Improving early detection and intervention for young infants at high risk of neurodevelopmental delay and disability in Uganda

Statistical Analysis Plan
Version 2.0
25th June 2019

This statistical analysis plan has been written based on information contained in the ABAaNA Early Intervention Trial protocol: Version 3.0, 19th February 2018

1. Overview of study design and setting

The study is being conducted at two sites in Uganda: Mulago Hospital and Kiwoko Hospital. The study is an open parallel arm individual randomised trial with two trial arms. Infants at high risk of neurodevelopmental delay and disability and their caregivers are enrolled and randomised to receive either an early intervention programme (the ABAaNA EIP) or standard of care.

The ABAaNA EIP consists of a 10-module parent training course delivered over a six month period and includes two home visits to ensure translation of the skills and learning to the home environment. Participatory group sessions with 6-10 families will be conducted by trained facilitators, who are themselves parents of children with neurodisability.

At enrolment, baseline characteristics of infants and their caregivers were obtained, including data on functioning, nutritional status and quality of life. Outcomes will be assessed by study staff blinded to trial allocation at two time points; at 6 months post enrolment (corresponding to ABAaNA EIP completion in the intervention arm) to assess the immediate impact, and at 12 months post enrolment (corresponding to 6 months post ABAaNA EIP completion in the intervention arm) to assess whether any impacts are sustained.

2. Objectives

The objectives of the study are to:

- Describe the feasibility and acceptability of the ABAaNA Early intervention programme (EIP) as an intervention for high-risk infants in Uganda with neurodevelopmental delay and impairment
- Obtain preliminary data on whether the ABAaNA EIP improves functioning, nutritional status and quality of life of high-risk infants and their carers when compared with standard care.
- Identify the main barriers and facilitating factors for scaling up of the programme.
- Determine the Cost and Cost-effectiveness of the ABAaNA EIP

This statistical analysis plan describes the quantitative analyses to be conducted for objectives 1 and 2. Objective 3 will be assessed through qualitative analyses and objective 4 will be assessed through economics analysis; both will be described separately.

3. Randomisation

Potential participants were screened for eligibility, and those that met the inclusion criteria and gave informed consent were enrolled and randomised. Randomisation was stratified by study site (Mulago and Kiwoko). Within each site, a block randomisation with block size 6 was used to allocate participants either to the ABAaNA EIP (intervention arm) or standard of care (control arm).

4. Outcomes

The primary outcomes of the study will be:

- Feasibility of participant recruitment and randomisation as assessed by the total number recruited and randomised to each arm. Qualitative tools will also be used to capture information on feasibility (details of qualitative analyses will be described in a separate document).
- Acceptability of the early intervention programme amongst caregivers and health care workers as assessed by the protocol violation rate (protocol violations may result from participants in the intervention arm being treated as if they were in the control arm or vice versa) at programme completion, and by the number of programme sessions attended between baseline and programme completion. Qualitative tools will also be used to capture information on acceptability (details of qualitative analyses will be described in a separate document).

- Quality of life as assessed using the scored Pediatric Quality of Life Family Impact module (PedsQL) (Varni 2003) at programme completion and at six months post programme completion.

The secondary outcomes of the study will be:

- Child functioning as assessed by the Pediatric Evaluation Disability Inventory (PEDI) (Haley SM, 1992). The PEDI is a standardised test designed to identify and describe functional impairment and monitor progress. Normative scaled scores are obtained for children ≥6 months to provide age-related expectations of ability.
- Cognitive function as assessed by the Griffiths Mental Developmental Scales II(Huntley M, 1996). This examination measures five areas of development for the 0-2 age group; locomotor, personal-social, hearing and language, eye and hand co-ordination, and performance.
- Growth and nutrition (weight-for-age, height-for-age, weight-for-height).
- Caregiver psychological distress as assessed using the Self-Referral Questionnaire (SRQ) and the Parenting Stress index (PSI) (Abidin RR, 2012). The tools will be translated into Luganda for non-English speakers. The SRQ consists of 20 items each scored 0 (symptom absent) or 1 (symptom present) and the total out of 20 is obtained. The PSI is a 120-item inventory that measures the magnitude of caregiver stress attributable to parent-child relationship (Total Stress Scale), and situational/demographics factors outside the parent-child relationship (Life Stress Scale).
- Caregiver-child attachment (Maternal Infant Responsiveness Instrument; MIRI). The MIRI is a 22-item scale designed to measure the parent's feelings about their infant and an appraisal of the infant's responses (Amankwaa L & Pickler R, 2002).
- Quality of the home environment assessed using the Home Observation for the Measurement of the Environment (HOME). This is composed of 45 items, based on observation and/or interview, assessing the physical environment of the home and the child's interaction within it (Caldwell B & Bradley R, 1984).

5. Sample size considerations

The trial will recruit 126 children and their caregivers, 63 per group. The planned study sample size was based on the primary outcome relating to impact on quality of life, and was estimated to give 90% power to detect a minimal relative improvement of 20% in PedQL Family Impact score between the control and intervention arms, at significance level 5% and accounting for a 20% dropout rate.

