Trials

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Statistical analysis plan for the Prenatal Iodine Supplementation and Early Childhood Neurodevelopment (PoppiE) randomised controlled trial

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Abstract

Background Observational evidence suggests both low and high iodine intakes in pregnancy are associated with poorer neurodevelopment in children. This raises concern that blanket recommendations for iodine supplementation in pregnancy may negatively impact child neurodevelopment in women with sufficient iodine intake from food alone.

Methods PoppiE (Prenatal Iodine Supplementation and Early Childhood Neurodevelopment) is a multi-centre, parallel, two-arm, clinician, researcher and participant blinded randomised controlled trial. Seven hundred fifty-four consenting pregnant women ≤ 13 weeks of gestation with an iodine intake of > 165 µg/day from food will be randomised to receive a multivitamin and mineral supplement containing 20 µg/day (intervention) or 200 µg/day (control) of iodine from enrolment until delivery. The primary outcome is the developmental quotient of infants at 24 months of age as assessed with the Cognitive Scale Score of the Bayley Scales of Infant Development, 4th Edition, to be analysed using linear regression with generalised estimating equations to account for multiple births. In this article, we comprehensively detail the planned statistical analyses of the PoppiE trial, including approaches to intercurrent events, methods for handling missing data and planned sensitivity analyses.

Conclusions PoppiE is the first trial to examine the effect of prenatal iodine supplementation on early childhood development in women with sufficient iodine intake from food. At the time of writing (February 2025), recruitment into the trial is complete and data collection is due to conclude in July 2026. The statistical analysis plan was finalised before the database lock, which will ensure study conclusions are not subject to bias due to data-driven analyses.

Trial registration ClinicalTrials.gov NCT04586348. Registered on October 14, 2020.

Keywords Iodine, Supplementation, Pregnancy, Cognitive development, Randomised controlled trial, Statistical analysis plan

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Introduction

Observational studies suggest both low and high maternal iodine intakes during pregnancy are associated with poorer neurodevelopmental outcomes in children [1–7]. Our recent cohort study involving 800 mother-infant pairs in Australia found that average iodine intakes below ~185 μg/day and above ~350 μg/day through pregnancy were associated with poorer cognitive and language scores in children at 18 months of age [8, 9]. These findings raise concern that blanket recommendations for iodine supplementation in pregnancy may negatively impact neurodevelopment in the offspring of iodine-sufficient women. The objective of the Prenatal Iodine Supplementation and Early Childhood Neurodevelopment (PoppiE) trial is to determine the effect of reducing iodine intake from supplements in women with adequate iodine intake from food early in pregnancy on the cognitive development of infants at 24 months of age.

This article describes the planned statistical analysis strategy for the PoppiE trial, to conform with the trial protocol. The statistical analysis plan (version 1, February 2025) was finalised before database lock and unblinding. Any deviations from the planned analysis strategy detailed in this article will be documented, with reasons, in an appendix to the primary publication of trial results.

Study methods

Trial design

A detailed description of the trial design has been published previously [10]. PoppiE is a multi-centre, parallel, two-arm (1:1 allocation), clinician, researcher and participant blinded partially clustered randomised controlled trial, with infants from a multiple birth clustered within mothers. Consenting pregnant women ≤13 weeks of gestation with an iodine intake of >165 μg/day from food, estimated using a validated iodine-specific food frequency questionnaire [11], are randomised to receive a multivitamin and mineral supplement containing 20 μg/day (intervention) or 200 μg/day (control) of iodine from enrolment until delivery. The primary outcome is the developmental quotient of infants at 24 months of age as assessed with the Cognitive Scale Score of the Bayley Scales of Infant Development, 4th Edition (Bayley-IV).

Randomisation and blinding

Pregnant women are assigned to receive 20 μg/day or 200 μg/day iodine supplements using a secure web-based randomisation service implemented via REDCap. The randomisation service allocates group assignments according to a computer-generated randomisation schedule prepared by an independent statistician using ralloc.ado version 3.7.6 in Stata version 16.1. Randomisation is stratified by state or territory at enrolment (South Australia, Victoria, New South Wales, Queensland, Western Australia, Australian Capital Territory and Tasmania) using randomly permuted blocks of varying sizes, with sizes to be disclosed at trial completion.

