



BMJ Open The ORVAC trial protocol: a phase IV, double-blind, randomised, placebo-controlled clinical trial of a third scheduled dose of Rotarix rotavirus vaccine in Australian Indigenous infants to improve protection against gastroenteritis

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ABSTRACT

Introduction Rotavirus vaccines were introduced into the Australian National Immunisation Program in 2007. Despite this, Northern Territory Indigenous children continue to be hospitalised with rotavirus at a rate more than 20 times higher than non-Indigenous children in other Australian jurisdictions, with evidence of waning protection in the second year of life. We hypothesised that scheduling an additional (third) dose of oral human rotavirus vaccine (Rotarix, GlaxoSmithKline) for children aged 6 to <12 months would improve protection against clinically significant all-cause gastroenteritis.

Methods and analysis This Bayesian adaptive clinical trial will investigate whether routinely scheduling an additional dose of Rotarix for Australian Indigenous children aged 6 to <12 months old confers significantly better protection against clinically important all-cause gastroenteritis than the current two-dose schedule at 2 and 4 months old. There are two coprimary endpoints: (1) seroconversion from baseline serum anti-rotavirus immunoglobulin A (IgA) titre <20 U/mL prior to an additional dose of Rotarix/placebo to serum anti-rotavirus IgA titre >20 U/mL following the administration of the additional dose of Rotarix/placebo and (2) time from randomisation to medical attendance (up to age 36 months old) for which the primary reason is acute gastroenteritis/diarrhoea. Secondary endpoints include the change in anti-rotavirus IgA log titre, time to hospitalisation for all-cause diarrhoea and for rotavirus-confirmed gastroenteritis/diarrhoea, and rotavirus notification. Analysis will be based on Bayesian inference with adaptive sample size.

Ethics, registration and dissemination Ethics approval has been granted by Central Australian Human Research Ethics Committee (HREC-16-426) and Human Research Ethics Committee of the Northern Territory

Strengths and limitations of this study

- The ORVAC study is one of the first studies to evaluate both the immunological and the clinical impact of an additional dose of oral Rotarix rotavirus vaccine administered to children between 6 and 12 months of age.
- This pragmatic randomised controlled trial is based on Bayesian adaptive design, an innovative trial design that uses interim analyses to inform decisions about trial progression.
- While Bayesian adaptive trials are becoming increasingly common, they are yet to be established and accepted as routine research practice.
- The pragmatic trial design conducted under real-world conditions aims to increase the likelihood that a positive trial result will be more rapidly translated into policy and practice in the Northern Territory.
- This study will not be able to capture all cases of gastroenteritis following the administration of additional dose Rotarix/placebo, only those presenting for clinical attendance; nor whether all cases of gastroenteritis presenting for medical attendance are caused by rotavirus.

Department of Health and Menzies School of Health Research (HREC-2016-2658). Study investigators will ensure the trial is conducted in accordance with the principles of the Declaration of Helsinki and with the ICH Guidelines for Good Clinical Practice. Individual participant consent will be obtained. Results will be disseminated via peer-reviewed publication. The trial is registered with Clinicaltrials.gov (NCT02941107) and important modifications to this protocol will be updated.
Trial registration number NCT02941107; Pre-results.