We assumed a mean caregiver PedQL score of 65 in the standard care arm and 78 in the intervention arm and SD of 20 in both arms. Assumptions are based on data from the pilot study showing a mean caregiver PedQL score for families before the intervention of 64.9 (SD:19.6) and mean score of 78.9 for families after receiving the intervention (SD 17.5).

This sample size will also provide 90% power to detect an absolute difference of 4 in mean PEDI (motor function, secondary outcome) between the two groups with an alpha value of 5% conservatively assuming a SD of 6 in both groups. This corresponds to a 10% relative improvement assuming a mean PEDI of 40 in the standard care group

6. Analysis for primary outcome 1 (feasibility of the EIP) and trial profile

The first primary outcome, feasibility of participant recruitment and randomisation, will be assessed by the total number recruited and randomised to each arm. Recruitment and randomisation feasibility will be demonstrated if the target sample size of 126 (63 per arm) is achieved. These figures will be displayed in a CONSORT diagram, which will illustrate the following:

- Number of participants assessed for eligibility
- Number of participants assessed but not enrolled, with reasons for non-enrolment
- Number of participants enrolled and providing baseline data
- Number of participants randomised, by trial arm
- Number of participants assessed at 6 months post enrolment, by trial arm
- Number of participants not assessed at 6 months post enrolment with reasons, by trial arm
- Number of participants assessed at 12 months post enrolment, by trial arm
- Number of participants not assessed at 12 months post enrolment with reasons, by trial arm

7. Analysis for primary outcome 2 (acceptability of the EIP)

The second primary outcome, acceptability of the early intervention programme amongst caregivers and health care workers, will be assessed quantitatively by (a) calculating the protocol violation rate, and, (b) summarising the number of programme sessions attended between baseline and programme completion for those in the intervention arm.

Protocol violations may result from (a) participants in the intervention arm being treated or behaving as if they were in the control arm, i.e. not being invited to or not attending any of the early intervention programme modules, or (b) participants in the control arm being treated or behaving as if they were in the intervention arm, e.g. by being invited to or attending any of the early intervention programme modules.

The protocol violation rate will be calculated as the number of participants for whom a protocol violation occurs divided by the total number of participants. It will be presented both overall, and by trial arm.

For participants in the EIP trial arm, attendance at each programme module will be tabulated. The overall number of modules attended by each participant will be summarised using median, range and interquartile range. Acceptability on the basis of this measure will be defined as attendance of at least 6 of the 10 modules.

8. Baseline characteristics and descriptive analyses

Characteristics of infants and their caregivers who are enrolled into the trial will be tabulated by trial arm. Characteristics tabulated will include, but may not be restricted to:

Infant characteristics:

- Age (median, interquartile range (IQR) and range)
- Sex (n(%))
- Birth order (median, IQR and range)
- Weight (mean, standard deviation (SD) and range)
- Weight-for-age z-score (mean, standard deviation (SD) and range)
- Length (mean, standard deviation (SD) and range)
- Length-for-age z-score (mean, SD and range)
- Head circumference (mean, standard deviation (SD) and range)
- Head circumference for age z-score (mean, SD and range)
- Mid upper arm circumference (MUAC) (mean, standard deviation (SD) and range)
- MUAC z-score (mean, SD and range)
- Moderate wasting, defined as weight-for-age z-score < - 2 and/or MUAC < 125mm (n(%))

- Severe wasting, defined as weight-for-age z-score <-3 and/or MUAC < 115mm (n(%))
- Haemoglobin level (mean, SD and range)
- Seizure frequency, categories (n(%))
- Hammersmith Infant Neurological Examination (HINE) score (median, IQR and range)
- Cerebral palsy (n(%))
- Griffiths Mental Developmental Scales (GMDS) Developmental Quotient (median, IQR and range)
- GMDS subscales (median, IQR and range)
- Pediatric Evaluation of Disability Inventory (PEDI) score (median, IQR and range)

Caregiver and household environment characteristics:

- Age (median, IQR and range)
- Sex (n(%))
- Marital status, categories (n(%))
- Relationship to infant, categories (n(%))
- Maternal parity (median, IQR and range)
- Maternal education, categories (n(%))
- Maternal occupation, categories (n(%))
- Caregiver's health (n(%))
- Household income, categories (n(%))
- Household SES, categories (n(%))
- Pediatric Quality of Life Family Impact module (PedsQL) score (median, IQR and range)
- Quality of home environment HOME score (median, IQR and range)
- Self-Reporting Questionnaire (SRQ) (median, IQR and range)
- Parent Stress Index (PSI) (median, IQR and range)
- Maternal Infant Responsiveness Instrument (MIR) (median, IQR and range)

9. Analysis for primary outcome 3 and secondary outcomes (effectiveness of the EIP)

9.1. Timing of outcome assessment

For the quality of life primary outcome and for the secondary outcomes, the analysis will be done at two time points. The first analysis will compare outcomes between intervention and control arms at the end of the programme, when the participants will be aged 12-17 months. The second analysis will compare outcomes between intervention and control arms 6 months after the intervention period has concluded (when participants will be aged 18-23 months).

