PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	ENACT (ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy): A randomised controlled trial of an innovative intervention for infants at risk of Autism Spectrum Disorder
AUTHORS	Whittingham, Koa; McGlade, Andrea; Kulasinghe, Kavindri; Mitchell, AE; Heussler, Honey; Boyd, Roslyn

VERSION 1 – REVIEW

REVIEWER	Lonnie Zwaigenbaum University of Alberta, Canada
REVIEW RETURNED	26-Oct-2019

GENERAL COMMENTS	Well-written summary of protocol for promising RCT of novel intervention for at-risk infants. Innovation includes target age group (<6 months), online delivery (cost-efficient, scalability) and application of 'Acceptance and Commitment Therapy'). Commendable effort to develop resilience by supporting parent-infant interactions. Several potential limitations in trial design, plus aspects that should further clarified, as follows: - Abstract should include more detail about the intervention (timing, intensity) - There is ambiguity in the primary outcome - bottom page 6 described as 'ASD symptomatology scores at 6 and 12 months' based on AOSI and Gap-Overlap task, whereas in description of Child Assessments (and Consort flow chart), AOSI is described as being administered at only 12 months. Published data would support the AOSI as a measure of ASD symptoms at 12 months, but not 6 months. Should also provide further detail re: Gap-Overlap task (e.g., what visual stimuli will be used?) - pg 7. no specific rationale for some of the hypothesized secondary outcomes (e.g., motor skills, visual reception skills). Hypothesis 9 relating movements assessed by the GMA at 3 months to the 12-month outcomes seems unrelated to the trial. - pg 10: should include rationale for limiting participation to mothers, who would then 'target' or teach other caregivers, including the father. - Statistical Analysis plan would benefit from further detail. For example, GLM or ANCOVA is proposed as 'standard methods'. What covariates would be incorporated? Any assessment of whether criteria met for parametric analyses, or whether transformation of data would be considered if not met? - Should add discussion of potential study limitations. Anticipated effect size may be optimistic, particularly given 'high-risk' design (i.e., a minority of participants anticipated to develop symptoms). Fidelity of clinicians but not of parents assessed, and degree to which intervention strategies implemented by mothers (and other

	caregivers) at home not assessed. Relatively heavy assessment burden on participants (in person assessments and questionnaires); should measure completion rates.

REVIEWER	Xiaoyi Hu Beijing Normal University, China ASD
REVIEW RETURNED	04-Nov-2019

GENERAL COMMENTS	1. The introduction should not so focus on the identification of ASD, instead, the authros should introduce more about this project, namely, the ENACT. More information on ACT of parents training should be elaborated. 2. The intervention/teachign content and fidelity of the intervention program should be more explained in the procedure. 3. The baseline assessments should include more on ACT knowledge or ACT parenting. Parenting behaviors/practices should also be included.

REVIEWER	Melanie Palmer King's College London, Institute of Psychiatry, Psychology & Neuroscience London, UK
REVIEW RETURNED	11-Nov-2019

GENERAL COMMENTS	The manuscript reports a study protocol for a randomised controlled trial of a novel parent-mediated intervention which aims to improve social reciprocity between parents and their infants who are at familial risk of autism, as well as supporting parental mental health and the parent-infant relationship. The novel intervention will be compared to care as usual. The trial will contribute to literature on interventions for children at increased risk of autism by intervening early during infancy to change trajectories in autism development. This is an important area of intervention given the increased rates of siblings of autistic children who later are diagnosed with autism themselves, and the substantial impact on the children and their families. The study protocol was well written and clear and the authors should be commended for their inclusion of a range of outcomes (including some blinded) from multiple informants. The manuscript could be further strengthened by including additional details on some of the procedures to understand exactly how these would be implemented. Comments on specific procedures are below: • The authors describe the use of four different primary outcome measures (the AOSI, the Gap-Overlap, the DASS-21 and the AAQ-II). The authors may want to consider including a rationale for the four different primary outcome measures. In addition, the power analysis appears to be based only on change on the AOSI. It was unclear how this would be accounted for and interpreted in the analyses for all the primary outcomes. • For the parent-infant interaction measure, it was unclear how this measure would be administered. Was the interaction conducted in the home? What will the parent be asked to do with their infant during this interaction? Will the observations be recorded and coded from videotape or live coded? Are the EAS scales used to assess the quality of the interaction scored on a Likert scale? • For hypothesis 4, further details about the timepoints of

