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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

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Title page
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Title page
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Title page

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6-7
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Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	17, figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10-11
	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10-11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
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Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-14
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Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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

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Running head: ENACT (ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy)

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Declaration of Interest:
None

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Author contributions All authors contributed to the conception and design of this study. All authors contributed to drafting and critical revision of the manuscript. All authors approved the final version of the manuscript to be submitted for publication.

Abstract

Introduction: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition with impacts on behaviour, cognition, communication, social interaction and family mental health. This paper reports the protocol of a randomised controlled trial (RCT) of a very early intervention ENACT (ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy) for families of infants at risk of ASD.

Methods and analysis: We aim to recruit 66 mothers of infants at risk of ASD (i.e., infants with a sibling or parent diagnosed with ASD) to this randomised controlled trial (RCT). Families will be randomly assigned to care-as-usual or ENACT. ENACT is a very early intervention, leveraging parent-child interactions to improve early social reciprocity, while supporting parental mental health and the parent-child relationship through Acceptance and Commitment Therapy (ACT). Intervention content is delivered online, supported by consultations with a clinician. Parents will perform the social reciprocity intervention with their child. Assessments at four time points (baseline; 3 months, 6 months and 12 months corrected age) will assess parent-infant interaction, parental mental health, infant development and early ASD markers. Analysis will be by intention to treat using general linear models for RCTs.

Ethics and dissemination: This protocol has been approved by the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/19/QCHQ/50131) and The University of Queensland (2019000558). If efficacy is demonstrated, the intervention has the potential for wide and accessible dissemination.

Registration details: This trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618002046280p).

Article Summary

Strengths and Limitations of this study

- First RCT to test a very early intervention for infants at risk of ASD implemented within the first 6 months of life.
- ENACT combines parent-mediated very early intervention with parental mental health support.
- Assessment includes neurodevelopmental and neurophysiological assessments, as well as observations of parent-child interaction.
- ENACT could, if effective, be widely disseminated at little cost.

Keywords: Autism Spectrum Disorder, early intervention, maternal mental health, parent-infant interaction, infant development

Word count: 3871

INTRODUCTION

Autism Spectrum Disorder and the Broader Autism Phenotype

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition defined by difficulties in social communication and interaction, and repetitive, restricted interests and activities[1 2]. It evolves from a complex interaction between genes and environment[3 4], and has substantial impact on affected individuals, with 65% having a profound or severe activity limitation, needing help or supervision with communication, self-care and/or mobility[5]. Prevalence rates are 0.7% and 1.7-2.5% in Australia and the United States, respectively[5-7]. Diagnosis rests on developmental assessment and behavioural observations with most children 2 years or older at diagnosis[8].

Infant siblings of children with ASD are at an increased risk of ASD themselves, with prevalence estimates of 18-20% from baby sibling studies[9 10]. A further 25% show elevated scores on the Autism Diagnostic Observation Schedule (ADOS), developmental delays and lower adaptive functioning[11-13]. Prospective sibling studies have identified a range of non-specific markers in infants at high-risk of ASD, including motor delays, poor visual reception, language delays, regulatory difficulties and changes in eye gaze at 6-12 months that precede the appearance of autism-specific features in the second year of life[14-18]. The diversity of early markers precludes a single developmental pathway to ASD and has been called 'the first year puzzle'[19-23]. Non-specific developmental markers may interact leading to increasingly abnormal trajectories of infant development. Visual, motor and regulatory difficulties may impact on emerging attention and emotional regulation[19 24-26]. Differences in visual, motor and regulatory abilities at six months of age correspond in timing with changes in whole-brain functional connectivity on MRI studies[27 28]. At 6 months of age, functional connectivity on diffusion tensor imaging MRI correctly predicted 9 of 11 infants that went on to be diagnosed with ASD at 24 months of age[29]. These findings support the conjecture that the developmental cascade leading to ASD begins early, *within the first six months of life*[28].

To date, six randomised controlled trials (RCTs) have tested parent-mediated early interventions with infants at risk of ASD implemented in the first 18 months, prior to confirmed ASD diagnosis[30-36]. Only one of these, an RCT of iBASIS-VIPP conducted with 54 infants at high familial risk of ASD recruited at 7-10 months of age has demonstrated sustained reduction of ASD related symptoms, but no change in the diagnostic outcome at 3 years[30 34]. To date, no RCT has commenced with at-risk infants *younger than six months of age*, before earliest ASD markers and commencement of the cascade.

ASD in the Family Context

Poor maternal mental health contributes to poorer long-term outcomes for infants, including those at risk of ASD[37]. Parents of children with ASD are at increased risk for depression and anxiety[38 39], both due to parenting challenges and pre-existing histories[40-42]. Parents of infants with ASD are more likely to have an ASD or the Broader Autism Phenotype (BAP)[43-46]. The BAP may include rigidity, aloofness, social and communication difficulties[46], with increased risk of depressive symptomatology, maladaptive coping and decreased social support[46].

Mental health difficulties can contribute to reductions in responsive parenting[47]. Responsive parenting— child-directed, contingent, prompt, and appropriate to the child's needs— is associated with better child outcomes[48 49]. Responsiveness is a dose-control system for environmental enrichment, enabling the child to obtain the necessary 'experience expectant development'[50 51]. If a child is difficult to read, sends atypical or unclear signals, as in ASD, it is more challenging for parents to cultivate responsive patterns of interaction[52].

By six months infants at risk of ASD may be showing an atypical style of interaction, with difficulty engaging in eye contact and joint attention[15 26 49 53 54]. Parent behaviour may shift towards intrusive parenting and high intensity approach behaviours in an attempt foster engagement and overcome the emerging social limitations of ASD[49 55]. The shift to directive parenting may impact further on the infant's social development[49 56]. Importantly, commencing parent focused intervention *prior to six months*, before the shift towards directive parenting, has not been tested.

Aim

To test the efficacy of ENACT (ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy) for families of infants at risk of ASD via an RCT comparing ENACT to care-as-usual (CAU). ENACT is a newly-developed, very early intervention that targets infants' social reciprocity through supported parent-infant interactions, while simultaneously supporting parental mental health and the parent-child relationship. ENACT commences prenatally.

Hypotheses

We predict that families allocated to ENACT will show better outcomes compared to families allocated to CAU in terms of having:

Primary outcomes

- H1**:** Lower scores for ASD symptomatology at 6 and 12 months of age, as assessed on (a) the AOSI[57 58] and (b) the Gap-Overlap task[59 60].

- 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)[61 62].

Secondary outcomes

- H3: Improved parent-infant interaction, with greater emotional availability and parental sensitivity, less parental intrusiveness, and greater child responsiveness, as assessed on the Emotional Availability Scales (EAS) Self-Report and Observed[63].
- H4: Higher scores on measures of (a) infants' cognitive development, assessed using the Mullen Scales of Early Learning- Early Learning Composite (MSEL-ELC; composite of the sub-domains of Visual Reception [VR], Fine Motor [FM], Receptive Language [RL] and Expressive Language [EL]),[64] and (b) infants' adaptive skills, assessed using the Vineland Adaptive Behaviour Scales Third Edition (VABS-3)[65].
- H5: Higher scores on measures of infants' (a) motor development (assessed using the Hammersmith Infant Neurological Examination; HINE[66 67]) and (b) fine and gross motor abilities (assessed using the MSEL)[68].
- H6: Higher scores on measures of infants' visual perceptual skills, assessed on the Visual Reception scores on the MSEL[24], and on symbolic cluster on the Communication and Symbolic Behaviour Scales – Developmental Profile (CSBS-DP)[69] and with reduced times on the Gap-Overlap task.
- H7: Higher scores on measures of infant language development, assessed by the Receptive Language and Expressive Language domains on the MSEL[70] and CSBS-DP[71].
- H8: Better scores on parent-report measures of infant regulation – specifically, (a) lower scores for Internalising and Externalising Behaviour, assessed on the Infant-Toddler Social and Emotional Assessment (ITSEA);[72] (b) lower scores on the Dysregulation scales of the ITSEA; (c) better sleep on the Brief Infant Sleep Questionnaire (BISQ);[73] and (d) less cry behaviours on the Crying Pattern Questionnaire (CPQ) at 3 and 6 months of age[74].

In addition, we will examine General Movements Assessment (GMA) as a predictor, testing the hypothesis that:

- H9: Infants who score as Absent Fidgety or Abnormal Fidgety on the GMA at 3 months of age (optimality scoring) will have a higher score on the AOSI at 12 months of age[75 76] and shorter latencies on the Gap-Overlap task[14]. Normal Fidgety movements on GMA will have a high negative predictive value for infants who do not go on to have ASD.

METHODS AND ANALYSIS

Design

The study is an RCT following CONSORT guidelines. After enrolment, and baseline assessments, mothers of infants at risk of ASD will be randomly allocated to intervention (ENACT) or CAU. Comparison to CAU is appropriate as ENACT is a newly developed intervention and this is a pilot trial. The CONSORT flow chart is depicted in Figure One.

[insert Figure One about here]

Recruitment

Families will be recruited via advertisements distributed through Queensland ASD family support groups, schools and clinics (e.g. Autism Queensland, AEIOU Foundation for Children with Autism, AspergerServices Australia, Minds and Hearts) and Queensland Health Antenatal and Child Development Clinics. Mothers will be recruited during the third trimester of pregnancy.

Inclusion criteria

Participants must meet the following inclusion criteria: (1) the infant must have one or more biological siblings or a biological parent (mother or father) diagnosed with ASD; (2) the mother must agree to the assessment requirements; (3) the mother must have reliable internet access (e.g. ADSL); and (4) the mother must have sufficient English to complete assessments.

Exclusion criteria

Any infant with known neurological or chromosomal disorder at the point of recruitment.

Sample size

The target number of participants is 66 (ENACT n=33, CAU n=33), which will provide power of 80% (two-tailed, α=0.05) to detect a difference between groups of 0.75 SD on the AOSI. In a previous study with a similar sample the observed SD=4;[30] consequently we should be able to observe a difference of ≥3 units in this study.

Blinding

Participants and intervention delivery facilitators cannot be blinded to group allocation. Assessors conducting the AOSI, Gap-Overlap task, MSEL and HINE assessments at 12 months CA will be blinded to group allocation, as will coders scoring the video/audio-recorded EAS observations, GMA, and Gap-Overlap task.

Care-as-Usual interventions for infants at risk of ASD

Participants allocated to CAU will receive usual postnatal care. As developmental and autism-related concerns generally present after 12 months of age, it is expected that any targeted interventions provided in the community by usual care providers will fall outside the timeframe of the study.

The ENACT Intervention

ENACT is a very early intervention targeting infant social reciprocity through supported parent-child interactions while simultaneously supporting parental mental health and the parent-child relationship using ACT. Core to ENACT is the social reciprocity intervention which teaches mothers to initiate and build sensitivity chains with their babies, with the goal that sensitivity chains become longer, increasingly complex and increasingly symbolic over time, and that the early social development of the infant is optimally supported. They should be mutually enjoyable, responsive and non-intrusive.

The three simple steps to building a sensitivity chain are for the mother to 1) stimulate an initial enjoyable interaction, 2) *wait* for the infant to signal their intent to continue, and 3) respond to the infant's signal, hence 'closing the loop' and building a link in the sensitivity chain. This will include a focus on: initially cultivating sensitivity chains through sensorimotor activities, using positive affect and predictable surprise to support the infant's involvement, maintaining reciprocal interactions withinfants with atypical responsiveness, and avoiding parental intrusiveness with atypically responsive infants. This intervention is specifically targeting the earliest documented abnormalities in social behaviour in infants at risk of ASD[77]. This aspect of the ENACT intervention was developed specifically for this trial by Andrea McGlade, with input from Koa Whittingham.

ENACT also incorporates parental mental health support grounded in ACT, including values, mindfulness, experiential acceptance and cognitive defusion (distancing from thoughts). The ACT component within ENACT draws from a previously trialled intervention[47]. ENACT also contains a small psychoeducation component on common early parenting challenges of sleep, crying and feeding, developed by Koa Whittingham[78]. This focusses on understanding the biological regulation of sleep via the circadian clock and the sleep-wake homeostat, understanding the developmental pattern of infant crying including the crying peak, and planning ahead on where to seek help for feeding challenges.

ENACT is delivered to mothers (i) via an online course (approximately 8 hours' duration) using the edX platform (www.edx.org/) and (ii) through telehealth (videoconferencing) consultations with a trained clinician. The edX course includes: videos and text explaining core concepts, interactive

exercises, multiple choice questions, and videos of real parent-and-baby interactions. The social reciprocity very early intervention is delivered to the infant through the mother and other caregivers. Intervention delivery to mothers will commence prenatally, and mothers will receive fortnightly sessions with the clinician to support consolidation of learning. Mothers will be encouraged to work through the edX course at their own pace, with completion before their babies reach 8 weeks of age.

Mothers will be encouraged to engage in regular practice of sensitivity chains, with a goal dose of 30 minutes per day/5 days per week from 2 weeks of age and throughout the first year (total dose approximately 125 hours). The social reciprocity intervention will be integrated into ordinary everyday interactions including feeding, nappy changes and playful interactions. Consultation sessions will be conducted when the infant is 4 weeks, 8 weeks, 12 weeks, 4 months, 6 months, 8 months and 10 months of age, with capacity for additional sessions as needed. Consultations will support mothers in finding opportunities to practice within everyday life, in tailoring interactions to their babies, and in adapting to their babies' developmental stage and skills. Mothers will be encouraged to initiate a sensitivity chain during the consultation, for the clinician's direct observation and feedback. In addition, clinical consultations will refer to ACT components, supporting maternal mental health throughout the first year. Clinical consultations will follow a specific protocol, and be recorded for fidelity.

The primary target for the intervention will be the mother, who will be encouraged to share ENACT with other caregivers (e.g. fathers, grandparents) and teach all other significant caregivers the sensitivity chain intervention through direct demonstration. The mother will therefore be used as a conduit to each infant's caregiving system.

Fidelity

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.

Patient and Public Involvement

Consumer feedback was sought on the protocol, the study forms and the intervention.

Study Procedure

Researchers will contact interested mothers to assess eligibility and provide detailed study information. Mothers will provide written consent prior to completing baseline assessments, and computer-

generated block randomisation will then be used to randomise families to intervention or CAU. Families allocated to intervention will receive immediate access to ENACT. Families allocated to CAU will receive routine antenatal and postnatal care.

Assessments will be conducted at baseline (prenatal), 3, 6, and 12 months CA. Parents will complete questionnaire measures online; mother-child relationship observations will be conducted via 20-minute video-recorded interactions; and child development assessments will be undertaken at [blinded for review] at 6 and 12 months of age. While completing ENACT, parents will be invited to provide feedback and suggestions for course improvement.

