Insika Yomama Trial
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Insika Yomama Trial

Cluster randomised controlled trial to evaluate an intervention for depressed HIV-positive women in the perinatal period, to enhance child development and reduce maternal depression

Statistical Analysis Plan

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ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Treatment
AHRI	African Health Research Institute
BA	Behavioural Activation
BSID-III	Bayley Scales of Infant and Toddler Development III
CBCL	Child Behaviour Checklist
eCRF	Electronic Case Report Form
DFID	Department for International Development
DSMB	Data Safety and Monitoring Board
EPDS	Edinburgh Postnatal Depression Scale
ESoC	Enhanced Standard of Care
GAD-7	Generalized Anxiety Disorder 7-item scale
HIV	Human Immunodeficiency Virus
MICS	Multiple Indicator Cluster Surveys
MRC	Medical Research Council
NPEU	National Perinatal Epidemiology Unit
PI	Principal Investigator
PSI	Parenting Stress Index
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
UNICEF	United Nations International Children's Emergency Fund
VAS	Visual Analogue Scale
WHO	World Health Organization

1 INTRODUCTION

This document details the proposed presentation and analysis for the main paper reporting results from the MRC funded cluster randomised controlled trial of an intervention for depressed HIV-positive women in the perinatal period, to enhance infant development and reduce maternal depression.

The results reported in these papers will follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (Example: to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (Example: data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis plan will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees will be considered carefully, and carried out as far as possible in line with the principles of this analysis plan; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

2 BACKGROUND INFORMATION

2.1 Rationale

Rates of HIV are very high amongst pregnant women in South Africa, 35% in antenatal clinics in some high prevalence areas. Wide access to antiretroviral treatment (ART) for treatment and prevention has reduced maternal morbidity and mortality, dramatically reduced vertical HIV transmission and substantially increased infant survival. As a result, most infants are now born HIV-exposed but HIV-negative, but these mothers and infants still face major challenges to their mental health and development. Depression is very common amongst HIV-positive perinatal women, with a recent Africa-wide systematic review finding that 23% met diagnostic criteria. Depression during the perinatal period is associated with poor adherence to ART, low clinic attendance, suicidal ideation, and low rates of exclusive breastfeeding in the postnatal period. Critically, perinatal depression is also associated with substantial negative effects on parenting, which in turn adversely impacts an infant's cognitive and behavioural development and growth. Improving the outcomes of these mothers and their infants requires both effective treatment of perinatal depression, and interventions to support parenting. Improving cognitive development by 2 years of age is important as it is a key predictor of school readiness and later life opportunities.

2.2 Objectives of the trial

To test whether a combined intervention of a psychological treatment for depression (behavioural activation) and a parenting programme adapted from UNICEF/WHO Care for Child Development for HIV-positive mothers with perinatal depression leads to improved infant cognitive development outcomes at 24 months postpartum and reduced levels of maternal depression at 12 months postpartum, compared to an enhanced standard of care.

2.3 Trial design

Two-arm cluster randomised controlled trial in 48-60 clusters of merged neighbourhoods ('geospatial' clusters).

2.4 Eligibility

Participants are pregnant women, at least 16 years of age, who are HIV-positive and meet criteria for depression, in a rural area of northern KwaZulu-Natal, South Africa.

2.4.1 Inclusion Criteria

- Pregnant women, 23-33 weeks gestation at time of enrolment
- Participant is willing and able to give informed consent for participation in the trial
- Aged 16 years and above
- Diagnosed HIV-positive
- Mother meets criteria for antenatal depression as defined by a score of 9 and greater on the Edinburgh Postnatal Depression Scale (EPDS)
- Living, or planning to live, within the study area at the time of delivery and for at least 9 months after delivery (the intensive treatment period)
- Mother conversant in isiZulu or English

2.4.2 Exclusion criteria

The participant may not enter the trial if ANY of the following apply:

- Any significant disease, disorder or disability which, in the opinion of the Principal Investigator (PI), may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial. This includes hospitalisation for at least three days for severe psychiatric illness (specifically bipolar disorder, schizophrenia, and any other psychoses), or a life-threatening or other serious physical illness (excluding HIV and tuberculosis).
- Current suicidal ideation/thoughts with specific plans and means identified
- Substance or alcohol use disorder
- Currently receiving a psychological treatment for mental health problems
- Participant planning to move away from the study area before 9 months postnatal
- Mother not planning to cohabit with the infant

2.5 Interventions

2.5.1 Enhanced Standard of Care (ESoC)

Participants in the control arm will receive an ESoC, delivered by trained lay counsellors (ESoC Callers). They will be assured access to the standard of care from the department of health services, plus four supportive advice and counselling telephone calls. This will include two phone calls during the antenatal period (2 weeks following enrolment and at 36 weeks gestation) and two after delivery, at 2 weeks and 4 months. During these phone calls the ESoC Caller will assess the participant's health and mental health status, provide supportive listening, encourage utilisation of existing social support, and provide advice. At their enrolment visit, participants will also be provided with a parenting leaflet developed by UNICEF South Africa, which is routinely distributed in maternal and child health clinics in the Department of Health.

2.5.2 Insika Yomama Intervention

The integrated intervention will be delivered by a trained lay counsellor and includes a psychological treatment for depression in combination with a parenting programme to enhance early infant development, which has been adapted from the Care for Child Development package developed by UNICEF and WHO. The first session, which includes an orientation to therapy lasts approximately 2 hours while the remaining sessions last approximately 1.5 hours. Aside from the first session, each treatment session will comprise of a mother-focused behavioural activation (BA) module and an infant-focused parenting component. The BA module focuses on two core principles; (i) increasing activities that are positively reinforcing for the individual (activation) and (ii) addressing processes that inhibit activation. The parenting module aims to promote parenting skills which enhance early infant development, especially cognitive development. Table 1 indicates the delivery of the BA and Parenting components across treatment sessions.

