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Keywords:	Respiratory infections < THORACIC MEDICINE, REGISTRIES, PAEDIATRICS, Clinical trials < THERAPEUTICS

The Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) Clinical Registry Protocol

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Abstract

Introduction

Acute Respiratory Infections (ARI) are the most common cause of paediatric hospitalisation. There is an urgent need to address ongoing critical knowledge gaps in ARI management. The Pragmatic Adaptive Trial for Respiratory Infections in Children (PATRIC) Clinical Registry will evaluate current treatments and outcomes for ARI in a variety of paediatric patient groups. The registry will provide a platform and data to inform a number of PATRIC clinical trials, testing various interventions in ARI treatment and management to optimise paediatric ARI care.

Methods and analysis

The PATRIC Clinical Registry is a single centre, prospective observational registry recruiting from a tertiary paediatric Emergency Department in Western Australia. Through characterising demographic, clinical, treatment and outcome data, the PATRIC Clinical Registry will improve our understanding of antibiotic utilisation and ARI outcomes in children.

Ethics and dissemination

The PATRIC Clinical Registry is conducted in accordance with the Declaration of Helsinki, and the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (CPMP/ICH/13595) July 1996. Approval is provided by the Child and Adolescent Health Service (CAHS) Human Research Ethics Committee (HREC). Study results will be communicated by presentation and publication (HREC: RGS0000003078.)

Trial registration number: Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12619000903189**.** UTN: U1111-1231-3365.

Keywords: Respiratory Tract Infections, Registries, Pediatrics, Pragmatic Clinical Trials

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Strengths and limitations of this study:

- This clinical registry promotes acute respiratory infections (ARI) care optimisation and provides a platform for future ARI intervention trials.

- Patient-reported outcomes and use of parent's hand-held devices enables a more flexible approach to registry data collection.
- Emergency department recruitment may result in the enrolment of children with more severe ARI
- Follow-up is dependent on parental recall and timely data entry by parents
- Current study materials may not be culturally appropriate for all patient groups (i.e., Aboriginal and Torres Strait Islander populations, who experience an increased burden of ARI)

Introduction

Acute respiratory infections (ARI), inclusive of both upper and lower respiratory tract infections (URTI, LRTI), are common in children. While URTI is mostly mild and self-limiting, LRTIs including pneumonia and bronchiolitis are frequent causes of paediatric hospital admissions. Outside the neonatal period, ARI remains the leading cause of childhood mortality (1) with global data (2019) estimating that LRTI resulted in 671,927 deaths, and 59.2 million disability-adjusted life years for children under 5 years (2). In Australia, ARI-associated mortality is rare, but the morbidity and economic burden of paediatric ARI remains substantial. It is estimated that, on average, Australian children experience thirteen ARI episodes in their first two years of life (3). In Western Australia (WA), ARI is the most common reason for childhood presentation to an emergency department and hospitalisation (4), with at least one in four Aboriginal children and one in fifteen non-Aboriginal children in WA hospitalised for a chest infection before their fifth birthday (5).

Most ARI episodes are secondary to respiratory viruses (6, 7). A recent case-control study investigating the viral and bacterial burden of pneumonia in WA children found that one or more respiratory virus was identified in 56% of cases versus 29% of controls (6). The population-attributable fraction for pneumonia by Respiratory Syncytial Virus (RSV), Human metapneumovirus (HMPV), influenza, and adenovirus was estimated to 20%, 10%, 6% and 4% respectively. This is compared with the most frequently detected bacterial species, *Mycoplasma*

pneumoniae (attributable fraction; 7%). *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Streptococcus pyogenes* are important bacterial causes of ARI.

Many of the current treatment recommendations for paediatric ARI have not been tested through clinical trials. Antibiotics are frequently prescribed for management of childhood pneumonia and many other ARIs (6, 8). However, given the substantial contribution of respiratory viruses to paediatric ARI, antibiotics may have little or no benefit in most ARI cases. Antimicrobial resistance (AMR) has been identified by the World Health Organization as a serious global threat. Injudicious use of antibiotics for ARI care contributes to the global concern of AMR (9). Well-designed antimicrobial trials for ARI management, conducted in the era of conjugate pneumococcal and HiB vaccination are few in number (10) and supportive care trials have been infrequently performed (11).

More than a decade ago, the Infectious Disease Society of America (IDSA) recommended robust time-to-event analyses in ARI trial design (12). However, despite numerous professional societies noting the limited trial data (10, 13), there has been slow progress towards evidence-based antimicrobial use in ARI management. Traditional randomised controlled trials have inherent design limitations, including increased expense, reduced generalisability, and delays in research translation. Provided the ongoing uncertainty about optimal ARI management strategies, the increasing threat of AMR and new therapeutic options expected; barriers to conducting clinical trials for ARI in paediatric populations must be overcome.