Measures

BASELINE ASSESSMENTS

The *Parent Questionnaire* collects (1) general demographic information (parent age, education, income, family composition) and (2) information relevant to the ASD context, such as parent health history, and details of the diagnosis of the first-degree relative (parent or sibling) with ASD. Further information regarding infant delivery, perinatal history, and feeding history will be collected postnatally by brief phone interview

The *Broad Autism Phenotype Questionnaire (BAPQ; 36-items)* assesses ASD-like features in adults through self-report or informant measure[79]. Participants rate how much each item applies to them on a 6-point Likert scale[80]. Internal consistency for the total scale is excellent (α=.95) and there is good inter-item reliability[80].

CHILD ASSESSMENTS

Autism symptomatology

The *Autism Observation Schedule in Infants (AOSI; 12 months)* will be the primary clinical outcome measure assessing intervention effect on infant development and severity of autism symptomatology at 12 months[58]. It is an experimenter-led, semi-structured observational assessment tool, developed for research purposes to study the emergence of ASD-related behavioural markers in infancy (6–18 months)[57 58]. Five standardised activities are delivered between two periods of free play, with a total of 18 items to be scored. Inter-rater reliability of total marker counts (number of items marked as atypical) and total scores, respectively, is good at 6 months (.68 and .74) and excellent at 12 months (.92 and .93)[57]. Test-retest reliability for total marker counts and total scores is fair to good at .68 and .61, respectively[57]. The AOSI differentiates between high-risk and low-risk infants at 12-14 months[81-83].

The *Gap-Overlap task (6 and 12 months)*[59] is used to assess visual attention by measuring differences in the efficiency of orienting towards peripheral stimuli. Two trial types will be contrasted: Gap and Overlap. In the Gap condition, an interval of 200-250ms separates the disappearance of the central stimulus and the appearance of the peripheral one (facilitation). In the Overlap condition, the central stimulus remains visible and overlaps with the peripheral stimulus. This measures the ability to disengage from a central stimulus and to orient to a peripheral one. This difference between the Gap and Overlap times is called the Gap effect. Gap-Overlap time, measured in milliseconds, decreases from 6 to 12 months for typically developing infants[15 84 85]. Infants who are later diagnosed with ASD consistently show an *increase* in Gap-Overlap time between 6 and 12 months of age[15 86 87]. This has been called 'sticky attention'. Test–retest reliability of the Gap-Overlap gap effect is r=.50 in infants at age 10 months[59].

Neurodevelopmental and motor assessments

The *Mullen Scales of Early Learning (MSEL; 6 and 12 months)* has been used in the cognitive assessment of infants and children from birth until 68 months of age[30 32 88-90]. The MSEL has five scales: Gross Motor [GM], Visual Reception [VR], Fine Motor [FM], Expressive Language [EL], and Receptive Language [RL], as well as an Early Learning Composite (ELC) score that is composed of the VR, FM, EL, and RL subscales. The MSEL has demonstrated convergent and divergent construct validity in infants and children with ASD[91-93]. Interrater reliability has been reported as high (r = .91-.99)[94].

The *General Movements Assessment (GMA; 3 months)* is a predictive and discriminative tool that assesses infants' spontaneous motor activity from pre-term to 20 weeks CA[95]. Scoring is completed from a videorecording with 2 full movement sequences required for pattern recognition (approximately 5 minutes)[95]. During the fidgety period from 9-20 weeks post-term, fidgety movements can be abnormal (exaggerated in amplitude and speed), sporadic (confined to a few body parts, never >3 seconds between 9-16 weeks CA), or absent (fidgety movements not present between 9-16 weeks CA) (optimality scoring)[95]. Abnormal fidgety movements that are absent or abnormal at 12-14 weeks C.A are highly predictive of cerebral palsy as well as other neurodevelopmental disabilities including ASD[75 76]. The Baby Moves app will be used to film the videos and transfer the videos for assessment. GMA will be scored by accredited blinded assessors.

The *Hammersmith Infant Neurological Examination (HINE; 6 and 12 months)* is a standardised clinical neurodevelopmental assessment for infants from 2-24 months of age[96]. The HINE contains 26 items across 5 domains, summed to provide a global optimality score, and can differentiate between low- and high-risk late preterm and term newborns at 6 and 12 months of age[97-99].

The *Vineland Adaptive Behaviour Scale (3rd ed.; VABS-III; 12 months)* is a standardised measure of adaptive behaviour, completed by caregivers and scored by a blinded assessor[65]. Standard scores are generated for the four domains (Communication, Daily Living Skills, Socialization, and Motor Skills) as well as a global score(Adaptive Behaviour Composite). It has good internal consistency, test–retest reliability, inter-interviewer reliability, and validity for young children including those with autism[65].

Infant regulation

The *Brief Infant Sleep Questionnaire (BISQ; 10-items; 3 and 6 months)* assesses parent-reported infant sleep patterns (nocturnal sleep duration, night waking and method of falling asleep), parent perception of infant sleep duration, and sleep-related (parent) behaviours for children from birth-36 months. It is well validated by comparisons with actigraphy, sleep diaries and caregiver-reported sleep[73 74].

The *Crying Patterns Questionnaire (CPQ; 6-items; 3 and 6 months)* is a parent-report measure assessing: (1) the amount and time of day when infant crying occurs; (2) situations in which crying occurs; (3) whether the mother finds the crying distressing and seeks advice and help; and (4) the mother's responses to crying. In comparison to 24 hour cry-fuss diaries kept by mothers, the CPQ showed moderate-to-good validity (.51-.68) for total duration of crying scores[74].

The *Infant Toddler Social & Emotional Assessment (ITSEA; 165-items; 12 months)* is a parent-report questionnaire used to assess social-emotional problems/competencies in the domains of behavioural dysregulation and competence. The ITSEA has established concurrent validity, strong test-retest reliability (α=.75-.91) and good internal reliability for each subscale (α=.86 for dysregulation, α=.87 for externalising, α=.85 for internalising, and α=.89 for competence)[100 101]. The ITSEA has been validated for 12 months CA and discriminates between low- and high-risk infants, particularly within the domain of dysregulation[72].

The Communication and Symbolic Behaviour Scales Developmental Profile (CSBS DP; 6 and 12 months) evaluates the symbolic abilities and communication skills of children aged 6-24 months[69]. It includes a 24-item Infant Toddler Checklist which is used as a developmental screening tool to detect

autism[102]. The CSBS DP has excellent internal consistency (α=.86-.92), good test-retest reliability and good construct and concurrent validity[69 103].

Mother-infant relationship

Emotional Availability Scales (EAS; 6 months). Coders blind to intervention condition will use the EAS to score 20-minute naturalistic observations of parent-child interactions[63]. The EAS is used to measure quality of parent-child relationships across six scales: parental sensitivity, parental structuring, parental non-intrusiveness, parental non-hostility, child responsiveness and child involvement[63]. The scales have high inter-rater reliability for the parent scales of sensitivity (.95), structuring (.87), non-intrusiveness (.81), non-hostility (.72) and the child scales of responsiveness (.87) and involvement (.87)[104].

The *Emotional Availability - Self Report* (*EA-SR; 36-items; 3, 6 and 12 months)* is a parent-report questionnaire used to measure emotional availability in a dyadic relationship across 5 subscales: Intrusiveness, Hostility, Mutual Attunement, Affect Quality and Capacity to Involve the Parent. Reliability ranges from .71-.84 for all subscales except affect quality (α=.49)[104]. All subscales (except for Intrusiveness) have moderate correlations with the corresponding EAS observed subscales, thus supporting the validity of the self-report measure[104 105].

Maternal mental health

The *Acceptance and Action Questionnaire (AAQ-II; 7-items; 3, 6 and 12 months)* is a self-report questionnaire measuring psychological flexibility, the key target of ACT[62]. The AAQ-II has good test-retest reliability and convergent validity and excellent internal consistency (α=.94)[62].

The *Depression Anxiety Stress Scales (DASS-21; 21-items; 3, 6 and 12 months)* assess symptoms of depression, anxiety, and stress in adults. The DASS-21 produces three subscales, each with good internal consistency: the Depression (α=.91-.97), Anxiety (α =.81-.92), and Stress (α=.88-.95) scales[106], and a Total score. The DASS-21 has good convergent validity and acceptable discriminative validity[106].

Comparison group

A comparison group of 30 healthy low risk infants will be recruited and assessed on the Gap-Overlap task and the HINE at 6 and 12 months, and the AOSI at 12 months. This comparison data will support the interpretation of results, particularly for the novel Gap-Overlap task.

Data Collection and Management

Data will be entered onto the REDCap database in a potentially individually identifiable format. Once de-identified, data will be stored in a re-identifiable format on a secure electronic database protected by the [blinded for review] secure server, and only accessible to members of the research team.

Statistical Analysis

Analysis (using STATA or SPSS) will follow standard methods for RCTs using comparisons between the two groups (e.g. general linear models, ANCOVA) and intention-to-treat analyses.

Monitoring

Data monitoring

As this is a trial of a very early intervention with low risk, a data monitoring committee is not required. Any adverse events will be recorded and reported in the published results.

Harms

This study should not pose risks beyond those of everyday living. Any participants experiencing undue psychological distress will be referred to their general practitioner. For infants scoring at high developmental risk on the GMA, HINE, MSEL or AOSI, infants' general practitioners/paediatricians and parents will be notified. All families will be sent a paediatrician's report detailing 12-month developmental assessment results.

ETHICS AND DISSEMINATION

ENACT should support mothers' mental health and may also support infant development. Ethical approval has been obtained ([blinded for review]) and the trial registered (Australian New Zealand Clinical Trials Registry, ACTRN12618002046280p). Study results will be disseminated through scientific journal publications and conference presentations. If shown to be effective, edX facilitates easy dissemination at minimal cost.

This study will test the efficacy of an innovative, very early intervention for infants at risk of ASD, integrating early social reciprocity intervention with parental mental health and parent-child relationship support.

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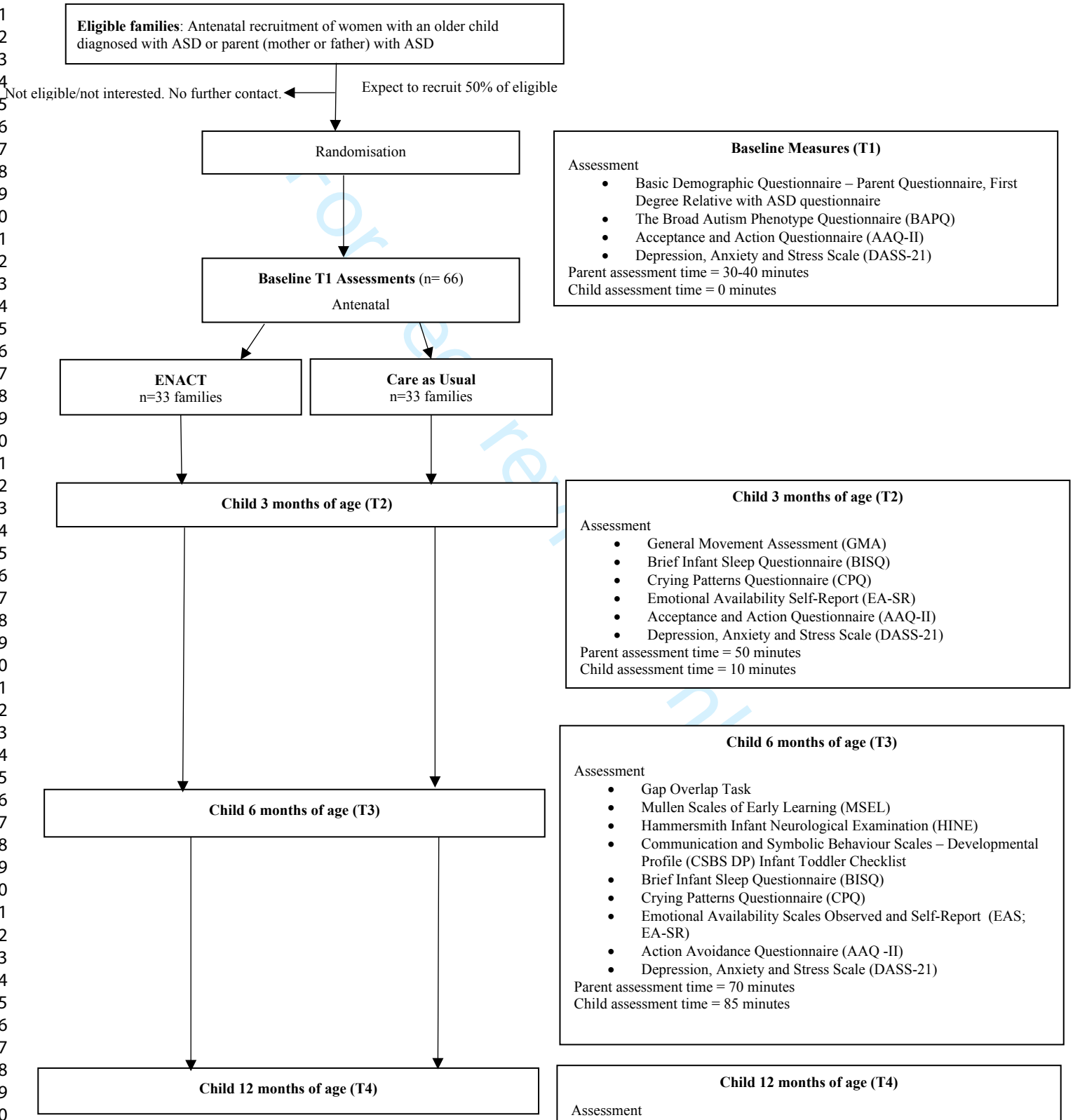
Competing Interests Statement: ENACT was developed from PACT, an intervention developed by researchers at The University of Queensland including Koa Whittingham and Roslyn Boyd. Andrea McGlade and Koa Whittingham developed the of the very early intervention component of edX. ENACT has been developed using the online platform edX.

Abbreviations:

AAQ-II	Acceptance and Action Questionnaire
ACT	Acceptance and Commitment Therapy
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
BAP	Broad Autism Phenotype
BISQ	Brief Infant Sleep Questionnaire
CA	Corrected age
CAU	Care as Usual
CSBS-DP	Communication and Symbolic Behaviour Scales – Developmental Profile
CPQ	Crying Pattern Questionnaire
DASS-21	Depression Anxiety Stress Scale
EAS	Emotional Availability Scales
EA-SR	Emotional Availability Scales – Self Report
EL	Expressive Language
ELC	Early Learning Composite
ENACT	ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy
FM	Fine Motor
GMA	General Movement Assessment
HINE	Hammersmith Infant Neurological Examination
ITSEA	Infant-Toddler Social and Emotional Assessment
MSEL	Mullen Scales of Early Learning
RCT	Randomised Controlled Trial
RL	Receptive Language
VABS-III	Vineland Adaptive Behaviour Scales Third Edition

VR Visual Reception

FIGURE 1: CONSORT flow chart of the ENACT study



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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

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None

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Abstract

Introduction: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition with impacts on behaviour, cognition, communication, social interaction and family mental health. This paper reports the protocol of a randomised controlled trial (RCT) of a very early intervention ENACT (ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy) for families of infants at risk of ASD.