Participants, care providers, outcome assessors, research personnel and data analysts are blinded to the randomisation group. In a medical emergency where knowledge of the investigational product is critical to a participant's clinical management, the blind for that participant may be broken. In such cases, the principal investigator (KPB) shall be notified of the need to approve an unblinding request but will remain blinded to the group allocation. The number of infants whose families are unblinded and reasons for unblinding will be reported as a post-randomisation characteristic.

Sample size

To detect a mean difference of 4 points in the Cognitive Scale Score of the Bayley-IV with 90% power (standard deviation 15 points, two-tailed $\alpha = 0.05$), 297 observations per group are required. No adjustment will be made for partial clustering [12] due to multiple births in sample size calculations, as the proportion of women expected to have a multiple birth is just 1.8% in this population and including women with a multiple birth will increase the effective sample size for the number of infants [13]. Assuming 6% losses due to miscarriage <20 weeks of gestation, termination <20 weeks of gestation, stillbirth and infant death, and allowing a further 15% loss to follow-up to 24 months, the planned sample size is 754 women (377 per group). A 4-point difference in the Cognitive Scale of the Bayley-IV is realistic based on the results of our cohort study [8] and would constitute a difference considered clinically important by developmental paediatricians. Similar effects on developmental quotients have prompted public health authorities to promote strategies to prevent iron deficiency anaemia and remove lead from petrol and paint [14, 15].

Framework

All statistical comparisons will be undertaken assuming a standard superiority hypothesis testing framework.

Statistical interim analyses and stopping guidance

An independent Data Safety and Monitoring Board has been appointed to safeguard the interests of participants in the trial; however, no formal interim analyses are planned.

Timing of final analysis

The database will be locked for analysis once data collection and cleaning are complete. Following database lock, blinded treatment codes (e.g. A and B) will be provided

to the trial statistician, with analysis of the outcomes listed in this analysis plan to be performed using these codes. After analyses have been completed and results presented to trial investigators, the treatment codes will be fully unblinded.

Timing of primary outcome assessment

The Cognitive Scale Score of the Bayley-IV is administered at 24 months chronological age for term-born infants and 24 months after the expected date of delivery for infants born < 37 weeks of gestation. We will endeavour to administer the Bayley-IV within a window of 24 months and 0 days to 24 months + 14 days. However, as the Cognitive Scale Score is age-standardised, data collected from assessments outside this target window will be retained in outcome comparisons.

Statistical principles

Confidence intervals and *p* values

For each outcome variable, a 95% confidence interval will be reported to express uncertainty about the estimated treatment effect, with the effect taken to be statistically significant if the p value for the two-sided comparative test is < 0.05. In describing the effectiveness of the intervention, multiple hypothesis tests will be performed due to numerous secondary outcomes, as well as subgroup analyses and sensitivity analyses for the primary outcome. No multiplicity adjustment will be made for the number of secondary analyses, as these are of less importance than the primary analysis of the primary outcome. Without a formal procedure for controlling the type I error rate, less emphasis will be placed on the results of secondary analyses.

Adherence and protocol deviations

Women are instructed to take one study supplement (tablet) daily from enrolment until delivery. At 7 days after randomisation and 16, 22, 28 and 36 weeks of gestation, women are asked how many days they have missed taking their study supplements in the previous week. During the first postnatal telephone call, scheduled for 2 weeks after the expected delivery date, women are asked what date they ceased taking the study supplements and how many supplements they have left. According to these responses, adherence with study supplements will be described as the median and interquartile range of supplements missed in the last week at each follow-up appointment and the percentage of supplements consumed during the intervention period (100 × number consumed/number expected to be consumed). A mid-pregnancy 'casual' urine sample will also be collected at 28 weeks of gestation to determine urinary iodine concentration; the median and interquartile range of urinary iodine concentration (measured in μg/L) will be calculated for each randomised group as an additional measure of adherence.