	measurement would be helpful here. Do the authors expect to see higher scores for cognitive development and adaptive behaviour at both 6 and 12 months for infants in ENACT in comparison to the CAU? This same comment applies for hypotheses five, six and seven. • For hypothesis nine, was a power calculation performed to explore whether the sample size was sufficient for this mediation analysis? • On page 8, the authors note that the trial is a pilot and it is common for data on the feasibility to conducting the trial to be reported in pilots. Will details on the feasibility be included? • In relation to the inclusion criteria, is there an age range for the biological siblings with autism and are there any criteria on the verbal ability (i.e. verbal and minimally verbal) of the sibling? It is possible that the verbal ability of the sibling may impact on intervention implementation? The authors may also like to consider adding how infant twins would be treated in terms of inclusion. Would one twin be randomly selected? • Further information on the randomisation process would also strengthen the manuscript. For example, who is randomisation done by and what is the process for informing the therapists and families of allocation to ensure researchers remain blind? Is it done using an online system? Is allocation to intervention on a 1:1 ratio? It was also unclear why blocked randomisation was being used and what the number of participants was within each block. • There were aspects about the ENACT interventions that could also be clarified in the manuscript. Were the fortnightly sessions with the clinicians conducted via the phone? The authors also state the mothers will be encouraged to initiate a sensitivity chain during consultation for the clinician's direct observation and feedback– will these consultations be individual home based sessions? A table displaying the different components and number and timepoints of consultation may help with understanding these details of the intervention. • For the measure of fidelity, the authors may like to consider adding further information on what exactly fidelity will cover (e.g. content, process). Will details of any other interventions received by the families be recorded? • For the primary analysis of the Gap-Overlap, it was unclear what exactly would be used as the primary outcome measure. Is it the difference in time between 6-12 months on this measure? • The authors also state that a comparison group of low risk infants will be recruited and assessed to aid with interpretation of scores on the AOSI, the Gap-Overlap task and the HINE. The authors might like to include information on how these families would be recruited and criteria used to assess whether they are low risk. • Further detail about the statistical analyses planned would also further strengthen the manuscript. For example, which variables will be used as co-variates in the analysis, how will missing data be treated? • The authors state that as this is a low risk trial, a data monitoring committee was not required. Did the authors use a trial steering committee to oversee the conduct of the trial? • In relation to the measurement of adverse events, which specific events will be recorded and at which time points? • The authors state that the efficacy of the intervention will be tested. Throughout the manuscript the authors may like to consider referring to this as pilot efficacy.

REVIEWER	Mayada Elsabbagh McGill University, Canada

REVIEW RETURNED	18-Nov-2019

GENERAL COMMENTS	The proposed protocol is innovative and has the potential to add new knowledge to an area where little research has been done to date. The following suggestions are intended to enhance reporting quality and capacity of the trial to yield solid and interpretable findings: - Background: The intro mentions that 6 studies have been done and the findings need to be reviewed and presented (including null results). It is important to understand current gaps and inconsistencies in the literature. The small number of existing studies allows for a thorough synthesis of past results. - Rationale: Previous studies with the same population were mostly parent mediated interventions. The adaptation of ACT approaches to this population is novel but it's unclear if the proposed approach is another parent-mediated intervention, i.e., targeted intervention for the child delivered through the parent or alternatively an intervention for parents' mental health. These are very different models that would motivate divergent designs and should be clearly distinguished. Another novel direction is delivery through and e-health platform. Here too, there is a need for a better review of existing literature and expected challenges. - Objectives & hypotheses: The sample size is under powered in so far as answering all of the questions included. A distinction needs to be made between hypotheses and exploratory analyses. Further, the hypotheses need to be simplified since some hypotheses phrased include multiple outcomes that are not logically related to each other. The authors present a nice mechanistic account in the introduction that can be used to improve selection and specificity of the hypotheses. - Participants: Recruitment through routine services is an asset. Exclusion criteria do not comment on cases with birth complications and/or those in NICU. The latter is another form of risk (in addition to familial risk) that should be considered as the experience of these families will be quite different. - The intervention: based on the description provided it appears that the intervention is comprehensive, covering parent mental health, parent-child interaction, daily challenges in sleep and feeding, psychoeducation, etc. This is fine but the mechanisms of intervention need to be clearer in so far as the target group is concerned. Also, the manuscript does not mention if the intervention is manualized. The criteria for fidelity can also be further detailed. - Measures: several measures differ from ones previously used in other studies, e.g., parent-child interaction coding. This is ok but it relates to the issue raised above regarding the importance of positioning this trial more clearly against existing ones. - One of the measures 'gap-overlap task' is an experimental one that differs from others in that it requires laboratory infrastructure. Also, the description of the task is not quite accurate. The 'gap effect' refers to the difference in the gap condition vs. a baseline task where a central stimulus disappears and a peripheral one appears immediately after. This facilitation effect is distinct from the overlap (or disengagement effect) that refers to the difference between a baseline and the overlap condition. Baseline measures are

	considered very important to measure in infants because there is a lot of variability in this early period. - Another concern is that most measures are parent report on infants' behavior which is a general limitation in this area of research in general given that the parents is mediating the intervention and also reporting on child outcomes. - Randomization: I am unclear if any factors are considered in randomization. These might include infant sex or any other child or family characteristics that are important to consider in this form of intervention - Analysis: I am unclear that GLM models are sufficient to address the complex set of variables included in the hypotheses. - Follow up: some studies show that positive intervention effects may be more distal, observed a few months post intervention. Is there a plan to measure such potential effects?