Methods and analysis: We aim to recruit 66 mothers of infants at risk of ASD (i.e., infants with a sibling or parent diagnosed with ASD) to this randomised controlled trial (RCT). Families will be randomly assigned to care-as-usual or ENACT. ENACT is a very early intervention, leveraging parent-child interactions to improve early social reciprocity, while supporting parental mental health and the parent-child relationship through Acceptance and Commitment Therapy (ACT). 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). Assessments at four time points (baseline; 3 months, 6 months and 12 months corrected age) will assess parent-infant interaction, parental mental health, infant development and early ASD markers. Analysis will be by intention to treat using general linear models for RCTs.

Ethics and dissemination: This protocol has been approved by the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/19/QCHQ/50131) and The University of Queensland Human Research Ethics Committee (2019000558). If efficacy is demonstrated, the intervention has the potential for wide and accessible dissemination.

Registration details: This trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618002046280p).

Article Summary

Strengths and Limitations of this study

- First RCT to test a very early intervention for infants at risk of ASD implemented within the first 6 months of life.
- ENACT combines parent-mediated very early intervention with parental mental health support.
- Assessment includes neurodevelopmental and neurophysiological assessments, as well as observations of parent-child interaction.
- ENACT could, if effective, be widely disseminated at little cost.

Keywords: Autism Spectrum Disorder, early intervention, maternal mental health, parent-infant interaction, infant development

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INTRODUCTION

Autism Spectrum Disorder and the Broader Autism Phenotype

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition defined by difficulties in social communication and interaction, and repetitive, restricted interests and activities[1 2]. It evolves from a complex interaction between genes and environment[3 4], and has substantial impact on affected individuals, with 65% having a profound or severe activity limitation, needing help or supervision with communication, self-care and/or mobility[5]. Prevalence rates are 0.7% and 1.7-2.5% in Australia and the United States, respectively[5-7]. Diagnosis rests on developmental assessment and behavioural observations with most children 2 years or older at diagnosis[8].

Infant siblings of children with ASD are at an increased risk of ASD themselves, with prevalence estimates of 18-20% from baby sibling studies[9 10]. A further 25% show elevated scores on the Autism Diagnostic Observation Schedule (ADOS), developmental delays and lower adaptive functioning[11-13]. Prospective sibling studies have identified a range of non-specific markers in infants at high-risk of ASD, including motor delays, poor visual reception, language delays, regulatory difficulties and changes in eye gaze at 6-12 months that precede the appearance of autism-specific features in the second year of life[14-18]. The diversity of early markers precludes a single developmental pathway to ASD and has been called 'the first year puzzle'[19-23]. Non-specific developmental markers may interact leading to increasingly abnormal trajectories of infant development. Visual, motor and regulatory difficulties may impact on emerging attention and emotional regulation[19 24-26]. Differences in visual, motor and regulatory abilities at six months of age correspond in timing with changes in whole-brain functional connectivity on MRI studies[27 28]. At 6 months of age, functional connectivity on diffusion tensor imaging MRI correctly predicted 9 of 11 infants that went on to be diagnosed with ASD at 24 months of age[29]. These findings support the conjecture that the developmental cascade leading to ASD begins early, *within the first six months of life*[28].

To date, nine randomised controlled trials (RCTs) have tested parent-mediated early interventions with infants at risk of ASD implemented in the first 24 months, prior to confirmed ASD diagnosis[30-36]. Only one of these, an RCT of iBASIS-VIPP conducted with 54 infants at high familial risk of ASD recruited at 7-10 months of age has demonstrated sustained reduction of ASD related symptoms, but no change in the diagnostic outcome at 3 years[30 34]. To date, no RCT has commenced with at-risk infants *younger than six months of age*, before earliest ASD markers and commencement of the cascade.

ASD in the Family Context

Poor maternal mental health contributes to poorer long-term outcomes for infants, including those at risk of ASD[37]. Parents of children with ASD are at increased risk for depression and anxiety[38 39], both due to parenting challenges and pre-existing histories[40-42]. Parents of infants with ASD are more likely to have an ASD or the Broader Autism Phenotype (BAP)[43-46]. The BAP may include rigidity, aloofness, social and communication difficulties[46], with increased risk of depressive symptomatology, maladaptive coping and decreased social support[46].

Mental health difficulties can contribute to reductions in responsive parenting[47]. Responsive parenting— child-directed, contingent, prompt, and appropriate to the child's needs— is associated with better child outcomes[48 49]. Responsiveness is a dose-control system for environmental enrichment, enabling the child to obtain the necessary 'experience expectant development'[50 51]. If a child is difficult to read, sends atypical or unclear signals, as in ASD, it is more challenging for parents to cultivate responsive patterns of interaction[52].

By six months infants at risk of ASD may be showing an atypical style of interaction, with difficulty engaging in eye contact and joint attention[15 26 49 53 54]. Parent behaviour may shift towards intrusive parenting and high intensity approach behaviours in an attempt foster engagement and overcome the emerging social limitations of ASD[49 55]. The shift to directive parenting may impact further on the infant's social development[49 56]. Importantly, commencing parent focused intervention *prior to six months*, before the shift towards directive parenting, has not been tested.

Aim

To test the efficacy of ENACT (ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy) for families of infants at risk of ASD via an RCT comparing ENACT to care-as-usual (CAU). ENACT is a newly-developed, very early intervention that targets infants' social reciprocity through supported parent-infant interactions, while simultaneously supporting parental mental health and the parent-child relationship. ENACT commences prenatally.

Hypotheses

We predict that families allocated to ENACT will show better outcomes compared to families allocated to CAU in terms of having:

Primary outcomes

- 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].

Secondary outcomes

- H2: Better scores on measures of parents' mental health at 3, 6 and 12 months as assessed on the Depression Anxiety and Stress Scales (DASS-21) and the Acceptance and Action Questionnaire (AAQ-II)[61 62].
- H3: Improved parent-infant interaction, with greater emotional availability and parental sensitivity, less parental intrusiveness, and greater child responsiveness, as assessed on the Emotional Availability Scales (EAS) Self-Report at 3, 6 and 12 months and Observed[63] at 6 months.
- H4: Higher scores on measures of (a) infants' cognitive development, assessed using the Mullen Scales of Early Learning- Early Learning Composite at 6 and 12 months (MSEL-ELC; composite of the sub-domains of Visual Reception [VR], Fine Motor [FM], Receptive Language [RL] and Expressive Language [EL]),[64] and (b) infants' adaptive skills, assessed using the Vineland Adaptive Behaviour Scales Third Edition (VABS-3)[65] at 12 months.
- H5: Higher scores on measures of infants' (a) motor development at 6 and 12 months assessed using the Hammersmith Infant Neurological Examination; (HINE[66 67]) and (b) fine and gross motor abilities (assessed using the MSEL)[68].
- H6: Higher scores on measures of infants' visual perceptual skills at 6 and 12 months, assessed on the Visual Reception scores on the MSEL[24], and on symbolic cluster on the Communication and Symbolic Behaviour Scales – Developmental Profile (CSBS-DP)[69] and with reduced times on the Gap-Overlap task.
- H7: Higher scores on measures of infant language development at 6 and 12 months, assessed by the Receptive Language and Expressive Language domains on the MSEL[70] and CSBS-DP[71].
- H8: Better scores on parent-report measures of infant regulation – specifically, (a) lower scores for Internalising and Externalising Behaviour, assessed on the Infant-Toddler Social and Emotional Assessment (ITSEA) at 12 months;[72] (b) lower scores on the Dysregulation scales of the ITSEA at 12 months; (c) better sleep on the Brief Infant Sleep Questionnaire (BISQ) at 3 and 6 months;[73] and (d) less cry behaviours on the Crying Pattern Questionnaire (CPQ) at 3 and 6 months of age[74].

METHODS AND ANALYSIS

Design

The study is an RCT following CONSORT guidelines. After enrolment, and baseline assessments, mothers of infants at risk of ASD will be randomly allocated to intervention (ENACT) or CAU. Comparison to CAU is appropriate as ENACT is a newly developed intervention and this is the first trial. The CONSORT flow chart is depicted in Figure One.

[insert Figure One about here]

Recruitment

Families will be recruited via advertisements distributed through Queensland ASD family support groups, schools and clinics (e.g. Autism Queensland, AEIOU Foundation for Children with Autism, Asperger Services Australia, Minds and Hearts) and Queensland Health Antenatal and Child Development Clinics. Mothers will be recruited during the third trimester of pregnancy.

Inclusion criteria

Participants must meet the following inclusion criteria: (1) the infant must have one or more biological siblings or a biological parent (mother or father) diagnosed with ASD; (2) the mother must agree to the assessment requirements; (3) the mother must have reliable internet access (e.g. ADSL); and (4) the mother must have sufficient English to complete assessments.

Exclusion criteria

Any infant with known neurological or chromosomal disorder at the point of recruitment.

Sample size

The target number of participants is 66 (ENACT n=33, CAU n=33), which will provide power of 80% (two-tailed, α=0.05) to detect a difference between groups of 0.75 SD on the AOSI. In a previous study with a similar sample the observed SD=4;[30] consequently we should be able to observe a difference of ≥3 units in this study.

Blinding

Participants and intervention delivery facilitators cannot be blinded to group allocation. Assessors conducting the AOSI, Gap-Overlap task, MSEL and HINE assessments at 12 months CA will be blinded to group allocation, as will coders scoring the video/audio-recorded EAS observations, GMA, and Gap-Overlap task.

Care-as-Usual interventions for infants at risk of ASD

Participants allocated to CAU will receive usual postnatal care. As developmental and autism-related concerns generally present after 12 months of age, it is expected that any targeted interventions provided in the community by usual care providers will fall outside the timeframe of the study.

The ENACT Intervention

ENACT is a very early intervention targeting infant social reciprocity through supported parent-child interactions while simultaneously supporting parental mental health and the parent-child relationship using ACT. Core to ENACT is the social reciprocity intervention which teaches mothers to initiate and build sensitivity chains with their babies, with the goal that sensitivity chains become longer, increasingly complex and increasingly symbolic over time, and that the early social development of the infant is optimally supported. They should be mutually enjoyable, responsive and non-intrusive.

The three simple steps to building a sensitivity chain are for the mother to 1) stimulate an initial enjoyable interaction, 2) *wait* for the infant to signal their intent to continue, and 3) respond to the infant's signal, hence 'closing the loop' and building a link in the sensitivity chain. This will include a focus on: initially cultivating sensitivity chains through sensorimotor activities, using positive affect and predictable surprise to support the infant's involvement, maintaining reciprocal interactions with infants with atypical responsiveness, and avoiding parental intrusiveness with atypically responsive infants. This intervention is specifically targeting the earliest documented abnormalities in social behaviour in infants at risk of ASD[75]. This aspect of the ENACT intervention was developed specifically for this trial by Andrea McGlade, with input from Koa Whittingham.

ENACT also incorporates parental mental health support grounded in ACT, including values, mindfulness, experiential acceptance and cognitive defusion (distancing from thoughts). The ACT component within ENACT draws from a previously trialled intervention[47]. ENACT also contains a small psychoeducation component on common early parenting challenges of sleep, crying and feeding, developed by Koa Whittingham[76]. This focusses on understanding the biological regulation of sleep via the circadian clock and the sleep-wake homeostat, understanding the developmental pattern of infant crying including the crying peak, and planning ahead on where to seek help for feeding challenges.

ENACT is delivered to mothers (i) via an online course (approximately 8 hours' duration) using the edX platform (www.edx.org/) and (ii) through telehealth (videoconferencing via Zoom) consultations with a trained clinician. The edX course includes: videos and text explaining core concepts, interactive

exercises, multiple choice questions, and videos of real parent-and-baby interactions. The social reciprocity very early intervention is delivered to the infant through the mother and other caregivers. Intervention delivery to mothers will commence prenatally, and mothers will receive fortnightly sessions with the clinician to support consolidation of learning. Mothers will be encouraged to work through the edX course at their own pace, with completion before their babies reach 8 weeks of age.

Mothers will be encouraged to engage in regular practice of sensitivity chains, with a goal dose of 30 minutes per day/5 days per week from 2 weeks of age and throughout the first year (total dose approximately 125 hours). The social reciprocity intervention will be integrated into ordinary everyday interactions including feeding, nappy changes and playful interactions. Consultation sessions will be conducted when the infant is 4 weeks, 8 weeks, 12 weeks, 4 months, 6 months, 8 months and 10 months of age, with capacity for additional sessions as needed. Consultations will support mothers in finding opportunities to practice within everyday life, in tailoring interactions to their babies, and in adapting to their babies' developmental stage and skills. Mothers will be encouraged to initiate a sensitivity chain during the consultation, for the clinician's direct observation and feedback. In addition, clinical consultations will refer to ACT components, supporting maternal mental health throughout the first year. Clinical consultations will follow a specific protocol, and be recorded for fidelity. See Table 1.

[insert Table 1 about here]

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.

Fidelity

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 (content and process) against the protocol.

Patient and Public Involvement

Consumer feedback was sought on the protocol, the study forms and the intervention.

Study Procedure

Researchers will contact interested mothers to assess eligibility and provide detailed study information (see supplementary file: study information sheet and consent form). Mothers will provide written consent prior to completing baseline assessments, and computer-generated block randomisation will then be used to randomise families (1:1) to intervention or CAU via REDcap. Families allocated to intervention will receive immediate access to ENACT. Families allocated to CAU will receive routine antenatal and postnatal care.

Assessments will be conducted at baseline (prenatal), 3, 6, and 12 months CA. Parents will complete questionnaire measures online; mother-child relationship observations will be conducted via 20-minute video-recorded interactions; and child development assessments will be undertaken at [blinded for review] at 6 and 12 months of age. While completing ENACT, parents will be invited to provide feedback and suggestions for course improvement.

Measures

BASELINE ASSESSMENTS

The *Parent Questionnaire* collects (1) general demographic information (parent age, education, income, family composition) and (2) information relevant to the ASD context, such as parent health history, and details of the diagnosis of the first-degree relative (parent or sibling) with ASD. Further information regarding infant delivery, perinatal history, and feeding history will be collected postnatally by brief phone interview

The *Broad Autism Phenotype Questionnaire (BAPQ; 36-items)* assesses ASD-like features in adults through self-report or informant measure[77]. Participants rate how much each item applies to them on a 6-point Likert scale[78]. Internal consistency for the total scale is excellent (α=.95) and there is good inter-item reliability[78].