Table 1: Intervention schedule

Session (S)	S1	S2	S3	S4	T1	S5	S6	S7	S8	S9	S10	S11
Timing	26w	28w	30w	32w	36-38w	2w	4w	6w	4m	6m	9m	16m
	Gestation weeks					Weeks and months post-delivery						
Behavioural Activation (BA)	BA1	BA2	BA3	BA4		BA5	BA6	BA7	BA8	BA9	BA10	Booster
Parenting (P)		P1 and P2	P3	P4		P5	P6	P7	P8	P9	P10	Booster
Telephone check-in call (T)					*							

For participants recruited between 26 and 33 weeks, this intervention schedule will be compressed. The times shown are targets and can be modified to fit the course of pregnancy and other antenatal clinic visits in the prenatal period.

The counselling in both arms was conducted by experienced lay counsellors who have at least 2 years of counselling experience, including working with women and children and in HIV counselling. Intervention counsellors received 2 weeks of intensive training based on the therapy manual and assessed for competence by the supervising psychologist. ESoC Callers received a 2-day training workshop followed by a mock telephone call competency assessment.

2.6 Definition of primary and secondary outcomes

2.6.1 Primary outcomes:

- **Child cognitive development measured at child age 24 months** - using the Bayley Scales of Infant and Toddler Development III (BSID-III) cognitive subscale;
- **Maternal depression at 12 months postnatal** - using the Edinburgh Postnatal Depression Scale (EPDS).

Domain	Measure	Metric	Method of aggregation	Timepoint
Child cognitive development at 24 months of age	Bayley Scales of Infant and Toddler Development III (BSID-III) cognitive subscale (Composite Score)	Mean Difference	Mean and SD	24 months postnatal
Maternal Depression	Edinburgh Postnatal Depression Scale (EPDS), total score	Mean Difference	Mean and SD	12 months postnatal

2.6.2 Secondary outcomes:

1. **Maternal Depression measured by the EPDS** - at the end of pregnancy and child age 24 months;
2. **Generalized Anxiety Disorder 7-item (GAD-7) scale** - at the end of pregnancy and child age 24 months;
3. **Maternal Antiretroviral Treatment Adherence** - measured as viral suppression (yes/no) over the entire trial period from clinical records and health questionnaires;
4. **Exclusive breastfeeding to six months postnatal** - measured as 'Exclusive Breast feeding at 6 months (Yes/No) from self-report questionnaire;
5. **Adherence to Infant Immunisation Schedule over the 24 month postnatal period** – measured as the number of immunisations recorded using health questionnaires and clinical records;
6. **Infant diarrhoea over the 24 month postnatal period** – measured as any maternal report of diarrhoea over the previous 14 days (defined as maternal report of child diarrhoea in the previous 14 days) from health questionnaires and clinical records;
7. **Cognitive and emotional stimulation** - within the home environment at child age 12 and 24 months measured by the Multiple Indicator Cluster Surveys (MICS);
8. **Infant behaviour -** at child age 12 months using the Parent-child dysfunctional interaction and the Difficult Child subscale of the Parenting Stress Index Short Form (PSI/SF), and the Child Behaviour Checklist externalising subscale (CBCL) at 24 months;
9. **Child language development at child age 24 months** - measured using the BSID-III language sub-scale;
10. **Child growth (Infant height and weight) at 24 months** - using clinical records and height and weight measurements for child age at 24 months.

	Domain	Measure	Metric	Method of aggregation	Timepoint
1	Maternal Depression	Edinburgh Postnatal Depression Scale (EPDS), total score	Mean Difference	Mean and SD	End of pregnancy; 24months postnatal
2	Maternal Anxiety	Generalized Anxiety Disorder 7-item (GAD-7) scale, total score	Mean Difference	Mean and SD	End of pregnancy, 24m postnatal
3	Maternal Antiretroviral Treatment Adherence	Viral Suppression (Yes/No)	Risk Ratio	Frequency and percentage	End of pregnancy; 12wk, 12m, 24m postnatal
4	Exclusive Breastfeeding	Exclusive breastfeeding at 6 months (Yes/No)	Risk Ratio	Frequency and percentage	6m postnatal
5	Adherence to Infant Immunisation Schedule over the 24m postnatal period	No. of immunisations recorded	Mean Difference	Mean and SD	12wk, 12m, 24m postnatal
6	Infant Diarrhoea	Any maternal report of diarrhoea over the previous 14 days.	Risk Ratio	Frequency and percentage	12wk, 6m, 12m, 24m postnatal
7	Cognitive and Emotional Stimulation within the home environment	Early Childhood Development section of Multiple Indicator Cluster Surveys (MICS6) Questionnaire for cognitive and emotional stimulation for children under five, total score	Mean Difference	Mean and SD	12m, 24m postnatal
8	Infant Behaviour	Parenting Stress Index, Short Form (PSI/SF) parent-child dysfunctional interaction subscale and difficult child subscale, total score	Mean Difference	Mean and SD	12m postnatal
		Externalising sub-scale of Child Behaviour Checklist (CBCL), total score	Mean Difference	Mean and SD	24m postnatal
9	Child Language Development	Language subscale of the Bayley Scales of Infant and Toddler Development III (BSID-III), Composite score	Mean Difference	Mean and SD	24m postnatal
10	Child Growth (Infant height and weight at 24 months)	Road to Health Book, study Weight and height measurements	Mean Difference	Mean and SD	24m postnatal

2.7 Hypothesis framework

This is a superiority trial in which outcomes in the intervention arm will be compared to the ESoC arm, and all comparisons will be analysed and presented on this basis.

