PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Middleton, Bianca; Jones, Mark; Waddington, Claire; Danchin, Margaret; McCallum, Carly; Gallagher, Sarah; Leach, Amanda; Andrews, Ross; Kirkwood, Carl; Cunliffe, Nigel; Carapetis, Jonathan; Marsh, Julie; Snelling, Tom

VERSION 1 – REVIEW

REVIEWER	Michelle Groome Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Johannesburg, South Africa
REVIEW RETURNED	16-Jul-2019

GENERAL COMMENTS	This study evaluates an additional dose of Rotarix given at 6-<12 months of age in indigenous children in Australia's Northern Territory. Both immunogenicity and clinical endpoints will be evaluated. A Bayesian adaptive trial design will be used. Full details of the statistical analysis are being submitted for publication in another journal. General: 1. Please review for minor grammatical errors e.g. abstract, pg 4, line 2: "children in continue…"; Pg 7, sentence starting "Reduced protection generated…". 2. Check that abbreviations are defined when used for the first time e.g. NT in the introduction; CPI on page 13 (only defined later). Introduction: 3. First sentence: add "globally" for clarity. 4. If possible, provide reference for sentence in 2nd paragraph on epidemics in northern and central Australia. Methods: 5. Has the study already starting enrolling? Provide date of study start or anticipated start date, as applicable. 6. How many locations are being used for the study? Please specify study sites. 7. Is there routine testing for rotavirus in Australia's NT? This seems to be a notifiable disease. It would be useful to have a sentence or two explaining when testing is done i.e. routine or physician-decision, especially as rotavirus gastroenteritis is one of the secondary endpoints. Are sites similar in terms of when stool testing for rotavirus is done?

	8. Abstract and pg 10: primary endpoints – when describing the IgA seroconversion from <20 U/ml, please add "prior to Rotarix/placebo". 9. Immunogenicity outcome: elsewhere it is described that children will be enrolled if they received one or two previous doses of Rotarix. For the immunogenicity endpoint, baseline is defined as before the third dose of Rotarix/placebo. Will those who received only one previous dose (i.e. receiving a second dose) also be included in the analysis? Please clarify is it only third dose or any additional dose and amend accordingly throughout. Sometimes says "additional dose" and other times "third dose". 10. Clinical endpoints: in the protocol it is clearly stated that enrolment=randomisation but in the manuscript it might be better to use randomisation rather than enrolment for clarity, or alternatively state that enrolment=randomisation, as in the protocol. 11. Follow-up: will participants always consult the same practitioner or clinic? Will multiple sources of health-care contact be checked for endpoints for each participant, in order to minimise the chance of missing outcomes? Is follow-up only passive i.e. record review or will participants also be contacted telephonically at the 6-monthly time points. What if participants relocate out of the area or die at home? This isn't clear in the manuscript. 12. Laboratory testing, pg 15, 2nd sentence seems incomplete – "Specific rotavirus IgA antibodies will be measured by enzyme immunoassays (EIA) using rabbit anti-RV poyclonal antisera as the coating antibody as a capture antigen."

REVIEWER	Expedito Luna Universidade de Sao Paulo, Brazil
REVIEW RETURNED	16-Aug-2019

GENERAL COMMENTS	The study addresses an unanswered issue, whether an additional dose of rotavirus (RV) vaccine is effective in reducing RV related disease. The methodology is sound. However, I believe two issues demand clarification: - Pg 22 "Randomisation will be performed by the Study Nurse ... Pg 24 "The stratified (urban vs remote), random allocation of two treatment arms called "A" and "B" to continuous randomisation numbers (1 to 1000) will be generated by the trial statistician ...". Aren't this lines contradictory? One of the trials' endpints is: "Time from randomisation to hospitalisation for which rotavirus confirmed diarrhoea illness occurs between randomisation and age 36 months". I did not find the definition of "RV confirmed diarrhoea". Which are the methods of aetiological confirmation that the trial will accept?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1		
Reviewer comment	Author's Response	Location of manuscript change
General: 1. Please review for minor grammatical errors e.g. abstract, pg 4, line 2: "children in continue…"; Pg 7, sentence starting "Reduced protection generated…".	thank you, have re-read & removed typographical & minor grammatical errors.	throughout manuscript; including page 4 & page 8 (marked copy)
2. Check that abbreviations are defined when used for the first time e.g. NT in the introduction; CPI on page 13 (only defined later).	thank you, have done so.	throughout manuscript; including page 8 & page 15 (marked copy)
Introduction: 3. First sentence: add "globally" for clarity.	thank you, have done so	page 8 (marked copy)
4. If possible, provide reference for sentence in 2nd paragraph on epidemics in northern and central Australia.	thank you, have added references for persisting epidemics of rotavirus post introduction of rotavirus vaccine and for the strain these epidemics cause on remote communities and health services	page 8 (marked copy)
Methods: 5. Has the study already starting enrolling? Provide date of study start or anticipated start date, as applicable.	thank you, have added detail about date of commencement of enrolment (March 2018)	page 10 (marked copy)
6. How many locations are being used for the study? Please specify study sites.	thank you, have added detail about the four participating communities, and plans to recruit patients from additional sites as the trial progresses.	page 10 (marked copy)
7. Is there routine testing for rotavirus in Australia's NT? This seems to be a notifiable disease. It would be useful to have a sentence or two explaining when testing is done i.e. routine or physician-decision, especially as rotavirus gastroenteritis is one of the secondary endpoints. Are sites similar in terms of when stool testing for rotavirus is done?	thank you, have added detail about laboratory testing for rotavirus (all stool samples from children < 5 years are routinely tested for rotavirus in the government laboratory) but have clarified that the decision to request/ send a stool sample for analysis remains at clinician discretion; have also clarified that all positive rotavirus stool results will be notified to the Northern Territory Centre for Disease Control.	page 10 (marked copy)
8. Abstract and pg 10: primary endpoints – when describing the IgA seroconversion from <20 U/ml, please add "prior to Rotarix/placebo".	thank you, have added 'prior to Rotarix/placebo'	page 4 & page 11 (marked copy)