CHILD ASSESSMENTS

Autism symptomatology

The *Autism Observation Schedule in Infants (AOSI; 12 months)* will be the primary clinical outcome measure assessing intervention effect on infant development and severity of autism symptomatology at 12 months[58]. It is an experimenter-led, semi-structured observational assessment tool, developed for research purposes to study the emergence of ASD-related behavioural markers in infancy (6–18

months)[57 58]. Five standardised activities are delivered between two periods of free play, with a total of 18 items to be scored. Inter-rater reliability of total marker counts (number of items marked as atypical) and total scores, respectively, is good at 6 months (.68 and .74) and excellent at 12 months (.92 and .93)[57]. Test-retest reliability for total marker counts and total scores is fair to good at .68 and .61, respectively[57]. The AOSI differentiates between high-risk and low-risk infants at 12-14 months[79-81].

The *Gap-Overlap task (6 and 12 months)*[59] is used to assess visual attention by measuring differences in the efficiency of orienting towards peripheral stimuli. A mix of social and non-social stimuli will be used. Two trial types will be contrasted: Gap and Overlap. In the Gap condition, an interval of 200-250ms separates the disappearance of the central stimulus and the appearance of the peripheral one (facilitation). In the Overlap condition, the central stimulus remains visible and overlaps with the peripheral stimulus. This measures the ability to disengage from a central stimulus and to orient to a peripheral one. This difference between the Gap and Overlap times is called the Gap effect. Gap-Overlap time, measured in milliseconds, decreases from 6 to 12 months for typically developing infants[15 82 83]. Infants who are later diagnosed with ASD consistently show an *increase* in Gap-Overlap time between 6 and 12 months of age[15 84 85]. This has been called 'sticky attention'. Test–retest reliability of the Gap-Overlap gap effect is r=.50 in infants at age 10 months[59].

Neurodevelopmental and motor assessments

The *Mullen Scales of Early Learning (MSEL; 6 and 12 months)* has been used in the cognitive assessment of infants and children from birth until 68 months of age[30 32 86-88]. The MSEL has five scales: Gross Motor [GM], Visual Reception [VR], Fine Motor [FM], Expressive Language [EL], and Receptive Language [RL], as well as an Early Learning Composite (ELC) score that is composed of the VR, FM, EL, and RL subscales. The MSEL has demonstrated convergent and divergent construct validity in infants and children with ASD[89-91]. Interrater reliability has been reported as high (r = .91-.99)[92].

The *General Movements Assessment (GMA; 3 months)* is a predictive and discriminative tool that assesses infants' spontaneous motor activity from pre-term to 20 weeks CA[93]. Scoring is completed from a videorecording with 2 full movement sequences required for pattern recognition (approximately 5 minutes)[93]. During the fidgety period from 9-20 weeks post-term, fidgety movements can be abnormal (exaggerated in amplitude and speed), sporadic (confined to a few body parts, never >3 seconds between 9-16 weeks CA), or absent (fidgety movements not present between 9-16 weeks CA)

(optimality scoring)[93]. Abnormal fidgety movements that are absent or abnormal at 12-14 weeks C.A are highly predictive of cerebral palsy as well as other neurodevelopmental disabilities including ASD[94 95]. The Baby Moves app will be used to film the videos and transfer the videos for assessment. GMA will be scored by accredited blinded assessors. It will be used as a predictive tool, to better understand the sample.

The *Hammersmith Infant Neurological Examination (HINE; 6 and 12 months)* is a standardised clinical neurodevelopmental assessment for infants from 2-24 months of age[96]. The HINE contains 26 items across 5 domains, summed to provide a global optimality score, and can differentiate between low- and high-risk late preterm and term newborns at 6 and 12 months of age[97-99].

The *Vineland Adaptive Behaviour Scale (3rd ed.; VABS-III; 12 months)* is a standardised measure of adaptive behaviour, completed by caregivers and scored by a blinded assessor[65]. Standard scores are generated for the four domains (Communication, Daily Living Skills, Socialization, and Motor Skills) as well as a global score(Adaptive Behaviour Composite). It has good internal consistency, test–retest reliability, inter-interviewer reliability, and validity for young children including those with autism[65].

Infant regulation

The *Brief Infant Sleep Questionnaire (BISQ; 10-items; 3 and 6 months)* assesses parent-reported infant sleep patterns (nocturnal sleep duration, night waking and method of falling asleep), parent perception of infant sleep duration, and sleep-related (parent) behaviours for children from birth-36 months. It is well validated by comparisons with actigraphy, sleep diaries and caregiver-reported sleep[73 74].

The *Crying Patterns Questionnaire (CPQ; 6-items; 3 and 6 months)* is a parent-report measure assessing: (1) the amount and time of day when infant crying occurs; (2) situations in which crying occurs; (3) whether the mother finds the crying distressing and seeks advice and help; and (4) the mother's responses to crying. In comparison to 24 hour cry-fuss diaries kept by mothers, the CPQ showed moderate-to-good validity (.51-.68) for total duration of crying scores[74].

The *Infant Toddler Social & Emotional Assessment (ITSEA; 165-items; 12 months)* is a parent-report questionnaire used to assess social-emotional problems/competencies in the domains of behavioural dysregulation and competence. The ITSEA has established concurrent validity, strong test-retest reliability (α=.75-.91) and good internal reliability for each subscale (α=.86 for dysregulation, α=.87 for externalising, α=.85 for internalising, and α=.89 for competence)[100 101]. The ITSEA has been

validated for 12 months CA and discriminates between low- and high-risk infants, particularly within the domain of dysregulation[72].

The Communication and Symbolic Behaviour Scales Developmental Profile (CSBS DP; 6 and 12 months) evaluates the symbolic abilities and communication skills of children aged 6-24 months[69]. It includes a 24-item Infant Toddler Checklist which is used as a developmental screening tool to detect autism[102]. The CSBS DP has excellent internal consistency (α=.86-.92), good test-retest reliability and good construct and concurrent validity[69 103].

Mother-infant relationship

Emotional Availability Scales (EAS; 6 months). Coders blind to intervention condition will use the EAS to score 20-minute naturalistic observations of parent-child interactions[63]. 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. The EAS is used to measure quality of parent-child relationships across six scales: parental sensitivity, parental structuring, parental non-intrusiveness, parental non-hostility, child responsiveness and child involvement[63]. The scales have high inter-rater reliability for the parent scales of sensitivity (.95), structuring (.87), non-intrusiveness (.81), non-hostility (.72) and the child scales of responsiveness (.87) and involvement (.87)[104].

The *Emotional Availability - Self Report* (*EA-SR; 36-items; 3, 6 and 12 months)* is a parent-report questionnaire used to measure emotional availability in a dyadic relationship across 5 subscales: Intrusiveness, Hostility, Mutual Attunement, Affect Quality and Capacity to Involve the Parent. Reliability ranges from .71-.84 for all subscales except affect quality (α=.49)[104]. All subscales (except for Intrusiveness) have moderate correlations with the corresponding EAS observed subscales, thus supporting the validity of the self-report measure[104 105].

Maternal mental health

The *Acceptance and Action Questionnaire (AAQ-II; 7-items; baseline, 3, 6 and 12 months)* is a self-report questionnaire measuring psychological flexibility, the key target of ACT[62]. The AAQ-II has good test-retest reliability and convergent validity and excellent internal consistency (α=.94)[62].

The *Depression Anxiety Stress Scales (DASS-21; 21-items; baseline, 3, 6 and 12 months)* assess symptoms of depression, anxiety, and stress in adults. The DASS-21 produces three subscales, each

with good internal consistency: the Depression (α=.91-.97), Anxiety (α =.81-.92), and Stress (α=.88-.95) scales[106], and a Total score. The DASS-21 has good convergent validity and acceptable discriminative validity[106].

Comparison group

A comparison group of 30 healthy low risk infants will be recruited and assessed on the Gap-Overlap task and the HINE at 6 and 12 months, and the AOSI at 12 months. This comparison data will support the interpretation of results, particularly for the novel Gap-Overlap task. 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.

Data Collection and Management

Data will be entered onto the REDCap database in a potentially individually identifiable format. Once de-identified, data will be stored in a re-identifiable format on a secure electronic database protected by the [blinded for review] secure server, and only accessible to members of the research team.

Statistical Analysis

Analysis (using STATA or SPSS) will follow standard methods for RCTs using comparisons between the two groups (e.g. general linear models, ANCOVA) and intention-to-treat analyses. 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.

Monitoring

Data monitoring

As this is a trial of a very early intervention with low risk, a data monitoring committee is not required. Any adverse events, particularly negative developmental outcomes, will be recorded and reported to the ethics committees and in the published results.

Harms

This study should not pose risks beyond those of everyday living. Any participants experiencing undue psychological distress will be referred to their general practitioner. For infants scoring at high developmental risk on the GMA, HINE, MSEL or AOSI, infants' general practitioners/paediatricians

and parents will be notified. All families will be sent a paediatrician's report detailing 12-month developmental assessment results.

Data Sharing Statement

Data will be made available in a public, open access repository. Deidentified data will be made conditionally available to other researchers with approval from the research team.

ETHICS AND DISSEMINATION

ENACT should support mothers' mental health and may also support infant development. Ethical approval has been obtained from the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/19/QCHQ/50131) and The University of Queensland Human Research Ethics Committee (2019000558) and the trial registered (Australian New Zealand Clinical Trials Registry, ACTRN12618002046280p). Study results will be disseminated through scientific journal publications and conference presentations. If shown to be effective, edX facilitates easy dissemination at minimal cost.

DISCUSSION

This study will test the efficacy of an innovative, very early intervention for infants at risk of ASD, integrating early social reciprocity intervention with parental mental health and parent-child relationship support. 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.

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Competing Interests Statement: ENACT was developed from PACT, an intervention developed by researchers at The University of Queensland including Koa Whittingham and Roslyn Boyd. Andrea McGlade and Koa Whittingham developed the of the very early intervention component of edX. ENACT has been developed using the online platform edX.

Abbreviations:

AAQ-II	Acceptance and Action Questionnaire
ACT	Acceptance and Commitment Therapy
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
BAP	Broad Autism Phenotype
BISQ	Brief Infant Sleep Questionnaire
CA	Corrected age
CAU	Care as Usual
CSBS-DP	Communication and Symbolic Behaviour Scales – Developmental Profile
CPQ	Crying Pattern Questionnaire
DASS-21	Depression Anxiety Stress Scale
EAS	Emotional Availability Scales
EA-SR	Emotional Availability Scales – Self Report
EL	Expressive Language
ELC	Early Learning Composite
ENACT	ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy
FM	Fine Motor
GMA	General Movement Assessment
HINE	Hammersmith Infant Neurological Examination
ITSEA	Infant-Toddler Social and Emotional Assessment
MSEL	Mullen Scales of Early Learning
RCT	Randomised Controlled Trial
RL	Receptive Language
VABS-III	Vineland Adaptive Behaviour Scales Third Edition
VR	Visual Reception

TABLE 1: ENACT Intervention Components

Component	Timing	Content
ENACT EdX Course		
Module 1: Very early intervention approach	Begins antenatally with completion before child is 8 weeks	Outlines the very early intervention approach or sensitivity chains and includes multiple videos of parents and babies. Includes advice on early parenting challenges.
Module 2: Living a meaningful life	Begins antenatally with completion before child is 8 weeks	Grounded in ACT, focuses on values and living a rewarding life.
Module 3: Willingness	Begins antenatally with completion before child is 8 weeks	Grounded in ACT, focuses on mindfulness, acceptance and defusion (undermining the literality of language) processes.
Module 4: Relating to others	Begins antenatally with completion before child is 8 weeks	Grounded in ACT, focuses on acceptance, compassion and flexible parenting.
Module 5: Extending early intervention	Begins antenatally with completion before child is 8 weeks	Extends sensitivity chain practice for older babies and provides advice for parents of babies experiencing challenges.
Teleconferencing clinical consultations		
ENACT EdX course completion support	As needed throughout course completion	Focuses on parental understanding of the EdX course, implementation of anything that is immediately relevant, and developing plans for the application of ENACT post-birth.
Developmental Consultations	At 4 weeks, 8 weeks, 12 weeks, 4 months, 6 months, 8 months and 10 months of age	Focuses on expanding and extending sensitivity chain practice, working through any challenges and flexibly supporting parents and parental implementation of sensitivity chain practice using ACT principles. Includes the demonstration of a sensitivity chain whenever possible with opportunities for reflection and feedback.

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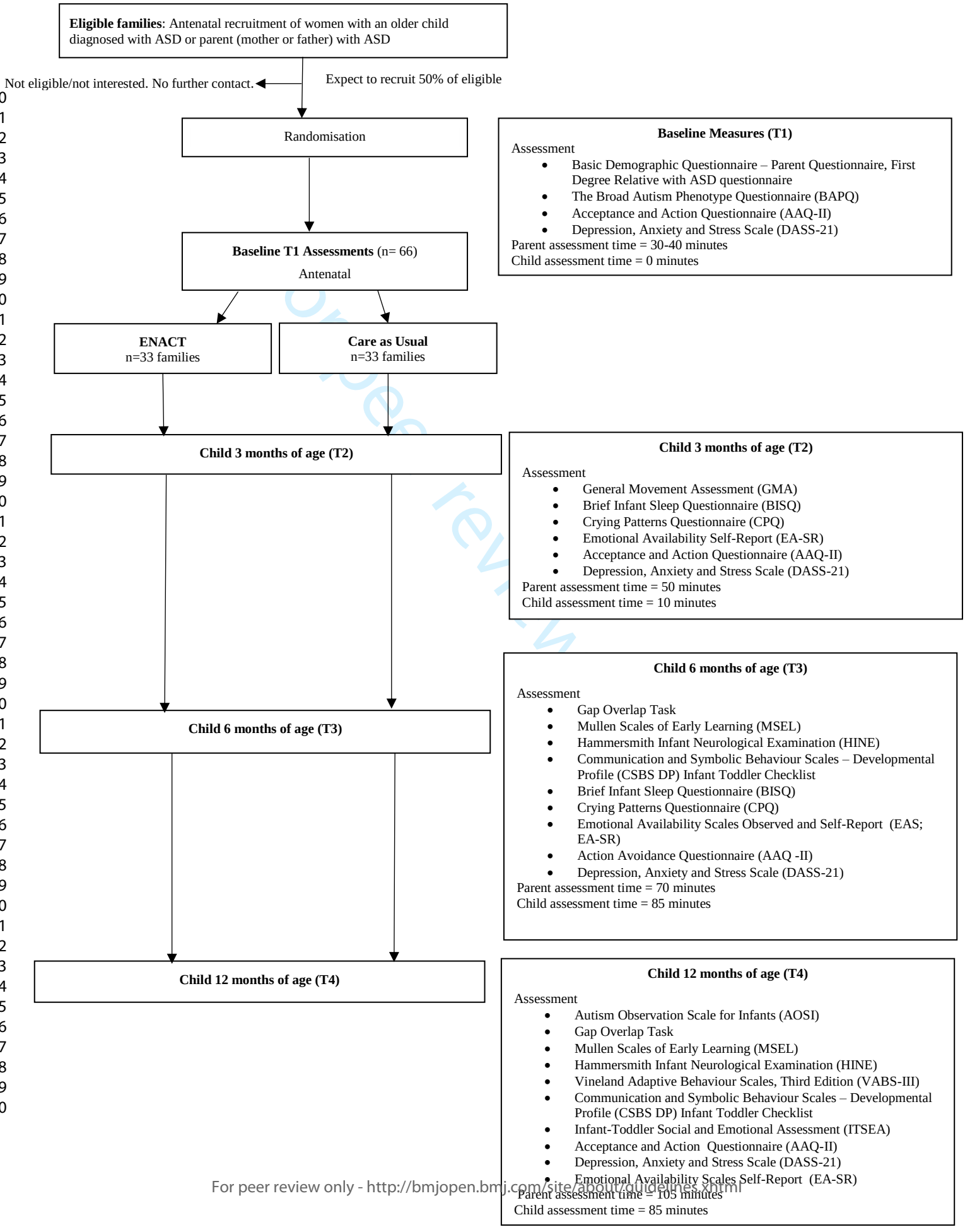
Figure 1: CONSORT flow chart of the ENACT study