VERSION 1 – AUTHOR RESPONSE

Reviewer One

Well-written summary of protocol for promising RCT of novel intervention for at-risk infants. Innovation includes target age group (<6 months), online delivery (cost-efficient, scalability) and application of 'Acceptance and Commitment Therapy'). Commendable effort to develop resilience by supporting parent-infant interactions.
Our response: Thank-you.

Several potential limitations in trial design, plus aspects that should further clarified, as follows:

Abstract should include more detail about the intervention (timing, intensity)
Our response: We have added timing and intensity of the intervention to the abstract. It now reads:

'Intervention content is delivered online (approximately 8 hours) and supported by consultations (7+) with a clinician. Parents will perform the social reciprocity intervention with their child (30 minutes per day).''

There is ambiguity in the primary outcome - bottom page 6 described as 'ASD symptomatology scores at 6 and 12 months' based on AOSI and Gap-Overlap task, whereas in description of Child Assessments (and Consort flow chart), AOSI is described as being administered at only 12 months. Published data would support the AOSI as a measure of ASD symptoms at 12 months, but not 6 months. Should also provide further detail re: Gap-Overlap task (e.g., what visual stimuli will be used?)
Our response: We are using the AOSI at 12 months only. We have corrected this in text. We have also provided detail about the visual stimuli used in the Gap-Overlap task which reads:

'A mix of social and non-social stimuli will be used.'

pg 7. no specific rationale for some of the hypothesized secondary outcomes (e.g., motor skills, visual reception skills). Hypothesis 9 relating movements assessed by the GMA at 3 months to the 12-month outcomes seems unrelated to the trial.
Our response: As we describe in the Introduction, non-specific markers in infants at high-risk of ASD include motor delays, poor visual reception, language delays, regulatory difficulties, and changes in eye gaze at 6-12 months. These markers may interact, leading to increasingly abnormal trajectories of infant development. Our intervention is designed to improve developmental outcomes for high-risk

infants, making these important secondary outcomes to assess. We agree that Hypothesis 9 does not relate to assessment of intervention effect and it has now been removed.

pg 10: should include rationale for limiting participation to mothers, who would then 'target' or teach other caregivers, including the father.
Our response: Participation is not limited to mothers. Rather, we are recruiting mothers. Fathers and other caregivers are free to participate. We have changed our wording to make this clearer. It now reads:

'The primary target for recruitment and the intervention will be the mother, who will act as conduit to each infant's caregiving system. Other caregivers (e.g. fathers, grandparents) will be given access to the ENACT edX course and will be welcome to participate in clinical consultations as applicable. Mothers will also be encouraged to teach all other significant caregivers the sensitivity chain intervention via direct demonstration.'

Statistical Analysis plan would benefit from further detail. For example, GLM or ANCOVA is proposed as 'standard methods'. What covariates would be incorporated? Any assessment of whether criteria met for parametric analyses, or whether transformation of data would be considered if not met?
Our response: The baseline variables will be entered as covariates. As is usual, the criteria for parametric analyses will be taken into account, and transformation considered if appropriate. We have added the following to the manuscript:

'Assumptions for parametric analyses will be assessed. Baseline scores will be included as covariates. Missing data will be handled using pro-rating and/or estimation maximisation depending upon the assessment and pattern of missingness.'

Should add discussion of potential study limitations. Anticipated effect size may be optimistic, particularly given 'high-risk' design (i.e., a minority of participants anticipated to develop symptoms). Fidelity of clinicians but not of parents assessed, and degree to which intervention strategies implemented by mothers (and other caregivers) at home not assessed. Relatively heavy assessment burden on participants (in person assessments and questionnaires); should measure completion rates.
Our response: We have now added a brief Discussion section to acknowledge these (and other) potential limitations. It reads:

'Potential limitations include recruitment and retention of parents with significant caregiving responsibilities; possible over-estimation of anticipated effect size; substantial burden of assessment for mothers; use of parent-report measures of infant regulation; and limited ability to assess day-to-day intervention implementation by mothers in the home environment.'

Reviewer Two

The introduction should not so focus on the identification of ASD, instead, the authors should introduce more about this project, namely, the ENACT. More information on ACT of parents training should be elaborated.
Our response: Thank-you for this suggestion. While we would be happy to provide detail regarding the theoretical foundation and content of the ACT component of the intervention in the Introduction, tight word limits preclude the addition of further detail. The ENACT intervention is, however, described in detail in the Methods section. Given that ENACT is a very early intervention for infants at risk of ASD, we consider the ASD literature as presented to be crucial to understanding the rationale for the intervention and the overall project.