2.8 Sample size & power

The first primary outcome will be the cognitive subscale on the Bayley Scales of Infant and Toddler Development, Third Edition (BSID III) at 24 months of age. A trial in Pakistan used a modified version of the CCD programme, and reported a 7.6 point difference between the groups on the same subscale at 24 months of age (effect size=0.6).[9] In order to achieve a power of over 90% (two-sided t-test with a significance level of 0.05), and assuming an estimated difference of 6 points (SD 15) on the BSID III cognitive subscale, a total sample size of 396 women (198 per arm) are required. This calculation takes into account geospatial clustering (24 clusters per arm with an intra-cluster correlation coefficient (ICC) of 0.05) and 'counsellor effect' in the intervention arm (4 lay counsellors with an ICC of 0.05). To take account of attrition of up to 25% a total sample size of 528 women will be recruited (264 per arm, 48-60 geospatial clusters, 9-11 women per cluster). Within each geospatial cluster in the intervention arm, women will also be clustered by lay counsellor (2-3 counsellors per geospatial cluster).

The second primary outcome will be the maternal depression at 12 months. Using the EPDS assessment with a standard deviation of 5, with the same assumptions of clustering as above, a difference of 2 points between trial arms (not adjusting for baseline or repeated measurements) could be detected with 90% power and a 5% 2-sided significance level. Analysis using repeated measures, taking into account within-participant correlation over time allows for smaller differences to be detected with the same power.

2.9 Intervention allocation

The unit of randomisation is the cluster using geospatial location of the participant's homestead. There are approximately 300 neighbourhoods in the region included in this trial; these are defined by geographical area as well as population density so that they are equivalent in terms of sample size. The distinct neighbourhoods were merged to form 48-60 clusters to ensure comparable clusters in terms of key indicators like population size. This clustering approach, and the important role of randomisation in this trial, has been presented to and approved by the Community Advisory Board.

The 48-60 geospatial clusters were randomly allocated to the intervention or ESoC with allocation ratio 1:1 using a random sequence generated by a senior NPEU statistician at the NPEU CTU (using Stata/SE version 13 for windows). The randomisation schedule was sent to the Africa Health Research Institute (AHRI) using a secure web-link and implemented by the data management team based there.

2.10 Data collection schedule

There are 7 planned assessments for this trial detailed in Table 2; A1 is the baseline assessment, and the timings for all the other assessments are as indicated. Trial data will be collected and managed using Research Electronic Data Capture (REDCap) hosted at the AHRI. The following electronic case report forms (eCRFs) will be used:

Recruitment

- Form 1 Pre-screen Verification Questions;
- Form 2 Contact Form;
- Form 3 Eligibility Checklist;
- Form 4a Screening;
- Form 4b Rescreening;
- Regiment Form

- Assessment of Capacity to Consent

Assessments A1-A7

- **A1 – Baseline Assessment**
  - Form 5a Enrollment
  - Form 5b Baseline Questionnaire;
- **A2 –** End of Pregnancy Assessment
  - Form 6 End of Pregnancy Assessment;
- **A3** – Six day postnatal Assessment
  - Form 7 Postnatal Six Day Screener;
- **A4** – 12-week postnatal assessment
  - Form 8 Postnatal Twelve Week Assessment;
- **A5 –** Postnatal 6-month assessment
  - Form 9 Postnatal Six Month Assessment;
- **A6 –** Postnatal 12-month assessment
  - Form 10 Postnatal Twelve Month Assessment;
- **A7** – Postnatal 24-month assessment
  - Form 11a Postnatal Twenty Four Month Assessment
  - Form 11b Postnatal Twenty Four Month Assessment

Other assessment forms

- 12-months Perception of Treatment.

Table 2: Trial assessment schedule

Assessment (A)		**A1**	**Allocation**	**A2**	**Birth**	**A3**	**A4**	**A5**	**A6**	**A7**
	Enrolment & Screening			**Post-Allocation Period**						
Timepoint	Screening & Enrolment	Baseline		End of pregnancy		6-12 days	12w	6m	12m	24m
Screening form and eligibility checklist	X									
Demographic & socioeconomic status		X								
Tracing and location information	X	X		X			X	X	X	X
GPS capture of home		X								
Allocation			x							
Primary Outcomes										
BSID-III cognitive										X
EPDS									X	
Secondary Outcomes										
EPDS	X			X			X			X
GAD-7		X		X					X	X
Maternal Antiretroviral treatment adherence		X		X			X		X	X
Exclusive Breastfeeding								X		
Infant immunisations							X		X	X
Infant diarrhoea							X	X	X	X
Cognitive & emotional stimulation (MICS)									X	X
Infant Behaviour (PSI/SF and Externalising subscale CBC)*									X	X
BSID-III language										X
Child Growth (weight and height)							X		X	X

* If the mother delivers early, this visit will be conducted between 12 and 21 days after delivery.

Additional information will be collected on mediator and other outcomes as listed in the protocol. These will be used in an exploratory analysis documented in a separate statistical analysis plan.

2.11 Interim analyses and stopping rules

An independent Data Safety and Monitoring Board (DSMB) has been established for the trial and the terms of reference for the DSMB were agreed at their first meeting and documented in DSMB charter. During the period of recruitment to the trial, interim analyses were supplied by the Trial Statistician, in strict confidence, to the DSMB, together with any other analyses the DSMB requested. Meetings of the DSMB were arranged periodically, as they considered appropriate.

In the light of interim data, and other evidence from relevant studies (including updated overviews of the relevant randomised controlled trials), the DSMB was to inform the Trial Steering Committee (TSC), if in their view there was proof beyond reasonable doubt that the data indicate that any part of the protocol under investigation was either clearly indicated or contra-indicated. A decision to inform the TSC was based on both statistical, clinical and ethical considerations. Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least 3 standard errors in the interim analysis of a major endpoint might have be needed to justify halting, or modifying, such a study prematurely.

2.12 Trial reporting

The trial will be reported according to the principles of the CONSORT statement for cluster randomised controlled trials.[1] The final analysis for the main results will be conducted once all of the 24 months assessments have been completed.

