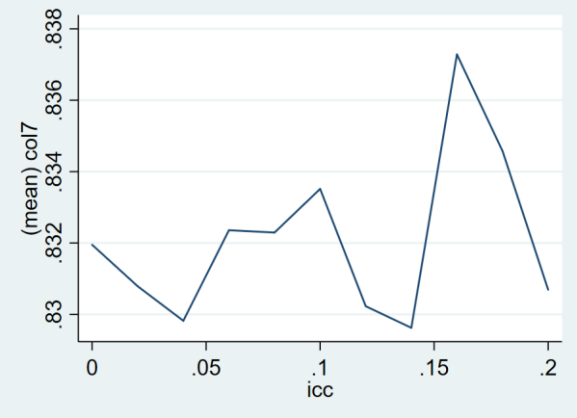


H1: 200 runs

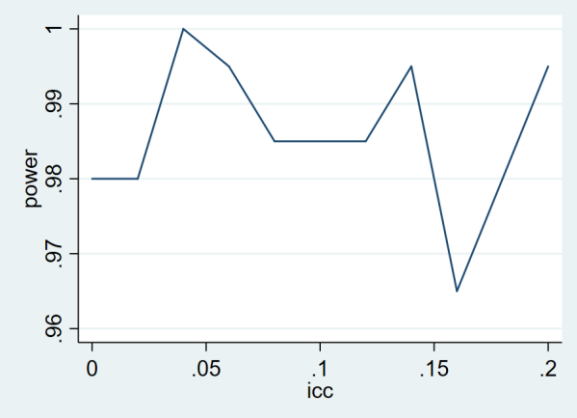
Effect Estimate



Effect SE



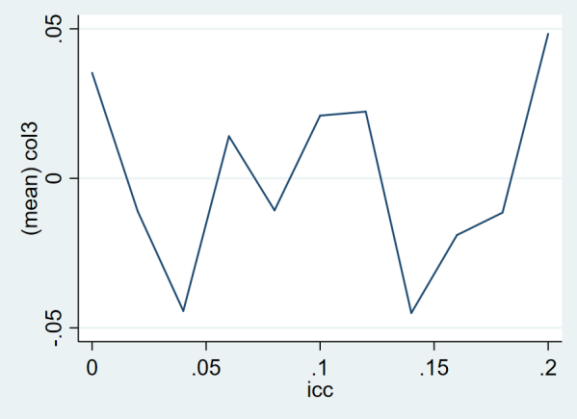
Power



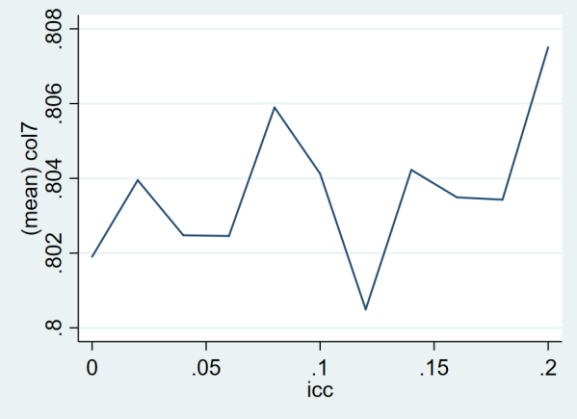
5 GEE, exchangeable correlation, robust se

Null: 500 runs

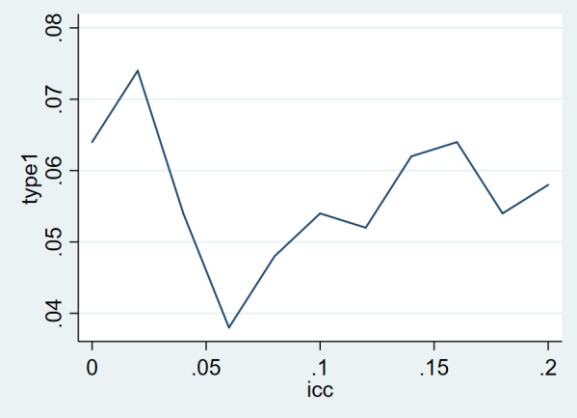
Effect Estimate



Effect SE

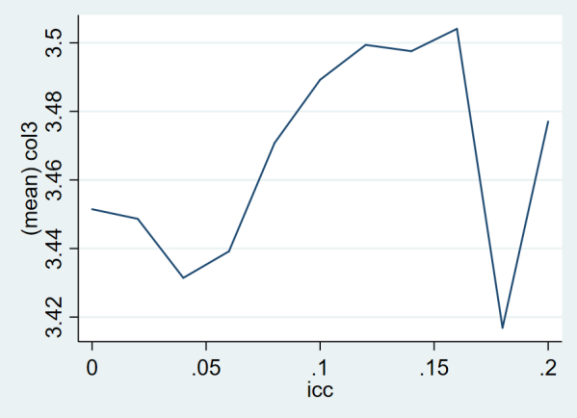


Type 1

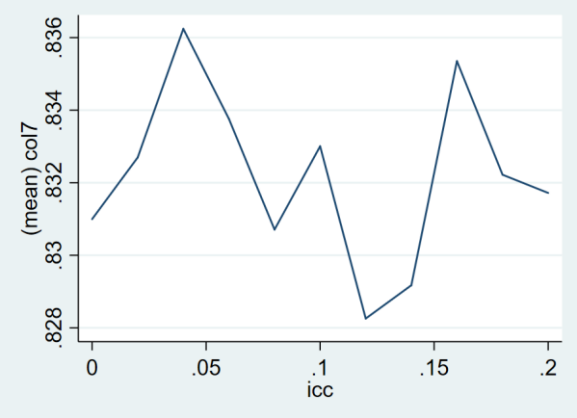


H1: 500 runs

Effect Estimate



Effect SE



Power