The intervention/teaching content and fidelity of the intervention program should be more explained in the procedure.
Our response: The processes for ensuring intervention fidelity are explained in detail. In specific it says:

'The study clinician will receive clinical supervision from Dr Koa Whittingham to support fidelity. Course completion will be checked by the clinician. Clinical consultations will follow a specific protocol and will be recorded; 20% will be checked for fidelity against the protocol.'

The baseline assessments should include more on ACT knowledge or ACT parenting. Parenting behaviors/practices should also be included.
Our response: The AAQ-II is a measure of psychological flexibility, the main clinical target of ACT. It is included in the baseline assessments. Parenting practices are not relevant until after the child is born. The particular parenting construct measured is emotional availability and it is measured by questionnaire at 3, 6 and 12 months and by observation at 6 months. Thus, we include well-validated and widely-used self-report and objective assessments of parenting behaviour.

Reviewer Three

The manuscript reports a study protocol for a randomised controlled trial of a novel parent-mediated intervention which aims to improve social reciprocity between parents and their infants who are at familial risk of autism, as well as supporting parental mental health and the parent-infant relationship. The novel intervention will be compared to care as usual. The trial will contribute to literature on interventions for children at increased risk of autism by intervening early during infancy to change trajectories in autism development. This is an important area of intervention given the increased rates of siblings of autistic children who later are diagnosed with autism themselves, and the substantial impact on the children and their families. The study protocol was well written and clear and the authors should be commended for their inclusion of a range of outcomes (including some blinded) from multiple informants. The manuscript could be further strengthened by including additional details on some of the procedures to understand exactly how these would be implemented.
Our response: Thank-you.

Comments on specific procedures are below:
The authors describe the use of four different primary outcome measures (the AOSI, the Gap-Overlap, the DASS-21 and the AAQ-II). The authors may want to consider including a rationale for the four different primary outcome measures. In addition, the power analysis appears to be based only on change on the AOSI. It was unclear how this would be accounted for and interpreted in the analyses for all the primary outcomes.
Our response: We agree that this was unclear. We have shifted H2 **(**Better scores on measures of parents' mental health as assessed on the Depression Anxiety and Stress Scales (DASS-21) and the Acceptance and Action Questionnaire (AAQ-II)) to the secondary outcomes. Now we have a single hypothesis for primary outcomes which is: lower scores for ASD symptomatology at 12 months of age as assessed on (a) the AOSI and (b) the Gap-Overlap task.

For the parent-infant interaction measure, it was unclear how this measure would be administered. Was the interaction conducted in the home? What will the parent be asked to do with their infant during this interaction? Will the observations be recorded and coded from videotape or live coded? Are the EAS scales used to assess the quality of the interaction scored on a Likert scale?
Our response: The interaction will be conducted in the family's home and the parent will be asked to interact as they normally would. The observations will be recorded. The EAS is not a Likert scale. Further details have been added to the manuscript and read:

'The parent-child interaction will occur in the family's own home, with the parent instructed to interact with their child as they normally would. The observations will be recorded via the videoconferencing software Zoom.'

For hypothesis 4, further details about the timepoints of measurement would be helpful here. Do the authors expect to see higher scores for cognitive development and adaptive behaviour at both 6 and 12 months for infants in ENACT in comparison to the CAU? This same comment applies for hypotheses five, six and seven.
Our response: The time points for all assessments have been added to all of the hypotheses.

For hypothesis nine, was a power calculation performed to explore whether the sample size was sufficient for this mediation analysis?
Our response: Hypothesis nine is highly exploratory and does not relate to the testing of the intervention. We have deleted it from the manuscript for clarity.

On page 8, the authors note that the trial is a pilot and it is common for data on the feasibility to conducting the trial to be reported in pilots. Will details on the feasibility be included?
Our response: As noted in our response to Reviewer 1, we recognise that the aims and design of the current trial deviate from the accepted definition of a pilot study, and this term has now been removed. We will, however, be reporting on the feasibility of all aspects of the trial, including participant recruitment and retention, intervention delivery and acceptability, parental engagement, and satisfaction.

In relation to the inclusion criteria, is there an age range for the biological siblings with autism and are there any criteria on the verbal ability (i.e. verbal and minimally verbal) of the sibling? It is possible that the verbal ability of the sibling may impact on intervention implementation? The authors may also like to consider adding how infant twins would be treated in terms of inclusion. Would one twin be randomly selected?
Our response: There is no age range or criteria for the biological sibling. We are unsure why the verbal ability of the sibling might impact on intervention implementation. Unless the reviewer is referring to the burden on the parent? That will vary due to a number of reasons. If infant twins enrol, one will be randomly selected as the participant (with the family free to implement the intervention for both).