The number of ineligible women randomised, women randomised in the wrong stratum, and women provided the wrong supplements according to their randomisation will be reported, with reasons, by randomised group.

Estimand for the primary outcome

The primary trial objective is to evaluate in women with adequate iodine intake from food early in pregnancy (> 165 μg/day) the effect of being randomised to receive 20 μg/day or 200 μg/day iodine supplementation during pregnancy on the Bayley-IV Cognitive Scale Scores in surviving offspring at 24 months of age. The defining attributes of the estimand [16] for addressing this objective are as follows. *Target population*: Infants of mothers with adequate iodine intake from food early in pregnancy (> 165 μg/day) who survive to 24 months of age. *Treatments*: 20 μg/day or 200 μg/day iodine supplementation during pregnancy. *Endpoint*: Bayley-IV Cognitive Scale Score. *Population summary*: Mean difference. *Handling of intercurrent events*: Non-compliance with the randomised supplement regime, including treatment discontinuation, taking other supplements, or being administered the wrong study supplements, will be ignored under a treatment policy strategy (consistent with the intention to treat approach detailed in the PoppiE trial protocol). Miscarriages, terminations, stillbirths and infant deaths will be excluded from the analysis according to the target population attribute.

Analysis population

Participants will be excluded from the analysis population for each trial outcome if the strategy for handling intercurrent events dictates their exclusion. For example, miscarriages, terminations, stillbirths and infant deaths will be excluded from the analysis population for the primary outcome as per its intercurrent event handling strategy. Participants found to be ineligible after randomisation (e.g. iodine intake from food early in pregnancy ≤ 165 μg/day, measured at baseline) will remain in the analysis population unless otherwise excluded due to intercurrent events. It will be assumed that infants lost to follow-up or withdrawn from the study who were last known to be alive will survive to 24 months and remain in the analysis population for all relevant outcomes. In the case of loss to follow-up or withdrawal during pregnancy before multiple birth status is confirmed, a singleton pregnancy will be assumed.

Trial population

Eligibility

Pregnant women are eligible to participate if they are ≤13 weeks of gestation; consume >165 µg/day of iodine from food alone, estimated using a validated iodine-specific food frequency questionnaire [11]; and English is the primary language spoken at home. Exclusion criteria include current treatment for thyroid disease or partial or complete thyroidectomy; previous child diagnosed with a thyroid dysfunction; and carrying a foetus with a known or suspected congenital abnormality that affects neurodevelopment.

Recruitment

Participant flow through the study will be described using a flowchart, as recommended by the Consolidated Standards of Reporting Trials (CONSORT) statement [17] (Fig. 1).

Withdrawal/follow-up

Participants are free to withdraw consent at any stage of the trial, after which time subsequent data are no longer collected. The number and percentage of participants withdrawing consent or lost to follow-up during both

Fig. 1 Consort flowchart for the PoppiE trial

the intervention (pregnancy) and follow-up phases of the trial will be reported by randomised group.

Baseline characteristics

A descriptive comparison of the randomised groups will be conducted on the baseline characteristics presented in Table 1. Comparisons will use all available data, with participant observations attributed to their randomised group irrespective of the occurrence of protocol deviations or intercurrent events. Means and standard deviations, or medians and interquartile ranges, will be reported for continuous variables. Frequencies and percentages will be reported for categorical variables. The clinical importance of any observed imbalances will be noted. Baseline urinary iodine concentration will also be descriptively compared by the state or territory at enrolment to confirm geographical differences in iodine status.