3 PROTOCOL NON-COMPLIANCES

A protocol non-compliance is defined as a failure to adhere to the protocol such as the wrong intervention being administered, incorrect data reported, errors in applying inclusion/exclusion criteria or missed follow-up visits due to error. Non-compliances are defined below. All protocol non-compliances will be listed in the final report.

3.1 Major

A major protocol non-compliance is any failure to comply with the final study protocol as approved by ethics committees, resulting from error, fraud or misconduct and results in the exclusion of a patient from the study. Fraudulent data will be defined as a major protocol non-compliance in this trial.

3.2 Minor

The following will be defined as minor protocol non-compliances:

3.2.1 Participants randomised in error

These include women:

- Over 33 weeks gestation at time of enrolment (visit window 1 week);
- Whose informed consent is not fully documented;
- Aged below 16 years;
- Not diagnosed HIV-positive;
- Whose EPDS score <9 points;
- Who are planning to move away from the study area before 9 months postnatal;
- Who do not speak English or Zulu as a first language;
- With severe psychiatric illness, or a life-threatening or other serious physical illness;
- With suicidal ideation/thoughts with specific plans and means identified;
- With a substance or alcohol use disorder;
- Who are receiving a psychological treatment for mental health problems;
- Who are not planning to cohabit with the infant.

3.2.2 Participants who do not receive the allocated intervention

These include women:

- In the intervention arm who did not receive the intervention as planned in the protocol;
- In the ESoC who received some or all of the intervention.

4 FIDELITY TO THE INTERVENTION

4.1 In-person treatment sessions

All in-person treatment sessions were audio recorded for quality purposes, if consent was provided by the woman. A 15% sample of audio recordings stratified by lay counsellor, and time period (antenatal, early- and late-postnatal) were scored by an independent assessor to provide a fidelity score for each time period.

4.2 Telephone-delivered treatment sessions

Telephone-delivered treatment sessions were introduced during the COVID-19 pandemic. These were recorded where possible, if consent was provided by the woman, and all were scored by an independent assessor to provide a fidelity score for each time period.

4.3 The fidelity score

A fidelity checklist assessed the presence or absence of key therapy features in the recorded session. The checklist for the antenatal period has 9 items, whilst the checklists for the early- and late- postnatal periods have 10 items each ('parenting' homework was not required for the antenatal sessions). The score for each checklist is derived as the proportion of features present.

5 ANALYSIS POPULATIONS

5.1 Post randomisation exclusions

The numbers (with percentages of the randomised population) of post-randomisation exclusions will be reported by trial arm, and reasons summarised. The following participants will be excluded from the baseline table and the analysis of all outcomes:

- Women for whom a consent form was not received;
- Women for whom consent to use any of their data was withdrawn;
- Women for whom an entire record of fraudulent data was detected.

5.2 Population definitions

The analysis will be on the modified intention to treat (modified ITT) population; women and infants of women will be categorised in the arm the women were randomised to, despite the allocation received, excluding the post-randomisation exclusions listed in section 5.1. For maternal outcomes, women whose infant died during the trial will be included in all analysis populations (unless they are classed as post randomisation exclusions as per section 5.1).

5.2.1 Descriptive analysis population

Baseline demographic and clinical characteristics will be reported for all women randomised minus post-randomisation exclusions.

5.2.2 Comparative analysis population

Maternal outcomes will be reported for all women randomised minus post-randomisation exclusions. Perinatal/developmental outcomes will be reported for infants (only the first-born child in cases of multiparous births) born to these women.

5.2.3 Safety population

Safety data will be reported for all women randomised (and the infants born to them).

5.2.4 Interim analysis population

Baseline data will be reported for all women randomised minus post-randomisation exclusions. Denominators for outcome data will only include women and infants who have reached the end of the time window at which the outcome assessment was planned.

6 DETAILED DEFINITION OF OUTCOMES

6.1 Primary outcomes

6.1.1 Child cognitive development at child age 24 months using the Bayley Scales of Infant Development-Third Edition (BSID-III) cognitive sub-scale

The BSID-III will be used when the infant is 24 months old to assess cognitive development. This is a comprehensive objective assessment administered face-to-face by a qualified independent assessor. Raw scores from the cognitive sub-scale will be converted into age-adjusted scaled scores that are then transformed using published normative data to a composite score equivalent (with mean 100, SD 15).[2] For children for whom a BSID-III could not be completed due to severe developmental delay, a score of 69 will be assigned (i.e. < 2 sds below the mean). [3] Inferential statistics will be based on the continuous outcome.

6.1.2 Maternal depression at 12 months postnatal measured by the Edinburgh Postnatal Depression Scale (EPDS)

The EPDS is a widely used and well established measure of perinatal depressive symptoms used to measure level of depression over the previous 7 days. Mothers will be asked to complete this scale at screening, end of pregnancy, and 3, 12 and 24 months postnatally. The questionnaire consists of 10 items with 4 response categories scored 0 to 3 (questions 3, 5-10 are reverse scored). The total score ranges from 0-30 with higher scores indicating greater severity of depressive symptoms. Missing items will be imputed if ≤20% (2/10) of the scale items are missing using the median score of available scale items for the woman at that time point. If >20% (more than 2/10) of the scale items are missing, an overall total score will not be derived for that participant. The threshold for depression at the screening visit are scored ≥9, and will be summarised using number (%). Inferential statistics will be based on the continuous outcome. The internal consistency of the scales will be assessed using Cronbach's Alpha for each time point.

6.2 Secondary Outcomes

6.2.1 Maternal depression at the end of pregnancy and child age 24 months measured by the EPDS.

This will be derived and analysed as described in section 6.1.2.

