PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) Clinical Registry Protocol
AUTHORS	Pavlos, Rebecca; Bhuiyan, Mejbah; Jones, Mark; Oakes, Daniel; O'Brien, Sharon; Borland, Meredith; Doyle, Sarah; Richmond, Peter; Martin, Andrew C.; Snelling, Thomas; Blyth, Christopher C.

VERSION 1 – REVIEW

REVIEWER	brown, nick Uppsala Universitet
REVIEW RETURNED	10-Jul-2023

GENERAL COMMENTS	Thanks for asking me to review this manuscript which is is very well written. The register seems to have been set up 3 years ago (feb 2020) and it´s, therefore, unclear why this ´statement of intent´ is only being submitted now- apologies if I have misunderstood the text The principle seems a good one, but the amalgamation of data with multiple outcomes and exposures is not sufficiently well described - examples would enhance The analysis (essentially descriptive variables) provided will not be nuanced enough to pick up times to recovery and the tool further blunted by the use of a 7 day parent report- many ARIs will recover well before this risking bias to the Null. There is no mention of allowing for clustering by centre. In many cases HRs and IRRS will be more informative It is unclear what the main exposure/outcome/focus test aims are I like the infographic flow chart ! Minor parent´s should be parents´

REVIEWER	Strand, Tor University of Bergen
REVIEW RETURNED	10-Oct-2023

GENERAL COMMENTS	This is a well-written protocol for a registry for respiratory infections in children. The scope and the methods are well described—a couple of minor issues.

	- the protocol mentions biological specimen, however it would have been helpful if it gave more information on what kind of specimen and for what kind of analyses - the registry can be used as a basis for add on studies such as randomized clincial trials, will there be a new consent process for such activities - what is the expected enrollment rate into the registry - the title and the abstract can be somewhat misleading as this is a registry and not yet a "trial." Please reconsider the title.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 comments The principle seems a good one, but the amalgamation of data with multiple outcomes and exposures is not sufficiently well described - examples would enhance. The analysis (essentially descriptive variables) provided will not be nuanced enough to pick up times to recovery The tool [is] further blunted by the use of a 7 day parent report- many ARIs will recover well before this risking bias to the Null. There is no mention of allowing for clustering by centre. In many cases HRs and IRRS will be more informative. It is unclear what the main exposure/outcome/focus test aims are. Parent´s should be parents´.	• To clarify for reviewers, this protocol is to introduce the platform and associated registry. • We clarified the role of the registry in the strengths and limitations section on page 3, line 2 and the methods on page 6, line 2. • Data are obtained from only two sources – parental surveys (obtained at recruitment and regular intervals thereafter) and case report forms (collected by research nurses). We have simplified the way this has been described under the data management subheading on page 10, line 13 to reduce confusion. • The decision to determine time to recovery from intermittent surveys (rather than daily symptom diaries) is pragmatic in an attempt to maximise recruitment and retention and therefore generalizability of registry data. Of importance, we request parents provide not only an assessment as to whether their child has recovered, but if so, when? We clarified this under the follow-up subheading on page 8, line 28. We acknowledge that there is a risk that this may be influenced by parent recall but believe that retention within the registry is of greater importance. As described in our example of a nested clinical trial (optimal duration of amoxycillin in community acquired pneumonia), additional surveys have been used to ensure greater resolution of time-dependent endpoints. • More detail has been added under the data analysis plan subheading on page 11, line 14, including proposed ways in which registry data will be used. Predictors for the primary and secondary outcomes will be determined from the registry data and will inform guideline development and future trial design. It is intended that both odds and hazards will be used depending on whether recovery (yes/no) or time to recovery (days) is the outcome being assessed, adjusted by multiple covariates, and refined to ensure best fit. • We thank the reviewer for their suggestion to consider clustering by center. This has been noted in the manuscript (page 11, line 16). • Additional detail has been introduced to the 'Use of the platform for nested clinical trials' subheading on page 11, line 23 to clarify an example of exposure, outcome and intervention during platform utilisation. • We revised Parent's to Parents' on page 3, line 5 of the manuscript.
Reviewer 2 comments	• While the platform is not actively salvaging biological specimens, we included a consent to salvage any already

The protocol mentions biological specimen, however it would have been helpful if it gave more information on what kind of specimen and for what kind of analyses. The registry can be used as a basis for add on studies such as randomized clinical trials, will there be a new consent process for such activities. What is the expected enrolment rate into the registry. The title and the abstract can be somewhat misleading as this is a registry and not yet a "trial." Please reconsider the title.	collected biological specimens to ensure current participants would be eligible for future HREC approved research. • Any trials introduced to the platform are subject to individual ethics and governance approval. Eligible participants will be required to sign a separate consent to be involved. • The registry is currently recruiting approximately 900 participants per year from a single centre with approximately 70% of registry participants completing surveys until recovery. Multi-centre expansion will increase the enrolment rate. • While the current manuscript is a protocol and statement of intent for the overall trial platform and registry, we include an example of an ongoing trial utilising the platform infrastructure on page 11. For this reason, the authors feel the title is appropriate.

VERSION 2 – REVIEW

REVIEWER	brown, nick Uppsala Universitet
REVIEW RETURNED	12-Dec-2023

GENERAL COMMENTS	thanks for your revision- all my comments have been addressed the manuscript reads very well good luck with the rest of the project

REVIEWER	Strand, Tor University of Bergen
REVIEW RETURNED	02-Jan-2024

GENERAL COMMENTS	The authors have responded to our initial queries well. The updated manuscript reads well and is ready for publication