Further information on the randomisation process would also strengthen the manuscript. For example, who is randomisation done by and what is the process for informing the therapists and families of allocation to ensure researchers remain blind? Is it done using an online system? Is allocation to intervention on a 1:1 ratio? It was also unclear why blocked randomisation was being used and what the number of participants was within each block.
Our response: Block randomisation is used to ensure approximately even numbers across groups. Only the outcome assessors will be blind to allocation, not all of the researchers. The randomisation process will be done via the research software REDcap and this has been added, so that it now reads:

'computer-generated block randomisation will then be used to randomise families (1:1) to intervention or CAU via REDcap.'

There were aspects about the ENACT interventions that could also be clarified in the manuscript. Were the fortnightly sessions with the clinicians conducted via the phone? The authors also state the mothers will be encouraged to initiate a sensitivity chain during consultation for the clinician's direct observation and feedback– will these consultations be individual home based sessions? A table displaying the different components and number and timepoints of consultation may help with understanding these details of the intervention.
Our response: All the consultations will be conducted through videoconferencing using the platform Zoom, thus allowing for live demonstrations. Including a table displaying the different components of the intervention with timepoints is an excellent idea and we have added such a table (Table 1, p.20).

For the measure of fidelity, the authors may like to consider adding further information on what exactly fidelity will cover (e.g. content, process). Will details of any other interventions received by the families be recorded?
Our response: Fidelity will cover both content and process – this is now made explicit on p.10. There are no other very early interventions for ASD as part of standard care; however, we will ask families about any other services sought or received at the conclusion of the follow-up period.

For the primary analysis of the Gap-Overlap, it was unclear what exactly would be used as the primary outcome measure. Is it the difference in time between 6-12 months on this measure?
Our response: Yes, the difference in overlap response time from 6 to 12 months will be the outcome. Where the gap effect is greater at 12 months than at 6 months, infants are at greater risk of later diagnosis of ASD. We hypothesise that intervention infants will show greater ease of disengagement and greater reduction in gap effect (reaction time at overlap minus reaction time at gap) on the Gap-Overlap task at 12 months in comparison to 6 months of age. The wording of the hypothesis has been changed for clarity and it now reads:

"H1**:** Lower scores for ASD symptomatology at as assessed on (a) the AOSI[57 58] at 12 months and (b) the greater ease of disengagement and greater reduction in the gap effect (reaction time at overlap minus reaction time at gap) on the Gap-Overlap task at 12 months in comparison to 6 months[59 60]."

The authors also state that a comparison group of low risk infants will be recruited and assessed to aid with interpretation of scores on the AOSI, the Gap-Overlap task and the HINE. The authors might like to include information on how these families would be recruited and criteria used to assess whether they are low risk.
Our response: The low risk infant would need to have no first degree relatives diagnosed with ASD, be born at term and have no other known developmental risk. The comparison group will be recruited through social media and word of mouth. We have added the following to the manuscript:

'To participate, the low risk infant would need to have no first degree relatives diagnosed with ASD, be born at term and have no other known developmental risk. The comparison group will be recruited through social media and word of mouth.'

Further detail about the statistical analyses planned would also further strengthen the manuscript. For example, which variables will be used as co-variates in the analysis, how will missing data be treated?
Our response: The baseline variables will be added as co-variates. A missing data analysis will be conducted and missing data will be handled through a pro-rating and/or estimation maximisation depending upon the assessment and pattern of missing data. It reads:

'Missing data will be handled using pro-rating and/or estimation maximisation depending upon the assessment and pattern of missingness.'

The authors state that as this is a low risk trial, a data monitoring committee was not required. Did the authors use a trial steering committee to oversee the conduct of the trial?
Our response: No, this trial does not have a steering committee. It is being conducted by two PhD scholars under the supervision of a team of experienced senior academics and specialist clinicians. This has been approved by the ethics review committees.

In relation to the measurement of adverse events, which specific events will be recorded and at which time points?
Our response: Any adverse events that come to light in the conduct of the trial will be recorded at the point at which they present. In particular, this trial may detect adverse developmental outcomes for the infant. We have added clarification and it now reads:

'Any adverse events, particularly negative developmental outcomes, will be recorded and reported to the ethics committees and in the published results.'

The authors state that the efficacy of the intervention will be tested. Throughout the manuscript the authors may like to consider referring to this as pilot efficacy.
Our response: As noted in our earlier response, we recognise that the aims and design of the current trial deviate from the accepted definition of a 'pilot' study, and this term has now been removed. The current trial does in fact aim to test the efficacy of this intervention.

Reviewer Four

The proposed protocol is innovative and has the potential to add new knowledge to an area where little research has been done to date.
Our response: Thank-you.

The following suggestions are intended to enhance reporting quality and capacity of the trial to yield solid and interpretable findings:

Background: The intro mentions that 6 studies have been done and the findings need to be reviewed and presented (including null results). It is important to understand current gaps and inconsistencies in the literature. The small number of existing studies allows for a thorough synthesis of past results.