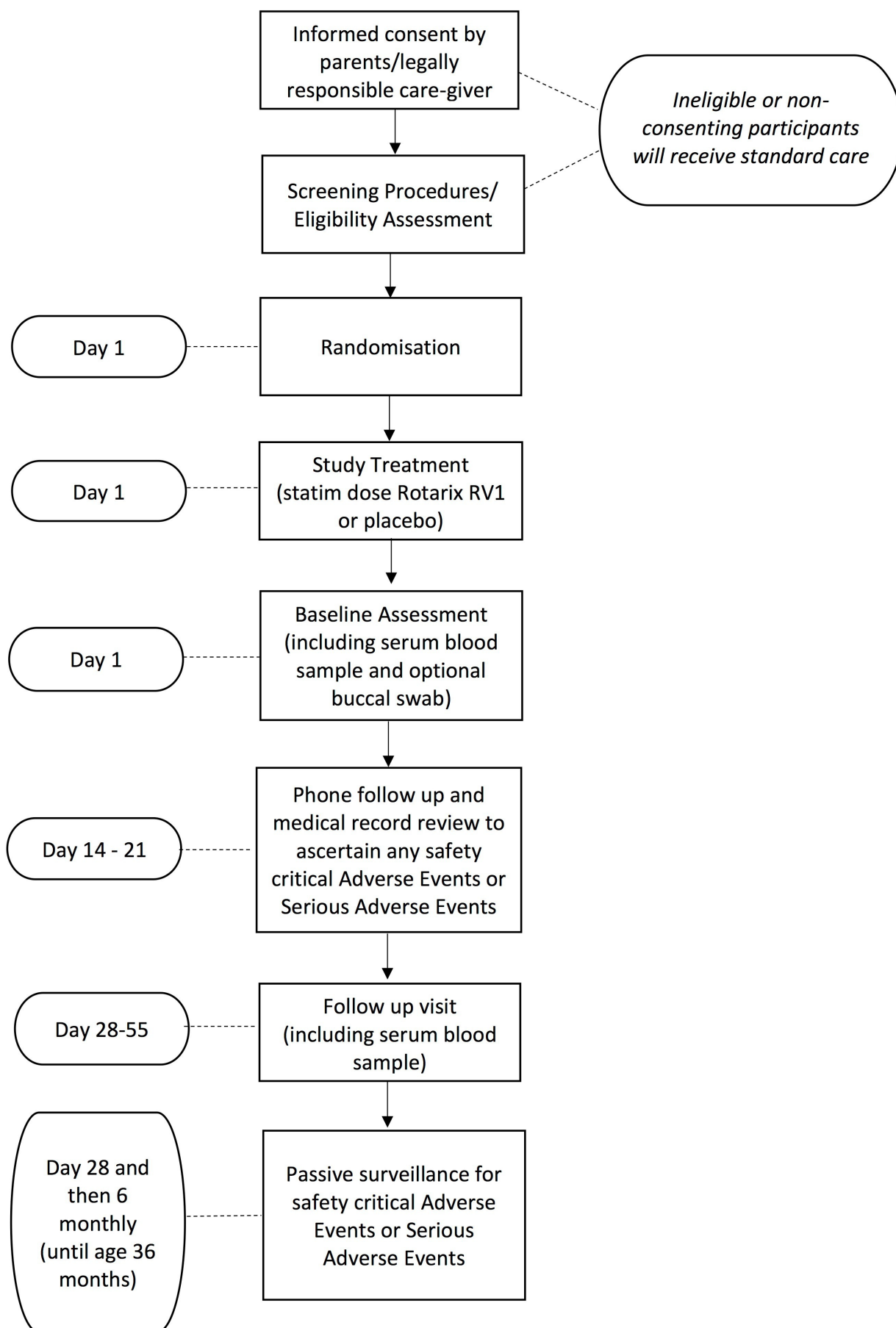


Figure 1 Trial flow chart.

INTRODUCTION

Rotavirus diarrhoeal disease is a leading cause of child mortality globally for children under 5 years of age and continues to be responsible for the death of 118 000–183 000 children annually, despite the availability of rotavirus vaccines.¹ Most of these deaths occur in resource-poor settings.