9. Immunogenicity outcome: elsewhere it is described that children will be enrolled if they received one or two previous doses of Rotarix. For the immunogenicity endpoint, baseline is defined as before the third dose of Rotarix/placebo. Will those who received only one previous dose (i.e. receiving a second dose) also be included in the analysis? Please clarify is it only third dose or any additional dose and amend accordingly throughout. Sometimes says “additional dose” and other times “third dose”.	thank you, we will be analysing children who have received either one or two doses of Rotarix prior to randomisation; have amended the manuscript to refer to ‘additional’ rather than ‘third’ dose; on two occasions the manuscript still refers to ‘third scheduled’ dose when attempting to illustrate that this is a change in the NT Immunisation Program; have also clarified that we will be analysing children who have received either one or two doses of Rotarix prior to randomisation at the end of the ‘outcomes’ section	page 11 & page 12 and throughout the manuscript (marked copy)
10. Clinical endpoints: in the protocol it is clearly stated that enrolment=randomisation but in the manuscript it might be better to use randomisation rather than enrolment for clarity, or alternatively state that enrolment=randomisation, as in the protocol.	thank you; have now used the term ‘randomisation’ throughout the manuscript to indicate the time point at which the child enters the trial	page 11 & throughout the manuscript (marked copy)
11. Follow-up: will participants always consult the same practitioner or clinic? Will multiple sources of health-care contact be checked for endpoints for each participant, in order to minimise the chance of missing outcomes? Is follow-up only passive i.e. record review or will participants also be contacted telephonically at the 6-monthly time points. What if participants relocate out of the area or die at home? This isn’t clear in the manuscript.	thank you, have added further detail about passive review of electronic medical records and attempts to contact patients who may have moved from the community from which they were originally recruited from	page 15 & page 16 (marked copy)
12. Laboratory testing, pg 15, 2nd sentence seems incomplete – “Specific rotavirus IgA antibodies will be measured by enzyme immunoassays (EIA) using rabbit anti-RV poyclonal antisera as the coating antibody as a capture antigen.”	thank you, have amended	page 17 (marked copy)
Reviewer 2		
Reviewer comment	Author’s Response	Location of manuscript change
Pg 22 "Randomisation will be performed by the Study Nurse ... Pg 24 "The stratified (urban vs remote), random allocation of two treatment arms called “A” and “B” to continuous randomisation numbers (1 to 1000) will be generated by the trial statistician ...". Aren't this lines contradictory?	thank you, we can see that the statement ‘Randomisation will be performed by the Study Nurse’ on page 22 of the ORVAC Protocol v6.0 is misleading; the manuscript states - 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) – we hope that this is a more	page 14 (marked copy)

	accurate and clear description of the study procedures for readers.	
One of the trials' endpoints is: "Time from randomisation to hospitalisation for which rotavirus confirmed diarrhoea illness occurs between randomisation and age 36 months". I did not find the definition of "RV confirmed diarrhoea". Which are the methods of aetiological confirmation that the trial will accept?	thank you; rotavirus confirmed gastroenteritis or diarrhea illness will be confirmed by reverse transcription polymerase chain reaction (RT-PCR) on stool samples processed in the government run NT Pathology service; this has been clarified in both the Outcomes and Laboratory Testing sections	page 12 & 17 (marked copy)

VERSION 2 – REVIEW

REVIEWER	Michelle Groome Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Johannesburg, South Africa
REVIEW RETURNED	19-Sep-2019

GENERAL COMMENTS	The authors have adequately addressed my comments. No further comments.

REVIEWER	Expedito Luna Faculdade de Medicina, Universidade de Sao Paulo, Brazil
REVIEW RETURNED	25-Sep-2019

GENERAL COMMENTS	The autthor have reviewed the manuscript, and the issues raised in the previous review have been addessed.