Post-randomisation characteristics

A descriptive comparison of the randomised groups will be conducted on the post-randomisation characteristics presented in Table 2. Comparisons will use all available data, with participant observations attributed to their randomised group irrespective of the occurrence of protocol deviations or intercurrent events. Means and standard deviations, or medians and interquartile ranges, will be reported for continuous and time-to-event variables. Frequencies and percentages will be reported for categorical variables. The clinical importance of any observed imbalances will be noted. The blindness index [18], which

Table 1 Baseline characteristics

Characteristic	Categories
Recruitment state or territory	Australian Capital Territory/ New South Wales/ Queensland/ South Australia/ Tasmania/ Victoria/ Western Australia
Age, years	–
Gestation at enrolment, weeks	–
Parity	0/1/> 1
Multiple pregnancy	Yes/no
Pre-pregnancy BMI, kg/m^2	–
Born in Australia	Yes/no
Aboriginal or Torres Strait Islander	Yes/no
Completed secondary education	Yes/no
Completed further study	Yes/no
Highest qualification completed	Certificate, apprenticeship or diploma/degree/higher degree/not applicable
Annual household income ($AUD)	≤ $25,000/$25,001 to $50,000/$50,001 to $100,000/$100,001 to $150,000/$150,001 to $250,000/> $250,001/undisclosed
Index of Relative Socioeconomic Disadvantage[a]	Quintile 1/2/3/4/5
Smoking at enrolment	Yes/no
Smoking in 3 months leading up to pregnancy	Yes/no
Smoking in household at enrolment	Yes/no
Alcohol use at enrolment	Yes/no
Alcohol use in 3 months leading up to pregnancy	Yes/no
Fertility treatment	Yes/no
Type 1 diabetes	Yes/no
Type 2 diabetes	Yes/no
Gestational diabetes in previous pregnancy	Yes/no/not applicable
Pre-eclampsia/eclampsia in previous pregnancy	Yes/no/not applicable
Urinary iodine concentration, µg/L	–
Iodine intake at screening, µg/day[b]	–
Pre-conception supplement use	Yes/no
Supplement use at enrolment	Yes/no
Infant sex	Female/male

[a] Australian Bureau of Statistics (2021), Socio-Economic Indexes for Areas (SEIFA), Australia, ABS Website, 'Postal Area, Indexes, SEIFA 2021, Table 1: Postal Area (POA) SEIFA Summary, 2021' [dataset]. Quintile 1 is the most disadvantaged

[b] Estimated using a validated iodine-specific food frequency questionnaire

Table 2 Post-randomisation characteristics

Characteristic	Categories
Maternal	
Iodine intake at 28 weeks of gestation, μg/day[a]	–
Took non-study nutritional supplements during intervention period	Yes/no
Diagnosed with thyroid problems during intervention period	Yes/no
Postnatal iodine supplementation if breastfeeding	Yes/no/not applicable
Which study group believed to be in	Intervention/control/unsure
Infant	
Apgar score at 5 min	–
Duration of breastfeeding[b]	–
Age commenced solids	–
Childcare attendance before primary outcome assessment	Yes/no
Home Screening Questionnaire score	–
Age at primary outcome assessment	–
Unblinded before primary outcome assessment	Yes/no

[a] Estimated using a validated iodine-specific food frequency questionnaire

[b] Treated as a time-to-event variable

quantifies the proportion of correct guesses on study group assignment beyond that expected by chance, will also be calculated.

Analysis

Outcome definitions

The primary and secondary outcomes for the trial are summarised in Table 3. All Bayley-IV raw scores are externally age-standardised to give scale scores with a mean of 100 and a standard deviation of 15. Standardised scores range from 50 to 150 and can be classified as within the normal range of development (85–115), delayed performance (< 85) or accelerated development (> 115). A clinical psychologist will review the case notes of children who are unable to undergo the Bayley-IV assessment due to deficit, disability or other impairment, to determine whether it is appropriate to assign the lowest score possible.

Estimands

The target population and strategy for handling intercurrent events for each outcome estimand vary according to the timing and level of measurement (infant or mother) of the outcome. Trial outcomes can be grouped as in Table 4, using outcome reference numbers from Table 3, to simplify the description of these two estimand attributes. For all outcomes, non-compliance with allocated treatment will be ignored under a treatment policy strategy, consistent with the intention to treat principle.

For all outcomes, the remaining attributes of the estimand are defined as follows. *Treatments*: 20 μg/day or 200 μg/day iodine supplementation during pregnancy. *Endpoint*: As defined in Table 3. *Population summary*: Mean difference for continuous outcomes, or adjusted odds ratio and risk difference for binary outcomes.