In 2006, two oral rotavirus vaccines—the human monovalent rotavirus vaccine (Rotarix) and the pentavalent human-bovine reassortant rotavirus vaccine (RotaTeq) were licensed for use, and in 2009 the World Health Organisation endorsed their use globally.² Despite the introduction of Rotarix into the Northern Territory (NT) childhood immunisation schedule in 2006, the rate of hospitalisation for rotavirus for NT Aboriginal and Torres Strait Islander (hereafter Indigenous) children remains more than 20 times higher than the rate of hospitalisation for non-Indigenous children,³ with evidence of waning protection in the second year of life.⁴ Epidemics of rotavirus remain common in remote northern and central Australia,^{4,5} and these epidemics have been shown to place enormous strain on remote communities and health services.⁶

This reduced protection generated by oral rotavirus vaccines has also been documented in low-income, high rotavirus burden settings in Africa and Southeast Asia (50%–64%),^{7–9} as has evidence of waning protection in the second year of life.^{9,10}

The reason for the suboptimal protection from oral rotavirus vaccine in these settings is not well understood, but is thought to be the result of one or more host and environmental factors.¹¹ A number of possible determinants of poor vaccine response have been proposed including high levels of maternal derived, vaccine-neutralising anti-rotavirus antibodies, poor nutrition, intestinal microbiota dysbiosis, environmental enteropathy, high prevalence of comorbid infections such as HIV, rotavirus strain heterogeneity and genetic determinants of immune responses and susceptibility to different rotavirus genotypes.¹¹

Programmatic restrictions unique to rotavirus vaccine may have also contributed to decreased vaccine programme effectiveness. An earlier tetravalent rhesus-human rotavirus vaccine was associated with an increased risk of intussusception; this was primarily with the first dose of vaccine and the highest attributable risk was in infants >3 months of age.² As a result, the manufacturers of the new generation oral rotavirus vaccines have recommended upper age limits for administration of their vaccines,¹² although large phase III clinical trials found no increased risk of intussusception.^{13,14} In practice, these upper age limits reduce the opportunity to catch-up missed vaccines in later infancy.

Here we provide the Optimising Rotavirus Vaccine in Aboriginal Children (ORVAC) clinical trial protocol specification (see Appendix One ORVAC Protocol Version 7.0). This is the first large-scale clinical trial to evaluate both the immunological and the clinical effects of administering an additional (third) dose of oral

Rotarix rotavirus vaccine to children older than 6 months. The pragmatic trial design seeks to evaluate the impact of administration of an additional dose of Rotarix under real-world conditions.

METHODS AND ANALYSIS

Design

ORVAC is a phase IV, double-blind, randomised, placebo-controlled, Bayesian adaptive clinical trial of a third scheduled dose of Rotarix rotavirus vaccine in Australian Indigenous children to improve immunological and clinical protection against gastroenteritis. The prespecified adaptive elements all pertain to the sample size with all analyses and inference undertaken in a Bayesian framework. The protocol for enrolment, intervention, endpoints and analyses is based on the principles of pragmatic trial design.¹⁵ The trial flow chart and trial events schedule are presented in figure 1 and table 1, respectively.

Study setting

The study is being conducted in urban, rural and remote locations of the tropical north and arid centre of Australia. In 2015, there were 3936 babies born in Australia's NT, 33% of whom were Indigenous.¹⁶ Study recruitment began in March 2018 in three large remote Aboriginal communities in the northern part of the NT (Wadeye, Wurrumiyanga and Maningrida) and in urban Darwin. Additional study sites will be added as the trial progresses. In the NT, the government-run NT Pathology service routinely tests all stool samples taken from children <5 years for rotavirus. However, the decision to request a stool sample at the time of medical attendance for diarrhoea or gastroenteritis remains at the discretion of the treating medical practitioner, nurse or aboriginal health worker. All laboratory-confirmed episodes of rotavirus infection (from both public and private laboratory services) are notified by the laboratory to the NT Department of Health Centre for Disease Control.

Objectives

The primary objective is to determine if routinely scheduling an additional dose of Rotarix for NT Indigenous children aged 6 to <12 months will confer significantly better protection against clinically important gastroenteritis in the context of the current schedule of two doses at age 2 and 4 months old.

Outcomes

There are two coprimary endpoints: (1) the primary immunological endpoint is seroconversion of serum anti-rotavirus IgA levels from <20 U/mL prior to additional Rotarix/placebo to >20 U/mL, 28–55 days following the administration of Rotarix or placebo, and (2) the primary clinical endpoint is the time from randomisation to medical attendance (hospitalisation, emergency department presentation, medical clinic presentation) for which the primary reason is acute gastroenteritis or acute diarrhoea, before the age of 36 months.