6.2.2 Maternal Anxiety measured by The Generalized Anxiety Disorder (GAD-7)

The GAD-7 is a seven-item questionnaire designed to assess the symptoms of generalised anxiety disorder over the previous 2 weeks. Mothers will be asked to complete this scale at baseline, end of pregnancy, and 3, 12 and 24 months postnatally. The GAD-7 total score for the seven items ranges from 0 to 21 and is calculated by assigning scores of 0, 1, 2, and 3, to the response categories [0-not at all, 1-several days, 2-more than half the days, 3-nearly every day]. Missing items will be imputed if ≤20% i.e. 1 item is missing, using the median score of completed items for the woman at that time point, a commonly used method

for imputation of missing items for psychometric scales. Higher scores represent increased anxiety: 0-4 mild; 5-9 moderate; 10-14 moderately severe anxiety; 15-21 severe anxiety, and will be summarised descriptively using number (%). Inferential statistics will be based on the continuous outcome. The internal consistency of the scales will be assessed using Cronbach's Alpha for each time point.

6.2.3 Maternal antiretroviral treatment (ART) adherence

This outcome will not be analysed or presented (see Section 11 for details).

6.2.4 Exclusive breastfeeding 6 months postnatal

This outcome will be derived using the following question measured at 24 months:
"Have you ever breastfed?" and "How long did you give your baby breast milk ONLY when feeding".
If the 24 month data is missing, then responses from questions on breastfeeding asked at 12 weeks, 6 months and 12 months will be used where available. This outcome will be analysed as a binary outcome.

6.2.5 Adherence to infant immunisation schedule over the 24m postnatal period

Information on vaccinations administered to the infant will be recorded from the child's 'Road to Health Card', at 3, 12 and 24 months postnatally. The following table lists the immunisation schedule and the trial assessments in which this information will be collected. The total number of vaccinations possible in the time period is 17. If a particular vaccination is not included on the 'Road to Health Card', it will be assumed that the vaccination was not received. This outcome will be reported as the sum of vaccinations received, and analysed as a continuous variable.

Infant age scheduled	Immunisation type	Data collection form
Birth	BCG OPV0	Postnatal Twelve Week Assessment Form
6 weeks	OPV1 RV1 DTaP-IPV-Hib1 Hep B1 PCV1	Postnatal Twelve Week Assessment Form
10 weeks	DTaP-IPV-Hib2 Hep B2	Postnatal Twelve Week Assessment Form
14 weeks	DTaP-IPV-Hib3 Hep B3 PCV2 RV2	Postnatal Twelve Week Assessment Form Postnatal Twelve Month Assessment Form
9 months	Measles 1 PVV3	Postnatal Twelve Month Assessment Form
18 months	DTaP-IPV-Hib4 Measles 2	Postnatal Twenty Four Month Assessment Form

6.2.6 Infant diarrhoea over the 24 month postnatal period

The mother will be asked if the infant has had any episodes of diarrhoea in the last 14 days at 3, 6, 12 and 24 months postnatally. This outcome will be analysed as a binary outcome defined as at least one episode at each time point, and analysed separately at each time point.

6.2.7 Cognitive and emotional stimulation within the home environment

This will be measured during the 12-month and 24 month assessment using questions selected from the Early Childhood Development section of the Multiple Indicator Cluster Surveys (MICS6) Under 5 survey. These indicators ask about play and communication activities mothers have done with their young children in the last three days, and have been used, with modification for children less than two years of age. [4] Six of the items are scored on a dichotomous scale with 0=mother did not read books/told stories/sang songs/played with/named, counted or drew thing/took child outside, and 1=mother did read books/told stories/sang songs/played with/named, counted or drew things/took child outside. These scores will be totalled and analysed as a continuous variable of exposure to cognitive and emotional stimulation. The score at 12 months will be summarised using descriptive statistics as some of the items are not applicable to infants aged 12 months; inferential statistics will be based on the score at 24 months.

6.2.8 Infant behaviour

Parenting Stress Index (PSI) Short Form

At 12 months of age, maternal perception of infant behaviour will be assessed using the Parent-child Dysfunctional Interaction subscale and the Difficult Child subscale of the PSI-Short Form. These subscales provide an indication of how easy or difficult the parent perceives their infant's behaviour to be. Each subscale has 12 items with 5 categories [strongly agree, agree, not sure, disagree, strongly disagree]. Total raw scores for each subscale are calculated directly from the mother's responses to the questions. For the difficult child subscale, higher scores indicate the perception of a more difficult child, while for the Parent-child dysfunctional interaction subscale, higher scores indicate more dysfunction in the parent-child relationship. Missing items will be imputed if ≤20% (2 items) are missing using the median score of completed subscale items. The 2 subscales will be analysed separately and as continuous variables.

Externalising sub-scale of Child Behaviour Checklist (CBCL)

At 24 months, child behaviour will be assessed using the externalising subscale of the CBCL questionnaire (1½-5 year-old version) which is widely-used and well-validated in South Africa. The Full CBCL for 1½ -5 year olds includes 100 items across 7 subscales. The items relate to child behaviour scored as 0=not true, 1=somewhat or sometimes true, and 2=very true or often true. This trial will use the externalising subscale only which covers 24 items. The externalising subscale compromises:

- Attention problems (5 items)
- Aggressive behaviour (19 items)

These will be summed and the summed raw score will be transformed to a normative score (T-score) using ASEBA software (https://aseba.org/aseba-pc/) and analysed as a continuous variable.

6.2.9 Child language development at child age 24 months using the BSID-III language sub-scale

See section 6.1.1. Raw scores from the language sub-scale will be converted into age-adjusted scaled scores that are then transformed using published normative data to a composite score equivalent (mean 100, SD 15).[2] For children for whom a BSID-III could not be completed due to severe developmental delay, a score of 69 will be assigned (i.e. < 2 sds below the mean).[3] Inferential statistics will be based on the continuous outcome.

6.2.10 Child growth (height and weight) at 24 months

The child's birth weight, and measurements of weight, length/height and head circumference will be recorded from the child's 'Road to Health Card', at 3, 12 and 24 months postnatally. Birthweight will be derived using the first non-missing measurement. Standard deviation scores (Z scores) at month 24 for sex and age will be calculated using the WHO Child Growth Standards,[5] and analysed as a continuous outcome.