FIGURE 1: CONSORT flow chart of the ENACT study



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Queensland Cerebral Palsy & Rehabilitation Research Centre (QCPRRC)
Faculty of Medicine

PARENT/GUARDIAN INFORMATION SHEET

Ethics Approval: HREC/19/QCHQ/50131, 2019000558

Title of Project: Environmental enrichment for infants; parenting with Acceptance and Commitment Therapy (**ENACT**)

Chief Investigators: Dr Koa Whittingham, Dr Andrea McGlade, Miss Kavindri Kulasinghe, Dr Amy Mitchell, Prof. Roslyn N. Boyd, Associate Professor Honey Heussler, Dr Kristelle Hudry

Associate Investigator: Dr Jacqui Barfoot

Thank you for taking the time to read this Information Sheet.
This information statement and consent form is 7 pages long. Please make sure you have all the pages. These pages contain information about a research project that we are inviting you to take part in. **It is okay to say no if you would not like to participate in this study.** Please read this information carefully as it explains clearly and openly what participation involves. Before you decide, you can ask us any questions you have about the project. If you decide you would like to participate in this study then you need to sign and return the consent form attached.

What is the Research Project about?
We have developed a new early intervention approach for infants who have an increased chance of having_Autism Spectrum Disorders (ASD), targeting social interaction from the earliest months through parent-child interactions. We have integrated support for parental mental health and parenting challenges into this early intervention, and developed a means of delivering the intervention online through an e-course combined with online consultations. We are calling our early intervention approach 'Environmental Enrichment for Infants: Parenting with ACT', or **'ENACT'**. The e- course we are trialing in this research project is called **'ENACT101'**. This research project is about trialing ENACT with families of infants who have an increased chance of having of developing an Autism Spectrum Disorder (ASD). We are aiming to discover whether ENACT is effective and whether or not families find it useful.

Can I participate?
You can participate in this study if you are **currently pregnant** with a **baby who has a first-degree relative (sibling or parent) with a diagnosis of an Autism Spectrum Disorder (ASD)**. This might mean that you, your baby's biological father, or your baby's sister or brother may have a diagnosis of an Autism Spectrum Disorder (ASD). As ENACT is delivered online, participation is restricted to families with **reliable internet access**. The intervention, ENACT, and the majority of assessments will be conducted via online questionnaires for your convenience. All participating families will **need to be able to travel to the Child Health Research Centre in Brisbane when their infant is 6 and 12 months of age** for their babies to have assessments in person.

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What does participating involve?
If you choose to participate in this study, you will be randomly allocated to one of two groups: ENACT or care-as-usual.

- **The ENACT group** will get immediate access to the ENACT101 e-course and online consultations with a clinician, who will answer any questions you might have and help to tailor the intervention to best meet your own individual needs and those of your baby. The ENACT intervention will include targeting your baby's social interaction from the earliest months during ordinary parent-child interactions. It also includes strategies to support your mental health and support you in coping with parenting challenges such as infant sleep. Our support for parental mental health is grounded in the psychological therapy Acceptance and Commitment Therapy (ACT). ENACT101 includes videos, text, questions and a discussion board.

- **The care-as-usual group** will receive their usual care without access to ENACT. This will allow us to determine if there are benefits to participating in ENACT.

Whether you are allocated to ENACT or to care-as-usual, you will still need to complete assessments **four times during the study: when you sign up and when your child is 3 months, 6 months, and 12 months old**. All of the assessments will include online questionnaires asking about family, feelings, wellbeing, and your relationship with your child, as well as your child's development.

At 3 months of age, you will be asked to record your baby's movements via the Baby Moves app, which we will ask you to download onto your phone. The Baby Moves app helps to record your baby's movements for the General Movements Assessment (GMA), which is a neurodevelopmental assessment tool. When your child is 6 months and 12 months old, we will ask you to bring your child for a visit to the **Centre for Children's Health Research in Brisbane** for a **comprehensive assessment of your baby's development with a developmental paediatrician**. **We will provide you with free parking.**

Can I get a copy of the assessment results and find out about my baby's development?
Absolutely! We hope that this is one of the benefits of participating, whether you are in the intervention group or not. We know that finding out about your baby's development is important to you. All participating families will receive a developmental report after their baby's 12 month assessments. If earlier assessments indicate neurodevelopmental risk, particularly the general movements assessment at 3-4 months of age and the HINE at 6 months then you will be informed and assisted in finding appropriate support. All babies participating in the study will have a report provided to their parent/s after their last assessment and a copy will also go to your baby's general practitioner. If there are any findings of concern you will also be informed via the report and your general practitioner. As these assessments have been performed as part of a study, we cannot provide individual recommendations for management. The report will be able to make some general recommendations though for you to be able to discuss further with your general practitioner (or your child's paediatrician if they have one), so that you know what management options are available.

Your involvement is genuinely appreciated.

Your active participation in refining ENACT is highly valued. We will ask you to share your thoughts and experiences with us as you work through the program.

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The steps of the study participation are summarised below:

✓Agree to participate in the study and sign the consent form
✓ Complete baseline questionnaires online *(30-40 minutes)*
✓ Be randomly assigned to **ENACT** or **Care as Usual** group

ENACT101
✓ e- course
(6-8 hours total over 8-10 weeks)

✓ Early intervention for social reciprocity
✓Supported by regular video conference sessions with clinician

Care as Usual
✓ Your usual postnatal medical care

When your child is 3 months old
✓ Complete questionnaires online
Parent assessment time = 50 minutes
Child assessment time = 10 minutes
✓***Baby Moves app recording at 12 and 14 weeks***
Child assessment time = 5 minutes each recording

When your child is 6 months old
✓ Complete questionnaires online
✓ Record a **20 minute** interaction with your child
✓ **Complete assessments in Brisbane**
Parent assessment time = 70 minutes
Child assessment time = 85 minutes

When your child is 12 months old
✓Complete questionnaires online
✓ Record a **20 minute** interaction with your child
✓ **Complete assessments in Brisbane**
✓ Get a comprehensive report of your child's developmental assessment

Parent assessment time = 105 minutes
Child assessment time = 85 minutes

What does ENACT involve?

ENACT101 is flexible online course, and participants will be able to move through the content at a pace that suits them. We estimate that it will take approximately 6-8 hours in total to complete the content, with most participants beginning antenatally. We aim to ensure that

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participants have worked through all of the ENACT101 content by the time their infant is 8 weeks of age. ENACT101 can be accessed from any device that can connect to the internet.

The social interaction component of ENACT should be practiced regularly from when your infant is 2 weeks old, with a target of 30 minutes per day/5 days per week. However, the social interaction practice is designed to be done during ordinary, everyday activities and interactions with your baby, and shouldn't take up extra time in your day. The clinical consultations will support you in finding ways to practice ENACT in the midst of everyday life.

How will this research help people in the future?
This is the first time an early intervention approach for ASD has been trialed from birth. With your help, we hope to refine ENACT. We have chosen to use an online delivery method, including the development of the e-course ENACT101, so that if ENACT is found to be effective, ENACT101 can be made accessible to families with children who have an increased chance of having Autism Spectrum Disorder across the world.

Are there any risks to participation?
ENACT101 will be exploring your relationship with your newborn child as well as your thoughts, feelings and general well-being. This study contains no risks beyond everyday living.

Will my information be confidential?
Yes! All information that we collect from you and your child, including your questionnaires, videoed parent-child interaction, child assessments and your feedback will be stored in a confidential manner. The information in this study will only be used in ways that will not reveal who you are. You will not be identified in any publication from this study or in any data files shared with other researchers. All information will be held in strict confidence, and will be used for statistical purposes only. Confidentiality will only be breached if a child is deemed at risk of harm or neglect. Data collected from you or your child will be de-identified, by replacing any identifying information (e.g. your name) with a participant number. Identified or de-identified research data may be made available for review by ethics review committees or other regulatory authorities for the purposes of monitoring ethical and scientific conduct of the study.

What if I change my mind?
You do not have to take part in this research project. Your participation will not affect any treatment that you or your child receives. If you do agree to participate, and change your mind at a later date, you are free to withdraw from the study at any time without any negative consequence.

Who is involved?
Chief Investigators

1. **Dr Koa Whittingham** is a clinical and developmental psychologist and a senior research fellow at the University of Queensland. She is experienced in working with parents of children with Autism Spectrum Disorder as well as in Acceptance and Commitment Therapy.
2. **Dr Andrea McGlade** is a developmental paediatrician and is undertaking this project as part of her PhD within the Faculty of Medicine at the University of Queensland.
3. **Miss Kavindri Kulasinghe** is a medical student within the Faculty of Medicine at the University of Queensland. She is undertaking this project as a part of her PhD.
4. **Dr Amy Mitchell** is a paediatric nurse and a research fellow at the University of Queensland with expertise in working with parents.

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5. **Professor Roslyn Boyd** is the Scientific Director of Queensland Cerebral Palsy and Rehabilitation Research Centre. She has clinical and scientific expertise in working with children with cerebral palsy and developmental delay and their families.
6. **Associate Professor Honey Heussler** is a developmental and behavioural paediatrician and a researcher with the Centre for Children's Health Research. She has extensive experience working with children with developmental and behavioural problems.
7. **Dr Kristelle Hudry** is a Senior Lecturer within the Department of Psychology and Counselling at the La Trobe University. She is experienced in working with parents of children with Autism Spectrum Disorder.

Associate Investigators

1. **Dr Jacqui Barfoot** is an occupational therapist with clinical and research experience in parent-infant relationship focussed interventions to support infant development. She is the clinician delivering the ENACT intervention.

Do you have any questions?

Please take the time to ask us any questions that you may have. You can contact:
Miss Kavindri Kulasinghe or Dr Andrea McGlade (Chief Investigators) on (07) 3069 7547 or email uqenact@uq.edu.au

University of Queensland Ethics Contact:

This study adheres to the Guidelines of the ethical review process of The University of Queensland and the National Statement on Ethical Conduct in Human Research. Whilst you are free to discuss your participation in this study with project staff, if you would like to speak to an officer of the University not involved in the study, you may contact the Ethics Coordinators on(07) 33653924 /(07) 34431656, or email humanethics@research.uq.edu.au.

HREC Information:

The Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC) has approved this study. If you have any concerns and/or complaints about the project, the way it is being conducted or your child's rights as a research participant, and would like to speak to someone independent of the project, please contact the HREC Co-ordinator on: 3069 7002 or email CHQETHICS@health.qld.gov.au

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PARTICIPANT CONSENT FORM

Project Number: HREC/19/QCHQ/50131, 2019000558

Title of Project: Environmental enrichment for infants; parenting with Acceptance and Commitment Therapy (ENACT)

Chief Investigators: Dr Koa Whittingham, Dr Andrea McGlade, Miss Kavindri Kulasinghe, Dr Amy Mitchell, Prof. Roslyn N. Boyd, Associate Professor Honey Heussler, Dr Kristelle Hudry

I/We,

_____

voluntarily consent to participate in the above titled Research Project explained to me by:

Mrs/Ms/Dr/Professor _____

- I/We have read the information statement for this study and I/we believe I/we understand the purpose, extent and possible effects of my involvement.
- I/We have had an opportunity to ask questions and I/we am satisfied with the answers I/we have received.
- I/We understand information collected will be stored confidentially and my/our identity will not be revealed.
- I/We understand that I/we can refuse to participate and can withdraw from this study at any time without any negative consequence. In particular, I/we understand that my/our participation will not affect my child's access to usual medical care.
- I/We understand that the purpose of this study is to pilot an innovative, online approach to early intervention and that my/our active involvement, including critical feedback, is valued.
- I/We understand that in order to evaluate the new early intervention I/we will be asked to complete online questionnaires as well as record an ordinary parent-child interaction during the study.
- I/We consent to having videos of my/our child recorded via the Baby Moves app when my/our child is 12 and 14 weeks of age and scored by an independent assessor.
- I/We understand that I/we will receive a developmental report covering my baby's 12 month assessments and that if neurodevelopmental risk is found at the earlier assessments particularly on the general movements assessment or the HINE I/we will be informed as soon as possible.
- I/We understand that in order to evaluate the new early intervention I/we will be asked to complete a developmental assessment at the Children's Health Research Centre in Brisbane when my child is 6 and 12 months of age.
- I/We understand that a report of my child's developmental assessments will be provided at the completion of the assessments and that in the event of any adverse findings I may be contacted by a member of the assessment team to notify me of these findings.

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- I/We consent to provide the name and contact details of my child's General Practitioner and Paediatrician (if your child has a paediatrician).
- I/We consent for my nominated General Practitioner (and paediatrician) to be contacted and a report provided to them for further follow up with your child, including any concerns identified in the assessments performed.
- **I/We consent to participate in this research project.**

My child's GP or Paediatrician:

Name: _____

Address: _____

Phone: _____

Signature _____ **Date** _____

I have explained this study and I believe that the participant/s understands the purpose, extent and possible effects of involvement.

Researcher's Signature _____ **Date** _____

Note: All parties signing the Consent Form must date their own signature.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Title page
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Title page
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Title page

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6-7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	17, figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10-11
	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10-11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

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

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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

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Running head: ENACT (ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy)

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Declaration of Interest:
None

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Author contributions All authors contributed to the conception and design of this study. KW and AM designed the ENACT intervention. KK, KW and AEM contributed to the design in terms of parental mental health and parent-child relationship assessment. AM, KW, HH and RNB contributed to the design in terms of motor, cognitive and autistic symptomatology assessment. All authors contributed to drafting and critical revision of the manuscript. All authors approved the final version of the manuscript to be submitted for publication.