Table 1 Schedule of events

Procedures	Preconsent (birth to 5 months)	On-study period			Long-term follow-up		
		Screening/ Baseline (day 1)	Follow-up visit 1	Follow-up visit 2*	Surveillance visit 1	6 monthly surveillance visit	End of trial surveillance visit (36 months of age)
Visit window		+3 days	Days 14–21	Days 28–55	Days 28–55	±2 weeks	+2 weeks
Study information and permission to contact	X (optional)	X					
Informed consent		X					
Eligibility assessment		X					
Vaccination history		X					
Demographics		X					
Randomisation allocation		X					
Pre-vaccination assessment†		X					
Study treatment administration (Rotarix or placebo)		X					
Baseline anthropometric indices assessment‡		X					
Baseline serum blood sample		X					
Telephone contact			X				
Assess elimination criteria				X			
Follow-up serum blood sample				X			
Active SAE/Safety critical AE assessment			X				
Passive SAE/Safety critical AE assessment §					X	X	X

*Follow-up blood collection visit will cease if immunogenicity interim analysis results meet one of the stopping rules, at which point no further venous blood samples will be collected.

† Pre-vaccination assessments performed are assessment of temporary exclusion criteria.

‡ Anthropometric indices performed are mid-upper arm circumference and weight.

§ From 28 days after Rotarix/placebo administration until 36 months, only intussusception and death will be recorded as SAEs regardless of causality.

SAE, serious adverse effect.

The secondary immunological endpoint is the change in anti-rotavirus immunoglobulin A (IgA) log titre from baseline (immediately before the additional dose of Rotarix or placebo) to 28–55 days following the administration of Rotarix/placebo. Secondary clinical endpoints are (1) time from randomisation to hospitalisation for all-cause diarrheal illness; (2) time from randomisation to hospitalisation for rotavirus-confirmed gastroenteritis or diarrhoea illness (confirmed by reverse transcription PCR (RT-PCR) on stool sample); and (3) notification for rotavirus-confirmed enteric infection.

Safety endpoint is the occurrence of intussusception (fulfilling Brighton criteria) within the first 28 days after

administration of an additional dose of Rotarix/placebo. Of note, the baseline incidence of intussusception appears to be much lower for NT Indigenous children than for non-Indigenous children (16/100 000 vs 92/100 000 live births).¹⁷

Children who have received either one or two prior doses of Rotarix will be included in the analyses of primary, secondary and safety outcomes.

Participants

Up to 1000 Australian Indigenous infants aged 6 to <12 months will be enrolled. Parents or legally responsible caregivers (hereafter parents) of newborn infants born

in two large NT hospitals (Royal Darwin Hospital and Alice Springs Hospital) will be provided with information about the ORVAC study after delivery, and we will seek permission to contact them again when their infant is approximately 5 months old to invite them to participate in the study. Enrolment will also be sought for age-eligible children (6 to <12 months) from other settings including hospital wards and outpatient clinics of participating hospitals, medical clinics and remote community health centres.

A verbal overview of the study, aided by use of pictorial representations of the study (flip chart), will be used to communicate to the parents of potential participants. A written information sheet will also be provided. These documents have been developed in consultation with the study's Indigenous cultural advisor and may be requested from the investigators. Written informed consent will be obtained from the parent or legally responsible caregiver.