Our response: While we would be happy to include a narrative synthesis of this group of studies in our Introduction, word limits preclude further elaboration. We are happy to take the editor's advice on this point.

Rationale: Previous studies with the same population were mostly parent mediated interventions. The adaptation of ACT approaches to this population is novel but it's unclear if the proposed approach is another parent-mediated intervention, i.e., targeted intervention for the child delivered through the parent or alternatively an intervention for parents' mental health. These are very different models that would motivate divergent designs and should be clearly distinguished. Another novel direction is delivery through and e-health platform. Here too, there is a need for a better review of existing literature and expected challenges.
Our response: ENACT incorporates both (1) a very early intervention for the infant that is parent-meditated and (2) a mental health intervention for the parent. The blending of early intervention for a child with mental health support for the parent is a key strength of our intervention approach. A discussion of the advantages and challenges of intervention delivery via e-health is beyond the scope of this protocol paper.

Objectives & hypotheses: The sample size is under powered in so far as answering all of the questions included. A distinction needs to be made between hypotheses and exploratory analyses. Further, the hypotheses need to be simplified since some hypotheses phrased include multiple outcomes that are not logically related to each other. The authors present a nice mechanistic account in the introduction that can be used to improve selection and specificity of the hypotheses.
Our response: The hypotheses are grouped according to construct, rather than specific assessment. We have changed H2 to a secondary hypothesis so that the primary hypothesis is now clear.

Participants: Recruitment through routine services is an asset. Exclusion criteria do not comment on cases with birth complications and/or those in NICU. The latter is another form of risk (in addition to familial risk) that should be considered as the experience of these families will be quite different.
Our response: Cases of birth complications and time spent in the NICU would not be excluded. We anticipate that there may be some incidental recruitment, however, they will not be targeted.

The intervention: based on the description provided it appears that the intervention is comprehensive, covering parent mental health, parent-child interaction, daily challenges in sleep and feeding, psychoeducation, etc. This is fine but the mechanisms of intervention need to be clearer in so far as the target group is concerned. Also, the manuscript does not mention if the intervention is manualized. The criteria for fidelity can also be further detailed.
Our response: The core mechanism in terms of impact on the infant is via the sensitivity chain practice, as a very early intervention. The other components, including parental mental health support and support around daily challenges in sleep and feeding, are intended to better support the parent in applying the sensitivity chain intervention. The intervention is partly via edX. The clinician consultations will focus on supporting the parent in regularly practicing the sensitivity chains, drawing upon ACT as relevant. A simple yet flexible manual will be followed.

Measures: several measures differ from ones previously used in other studies, e.g., parent-child interaction coding. This is ok but it relates to the issue raised above regarding the importance of positioning this trial more clearly against existing ones.
Our response: As stated in the previous point, while we would be happy to include a narrative synthesis of this group of studies in our Introduction, word limits preclude further elaboration. We are happy to take the editor's advice on this point.

One of the measures 'gap-overlap task' is an experimental one that differs from others in that it requires laboratory infrastructure. Also, the description of the task is not quite accurate. The 'gap effect' refers to the difference in the gap condition vs. a baseline task where a central stimulus disappears and a peripheral one appears immediately after. This facilitation effect is distinct from the overlap (or disengagement effect) that refers to the difference between a baseline and the overlap condition. Baseline measures are considered very important to measure in infants because there is a lot of variability in this early period.
Our response: There is some variation in nomenclature across researchers. We are defining the gap effect as the gap-overlap condition, based on the research of Cousijns et al (2017) who compared the psychometric properties of the baseline-overlap condition to the gap-overlap condition.

Another concern is that most measures are parent report on infants' behavior which is a general limitation in this area of research in general given that the parents is mediating the intervention and also reporting on child outcomes.
Our response: This study contains a number of significant assessments that are not parent-report, namely: the Autism Observation Schedule in Infants *(*AOSI), the Gap-Overlap, the Hammersmith Infant Neurological Examination (HINE), the Mullen Scales of Early Learning (MSEL), the General Movements Assessment (GMA) and the Emotional Availability Scales (EAS) observational assessment. However, reliance on parent-report measures for infant regulation is a potential limitation, and this has been added to the Discussion, and reads:

'Potential limitations include recruitment and retention of parents with significant caregiving responsibilities; possible over-estimation of anticipated effect size; substantial burden of assessment for mothers; use of parent-report measures of infant regulation; and limited ability to assess day-to-day intervention implementation by mothers in the home environment.'.

Randomization: I am unclear if any factors are considered in randomization. These might include infant sex or any other child or family characteristics that are important to consider in this form of intervention
Our response: Our randomisation procedures employ blocked randomisation without stratification. As the reviewer notes, there are numerous factors that could be used to stratify this type of sample. Post-hoc analyses may be used to compare intervention effects for different subgroups depending on the distributions of the final sample.