Analysis methods

The primary outcome and continuous secondary outcomes will be analysed using linear regression, with the effect of treatment described as a mean difference with a 95% confidence interval. To account for clustering due to multiple births within the same family, generalised estimating equations assuming an independence working correlation structure will be used [19]. All binary secondary outcomes will be analysed using logistic regression, with the effect of treatment described as an adjusted odds ratio with a 95% confidence interval; generalised estimating equations assuming an independence working correlation structure will be used in the case of infant-level binary secondary outcomes to account for clustering due to multiple births. A risk difference and 95% confidence interval will also be presented for binary secondary outcomes, estimated using standardisation following analysis via logistic regression (with the delta method used to calculate standard errors). If the number of infants or mothers experiencing a binary secondary outcome is less than 10 in either randomised group, then, regardless of convergence, a Fisher exact test will be performed instead of logistic regression.

Given recommendations to adjust for variables used to stratify the randomisation when estimating treatment effects [20, 21], analyses will be adjusted for location of enrolment (South Australia, Victoria, New South Wales, Queensland, Western Australia, Australian Capital

Table 3 Primary and secondary trial outcomes

#	Outcome	Time-point measured	Variable type
	Primary		
1	Bayley-IV[a] Cognitive Scale Score	24 months	Continuous
	Secondary infant		
2	Bayley-IV Cognitive Scale Score < 85	24 months	Binary
3	Bayley-IV Motor Scale Score	24 months	Continuous
4	Bayley-IV Motor Scale Score < 85	24 months	Binary
5	Bayley-IV Language Scale Score	24 months	Continuous
6	Bayley-IV Language Scale Score < 85	24 months	Binary
7	ITSEA externalising *T* score	24 months	Continuous
8	ITSEA internalising *T* score	24 months	Continuous
9	ITSEA dysregulation *T* score	24 months	Continuous
10	ITSEA competence *T* score	24 months	Continuous
11	ITSEA externalising *T* score ≥ 65	24 months	Binary
12	ITSEA internalising *T* score ≥ 65	24 months	Binary
13	ITSEA dysregulation *T* score ≥ 65	24 months	Binary
14	ITSEA competence *T* score ≤ 35	24 months	Binary
15	Weight *z*-score[b]	24 months	Continuous
16	Length *z*-score[b]	24 months	Continuous
17	Head circumference *z*-score[b]	24 months	Continuous
18	Weight *z*-score[b]	Birth	Continuous
19	Length *z*-score[b]	Birth	Continuous
20	Head circumference *z*-score[b]	Birth	Continuous
21	Length of gestation (days)	Birth	Continuous
22	Preterm birth < 37 weeks of gestation	Birth	Binary
23	Thyroid-stimulating hormone level[c]	Birth	Continuous
24	Admission to special care nursery	Birth hospitalisation	Binary
	Secondary maternal		
25	Hypertension/pre-eclampsia	Pregnancy	Binary
26	Gestational diabetes	Pregnancy	Binary
27	Vaginal delivery	Birth	Binary
28	Postpartum haemorrhage	Postpartum stage	Binary

Abbreviations: ITSEA Infant Toddler Social Emotional Assessment

[a] If a Bayley-IV assessment is unavailable, scores of an alternative robust developmental assessment with an age-standardised cognitive score will be accepted, if available (e.g. earlier versions of the Bayley scales or the Wechsler Preschool and Primary Scale of Intelligence)

[b] Calculated according to WHO growth standards based on an average of 2 measures (average of closest 2 measures if a 3rd measure taken)

[c] Measured only in infants from South Australia

Territory and Tasmania), treated as a fixed effect in each analysis model. However, adjustment is not expected to lead to efficiency gains, as stratification was performed predominantly for logistic reasons rather than expected associations with outcome variables. For binary outcomes with low to moderate prevalence, adjustment for location of enrolment may lead to model non-convergence. In these instances, the Australian Capital Territory, Tasmania and Western Australia enrolment locations will be collapsed together; these locations correspond to the smallest strata and the last to join the trial. If convergence remains an issue following collapsing of enrolment locations, an unadjusted analysis will be performed instead. Adjusted analyses will not be considered for binary secondary outcomes analysed using a Fisher exact test. An adjusted analysis will not be performed for thyroid-stimulating hormone levels as this outcome will only be measured in South Australian participants.