In keeping with the pragmatic objectives, all Indigenous children aged 6 and <12 months who are not contraindicated for rotavirus vaccine and who have received either one or two prior doses of Rotarix will be eligible for enrolment. Ethnicity will be determined by self-report of the parent. Additional requirements for eligibility include permission from the parent to (1) notify healthcare practitioners involved in their child's care about participation; (2) ascertain vaccination history from the Australian Immunisation Register and/or local vaccination provider; and (3) obtain medical data from the medical records and/or primary healthcare provider. Exclusion criteria are consistent with standard Australian recommendations for Rotarix, namely (1) severe immunosuppression, for example, due to severe combined immunodeficiency, more than 2 weeks of immunosuppressive or immune modifying drugs within 28 days of randomisation, or other suspected severe immunodeficient conditions; (2) heightened risk of intussusception, for example, due to history of intussusception or uncorrected gastrointestinal malformation; (3) history of allergy or hypersensitivity to any Rotarix component; (4) receipt of any blood products including immunoglobulin in the previous 3 months. Additional exclusion criteria are (5) receipt of either no prior doses or more than two prior doses of Rotarix; (6) receipt of a rotavirus vaccine other than Rotarix; (7) medical condition or treatment with medication which in the opinion of the trial investigators would make the child unsuitable for the trial; and (8) previous randomisation. Temporary exclusion criteria are (1) acute diarrhoea or gastrointestinal illness; (2) acute systemic illness or fever $\geq 38.5^{\circ}\text{C}$; and (3) receipt of a dose of Rotarix in the preceding 28 days.

Study procedures

Baseline assessment

To assess eligibility and to allow description of the study population, demographic data (including usual place of residence), medical history (including rotavirus vaccination history), details of any current illness, breastfeeding

status and anthropometric indices (weight, mid-upper arm circumference) will be collected. A baseline blood sample of up to 5 mL will be taken from up to the first 250 participants to measure anti-rotavirus serum IgA levels before administration of the additional dose of Rotarix/placebo. If attempts to collect the blood sample are unsuccessful or a parent declines this procedure, the child will remain enrolled in the study for determination of the clinical endpoint.

Randomisation, intervention and blinding

Randomisation of eligible participants will be by computer-generated allocation sequence. The study nurse will allocate the next sequential product identifier with stratification by usual place of residence (urban or rural/remote). Participants will be randomised 1:1 within the two strata to receive either Rotarix or placebo. Where possible, the dose of Rotarix/placebo will be given within 12 hours of randomisation. In an inpatient setting, consent and other baseline assessments may be done up to 72 hours before randomisation. If most of an oral Rotarix/placebo dose is spat out or vomited within minutes of administration, a single repeat dose can be administered during the same visit. The placebo for this trial is a clear and flavoured solution used as a pharmaceutical excipient which has been repackaged into a labelled syringe, identical to the active vaccine product once prepared by the unblinded study nurse.

Randomisation codes are held by the trial statistician and are password protected. Code breaks are only to be used if a situation arises where the coordinating principal investigator (CPI) deems it necessary to break the blinding process for compelling medical or safety reasons.

Follow-up

Medical record and hospital admission review and/or attempted telephone contact of the parents of participants will occur between 14 and 21 days after receipt of Rotarix/placebo to ascertain any adverse events (AEs) that have occurred since administration. For infants who have had a baseline blood sample taken, a follow-up blood sample will be collected 28–55 days following the administration of the Rotarix/placebo. A review of the participant's medical records by a study team member will occur within 28–55 days of vaccination to ascertain whether any AEs including hospitalisations have occurred. Subsequent review of clinic and hospital medical records will occur every 6 months (± 2 weeks) after randomisation to ascertain medical attendances for diarrhoea or gastroenteritis, episodes of intussusception or death. Review of electronic medical records will include review of medical records from all remote community health centres run by the NT Government and from all five NT Public Hospitals. If the participant moves to a remote community without a health centre run by the NT Government during the defined follow-up period, information about medical attendances will be requested from the applicable Aboriginal Medical Service and/or private medical

practitioner. Of note, the NT Notifiable Disease System records all positive rotavirus samples notified across the NT (from both public and private pathology providers).

The final surveillance review will occur when the child is 36 months old (window period 36 months+4 weeks).

Data collection

Information from source documents (including but not limited to hospital records, clinical charts, clinic records, laboratory and pharmacy records, radiographs and correspondence) and all deidentified trial data will be entered directly onto the password protected online database built in Medrio eClinical with CloudEDC. Study documents (including the signed consent form) will be stored securely at each study site, both hard copy and electronic data will be archived until the youngest participant reaches 25 years old, or until 15 years after the end of the trial, whichever is later.