Abstract

Introduction: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition with impacts on behaviour, cognition, communication, social interaction and family mental health. This paper reports the protocol of a randomised controlled trial (RCT) of a very early intervention ENACT (ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy) for families of infants at risk of ASD.

Methods and analysis: We aim to recruit 66 mothers of infants at risk of ASD (i.e., infants with a sibling or parent diagnosed with ASD) to this randomised controlled trial (RCT). Families will be randomly assigned to care-as-usual or ENACT. ENACT is a very early intervention, leveraging parent-child interactions to improve early social reciprocity, while supporting parental mental health and the parent-child relationship through Acceptance and Commitment Therapy (ACT). 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). Assessments at four time points (baseline; 3 months, 6 months and 12 months corrected age) will assess parent-infant interaction, parental mental health, infant development and early ASD markers. Analysis will be by intention to treat using general linear models for RCTs.

Ethics and dissemination: This protocol has been approved by the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/19/QCHQ/50131) and The University of Queensland Human Research Ethics Committee (2019000558). If efficacy is demonstrated, the intervention has the potential for wide and accessible dissemination.

Registration details: This trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618002046280).

Article Summary

Strengths and Limitations of this study

- First RCT to test a very early intervention for infants at risk of ASD implemented within the first 6 months of life.
- ENACT combines parent-mediated very early intervention with parental mental health support.
- Assessment includes neurodevelopmental assessments, as well as observations of parent-child interaction.

- 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.

Keywords: Autism Spectrum Disorder, early intervention, maternal mental health, parent-infant interaction, infant development

Word count: 3871

INTRODUCTION

Autism Spectrum Disorder and the Broader Autism Phenotype

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition defined by difficulties in social communication and interaction, and repetitive, restricted interests and activities[1 2]. It evolves from a complex interaction between genes and environment[3 4], and has substantial impact on affected individuals, with 65% having a profound or severe activity limitation, needing help or supervision with communication, self-care and/or mobility[5]. Prevalence rates are 0.7% and 1.7-2.5% in Australia and the United States, respectively[5-7]. Diagnosis rests on developmental assessment and behavioural observations with most children 2 years or older at diagnosis[8].

Infant siblings of children with ASD are at an increased risk of ASD themselves, with prevalence estimates of 18-20% from baby sibling studies[9 10]. A further 25% show elevated scores on the Autism Diagnostic Observation Schedule (ADOS), developmental delays and lower adaptive functioning[11-13]. Prospective sibling studies have identified a range of non-specific markers in infants at high-risk of ASD, including motor delays, poor visual reception, language delays, regulatory difficulties and changes in eye gaze at 6-12 months that precede the appearance of autism-specific features in the second year of life[14-18]. The diversity of early markers precludes a single developmental pathway to ASD and has been called 'the first year puzzle'[19-23]. Non-specific developmental markers may interact leading to increasingly abnormal trajectories of infant development. Visual, motor and regulatory difficulties may impact on emerging attention and emotional regulation[19 24-26]. Differences in visual, motor and regulatory abilities at six months of age correspond in timing with changes in whole-brain functional connectivity on MRI studies[27 28]. At 6 months of age, functional connectivity on diffusion tensor imaging MRI correctly predicted 9 of 11 infants that went on to be diagnosed with ASD at 24 months of age[29]. These findings support the conjecture that the developmental cascade leading to ASD begins early, *within the first six months of life*[28].

To date, nine randomised controlled trials (RCTs) have tested parent-mediated early interventions with infants at risk of ASD implemented in the first 24 months, prior to confirmed ASD diagnosis[30-36]. Only one of these, an RCT of iBASIS-VIPP conducted with 54 infants at high familial risk of ASD recruited at 7-10 months of age has demonstrated sustained reduction of ASD related symptoms, but no change in the diagnostic outcome at 3 years[30 34]. iBASIS-VIPP begins after the infant is 6 months of age and focusses on changing parent behaviour. To date, no RCT has commenced with at-risk infants *younger than six months of age*, before earliest ASD markers and commencement of the cascade.

ASD in the Family Context

Poor maternal mental health contributes to poorer long-term outcomes for infants, including those at risk of ASD[37 38]. Parents of children with ASD are at increased risk for depression and anxiety[39 40], both due to parenting challenges and pre-existing histories[41-43]. Parents of infants with ASD are more likely to have an ASD or the Broader Autism Phenotype (BAP)[44-47]. The BAP may include rigidity, aloofness, social and communication difficulties[47], with increased risk of depressive symptomatology, maladaptive coping and decreased social support[47].

Mental health difficulties can contribute to reductions in responsive parenting[48]. Responsive parenting— child-directed, contingent, prompt, and appropriate to the child's needs— is associated with better child outcomes[49 50]. Responsiveness is a dose-control system for environmental enrichment, enabling the child to obtain the necessary 'experience expectant development'[51 52]. If a child is difficult to read, sends atypical or unclear signals, as in ASD, it is more challenging for parents to cultivate responsive patterns of interaction[53].

By six months infants at risk of ASD may be showing an atypical style of interaction, with difficulty engaging in eye contact and joint attention[15 26 50 54 55]. Parent behaviour may shift towards intrusive parenting and high intensity approach behaviours in an attempt foster engagement and overcome the emerging social limitations of ASD[50 56]. The shift to directive parenting may impact further on the infant's social development[50 57]. Importantly, commencing parent focused intervention *prior to six months*, before the shift towards directive parenting, has not been tested.

Aim

To test the efficacy of ENACT (ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy) for families of infants at risk of ASD via an RCT comparing ENACT to care-as-usual (CAU). ENACT is a newly-developed, very early intervention that targets infants' social reciprocity through supported parent-infant interactions, while simultaneously supporting parental mental health and the parent-child relationship. ENACT commences prenatally.

Hypotheses

We predict that families allocated to ENACT will show better outcomes compared to families allocated to CAU in terms of having:

Primary outcomes

- H1**:** Lower scores for ASD symptomatology at as assessed on (a) the AOSI[58 59] 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[60 61].

Secondary outcomes

- H2: Better scores on measures of parents' mental health at 3, 6 and 12 months as assessed on the Depression Anxiety and Stress Scales (DASS-21) and the Acceptance and Action Questionnaire (AAQ-II)[62 63].
- H3: Improved parent-infant interaction, with greater emotional availability and parental sensitivity, less parental intrusiveness, and greater child responsiveness, as assessed on the Emotional Availability Scales (EAS) Self-Report at 3, 6 and 12 months and Observed[64] at 6 months.
- H4: Higher scores on measures of (a) infants' cognitive development, assessed using the Mullen Scales of Early Learning- Early Learning Composite at 6 and 12 months (MSEL-ELC; composite of the sub-domains of Visual Reception [VR], Fine Motor [FM], Receptive Language [RL] and Expressive Language [EL]),[65] and (b) infants' adaptive skills, assessed using the Vineland Adaptive Behaviour Scales Third Edition (VABS-3)[66] at 12 months.
- H5: Higher scores on measures of infants' (a) motor development at 6 and 12 months assessed using the Hammersmith Infant Neurological Examination; (HINE[67 68]) and (b) fine and gross motor abilities (assessed using the MSEL)[69].
- H6: Higher scores on measures of infants' visual perceptual skills at 6 and 12 months, assessed on the Visual Reception scores on the MSEL[24], and on symbolic cluster on the Communication and Symbolic Behaviour Scales – Developmental Profile (CSBS-DP)[70] and with reduced times on the Gap-Overlap task.
- H7: Higher scores on measures of infant language development at 6 and 12 months, assessed by the Receptive Language and Expressive Language domains on the MSEL[71] and CSBS-DP[72].
- H8: Better scores on parent-report measures of infant regulation – specifically, (a) lower scores for Internalising and Externalising Behaviour, assessed on the Infant-Toddler Social and Emotional Assessment (ITSEA) at 12 months;[73] (b) lower scores on the Dysregulation scales of the ITSEA at 12 months; (c) better sleep on the Brief Infant Sleep Questionnaire (BISQ) at 3 and 6 months;[74] and (d) less cry behaviours on the Crying Pattern Questionnaire (CPQ) at 3 and 6 months of age[75].

METHODS AND ANALYSIS

Design

The study is an RCT following CONSORT guidelines. After enrolment, and baseline assessments, mothers of infants at risk of ASD will be randomly allocated to intervention (ENACT) or CAU. Comparison to CAU is appropriate as ENACT is a newly developed intervention and this is the first trial. The CONSORT flow chart is depicted in Figure One.

[insert Figure One about here]

Recruitment

Families will be recruited via advertisements distributed through Queensland ASD family support groups, schools and clinics (e.g. Autism Queensland, AEIOU Foundation for Children with Autism, Asperger Services Australia, Minds and Hearts) and Queensland Health Antenatal and Child Development Clinics. Families will be recruited during pregnancy and up to the infant reaching 7 weeks corrected age then followed over the first 12 months.

Inclusion criteria

Participants must meet the following inclusion criteria: (1) the infant must have one or more biological siblings or a biological parent (mother or father) diagnosed with ASD; (2) the mother must agree to the assessment requirements; (3) the mother must have reliable internet access (e.g. ADSL); and (4) the mother must have sufficient English to complete assessments.

Exclusion criteria

Any infant with known neurological or chromosomal disorder at the point of recruitment.

Sample size

The target number of participants is 66 (ENACT n=33, CAU n=33), which will provide power of 80% (two-tailed, α=0.05) to detect a difference between groups of 0.75 SD on the AOSI. In a previous study with a similar sample the observed SD=4;[30] consequently we should be able to observe a difference of ≥3 units in this study.

Blinding

Participants and intervention delivery facilitators cannot be blinded to group allocation. Assessors conducting the AOSI, Gap-Overlap task, MSEL and HINE assessments at 12 months CA will be blinded to group allocation, as will coders scoring the video/audio-recorded EAS observations, GMA, and Gap-Overlap task.

Care-as-Usual interventions for infants at risk of ASD

Participants allocated to CAU will receive usual postnatal care. As developmental and autism-related concerns generally present after 12 months of age, it is expected that any targeted interventions provided in the community by usual care providers will fall outside the timeframe of the study.

The ENACT Intervention

ENACT is a very early intervention targeting infant social reciprocity through supported parent-child interactions while simultaneously supporting parental mental health and the parent-child relationship using ACT. Core to ENACT is the social reciprocity intervention which teaches mothers to initiate and build sensitivity chains with their babies, with the goal that sensitivity chains become longer, increasingly complex and increasingly symbolic over time, and that the early social development of the infant is optimally supported. They should be mutually enjoyable, responsive and non-intrusive.

The three simple steps to building a sensitivity chain are for the mother to 1) stimulate an initial enjoyable interaction, 2) *wait* for the infant to signal their intent to continue, and 3) respond to the infant's signal, hence 'closing the loop' and building a link in the sensitivity chain. This will include a focus on: initially cultivating sensitivity chains through sensorimotor activities, using positive affect and predictable surprise to support the infant's involvement, maintaining reciprocal interactions with infants with atypical responsiveness, and avoiding parental intrusiveness with atypically responsive infants. This intervention is specifically targeting the earliest documented abnormalities in social behaviour in infants at risk of ASD[76]. This aspect of the ENACT intervention was developed specifically for this trial by Andrea McGlade, with input from Koa Whittingham.

ENACT also incorporates parental mental health support grounded in ACT, including values, mindfulness, experiential acceptance and cognitive defusion (distancing from thoughts). The ACT component within ENACT contains material previously trialled as the online intervention entitled Parenting Acceptance and Commitment Therapy or PACT[48]. The development of PACT was itself grounded in RCTs demonstrating the efficacy of a group ACT intervention for parents of children with neurodevelopmental disabilities[77-80]. ENACT also contains a small psychoeducation component on common early parenting challenges of sleep, crying and feeding, developed by Koa Whittingham and grounded in the existing literature and her previous work.[81-84] This focusses on understanding the biological regulation of sleep via the circadian clock and the sleep-wake homeostat, understanding the developmental pattern of infant crying including the crying peak, and planning ahead on where to seek help for feeding challenges.

ENACT is delivered to mothers (i) via an online course (approximately 8 hours' duration) using the edX platform (www.edx.org/) and (ii) through telehealth (videoconferencing via Zoom) consultations with a trained clinician. The edX course includes: videos and text explaining core concepts, interactive exercises, multiple choice questions, and videos of real parent-and-baby interactions. The social reciprocity very early intervention is delivered to the infant through the mother and other caregivers. Intervention delivery to mothers will commence prenatally, and mothers will receive fortnightly sessions with the clinician to support consolidation of learning. Mothers will be encouraged to work through the edX course at their own pace, with completion before their babies reach 8 weeks of age.

Mothers will be encouraged to engage in regular practice of sensitivity chains, with a goal dose of 30 minutes per day/5 days per week from 2 weeks of age and throughout the first year (total dose approximately 125 hours). The social reciprocity intervention will be integrated into ordinary everyday interactions including feeding, nappy changes and playful interactions. Consultation sessions will be conducted when the infant is 4 weeks, 8 weeks, 12 weeks, 4 months, 6 months, 8 months and 10 months of age, with capacity for additional sessions as needed. Consultations will support mothers in finding opportunities to practice within everyday life, in tailoring interactions to their babies, and in adapting to their babies' developmental stage and skills. Mothers will be encouraged to initiate a sensitivity chain during the consultation, for the clinician's direct observation and feedback. In addition, clinical consultations will refer to ACT components, supporting maternal mental health throughout the first year. Clinical consultations will follow a specific protocol, and be recorded for fidelity. See Table 1.

[insert Table 1 about here]

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.

Fidelity

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. The 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 (content and process) against the protocol. Qualitative feedback will be collected.

Patient and Public Involvement

Consumer feedback was sought on the protocol, the study forms and the intervention. Consumer feedback was positive, with some changes to wording made following input.

Study Procedure

Researchers will contact interested mothers to assess eligibility and provide detailed study information (see supplementary file: study information sheet and consent form). Mothers will provide written consent prior to completing baseline assessments, and computer-generated block randomisation will then be used to randomise families (1:1) to intervention or CAU via REDcap. Families allocated to intervention will receive immediate access to ENACT. Families allocated to CAU will receive routine antenatal and postnatal care.

Assessments will be conducted at baseline (prenatal), 3, 6, and 12 months CA. Parents will complete questionnaire measures online; mother-child relationship observations will be conducted via 20-minute video-recorded interactions; and child development assessments will be undertaken at [blinded for review] at 6 and 12 months of age. While completing ENACT, parents will be invited to provide feedback and suggestions for course improvement.