7 DESCRIPTIVE ANALYSES

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented. If any important differences are detected in a pre-specified subset of these variables, these will be adjusted for in a sensitivity analysis (see section 8.4).

Baseline variables (as listed in section 7.2) will be presented for those women assessed within and outside the time window for EPDS at 12 months (+/- 3 months - delay most likely due to the impact of the COVID-19 pandemic), by trial arm.

7.1 Representativeness of trial population and participant throughput

The flow of participants through each stage of the trial will be summarised using a CONSORT diagram.[1] This will report the number of:

- Clusters and women randomly assigned
- Women in each cluster (mean (SD) and range)
- Clusters that did not recruit
- Women who received the allocated intervention
- Infants born to women who received the allocated intervention
- Women randomised in error
- Women withdrawn from the intervention
- Women who withdrew consent to use their data
- Women assessed at 12 and 24 months
- Women lost to follow-up
- Women included in the analysis at 12 months
- Infants assessed at 12 and 24 months

7.2 Baseline comparability of randomised groups

The following maternal characteristics at trial entry will be described separately for the two randomised groups using summary statistics:

Financial variables

- Adult food insecurity in the past 4 weeks
- Child food insecurity in the past 4 weeks
- Highest educational level
- Paid employment
- Main household income provider
- Household access to a support grant
- Household access to a child support grant
- Household fridge ownership
- Current household financial situation
- Unable to pay debt repayments in the last 6 months
- Too little money for basics in the last 6 months

Maternal variables

- Maternal age

Mental health variables
- EPDS score (as a continuous and categorical variable: 9-12, ≥13)
- GAD-7 score

Physical health variables
- Gestational diabetes during this pregnancy
- Anaemia diagnosed during this pregnancy
- High blood pressure during pregnancy
- Ever smoked since discovering being pregnant (during this pregnancy), and maximum number smoked on any one day
- Ever consumed alcohol since discovering being pregnant (during this pregnancy), and number of units per week
- Currently on Antiretroviral treatment

Gestation variables
- Completed weeks of gestation at baseline
- Parity (nulliparous/multiparous)
- Number of live births
- Number of miscarriages/stillbirths
- Number of antenatal visits during this pregnancy
- Current pregnancy planned
- Type of milk intend to give baby during first 4 weeks
- If breastmilk only, intended duration (<6 months, ≥6 months)

Household variables
- Current family situation
- Number of resident adults (≥18 years) in the household (as a continuous variable and categorical variable: 1, 2-5, >5 adults)
- Number of resident adolescents (11-17 years) in the household (as a continuous variable and categorical variable: 0, 1, 2-5, >5 adolescents)
- Number of resident children (0-10 years) in the household as a continuous variable and categorical variable: 0, 1, 2-5, >5 children)
- Father of baby lives with participant (mother) in the household

7.3 Infant characteristics at birth
The following infant characteristics at birth will be described separately for the two randomised groups using summary statistics:
- Infant birth weight standardised score
- Infant birth length standardised score

7.4 Follow-up assessments
The following assessment time points will be described separately for the two randomised groups, using summary statistics and histograms:
- Time of EPDS completion from date of delivery, overall and by whether they were completed within or outside the time window of 12 months ± 3 months post-delivery
- Age of child when 24 month assessment was carried out (based on date of completion of BSID-III), overall and by whether they were completed within or outside the window of infant age 24 months ± 3 months post-delivery

7.5 Unblinding of assessor

The following unblinding variable will be described separately for the two randomised groups using summary statistics:

- Assessor becomes unblinded (Y/N) by assessment time point

7.6 Losses to follow-up/withdrawals

The number and percentage of losses to follow up and withdrawals among women will be reported for the two trial arms, and the reasons will be presented where available. All deaths of the woman or infant will be reported separately.

Baseline characteristics (see section 7.2), and maternal short term outcomes (EPDS at end of pregnancy and 12 weeks post-natally, GAD-7 at end of pregnancy), will be described using summary statistics for women with and without the 12 month EPDS (excluding women who have died), and for infants of women with and without the 24 month BSID-III (excluding infants of women who have died), summarised by trial arm. Any imbalance in a pre-specified subset of the baseline variables will be adjusted for in a sensitivity analysis (see section 8.4).

7.7 Fidelity to intervention

The following measures will be reported in the group of women randomised to the integrated intervention (all measures will exclude the booster session):

- Median {IQR} [Range] number of sessions received per woman
- Number (%) of women receiving fewer than 6 out of the 10 therapy sessions
- Mean (sd) of the fidelity scores for each time period (antenatal, early- and late-postnatal) for each of the sample of audio recordings for in-person sessions, and the telephone-delivered recordings (see section 4)
- Overall mean (sd) of the fidelity scores across all time periods separately for the audio recordings of the in-person sessions and the telephone-delivered recordings (overall fidelity scores represent quality of sessions combining scores from different women)

In addition, the number (%) of women who received a booster session will be presented.

The following descriptive analysis to explore the impact of the COVID-19 pandemic on the delivery of the intervention will also be undertaken, presenting the delivery of the intervention telephonically versus in-person. The date indicating the start of the impact of the pandemic is specified as 16/03/2020.

- Number of telephonic sessions after 16/03/2020 for each visit (Sessions 1-11);
- Number of in-person sessions on or before 16/03/2020 and after 16/03/2020 for each visit (Sessions 1-11);
- Number of telephonic sessions per woman after 16/03/2020;
- Number of in-person sessions per woman on or before 16/03/2020 and after 16/03/2020

8 COMPARATIVE ANALYSES

Women and infants of women will be analysed in the groups to which the women were randomly assigned, regardless of deviation from the protocol or treatment received, excluding the post-randomisation exclusions listed in section 5.1 (modified ITT population). The ESoC group will be used as the reference group in all analyses.