9.2. Analysis populations

The primary analysis will be an intention-to-treat analysis. The population for this will consist of all infants and their caregivers who are randomised and for whom outcome data are available, regardless of whether they have taken part in the trial interventions (where applicable, i.e. for those in the intervention arm).

9.3. Statistical methods

Data from each outcome measure will be summarised by trial arm. Binary outcomes will be summarised as proportions (number experiencing the outcome divided by number assessed for the outcome). Quantitative outcomes will be summarised as means if approximately normally distributed, or as medians if non-normally distributed. Log transformation of non-normally distributed quantitative outcomes will be investigated, and implemented if it normalises the distribution.

For each outcome, both crude and adjusted analyses will be done. Differences in means/proportions between trial arms together with 95% confidence intervals will be calculated. We do not plan any formal statistical tests due to the preliminary nature of the trial; instead confidence intervals will provide a possible range of effect sizes.

Analyses adjusting for baseline measures of the outcomes, which were collected at enrolment into the trial, will be done using regression models, in order to improve precision of effectiveness estimates. Adjusted analysis may also incorporate other baseline characteristics that were not balanced by the randomisation (if any). Logistic regression will be used for binary outcomes. Linear regression will be used for quantitative outcomes that are approximately normally distributed, or that are approximately normally distributed after transformation (in which case linear regression will be applied to the transformed data). For skewed quantitative outcomes with distributions that are

not normalised by suitable transformation, linear regression using bootstrapping to estimate confidence intervals or quantile regression models will be considered.

9.4. Checking model assumptions

For statistical analyses that require data to be normally distributed, the normality assumption of the data will be checked using graphical assessment of normality (Q-Q plot) and a Kolmogorov-Smirnov test for normality. If the data are found to be non-normal, medians (IQR) will be presented instead of means (SD). A log transformation will be applied to achieve normality and if not achieved, alternative tests such as the Wilcoxon rank sum test will be used. The assumption of equal variances will be checked by testing if standard deviations of the two sample counts are approximately equal e.g. using the F test. If the variances are found to differ, a t test allowing for unequal variance will be used.

9.5. Missing data

Participants with missing outcome data at the end of the programme will be excluded from effectiveness analyses at this time point. Participants with missing outcome data at 6 months post programme completion (12 months post enrolment) will be excluded from effectiveness analyses at this time point. Participants who miss one of the two outcome assessment visits but attend the other outcome assessment visit will only be excluded from the outcome time point that they did not attend. There will be no imputation of missing data.

10. Shell tables

Table 1. Protocol violations

Trial arm	Date of protocol violation	Description of protocol violation

Table 2. Protocol violation rate

Trial arm	Number of participants	Number of protocol violations	Protocol violation %
Control			
EIP			
Overall			

Table 3. Early intervention programme module attendance, by module

Module number	Total number participants expected[1]	Total number participants attended	% attendance
1			
2			
…			
10			

[1]Numbers of participants permanently lost to follow-up, withdrawn, died, or otherwise no longer expected to attend module for any other reason will be described in a footnote, with reasons.

Table 4. Early intervention programme module attendance, by participant

Number of modules attended	Number participants	% participants
1		
2		
…		
10		
Total		

Table 5a: Baseline characteristics of infants by trial arm

	Standard care (N=xx)	Early intervention programme (N=xx)
Characteristic	N (%) mean (SD), range median (IQR), range	N (%) mean (SD), range median (IQR), range
Sex (male)		
Age		

Table 5b: Baseline characteristics of caregivers and home environment by trial arm

	Standard care (N=xx)	Early intervention programme (N=xx)
Characteristic	N (%) mean (SD), range median (IQR), range	N (%) mean (SD), range median (IQR), range
Sex (male)		
Age		

Table 6: Effect of EIP on PedsQL and secondary effectiveness outcomes, at programme completion (6 months post enrolment)

Outcome	Standard care	EIP	Crude difference/	Adjusted difference/
	mean (SD) / n (%)[1]	mean (SD) / n (%)[1]	odds ratio (95% CI)[2]	odds ratio (95% CI)[2]
PedsQL				
PEDI				
GMDS DQ				
GMDS sub-scales				
…continued				

[1]Mean (SD) will be presented for continuous outcome variables, n (%) will be presented for binary outcome variables; [2]Mean difference will be presented for continuous outcome variables, odds ratios will be presented for binary outcome variables

Table 7: Effect of EIP on PedsQL and secondary effectiveness outcomes, at 6 months post programme completion (12 months post enrolment)

Outcome	Standard care	EIP	Crude difference/	Adjusted difference/
	mean (SD) / n (%)[1]	mean (SD) / n (%)[1]	odds ratio (95% CI)[2]	odds ratio (95% CI)[2]
PedsQL				
PEDI				
GMDS DQ				
GMDS sub-scales				
…continued				

[1]Mean (SD) will be presented for continuous outcome variables, n (%) will be presented for binary outcome variables; [2]Mean difference will be presented for continuous outcome variables, odds ratios will be presented for binary outcome variables