Measures

BASELINE ASSESSMENTS

The *Parent Questionnaire* collects (1) general demographic information (parent age, education, income, family composition) and (2) information relevant to the ASD context, such as parent health history, and details of the diagnosis of the first-degree relative (parent or sibling) with ASD. Further information regarding infant delivery, perinatal history, and feeding history will be collected postnatally by brief phone interview

The *Broad Autism Phenotype Questionnaire (BAPQ; 36-items)* assesses ASD-like features in adults through self-report or informant measure[85]. Participants rate how much each item applies to them on a 6-point Likert scale[86]. Internal consistency for the total scale is excellent (α=.95) and there is good inter-item reliability[86].

CHILD ASSESSMENTS

Autism symptomatology

The *Autism Observation Schedule in Infants (AOSI; 12 months)* will be the primary clinical outcome measure assessing intervention effect on infant development and severity of autism symptomatology at 12 months[59]. It is an experimenter-led, semi-structured observational assessment tool, developed for research purposes to study the emergence of ASD-related behavioural markers in infancy (6–18 months)[58 59]. Five standardised activities are delivered between two periods of free play, with a total of 18 items to be scored. Inter-rater reliability of total marker counts (number of items marked as atypical) and total scores, respectively, is good at 6 months (.68 and .74) and excellent at 12 months (.92 and .93)[58]. Test-retest reliability for total marker counts and total scores is fair to good at .68 and .61, respectively[58]. The AOSI differentiates between high-risk and low-risk infants at 12-14 months[87-89].

The *Gap-Overlap task (6 and 12 months)*[60] is used to assess visual attention by measuring differences in the efficiency of orienting towards peripheral stimuli. A mix of social and non-social stimuli will be used. Two trial types will be contrasted: Gap and Overlap. In the Gap condition, an interval of 200-250ms separates the disappearance of the central stimulus and the appearance of the peripheral one (facilitation). In the Overlap condition, the central stimulus remains visible and overlaps with the peripheral stimulus. This measures the ability to disengage from a central stimulus and to orient to a peripheral one. This difference between the Gap and Overlap times is called the Gap effect. Gap-Overlap time, measured in milliseconds, decreases from 6 to 12 months for typically developing infants[15 90 91]. Infants who are later diagnosed with ASD consistently show an *increase* in Gap-Overlap time between 6 and 12 months of age[15 92 93]. This has been called 'sticky attention'. Test–retest reliability of the Gap-Overlap gap effect is r=.50 in infants at age 10 months[60].

Neurodevelopmental and motor assessments

The *Mullen Scales of Early Learning (MSEL; 6 and 12 months)* has been used in the cognitive assessment of infants and children from birth until 68 months of age[30 32 94-96]. The MSEL has five scales: Gross Motor [GM], Visual Reception [VR], Fine Motor [FM], Expressive Language [EL], and Receptive Language [RL], as well as an Early Learning Composite (ELC) score that is composed of the VR, FM, EL, and RL subscales. The MSEL has demonstrated convergent and divergent construct validity in infants and children with ASD[97-99]. Interrater reliability has been reported as high (r = .91-.99)[100].

The *General Movements Assessment (GMA; 3 months)* is a predictive and discriminative tool that assesses infants' spontaneous motor activity from pre-term to 20 weeks CA[101]. Scoring is completed from a videorecording with 2 full movement sequences required for pattern recognition (approximately 5 minutes)[101]. During the fidgety period from 9-20 weeks post-term, fidgety movements can be abnormal (exaggerated in amplitude and speed), sporadic (confined to a few body parts, never >3 seconds between 9-16 weeks CA), or absent (fidgety movements not present between 9-16 weeks CA) (optimality scoring)[101]. Abnormal fidgety movements that are absent or abnormal at 12-14 weeks C.A are highly predictive of cerebral palsy as well as other neurodevelopmental disabilities including ASD[102 103]. The Baby Moves app will be used to film the videos and transfer the videos for assessment. GMA will be scored by accredited blinded assessors. It will be used as a predictive tool, to better understand the sample.

The *Hammersmith Infant Neurological Examination (HINE; 6 and 12 months)* is a standardised clinical neurodevelopmental assessment for infants from 2-24 months of age[104]. The HINE contains 26 items across 5 domains, summed to provide a global optimality score, and can differentiate between low- and high-risk late preterm and term newborns at 6 and 12 months of age[105-107].

The *Vineland Adaptive Behaviour Scale (3rd ed.; VABS-III; 12 months)* is a standardised measure of adaptive behaviour, completed by caregivers and scored by a blinded assessor[66]. Standard scores are generated for the four domains (Communication, Daily Living Skills, Socialization, and Motor Skills) as well as a global score(Adaptive Behaviour Composite). It has good internal consistency, test–retest reliability, inter-interviewer reliability, and validity for young children including those with autism[66].

Infant regulation

The *Brief Infant Sleep Questionnaire (BISQ; 10-items; 3 and 6 months)* assesses parent-reported infant sleep patterns (nocturnal sleep duration, night waking and method of falling asleep), parent perception of infant sleep duration, and sleep-related (parent) behaviours for children from birth-36 months. It is well validated by comparisons with actigraphy, sleep diaries and caregiver-reported sleep[74 75].

The *Crying Patterns Questionnaire (CPQ; 6-items; 3 and 6 months)* is a parent-report measure assessing: (1) the amount and time of day when infant crying occurs; (2) situations in which crying occurs; (3) whether the mother finds the crying distressing and seeks advice and help; and (4) the mother's responses to crying. In comparison to 24 hour cry-fuss diaries kept by mothers, the CPQ showed moderate-to-good validity (.51-.68) for total duration of crying scores[75].

The *Infant Toddler Social & Emotional Assessment (ITSEA; 165-items; 12 months)* is a parent-report questionnaire used to assess social-emotional problems/competencies in the domains of behavioural dysregulation and competence. The ITSEA has established concurrent validity, strong test-retest reliability (α=.75-.91) and good internal reliability for each subscale (α=.86 for dysregulation, α=.87 for externalising, α=.85 for internalising, and α=.89 for competence)[108 109]. The ITSEA has been validated for 12 months CA and discriminates between low- and high-risk infants, particularly within the domain of dysregulation[73].

The Communication and Symbolic Behaviour Scales Developmental Profile (CSBS DP; 6 and 12 months) evaluates the symbolic abilities and communication skills of children aged 6-24 months[70]. It includes a 24-item Infant Toddler Checklist which is used as a developmental screening tool to detect autism[110]. The CSBS DP has excellent internal consistency (α=.86-.92), good test-retest reliability and good construct and concurrent validity[70 111].

Mother-infant relationship

Emotional Availability Scales (EAS; 6 months). Coders blind to intervention condition will use the EAS to score 20-minute naturalistic observations of parent-child interactions[64]. 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. The EAS is used to measure quality of parent-child relationships across six scales: parental sensitivity, parental structuring, parental non-intrusiveness, parental non-hostility, child responsiveness and child involvement[64]. The scales have high inter-rater reliability for the parent scales of sensitivity (.95), structuring (.87), non-intrusiveness (.81), non-hostility (.72) and the child scales of responsiveness (.87) and involvement (.87)[112].

The *Emotional Availability - Self Report* (*EA-SR; 36-items; 3, 6 and 12 months)* is a parent-report questionnaire used to measure emotional availability in a dyadic relationship across 5 subscales: Intrusiveness, Hostility, Mutual Attunement, Affect Quality and Capacity to Involve the Parent. Reliability ranges from .71-.84 for all subscales except affect quality (α=.49)[112]. All subscales (except for Intrusiveness) have moderate correlations with the corresponding EAS observed subscales, thus supporting the validity of the self-report measure[112 113].

Maternal mental health

The *Acceptance and Action Questionnaire (AAQ-II; 7-items; baseline, 3, 6 and 12 months)* is a self-report questionnaire measuring psychological flexibility, the key target of ACT[63]. The AAQ-II has good test-retest reliability and convergent validity and excellent internal consistency (α=.94)[63].

The *Depression Anxiety Stress Scales (DASS-21; 21-items; baseline, 3, 6 and 12 months)* assess symptoms of depression, anxiety, and stress in adults. The DASS-21 produces three subscales, each with good internal consistency: the Depression (α=.91-.97), Anxiety (α =.81-.92), and Stress (α=.88-.95) scales[114], and a Total score. The DASS-21 has good convergent validity and acceptable discriminative validity[114].

Comparison group

A comparison group of 30 healthy low risk infants will be recruited and assessed on the Gap-Overlap task and the HINE at 6 and 12 months, and the AOSI at 12 months. This comparison data will support the interpretation of results, particularly for the novel Gap-Overlap task. 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.

Data Collection and Management

Data will be entered onto the REDCap database in a potentially individually identifiable format. Once de-identified, data will be stored in a re-identifiable format on a secure electronic database protected by the [blinded for review] secure server, and only accessible to members of the research team.

Statistical Analysis

Analysis (using STATA or SPSS) will follow standard methods for RCTs using comparisons between the two groups (e.g. general linear models, ANCOVA) and intention-to-treat analyses. 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.

Monitoring

Data monitoring

As this is a trial of a very early intervention with low risk, a data monitoring committee is not required. Any adverse events, particularly negative developmental outcomes, will be recorded and reported to the ethics committees and in the published results.

Harms

This study should not pose risks beyond those of everyday living. Any participants experiencing undue psychological distress will be referred to their general practitioner. For infants scoring at high developmental risk on the GMA, HINE, MSEL or AOSI, infants' general practitioners/paediatricians and parents will be notified. All families will be sent a paediatrician's report detailing 12-month developmental assessment results.

Data Sharing Statement

Data will be made available in a public, open access repository. Deidentified data will be made conditionally available to other researchers with approval from the research team.

ETHICS AND DISSEMINATION

ENACT should support mothers' mental health and may also support infant development. Ethical approval has been obtained from the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/19/QCHQ/50131) and The University of Queensland Human Research Ethics Committee (2019000558) and the trial registered (Australian New Zealand Clinical Trials Registry, ACTRN12618002046280). Study results will be disseminated through scientific journal publications and conference presentations. If shown to be effective, edX facilitates easy dissemination at minimal cost.

DISCUSSION

This study will test the efficacy of an innovative, very early intervention for infants at risk of ASD, integrating early social reciprocity intervention with parental mental health and parent-child relationship support. 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.

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Competing Interests Statement: ENACT was developed from PACT, an intervention developed by researchers at The University of Queensland including Koa Whittingham and Roslyn Boyd. Andrea McGlade and Koa Whittingham developed the of the very early intervention component of edX. ENACT has been developed using the online platform edX.

Abbreviations:

AAQ-II	Acceptance and Action Questionnaire
ACT	Acceptance and Commitment Therapy
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism Spectrum Disorder
BAP	Broad Autism Phenotype
BISQ	Brief Infant Sleep Questionnaire
CA	Corrected age
CAU	Care as Usual
CSBS-DP	Communication and Symbolic Behaviour Scales – Developmental Profile
CPQ	Crying Pattern Questionnaire
DASS-21	Depression Anxiety Stress Scale
EAS	Emotional Availability Scales
EA-SR	Emotional Availability Scales – Self Report
EL	Expressive Language
ELC	Early Learning Composite
ENACT	ENvironmental enrichment for infants; parenting with Acceptance and Commitment Therapy
FM	Fine Motor
GMA	General Movement Assessment
HINE	Hammersmith Infant Neurological Examination
ITSEA	Infant-Toddler Social and Emotional Assessment
MSEL	Mullen Scales of Early Learning
RCT	Randomised Controlled Trial
RL	Receptive Language
VABS-III	Vineland Adaptive Behaviour Scales Third Edition

VR	Visual Reception

TABLE 1: ENACT Intervention Components

Component	Timing	Content
ENACT EdX Course		
Module 1: Very early intervention approach	Begins antenatally with completion before child is 8 weeks	Outlines the very early intervention approach or sensitivity chains and includes multiple videos of parents and babies. Includes advice on early parenting challenges.
Module 2: Living a meaningful life	Begins antenatally with completion before child is 8 weeks	Grounded in ACT, focuses on values and living a rewarding life.
Module 3: Willingness	Begins antenatally with completion before child is 8 weeks	Grounded in ACT, focuses on mindfulness, acceptance and defusion (undermining the literality of language) processes.
Module 4: Relating to others	Begins antenatally with completion before child is 8 weeks	Grounded in ACT, focuses on acceptance, compassion and flexible parenting.
Module 5: Extending early intervention	Begins antenatally with completion before child is 8 weeks	Extends sensitivity chain practice for older babies and provides advice for parents of babies experiencing challenges.
Teleconferencing clinical consultations		
ENACT EdX course completion support	As needed throughout course completion	Focuses on parental understanding of the EdX course, implementation of anything that is immediately relevant, and developing plans for the application of ENACT post-birth.
Developmental Consultations	At 4 weeks, 8 weeks, 12 weeks, 4 months, 6 months, 8 months and 10 months of age	Focuses on expanding and extending sensitivity chain practice, working through any challenges and flexibly supporting parents and parental implementation of sensitivity chain practice using ACT principles. Includes the demonstration of a sensitivity chain whenever possible with opportunities for reflection and feedback.