Laboratory testing

A blood sample will be collected at the time of baseline assessment immediately prior to the dose of Rotarix/placebo and at a follow-up visit 28–55 days following the administration of the Rotarix/placebo. Blood will be centrifuged within 24 hours of collection and serum collected and separated into appropriate-sized aliquots and stored at -70°C . The investigational analysis will be conducted at Telethon Kids Institute, Perth, Western Australia, Australia. Shipments of samples will occur at regular intervals to allow regular interim analyses as per the protocol. Specific rotavirus IgA antibodies will be measured by enzyme immunoassays using rabbit anti-RV polyclonal antisera as the coating antibody and as a capture antigen. The antigen-antibody complexes will be detected with biotinylated anti-human IgA and avidin-biotin-peroxidase and developed using an *o*-Phenylenediamine substrate. Concentrations of rotavirus-specific IgA will be measured using a standard curve generated with a validated pooled reference sera.

Hospitalisation with rotavirus-confirmed gastroenteritis or diarrhoea illness will be confirmed by RT-PCR performed on stool samples processed in the government-run NT Pathology service.

Withdrawal of participants

Parents will have the right to withdraw their child from the trial at any time. In addition, the CPI or site principal investigator may discontinue participant involvement in the trial if (1) the child is found to be ineligible following randomisation, or if (2) a significant protocol violation, (3) withdrawal of consent or (4) loss to follow-up occurs. Participant withdrawal from the study will not result in automatic exclusion from the analysis.

Data analyses and sample size

Participant demographics and baseline characteristics will be summarised and tabulated by treatment group and location of residence. For the immunological endpoint, multivariate logistic regression will be used to compute

the log odds of the treatment effect. For the clinical endpoint, a Weibull parametric survival model will be used to compute the treatment effect, obtaining an absolute measure of median time to medical attendance in each arm. All analyses will occur within a Bayesian framework.

In addition to modelling the treatment effects, we will include parameters to account for locality of residence, breastfeeding status in the 7 days prior to randomisation and, where applicable, indicator variables for gastroenteritis outbreaks.

Secondary endpoints will be analysed using the same methods. Hypotheses, methods, prior distribution specification and probability thresholds that are alluded to here but omitted for brevity and accessibility will be detailed in a separately published statistical analysis plan.

The first interim analysis will occur when 70 participants have immunogenicity results available. Further interim analyses will occur after every subsequent 50th child is enrolled or after every 3 months, whichever occurs sooner. If fewer than 25 children are enrolled in the 3-month interval, then the analyses will be deferred until the next scheduled interim. Analysis of the clinical endpoint will start when 200 children are enrolled in order that there are enough events to meaningfully undertake a time to event analysis. At each interim analysis, we will independently estimate:

1. The posterior probability that the proportion of children achieving an IgA seroconversion in one arm is greater than in the other arm.
2. The posterior probability that the median time to first medical attendance is greater in one arm than in the other arm.

To assess futility, we will compute the predicted probability of trial success in both endpoints as if all resources were fully expended. If there is a very low chance of observing a greater proportion of seroconversion in the treatment arm OR there is very low chance of observing a greater median time to medical attendance in the treatment arm, then the trial will be stopped. Futility can be determined based on the results from either the immunological or the clinical endpoint. If futility is not concluded, we will then evaluate (1) whether the treatment arm has a higher rate of seroconversion compared with the placebo arm, and (2) whether a treatment effect is apparent in the clinical endpoint.

If the probability that the rate of seroconversion in the Rotarix group is higher than in the placebo group, above a threshold level chosen to control the type I error, then we will cease collecting blood samples. Enrolment into the trial will continue, as will interim analyses, in order to assess the clinical endpoint until a decision rule is triggered for expected success or futility, or until we reach the maximum sample size of 1000 participants. If 250 infants with immunogenicity results have been enrolled without the above stopping rules having been met, no further venous blood samples will be collected.