For all outcomes at all time-points, the primary analysis will be based on all available outcome data (i.e., a complete-case-analysis), with no imputation other than described in section 6.

8.1 Primary analysis

For the primary outcomes and other continuous outcomes, the mean (SD) will be presented for normally distributed continuous variables, or median and interquartile range for other non-normally distributed continuous variables, by allocation group, and the mean difference (plus 95% confidence interval (CI)) will be estimated using mixed effects linear regression assuming residuals are normally distributed. Should this assumption be considered unmet, a log transformation will be applied in the first instance and the geometric mean ratio (with 95% CI) will be presented. If model assumptions are still unmet, quantile regression methods will be used and the median difference (with 95% CI) will be presented.

For binary outcomes, the number and percentage with the outcome will be presented by allocation group, and the risk ratio (plus 95% confidence interval) will be estimated using a mixed effect model. Adjusted risk ratios and confidence intervals will be calculated using binomial regression with a log link, and if a model fails to converge, a Poisson regression model with a robust variance estimator will be used.[6]

The unit of randomisation is geospatial cluster, however outcomes are collected at the individual level, hence the unit of analysis will be the mother and the infant(s). There is also an additional level of clustering by lay counsellor in the intervention and the control groups. Hence there is a lack of independence among individuals in the same geospatial cluster and/or lay counsellor cluster, and standard methods of analysis will underestimate the standard error of the treatment difference yielding p-values that are too small. To account for the correlation of outcomes within geospatial and lay counsellor clusters, geospatial cluster and lay counsellor identifier will be fitted as random effects, with lay counsellor crossed with geospatial cluster (since lay counsellors worked across clusters).[7] In cases where women had more than one lay counsellor, the lay counsellor who makes the first contact with the woman will be used. The intra-class correlation coefficients for geospatial cluster and lay counsellor will be estimated from the final model for the primary outcomes.

For cognitive and emotional simulation and infant behaviour outcomes (secondary outcomes 7 and 8 in section 2.6.2), models will be additionally adjusted for age of the child at which the assessment took place.

For the EPDS and the GAD-7, a repeated measures model will be fitted, including the baseline, and all follow-up assessments up until the time point of the outcome of interest (e.g. up to 12 months for the 12-month outcomes). Time-treatment interactions will be included in all repeated measures models, under a constrained baseline analysis.[8] Mixed effects models with maximum-likelihood estimation allow participants with incomplete repeated measures data to be included in the model, contributing to the estimation of model parameters. The mean scores with 95% confidence intervals will be plotted over time by allocation group.

8.2 Secondary analyses

None specified.

8.3 Pre-specified subgroup analyses

The consistency of the treatment effect on the primary outcomes will be assessed across specific subgroups using the statistical test of interaction. Effect estimates and 95% confidence intervals will be presented for each subgroup, plus the interaction p-value.

Pre-specified subgroup analyses based on maternal education, socio-economic status, severity of depression at trial entry, child's sex and time point of randomisation will be performed for the infant cognitive development outcome at 24 months; these factors are known to be associated with infant cognitive development. Pre-specified sub-group analyses based on maternal education, socio-economic class, child's sex and time point of randomisation in relation to maternal depression at 12 months will also be performed. The subgroups will be categorised as follows:

- Maternal education (primary completed or below; grade 10; matriculation or above);
- Socio-economic status (Unable to pay debt repayments in the last 6 months yes/no);
- Severity of depression at trial entry (EPDS score 9-12, ≥13);
- Child's sex (male/female).
- Time point of randomisation (on or before 16/03/2020; after 16/03/2020) (to address the impact of the COVID-19 pandemic on the treatment effect)

8.4 Sensitivity analyses

The following sensitivity analyses will be performed:

- A multiple imputation analysis (or other appropriate approach to handling missing data) will be performed for each primary outcome if attrition in each exceeds 5%, assuming data are missing at random. The multiple imputation model will include baseline characteristics and outcome measures collected prior to the missing assessment, which are associated with missing status.[9, 10]
- The final analysis models for both primary outcomes will be additionally adjusted for any or all of the following baseline variables (unless already adjusted for), if important differences between randomised groups are detected, or any important differences are detected between women with non-missing EPDS at 12 months or infants of women with non-missing BSID-III at 24 months and those with corresponding missing outcome data in these baseline variables:
    - EPDS
    - Maternal education
    - Maternal age
    - No. of previous pregnancies
    - Unable to pay debt repayments in the last 6 months
    - Too little money for basics in the last 6 months
- Restricted analysis for the maternal primary outcome only excluding women assessed outside the time window for EPDS (+/- 3 months - delay most likely due to the impact of the COVID-19 pandemic).
- A restricted analysis for the following outcomes measured at 24 months (primary and secondary) excluding women and children for whom the 24 month assessment took place after 36 months postnatal, or, for repeated measures outcomes (EPDS, GAD-7) excluding their 24 month measurements:
    - Child cognitive development at child age 24 months
    - Maternal depression at child age 24 months
    - Maternal Anxiety measured by the GAD-7 at child age 24 months
    - Infant diarrhoea at child age 24 months
    - Cognitive and emotional stimulation within the home environment at child age 24 months
    - Externalising sub-scale of CBCL at child age 24 months

  - Child language development at child age 24 months
  - Child growth (height and weight) at child age 24 months
- A restricted analysis for the following outcomes measured at 12 months (primary and secondary) excluding women and children for whom the 12 month assessment took place after 15 months postnatal, or, for repeated measures outcomes (EPDS) excluding their 12 month measurements:
  - Maternal depression at child age 12 months
  - Cognitive and emotional stimulation within the home environment at child age 12 months
  - Infant behaviour at child age 12 months

8.5 Significance levels and adjustment of p-values for multiplicity

For all pre-specified primary and secondary outcomes, and subgroup analyses, 95% confidence intervals will be used. No adjustments will be made for multiple testing. Precise interpretation of individual secondary outcome results will be made, and therefore no adjustment of the family wise error rate is required.[11]

8.6 Unknown data

Missing data will be described by presenting the number and percentage of individuals in the missing category for every outcome. For missing items in the outcome measurements that are based on summing items to give an overall scores (EPDS, GAD-7, PSI, CBCL) refer to section 6 for the treatment of missing data and prorating rules.