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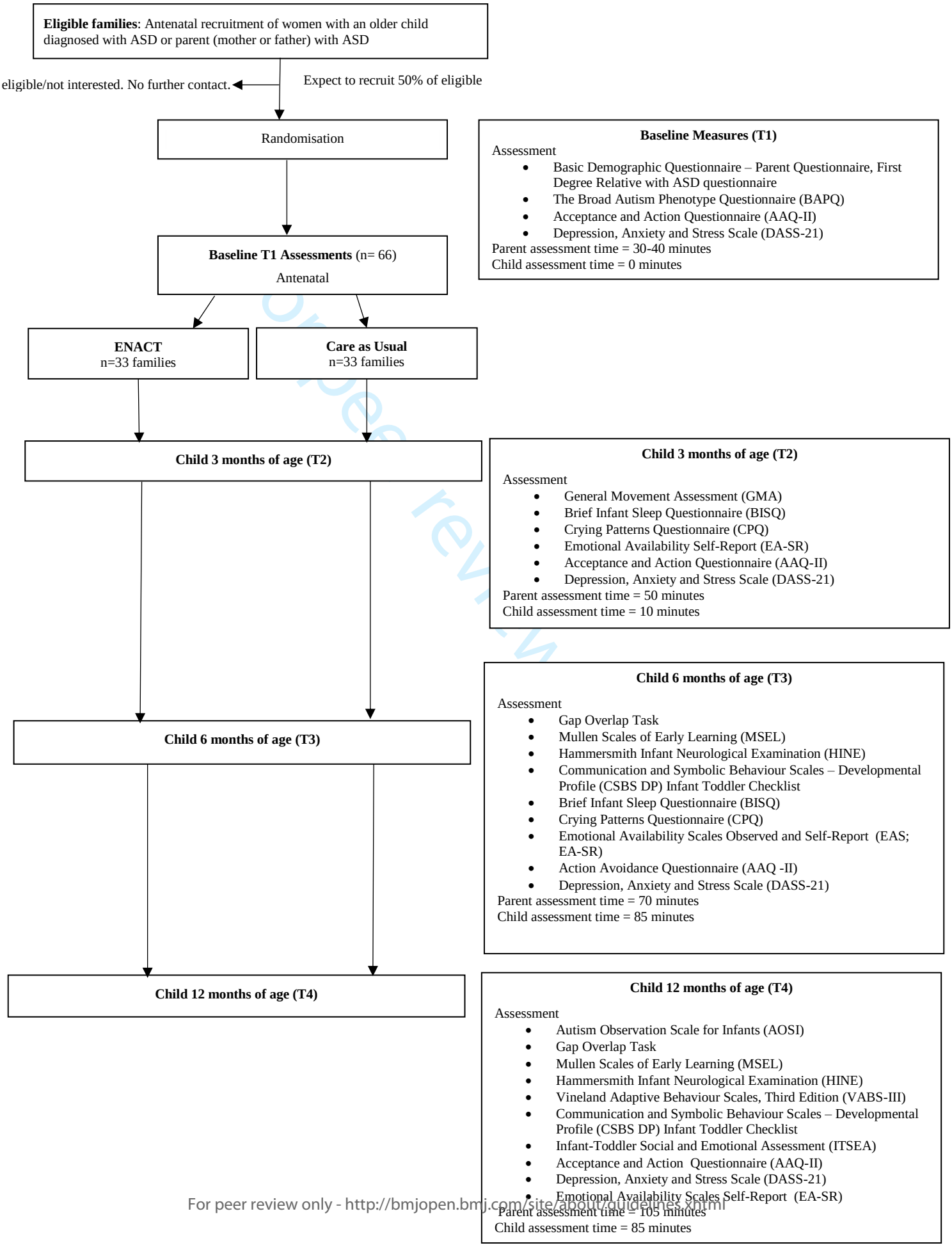
Figure 1: CONSORT flow chart of the ENACT study

FIGURE 1: CONSORT flow chart of the ENACT study



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PARENT/GUARDIAN INFORMATION SHEET

Ethics Approval: HREC/19/QCHQ/50131, 2019000558

Title of Project: Environmental enrichment for infants; parenting with Acceptance and Commitment Therapy (**ENACT**)

Chief Investigators: Dr Koa Whittingham, Dr Andrea McGlade, Miss Kavindri Kulasinghe, Dr Amy Mitchell, Prof. Roslyn N. Boyd, Associate Professor Honey Heussler, Dr Kristelle Hudry

Associate Investigator: Dr Jacqui Barfoot

Thank you for taking the time to read this Information Sheet.
This information statement and consent form is 7 pages long. Please make sure you have all the pages. These pages contain information about a research project that we are inviting you to take part in. **It is okay to say no if you would not like to participate in this study.** Please read this information carefully as it explains clearly and openly what participation involves. Before you decide, you can ask us any questions you have about the project. If you decide you would like to participate in this study then you need to sign and return the consent form attached.

What is the Research Project about?
We have developed a new early intervention approach for infants who have an increased chance of having Autism Spectrum Disorders (ASD), targeting social interaction from the earliest months through parent-child interactions. We have integrated support for parental mental health and parenting challenges into this early intervention, and developed a means of delivering the intervention online through an e-course combined with online consultations. We are calling our early intervention approach 'Environmental Enrichment for Infants: Parenting with ACT', or **'ENACT'**. The e- course we are trialing in this research project is called **'ENACT101'**. This research project is about trialing ENACT with families of infants who have an increased chance of having of developing an Autism Spectrum Disorder (ASD). We are aiming to discover whether ENACT is effective and whether or not families find it useful.

Can I participate?
You can participate in this study if you are **currently pregnant** with a **baby who has a first-degree relative (sibling or parent) with a diagnosis of an Autism Spectrum Disorder (ASD)**. This might mean that you, your baby's biological father, or your baby's sister or brother may have a diagnosis of an Autism Spectrum Disorder (ASD). As ENACT is delivered online, participation is restricted to families with **reliable internet access**. The intervention, ENACT, and the majority of assessments will be conducted via online questionnaires for your convenience. All participating families will **need to be able to travel to the Child Health Research Centre in Brisbane when their infant is 6 and 12 months of age** for their babies to have assessments in person.

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What does participating involve?

If you choose to participate in this study, you will be randomly allocated to one of two groups: ENACT or care-as-usual.

- **The ENACT group** will get immediate access to the ENACT101 e-course and online consultations with a clinician, who will answer any questions you might have and help to tailor the intervention to best meet your own individual needs and those of your baby. The ENACT intervention will include targeting your baby's social interaction from the earliest months during ordinary parent-child interactions. It also includes strategies to support your mental health and support you in coping with parenting challenges such as infant sleep. Our support for parental mental health is grounded in the psychological therapy Acceptance and Commitment Therapy (ACT). ENACT101 includes videos, text, questions and a discussion board.

- **The care-as-usual group** will receive their usual care without access to ENACT. This will allow us to determine if there are benefits to participating in ENACT.

Whether you are allocated to ENACT or to care-as-usual, you will still need to complete assessments **four times during the study: when you sign up and when your child is 3 months, 6 months, and 12 months old**. All of the assessments will include online questionnaires asking about family, feelings, wellbeing, and your relationship with your child, as well as your child's development.

At 3 months of age, you will be asked to record your baby's movements via the Baby Moves app, which we will ask you to download onto your phone. The Baby Moves app helps to record your baby's movements for the General Movements Assessment (GMA), which is a neurodevelopmental assessment tool. When your child is 6 months and 12 months old, we will ask you to bring your child for a visit to the **Centre for Children's Health Research in Brisbane** for a **comprehensive assessment of your baby's development with a developmental paediatrician**. **We will provide you with free parking.**

Can I get a copy of the assessment results and find out about my baby's development?

Absolutely! We hope that this is one of the benefits of participating, whether you are in the intervention group or not. We know that finding out about your baby's development is important to you. All participating families will receive a developmental report after their baby's 12 month assessments. If earlier assessments indicate neurodevelopmental risk, particularly the general movements assessment at 3-4 months of age and the HINE at 6 months then you will be informed and assisted in finding appropriate support. All babies participating in the study will have a report provided to their parent/s after their last assessment and a copy will also go to your baby's general practitioner. If there are any findings of concern you will also be informed via the report and your general practitioner. As these assessments have been performed as part of a study, we cannot provide individual recommendations for management. The report will be able to make some general recommendations though for you to be able to discuss further with your general practitioner (or your child's paediatrician if they have one), so that you know what management options are available.

Your involvement is genuinely appreciated.

Your active participation in refining ENACT is highly valued. We will ask you to share your thoughts and experiences with us as you work through the program.

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The steps of the study participation are summarised below:

✓Agree to participate in the study and sign the consent form
✓ Complete baseline questionnaires online *(30-40 minutes)*
✓ Be randomly assigned to **ENACT** or **Care as Usual** group

ENACT101
✓ e- course
(6-8 hours total over 8-10 weeks)

✓ Early intervention for social reciprocity
✓Supported by regular video conference sessions with clinician

Care as Usual
✓ Your usual postnatal medical care

When your child is 3 months old
✓ Complete questionnaires online
Parent assessment time = 50 minutes
Child assessment time = 10 minutes
✓***Baby Moves app recording at 12 and 14 weeks***
Child assessment time = 5 minutes each recording

When your child is 6 months old
✓ Complete questionnaires online
✓ Record a **20 minute** interaction with your child
✓ **Complete assessments in Brisbane**
Parent assessment time = 70 minutes
Child assessment time = 85 minutes

When your child is 12 months old
✓Complete questionnaires online
✓ Record a **20 minute** interaction with your child
✓ **Complete assessments in Brisbane**
✓ Get a comprehensive report of your child's developmental assessment

Parent assessment time = 105 minutes
Child assessment time = 85 minutes

What does ENACT involve?

ENACT101 is flexible online course, and participants will be able to move through the content at a pace that suits them. We estimate that it will take approximately 6-8 hours in total to complete the content, with most participants beginning antenatally. We aim to ensure that

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participants have worked through all of the ENACT101 content by the time their infant is 8 weeks of age. ENACT101 can be accessed from any device that can connect to the internet.

The social interaction component of ENACT should be practiced regularly from when your infant is 2 weeks old, with a target of 30 minutes per day/5 days per week. However, the social interaction practice is designed to be done during ordinary, everyday activities and interactions with your baby, and shouldn't take up extra time in your day. The clinical consultations will support you in finding ways to practice ENACT in the midst of everyday life.

How will this research help people in the future?
This is the first time an early intervention approach for ASD has been trialed from birth. With your help, we hope to refine ENACT. We have chosen to use an online delivery method, including the development of the e-course ENACT101, so that if ENACT is found to be effective, ENACT101 can be made accessible to families with children who have an increased chance of having Autism Spectrum Disorder across the world.

Are there any risks to participation?
ENACT101 will be exploring your relationship with your newborn child as well as your thoughts, feelings and general well-being. This study contains no risks beyond everyday living.

Will my information be confidential?
Yes! All information that we collect from you and your child, including your questionnaires, videoed parent-child interaction, child assessments and your feedback will be stored in a confidential manner. The information in this study will only be used in ways that will not reveal who you are. You will not be identified in any publication from this study or in any data files shared with other researchers. All information will be held in strict confidence, and will be used for statistical purposes only. Confidentiality will only be breached if a child is deemed at risk of harm or neglect. Data collected from you or your child will be de-identified, by replacing any identifying information (e.g. your name) with a participant number. Identified or de-identified research data may be made available for review by ethics review committees or other regulatory authorities for the purposes of monitoring ethical and scientific conduct of the study.

What if I change my mind?
You do not have to take part in this research project. Your participation will not affect any treatment that you or your child receives. If you do agree to participate, and change your mind at a later date, you are free to withdraw from the study at any time without any negative consequence.

Who is involved?
Chief Investigators

1. **Dr Koa Whittingham** is a clinical and developmental psychologist and a senior research fellow at the University of Queensland. She is experienced in working with parents of children with Autism Spectrum Disorder as well as in Acceptance and Commitment Therapy.
2. **Dr Andrea McGlade** is a developmental paediatrician and is undertaking this project as part of her PhD within the Faculty of Medicine at the University of Queensland.
3. **Miss Kavindri Kulasinghe** is a medical student within the Faculty of Medicine at the University of Queensland. She is undertaking this project as a part of her PhD.
4. **Dr Amy Mitchell** is a paediatic nurse and a research fellow at the University of Queensland with expertise in working with parents.

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5. **Professor Roslyn Boyd** is the Scientific Director of Queensland Cerebral Palsy and Rehabilitation Research Centre. She has clinical and scientific expertise in working with children with cerebral palsy and developmental delay and their families.
6. **Associate Professor Honey Heussler** is a developmental and behavioural paediatrician and a researcher with the Centre for Children's Health Research. She has extensive experience working with children with developmental and behavioural problems.
7. **Dr Kristelle Hudry** is a Senior Lecturer within the Department of Psychology and Counselling at the La Trobe University. She is experienced in working with parents of children with Autism Spectrum Disorder.

Associate Investigators

1. **Dr Jacqui Barfoot** is an occupational therapist with clinical and research experience in parent-infant relationship focussed interventions to support infant development. She is the clinician delivering the ENACT intervention.

Do you have any questions?

Please take the time to ask us any questions that you may have. You can contact:
Miss Kavindri Kulasinghe or Dr Andrea McGlade (Chief Investigators) on (07) 3069 7547 or email uqenact@uq.edu.au

University of Queensland Ethics Contact:

This study adheres to the Guidelines of the ethical review process of The University of Queensland and the National Statement on Ethical Conduct in Human Research. Whilst you are free to discuss your participation in this study with project staff, if you would like to speak to an officer of the University not involved in the study, you may contact the Ethics Coordinators on(07) 33653924 /(07) 34431656, or email humanethics@research.uq.edu.au.

HREC Information:

The Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC) has approved this study. If you have any concerns and/or complaints about the project, the way it is being conducted or your child's rights as a research participant, and would like to speak to someone independent of the project, please contact the HREC Co-ordinator on: 3069 7002 or email CHQETHICS@health.qld.gov.au

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PARTICIPANT CONSENT FORM

Project Number: HREC/19/QCHQ/50131, 2019000558

Title of Project: Environmental enrichment for infants; parenting with Acceptance and Commitment Therapy (ENACT)

Chief Investigators: Dr Koa Whittingham, Dr Andrea McGlade, Miss Kavindri Kulasinghe, Dr Amy Mitchell, Prof. Roslyn N. Boyd, Associate Professor Honey Heussler, Dr Kristelle Hudry

I/We,

_____

voluntarily consent to participate in the above titled Research Project explained to me by:

Mrs/Ms/Dr/Professor _____

- I/We have read the information statement for this study and I/we believe I/we understand the purpose, extent and possible effects of my involvement.
- I/We have had an opportunity to ask questions and I/we am satisfied with the answers I/we have received.
- I/We understand information collected will be stored confidentially and my/our identity will not be revealed.
- I/We understand that I/we can refuse to participate and can withdraw from this study at any time without any negative consequence. In particular, I/we understand that my/our participation will not affect my child's access to usual medical care.
- I/We understand that the purpose of this study is to pilot an innovative, online approach to early intervention and that my/our active involvement, including critical feedback, is valued.
- I/We understand that in order to evaluate the new early intervention I/we will be asked to complete online questionnaires as well as record an ordinary parent-child interaction during the study.
- I/We consent to having videos of my/our child recorded via the Baby Moves app when my/our child is 12 and 14 weeks of age and scored by an independent assessor.
- I/We understand that I/we will receive a developmental report covering my baby's 12 month assessments and that if neurodevelopmental risk is found at the earlier assessments particularly on the general movements assessment or the HINE I/we will be informed as soon as possible.
- I/We understand that in order to evaluate the new early intervention I/we will be asked to complete a developmental assessment at the Children's Health Research Centre in Brisbane when my child is 6 and 12 months of age.
- I/We understand that a report of my child's developmental assessments will be provided at the completion of the assessments and that in the event of any adverse findings I may be contacted by a member of the assessment team to notify me of these findings.

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- I/We consent to provide the name and contact details of my child's General Practitioner and Paediatrician (if your child has a paediatrician).
- I/We consent for my nominated General Practitioner (and paediatrician) to be contacted and a report provided to them for further follow up with your child, including any concerns identified in the assessments performed.
- **I/We consent to participate in this research project.**

My child's GP or Paediatrician:

Name: _____

Address: _____

Phone: _____

Signature _____ **Date** _____

I have explained this study and I believe that the participant/s understands the purpose, extent and possible effects of involvement.

Researcher's Signature _____ **Date** _____

Note: All parties signing the Consent Form must date their own signature.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Title page
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Title page
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Title page

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6-7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6-7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8-9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	17, figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10-11
	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10-11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A