If the probability that the median time to event in the Rotarix group is greater than in the placebo group, above a threshold level chosen to control the type I error, then

we will cease enrolment into the trial for expected success. We will continue to process any outstanding immunological results and follow patients up to 36 months old at which point we will undertake the final analysis and publish our findings. We note that expected success can only be determined based on the clinical endpoint.

After 1000 infants have been enrolled without meeting a trial stopping rule, no further participants will be enrolled. Regardless of whether the trial is ceased for superiority or futility or continues to the maximum sample size, we will complete a final analysis once all follow-up data have been received.

With the necessary governance and ethics approvals, access will be granted to the full protocol, Statistical Analysis Plan (SAP), analysis code and final dataset to allow for independent validation of the analysis.

Safety reporting and trial oversight

Telethon Kids Institute is the trial sponsor. Sponsor duties are delegated to a trial steering committee comprising the CPI, other investigators and key stakeholders.

The funder, National Health and Medical Research Council, approved the study plan for funding (1086952) administered via Curtin University, but will have no role in the collection, management, analysis, interpretation, reporting or decision to submit for publication which rests entirely with the steering committee.

All serious adverse events (SAEs), regardless of cause or relationship, that occur following the administration of the Rotarix/placebo up until 28 days will be reported to the sponsor within 24 hours. From 28 days after Rotarix/placebo administration until 36 months old, only intussusception or death will be recorded as SAEs, regardless of causality. All SAEs are reported in accordance with the approving ethics committees' and the sponsor's requirements. Any suspected, unexpected serious adverse reactions will be reported to the Australian Therapeutic Goods Administration by the sponsor within 7 days.

A Data and Safety Monitoring Committee (DSMC), which is independent of the sponsor, the trial steering committee and vaccine manufacturer will receive quarterly safety reports and convene at least twice per year to provide safety oversight and to monitor the overall conduct of the trial including adherence to the stopping rules prespecified in the trial protocol and SAP. The DSMC will make recommendations to the trial steering committee via the CPI.

Patient and public involvement

This study was informed by consultations with the Aboriginal Health Research Forum of the Telethon Kids Institute (May 2016) and with the Menzies Child Health Indigenous Reference Group (November 2013) who continue to provide advice to the study team. Studies to improve rotavirus vaccine performance were also considered and supported as a priority at the Round Table meeting of delegates from Aboriginal Community-Controlled Health Organisations convened by the Centre for Research

Excellence in Immunisation in Understudied and Disadvantaged Populations (November 2012) and also at the third National Indigenous Immunisation Research Workshop (November 2013) attended by 130 Indigenous vaccine and healthcare providers, immunisation researchers, and jurisdictional and national policymakers. The study protocol, procedures and evaluation of the burden of intervention has also been informed by the advice from the Menzies School of Health Research Child Health Indigenous Reference Group, Aboriginal Elders and Aboriginal Health Workers employed to work on the study in both a cultural advisor and project officer capacity, and by Aboriginal members of the Steering Committee. Results from the study will be presented at conferences and published in peer-reviewed journals. Results will be communicated to the wider community with the assistance of the Menzies Child Health Indigenous Reference Group. Results will also be available to individual participants on request, as per participant consent form.

DISCUSSION

There is a compelling need to identify practical, ethical and implementable strategies to improve the performance and extend the protection of oral rotavirus vaccine among Australian Indigenous children, especially those living in rural and remote areas, where severe rotavirus gastroenteritis remains unacceptably common.