Analysis: I am unclear that GLM models are sufficient to address the complex set of variables included in the hypotheses.
Our response: We do not anticipate the need for complex models to test our hypotheses, which primarily comprise continuous-level variables; we will, or course, be able to commit to a final plan for analyses once the final sample size and distributions on outcome variables are known.

Follow up: some studies show that positive intervention effects may be more distal, observed a few months post intervention. Is there a plan to measure such potential effects?
Our response: Intervention effects will be assessed at 3, 6, and 12 months of age. Although intermittent clinician contact continues until infants are 10 months of age, the online ENACT intervention is intended to be completed by the time infants are 8 weeks old; thus, the 6- and 12-month assessment timepoints are situated approximately 4- and 10-months post-completion of ENACT, respectively, to allow for the assessment of the effects to which the reviewer refers.

VERSION 2 – REVIEW

REVIEWER	Lonnie Zwaigenbaum University of Alberta
REVIEW RETURNED	27-Mar-2020

GENERAL COMMENTS	Outstanding manuscript describing novel intervention targeting very young infants at risk of ASD due to positive family history. The manuscript is extremely well-written, providing a thorough review of the relevant literature (see one question below), the study protocol is clearly described, and has several strengths including novel age focus, strong theoretical foundation, and online delivery platform potentially making the intervention highly cost-efficient and scalable. There are several minor points that should be addressed for further clarity, summarized below. 1. Page 6, para 1: the authors state, 'Poor maternal mental health contributes to poorer long-term outcomes for infants, including those at risk of ASD (37)'. However, ref 37 is a study of older preschool children. Please change the reference or clarify the point.

	2. Page 8 (Methods Section) a. Although the abstract/intro refers repeatedly to the intervention targeting 'infants in the first 6 months', there should be a clearer statement of age in the Methods section (e.g., as part of eligibility criteria). Sorry if I've missed this. b. In reference to the summary of 'strengths and limitations' below the abstract, there does not appear to be a specific measure of neurophysiology. There is a neurological exam and measures of regulation (parent report and focused on behavior), but not neurophysiology. Please clarify, for consistency. c. Re: 'care as usual' group; although it is reasonable to assume few parents in this group will have access to community interventions, would the authors consider collecting some simple data to confirm? d. Inclusion criteria – while there is unique value in including mothers diagnosed with ASD, consider whether there may be implications for collapsing data with other participating mothers who do are not diagnosed. e. Consider describing intervention study in ref 30 in Introduction, so reader can judge similarity to current protocol f. Please add detail regarding training/supervision model for the therapists; relevant to summary point re: strengths related to cost and scalability 3. Page 10: 'Consumer feedback sought' – should comment further (i.e., was feedback obtained that influenced the study protocol?) 4. Page 15: there should be further consideration of potential risk for psychological harm to parents. I agree that a Safety Monitoring Committee is not needed, but there is potential anxiety that could be generated regarding focus on risk status, difficulties learning the intervention techniques etc. Could there be some assessment via post-treatment debrief interview? It is reasonable to consider whether there is risk of both potential benefit but also risk to parent mental health. 5. Page 22: Should provide full reference for ref 58.

REVIEWER	Xiaoyi Hu Beijing Normal University, China
REVIEW RETURNED	20-Feb-2020

GENERAL COMMENTS	I think this round of revision address all the points I mentioned. I think it can benefit the ACT audience with ASD.

REVIEWER	Melanie Palmer King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK
REVIEW RETURNED	16-Mar-2020

GENERAL COMMENTS	The authors have responded to my previous comments in a thoughtful and through way with the addition of further details about outcome measurement and administration of measures. This has enabled the reader to have a greater understanding of what procedures will be completed when. As this is the first trial of the ENACT therapy, it may be helpful for the authors to also report on feasibility of the trial (e.g. recruitment, completion rates and acceptability of measures, ease of administration of measures), to assist with the planning of possible future trials of ENACT or other similar interventions. I wish the authors all the best in conducting the study and look forward to reading the results in due course.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

I think this round of revision address all the points I mentioned. I think it can benefit the ACT audience with ASD.

Our response: Thank-you.

Reviewer: 3

The authors have responded to my previous comments in a thoughtful and through way with the addition of further details about outcome measurement and administration of measures. This has enabled the reader to have a greater understanding of what procedures will be completed when. As this is the first trial of the ENACT therapy, it may be helpful for the authors to also report on feasibility of the trial (e.g. recruitment, completion rates and acceptability of measures, ease of administration of measures), to assist with the planning of possible future trials of ENACT or other similar interventions. I wish the authors all the best in conducting the study and look forward to reading the results in due course.

Our comments: Thank-you. We will endeavour to report upon feasibility considerations as much as possible. Thank-you for this suggestion.