8.7 Statistical software employed

The statistical software Stata/SE version 17 (or later) for Windows will be used for all analyses.

9 SAFETY DATA ANALYSIS

All serious adverse events (SAEs) and adverse events (AEs), their relationship to research procedures, expectedness and date of occurrence will be listed by trial arm, along with number (%) of SAEs and AEs, overall and by type and trial arm. As the trial intervention involves increased visits and face-to-face contact, the number of safety events detected and reported is likely to be higher in the intervention arm. Inferential statistics will therefore not be performed due to the unavoidable bias in reporting methods.

10 ADDITIONAL EXPLORATORY ANALYSIS

The mechanisms by which the intervention improves infant outcomes and maternal responsiveness will be evaluated in an exploratory analysis. The details of this analysis and other subsequent exploratory analysis will be documented in a separate analysis plan.

Any other additional analyses not specified in the analysis plan will be exploratory in nature and 99% confidence intervals will be used. All such analyses will be approved by the Co-investigator Group.

11 DEVIATION FROM ANALYSIS DESCRIBED IN PROTOCOL

Maternal ART adherence will not be analysed or presented, for the following reasons:

- On review of data completeness of the clinical records, very few women had viral load data at the trial specific time points.
- In addition, a very small proportion of the women (<20%) had data at any one particular time point.
- Self-report data from the health questionnaires on adherence to ART was collected but on discussion with experts on ART adherence, this was not considered sufficiently reliable to report on.
- Potential for bias with either method of measuring ART adherence.

The following additional subgroup analysis has been included to assess the homogeneity of the treatment effect before and after the onset of the COVID19 pandemic:

- Time point of randomisation (on or before 16/03/2020; after 16/03/2020)

12 REFERENCES

12.1 Trial documents

Insika Yomama Clinical Trial Protocol Version 1.07 11th Nov 2022
NPEU SOP ST105 v4.0 Statistical Analysis Plan
NPEU SOP ST 107 v3.0 Statistical Analysis and Reporting

12.2 Other references

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9. Enders CK. *Applied Missing Data Analysis.* New York: Guilford Press, 2010.
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11. Parker, R.A., Weir, C.J. Multiple secondary outcome analyses: precise interpretation is important. *Trials* 23, 27 (2022). https://doi.org/10.1186/s13063-021-05975-2

13 APPROVAL

Senior Statistician	Name: Pollyanna Hardy	
	Signature 	Date Nov 6, 2023
Chief Investigator	Name: Professor Alan Stein	
	Signature Alan Stein Alan Stein (Nov 7, 2023 11:02 GMT)	Date Nov 7, 2023
Chair of Trial Steering Committee (or delegate)	Name: Professor Stephen Tollman	
	Signature Stephen Tollman Stephen Tollman (Nov 22, 2023 17:55 GMT+2)	Date Nov 22, 2023

14 DOCUMENT HISTORY

Version	Date	Edited by	Comments/Justification	Timing in relation to interim analysis/unblinding
0.1	14.09.17	LL	First draft	Prior to interim analysis and aggregation of data.
0.2	29.03.19	LL	Reviewed by FvL and AS	Prior to interim analysis and aggregation of data.
0.3	18.11.19	LL	Reviewed by FvL, SR, TE, AS, AY and TR	Prior to interim analysis and aggregation of data.
0.4	08.04.20	LL	Window for f-up assessments changed to +/-3m. Adherence based on viral load only. Subgroup analysis updated. Sensitivity analysis updated. Added SAE table.	Prior to interim analysis and aggregation of data.
0.5	15.07.20	LL	Removal of duration of session from adherence outcomes. Adherence table 6 amended. Addition of AE table 7. Testing of baseline characteristics added.	Prior to interim analysis and aggregation of data.
0.6	02.10.20	LL	Minor edits following suggestions made at DSMB meeting on 01.10.20. Additional analysis to address the impact of the COVID-19 pandemic on the trial.	After interim analysis and aggregation of data.
0.7	Nov 21 to Nov 22	PH	Updates made following a series of meetings with the CI, TM and the stats team appointed to carry out the final analysis.	After interim analysis and aggregation of data.
0.8	07.12.22	PH	Changes accepted and comments addressed	After interim analysis and aggregation of data
0.9	03.03.23	PH	Added responses to comments and additional corresponding amendments.	After interim analysis and aggregation of data
0.10	23.03.23	PH	Edits made during discussions with team at meeting in Oxford on 23rd March 23.	After interim analysis and aggregation of data
0.11	19.05.23	PH	Edits made during discussions with team at meeting in AHRI 19th/20th May 23 including:	After interim analysis and aggregation of data

			accepting changes and deleting/responding to comments from previous version; adding details on assessment of fidelity; adding model adjustment for age for 'Cognitive and emotional stimulation within the home environment' and 'Infant behaviour'; decision to not present 'adherence to ART' with explanation;	
0.12	02.07.23	PH	Changes accepted, minor edits made, references updated.	After interim analysis and aggregation of data
0.13	08.07.23	PH	Changes accepted, minor edits made after generation of dummy tables, references updated.	After interim analysis and aggregation of data
0.14	20.07.23	PH	During discussions with the team on 20/07/23: additional sensitivity analyses added to assess robustness of conclusions removing assessments made much later than planned; ref added for scoring Bayley when assessments were not possible; minor edits made.	After interim analysis and aggregation of data
0.15	06.11.23	PH	Amendments made in response to TSC/DMC/co-investigator review.	After interim analysis and aggregation of data
1.0	06.11.23	PH	Final version	After interim analysis and aggregation of data

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