Post-licensure effectiveness studies have shown a large decrease in rotavirus morbidity in high-income and middle-income countries,¹⁸ but real-world vaccine effectiveness, measured as a proportional reduction in rotavirus disease, appears to be much lower in low-income high rotavirus burden settings.⁷⁻⁹ Data from studies in low-income countries in Africa and Asia have shown a correlation between baseline rotavirus disease burden and measures of real-world vaccine effectiveness with highest disease burden populations experiencing the lowest vaccine effectiveness and vice versa.¹⁹ There is also evidence of waning protection in the second year of life.^{7 10} While rotavirus vaccination has achieved a very large absolute reduction in the number of global deaths due to rotavirus infection, there is still a need to find effective, safe and implementable strategies to further decrease the burden of gastroenteritis in high burden settings, including among Australian Indigenous children. A recent systematic review found no evidence for improved performance of oral rotavirus vaccine in low resource settings when coadministered with zinc or probiotics, or withholding breast feeding at the time of rotavirus vaccine delivery.²⁰ However, changes in vaccine scheduling and the development of novel vaccine formulations still hold promise.

Clinical trials in remote populations and high-disease burden settings present many logistical challenges. The pragmatic design of the ORVAC study aims to evaluate the scheduling of an additional dose of Rotarix under real-world conditions. There are therefore few exclusion

criteria apart from medical contraindication for Rotarix and prior receipt of another rotavirus vaccine. It is proposed that this inclusive pragmatic trial design will increase the likelihood of a positive trial outcome being translated into clinical practice in Australia and potentially enable the extrapolation of trial outcomes to other high burden settings.

Studies from Africa support the hypothesis that administering an additional (third) dose of oral Rotarix may be a safe and effective strategy for increasing protection against severe rotavirus gastroenteritis diarrhoea in developing country settings.^{10 21} However, previous studies have given additional doses of Rotarix before 6 months of age. Given that maternally derived antibodies, particularly cord IgG, have been suggested to interfere with oral vaccine performance in early infancy,²² we propose that an improvement in protection against rotavirus may be achieved by scheduling an additional dose of Rotarix in the second 6 months of life. More importantly, we propose that this later administration of Rotarix will help extend protection into the second and third years of life.

Ensuring valid informed consent that meets the standards outlined in the Declaration of Helsinki is of paramount importance, especially in a vulnerable population with low levels of health literacy and different cultural concepts of individual versus community-level determination. For this reason, study design, consent procedures, study procedures and community engagement have been informed by a cultural advisor employed on the study, with additional involvement of an Indigenous child health research community reference group.²³

This will be one of the first clinical trials among Indigenous children to employ a Bayesian adaptive approach, meaning that no fixed sample size will be set and only as many children are required to determine the study objectives will be enrolled. Traditional 'frequentist' methods for analysing clinical trials determine the sample size in advance, based on an anticipated treatment response rate among controls and a usually arbitrary judgement about what constitutes a 'minimum clinically important difference'. These design decisions are often based on a 'best guess' and consequently many trials fail to answer the question they set out to address with certainty, or alternatively, continue to enrol participants beyond the point where conclusive evidence of an effect has already been obtained. In ORVAC, decisions on prespecified sample size adaptations use accumulated data and Bayesian inference, and can therefore increase the probability of a conclusive trial result while ensuring the trial does not continue beyond the point where either futility or success can be reasonably concluded. We expect it will also help ensure timely translation of any positive clinical trial findings into clinical practice or help inform and expedite evaluation of alternative strategies if the trial results are negative.

It is anticipated that ORVAC's Bayesian design will provide a flexible and pragmatic study that represents a practical way to conduct research among the vulnerable

population of Indigenous children. It is proposed that a successful study outcome will lead to the incorporation of an additional dose of oral Rotarix into the existing immunisation schedule for Indigenous children in Australia.

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Contributors BFM, TS, MD and MAJ contributed to the preparation of the manuscript. BFM and TS developed the study processes and procedures and primarily authored the initial trial protocol. CM and SG have authored further protocol revisions. TS conceived the study and JAM devised the Bayesian approach, which was revised by MAJ. CSW, RA, CK, MD, NC JC and AJL contributed to the clinical aspects of the protocol. MD and JAM contributed to the study design. All authors have reviewed and approved the manuscript. All authors meet the BMJ uniform requirements for authorship inclusion and have seen and approved the final version of this manuscript.

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