Reviewer: 1

Outstanding manuscript describing novel intervention targeting very young infants at risk of ASD due to positive family history. The manuscript is extremely well-written, providing a thorough review of the relevant literature (see one question below), the study protocol is clearly described, and has several strengths including novel age focus, strong theoretical foundation, and online delivery platform potentially making the intervention highly cost-efficient and scalable. There are several minor points that should be addressed for further clarity, summarized below.

Our response: Thank-you.

1. Page 6, para 1: the authors state, 'Poor maternal mental health contributes to poorer long-term outcomes for infants, including those at risk of ASD (37)'. However, ref 37 is a study of older preschool children. Please change the reference or clarify the point.

Our response: We have removed the reference to a study of older preschool children and replaced it with the following references that demonstrated the effect of maternal depression on infant development as well as the effect of maternal well-being on siblings of children with ASD. The changes are highlighted in text:

37. Field T. Infants of depressed mothers. Development and psychopathology 1992;4(1):49-66. doi: 10.1017/S0954579400005551 [published Online First: 2008/10/31]

38. Quintero N, McIntyre LL. Sibling Adjustment and Maternal Well-Being: An Examination of Families With and Without a Child With an Autism Spectrum Disorder. Focus Autism Other Dev Disabl 2010;25(1):37-46. doi: 10.1177/1088357609350367"

2. Page 8 (Methods Section)

a. Although the abstract/intro refers repeatedly to the intervention targeting 'infants in the first 6 months', there should be a clearer statement of age in the Methods section (e.g., as part of eligibility criteria). Sorry if I've missed this.

Our response: Thank-you. For clarity we have added the following sentence to the section describing recruitment:

‘Families will be recruited during pregnancy and up to the infant reaching 7 weeks corrected age then followed over the first 12 months.’

b. In reference to the summary of ‘strengths and limitations’ below the abstract, there does not appear to be a specific measure of neurophysiology. There is a neurological exam and measures of regulation (parent report and focused on behavior), but not neurophysiology. Please clarify, for consistency.

Our response: Agreed. We have amended the strengths and limitations section accordingly.

c. Re: ‘care as usual’ group; although it is reasonable to assume few parents in this group will have access to community interventions, would the authors consider collecting some simple data to confirm?

Our response: Thank-you. That is a good idea. We will do so.

d. Inclusion criteria – while there is unique value in including mothers diagnosed with ASD, consider whether there may be implications for collapsing data with other participating mothers who do are not diagnosed.

Our response: Thank-you. We will consider sub-group analyses as appropriate.

e. Consider describing intervention study in ref 30 in Introduction, so reader can judge similarity to current protocol

Our response: We have added the following sentence for further detail:

‘iBASIS-VIPP begins after the infant is 6 months of age and focuses on changing parent behaviour.’

f. Please add detail regarding training/supervision model for the therapists; relevant to summary point re: strengths related to cost and scalability

Our response: ENACT is designed to be delivered by clinicians with clinical training in ACT and experience in working with parents of children with neurodevelopmental disabilities. This has now been clarified. The clarification now reads:

‘ENACT is designed to be delivered by health professionals with relevant clinical experience in working with parents and in ACT, and could, if effective, be widely disseminated at little cost.’

‘The study clinician is experienced in working with families of children with neurodevelopmental disabilities, completed general training in ACT and also completed project-specific training via the ENACT intervention manual.’

3. Page 10: ‘Consumer feedback sought’ – should comment further (i.e., was feedback obtained that influenced the study protocol?)

Our response: We have added the following sentence to give further details:

‘Consumer feedback was positive, with some changes to wording made following input.’

4. Page 15: there should be further consideration of potential risk for psychological harm to parents. I agree that a Safety Monitoring Committee is not needed, but there is potential anxiety that could be generated regarding focus on risk status, difficulties learning the intervention techniques etc. Could there be some assessment via post-treatment debrief interview? It is reasonable to consider whether there is risk of both potential benefit but also risk to parent mental health.

Our response: It is important to note that this study does not inform parents that their infant may be at increased risk of developing ASD. Rather, families are already aware of their infant’s at risk status, in most cases, even before conception. Parental mental health is measured throughout the study and informally monitored via sessions with the intervention clinician; parents with mental health concerns will be contacted and advised on how to seek support relevant to their needs and circumstances.

5. Page 22: Should provide full reference for ref 58.

Our response: This reference has been corrected and the changes are highlighted in the reference list. It now reads as:

"Bryson S, Zwaigenbaum L. Autism Observation Scale for Infants. In Patel V, Preedy V, Martin C (eds) Comprehensive Guide to Autism: Springer, New York, NY 2014:299-310."

Thanks again for the opportunity to provide revisions.

VERSION 3 – REVIEW

REVIEWER	Lonnie Zwaigenbaum University of Alberta
REVIEW RETURNED	07-May-2020

GENERAL COMMENTS	No further concerns. Many thanks to the authors for their careful attention to the previous set of reviews. Excited to see this trial move forward, and appreciate the authors sharing the details of their innovative trial.