For the primary outcome only, exploratory analyses will be performed to test for evidence of effect modification by enrolment location (South Australia, Victoria, New South Wales, Queensland, Western Australia, Australian Capital Territory and Tasmania) and iodine intake at screening. Effect modification by enrolment

Table 4 Target population and intercurrent event handling by outcome variable groupings

Outcomes	Estimand attributes
1–17: Infant cognitive development and anthropometrics at 24 months of age	Target population: Infants of mothers with adequate iodine intake from food early in pregnancy (> 165 µg/day) who survive to 24 months of age Intercurrent events: Non-compliance with the randomised supplement regime will be ignored under a treatment policy strategy. Miscarriages, terminations, stillbirths and infant deaths will be excluded from analysis according to the target population attribute
18–24: Infant birth and birth hospitalisation characteristics	Target population: Infants of mothers with adequate iodine intake from food early in pregnancy (> 165 µg/day) who are live-born Intercurrent events: Non-compliance with the randomised supplement regime will be ignored under a treatment policy strategy. Miscarriages, terminations and stillbirths will be excluded from analysis according to the target population attribute
25–28: Maternal complications during pregnancy, delivery type and postpartum haemorrhage	Target population: Mothers with adequate iodine intake from food early in pregnancy (> 165 µg/day) who deliver a live-born infant Intercurrent events: Non-compliance with the randomised supplement regime will be ignored under a treatment policy strategy. Miscarriages, terminations and stillbirths will be excluded from analysis according to the target population attribute

location will be assessed by including this subgroup variable and its interaction with treatment group into the linear regression model for the primary outcome. Effect modification by iodine intake will be assessed in a similar fashion, but with this variable treated as continuous rather than categorical in the analysis. To account for potential non-linear effects, two-term fractional polynomials will be fitted using the 'mfpi' command in Stata v18 (or later) using default settings [22]. For each potential effect modifier, the p value for the interaction term with treatment group will be reported. Independent of the statistical significance of the interaction p value, estimates of the treatment effect with 95% confidence intervals will be reported for each enrolment location or in a treatment effect plot for iodine intake in early pregnancy.

The statistical analysis approach for continuous outcomes is based on assumptions about the distribution of model residuals. Should these assumptions turn out to be unreasonable, data transformations are not planned since the sample size will be large enough for the central limit to apply in the case of departures from normality, and the use of generalised estimating equations with an independence working correlation structure ensures robustness to unequal residual variances across treatment groups.

Missing data

Missing data will be summarised descriptively by treatment group for all baseline characteristics, post-randomisation characteristics and outcome variables. To address missing outcome data, multiple imputation implemented under a missing at random assumption will be used to estimate treatment effects. Imputation will be performed separately by treatment group [23] using fully conditional specification, also known as chained equations [24], with 50 burn-in iterations used and a total of 100 complete datasets generated for analysis. Linear and logistic regression models will be used to impute incomplete continuous and binary outcomes, respectively. For dichotomised scale scores (e.g. Bayley-IV Cognitive Scale Score < 85), linear regression models will be used to impute the underlying continuous score and the dichotomised outcome will be derived following imputation.

All conditional imputation models will include state or territory at enrolment, given its use an adjustment variable, while the conditional imputation model for the primary outcome will also include iodine intake in early pregnancy to facilitate subgroup analyses. Auxiliary variables will be added to imputation models as appropriate to improve the prediction of missing values and the plausibility of the missing at random assumption. Candidate auxiliary variables will be restricted to other outcomes (excluding dichotomised outcomes), adherence measures, safety and tolerability measures, and baseline and post-randomisation characteristics presented in this analysis plan. All auxiliary variables will be in the same functional form as detailed in this analysis plan and assumed to be linearly related to incomplete outcomes via the link function, excepting iodine intake in pregnancy when imputing the primary outcome. For each incomplete outcome, selected auxiliary variables will be those that (a) are observed in more than 50% of cases where the outcome is missing and (b) are predictive ($p < 0.10$) in a univariate complete case analysis for the outcome. The appropriateness of the chosen imputation model will be confirmed through trace plots and

summaries of imputed and observed data before any outcome comparisons are performed [25]. Imputation will not be performed for binary outcomes with less than 30 events/non-events in either treatment group, given the limited scope for incorporating auxiliary variables. Additionally, imputation will not be implemented for thyroid-stimulating hormone levels, given this outcome is only measured in a subset of infants.

For the primary outcome, the sensitivity of results to the missing at random assumption will be explored by considering missing not at random mechanisms in sensitivity analyses. Using pattern mixture models, the mean Cognitive Scale Score will be assumed to be up to 4 points lower or 4 points higher in children with missing data compared to children with observed data, conditional on other observed data included in the imputation model. This is a large departure from the 0-point difference expected under a missing at random assumption given the information available to help satisfy this assumption. The differences will be applied independently to control and intervention group children in increments of 2 points, resulting in an additional 24 scenarios for investigation. The statistical significance of treatment effects in these sensitivity analyses will be plotted in a 5×5 grid and 'tipping points' where study conclusions qualitatively change identified.

Additional analyses

Miscarriages, terminations, stillbirths and infant deaths will be excluded from the analysis of the primary outcome according to the target population attribute, corresponding to a survivor's analysis. If there is any evidence to suggest the overall incidence of these intercurrent events is influenced by the treatment group ($p < 0.20$ according to a Fisher exact test), the principal stratum effect in the subgroup of infants who would survive to 24 months under either treatment will be estimated in a sensitivity analysis.

Safety and tolerability

The number and percentage of infants and mothers experiencing a serious adverse event will be reported for each treatment group, irrespective of eligibility or compliance with the protocol, and compared across groups using Fisher exact tests. The denominator for comparisons will be all randomised infants or mothers, as appropriate. The following serious adverse events will be evaluated: infant major congenital anomaly; foetal mortality (miscarriage, termination and stillbirth); infant mortality, excluding lethal congenital anomalies (death of a live-born infant in first 28 days of life, after first 28 days); infant admission to intensive care unit; maternal admission to intensive care unit during the intervention period; and maternal death in the intervention period. The tolerability of the intervention will be described by reporting the number and percentage of mothers in each group (based on available data) stopping supplements due to a perceived adverse event or difficulty swallowing the tablets or reporting diarrhoea, nausea, constipation, burping and vomiting at different stages of the intervention period (7 days after randomisation and at 16, 22, 28 and 36 weeks of gestation).

Statistical software

All analyses will be performed using Stata v18 or later (College Station, TX: StataCorp LP).

Discussion

To avoid bias due to data-driven analyses, in this paper we attempt to completely and unambiguously detail the planned statistical analyses of the PoppiE trial. The statistical analysis plan was finalised in advance of the database lock, unblinding or any analysis of study outcome data. At the time of writing (February 2025), recruitment into PoppiE has been completed and the trial is in the follow-up phase, with data collection expected to be completed in July 2026.

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Not applicable.

Authors' contributions

TRS (trial statistician) drafted the first version of the statistical analysis plan manuscript. JFG (chief investigator), TJG (chief investigator), MMM (chief investigator) and KPB (principal investigator) conceived the trial and critically revised the manuscript. All authors read and approved the final manuscript.

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Data availability

Deidentified individual participant data may be shared on reasonable request. Proposals to access the data must be scientifically sound and approved by the PoppiE trial steering committee and the Women's and Children's Human Research Ethics Committee. Proposals should be directed to the Chair of the PoppiE Steering Committee, KPB, via email (karen.best@sahmri.com).

Declarations

Ethics approval and consent to participate

The trial has been approved by the Women's and Children's Health Network Research Ethics Committee (HREC/17/WCHN/187). All participants provided written informed consent and were made away they were free to withdraw consent at any stage of the trial.

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no competing interests.

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