To drive and inform evidence-based ARI care, we have established a prospective clinical registry recruiting children with ARI presenting for urgent care at the emergency department (ED). This has been developed to document risk factors, symptoms, severity and duration of illness, microbiology (when obtained), treatment adherence and disease outcomes and to explore factors associated with rapid symptom resolution. The Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) Clinical Registry serves as a research platform, generating critical baseline data for future clinical trials in ARI, focusing on time-to-event endpoints. Commencing in a single centre, the registry has been designed to expand into a multicentre registry and adaptive clinical trial platform.

Primary objective

The PATRIC Clinical Registry aims to: (i) accurately and efficiently characterise demographic, clinical, treatment, and outcome data from eligible participants in order to optimise the care of children with ARI and, (ii) provide the underlying preliminary evidence and platform for a pragmatic adaptive clinical trial on childhood ARI, a critical step towards evidence-based ARI care.

Secondary objectives

Secondary objectives are to: (i) demonstrate the willingness of parents and/or guardians (hereafter referred to as parents) to enrol their children in an electronic prospective ARI registry; (ii) estimate the distribution of treatment response under alternative management options within different ARI patient subgroups; (iii) optimise parent-reported outcomes and refine patient-reported outcome measures for ARI treatment and (iv) provide surveillance data to characterise seasonal trends in ARI and real-time data for ARI epidemics as they arise.

Methods and analysis

Study design

The PATRIC Clinical Registry is an observational, prospective cohort of patients who present to an emergency department with an ARI. Information including demographic, symptoms, vaccination history, medical history, treatment, and follow-up responses are collected.

The PATRIC Clinical Registry provides the foundation for the PATRIC platform, collecting baseline data and enabling future trials evaluating ARI interventions to be nested within the platform. While this manuscript describes the methodology for the PATRIC Clinical Registry, each individual trial to be conducted within the PATRIC platform will have an independent protocol, with unique objectives and outcomes. Each PATRIC trial will also have individual ethics

and regulatory approvals as required. It is proposed that trials may involve antimicrobial, immunomodulatory, and supportive care interventions.

Patient and community involvement

The objectives of the PATRIC Clinical Registry have been discussed with, and supported by, the *Wesfarmers Centre of Vaccines and Infectious Diseases (WCVID) Consumer Reference Group* to ensure the study objectives and procedures are relevant and acceptable for the ARI patient community. An information video, participant information sheet, e-consent forms, e-survey, and supportive information sheets were co-designed with input from consumers and tested for usability and acceptance with a pilot group of parents of young children (14). Intervention in the future PATRIC trials will also be guided by discussions and the priorities of the WCVID consumer reference group as well as other consumer groups.

Study setting

Participants are enrolled from children presenting with physician-diagnosed ARI to the emergency department. At time of writing, recruitment is underway at Perth Children's Hospital (PCH), Western Australia (WA). The PCH is the only tertiary paediatric hospital for the state of WA (population: 2.6 million (15)). It is intended that the PATRIC Clinical Registry will be implemented across multiple sites in Australia, initially focusing on paediatric emergency departments. Recruitment started in February 2020 and is ongoing. The PATRIC Clinical Registry is designed to prospectively collect data on eligible participants.

Eligibility criteria, sample size and recruitment procedures

Inclusion Criteria

Children and adolescents who meet the following criteria are eligible for registry enrolment:

(i) aged ≥ 1 months and <18 years AND

(ii) symptoms and signs of ARI: a documented fever ≥37.5^{0}C or history of fever in the past 96 hours AND cough, and/or shortness of breath and/or influenza-like symptoms such as sore throat or fatigue AND

(iii) total duration of symptoms <21 days at time of enrolment.

Exclusion criteria

A potentially eligible child who meets any of the following criteria will be excluded from participation:

(i) children < 1 months old or 18 years and older OR

(ii) previous participation in PATRIC within the last 3 months OR

(iii) parents whose English is insufficient to understand study materials, OR

(iv) parents do not complete the baseline survey, OR

(v) parents not willing or able to provide consent.

Patient recruitment and consent

The registry does not have a fixed sample size. ED research nurses will identify and approach parents whose children meet the eligibility criteria. Parents are then presented a departmental electronic tablet to view the 3min participant information video, information form and electronic consent form. They are also able to access these materials on their own hand-held device using a QR code. Upon completion of the electronic consent a copy of the participant information sheet, and signed electronic consent is sent to the parents' email address. As shown in Figure 1, The Day 0 baseline survey is then sent immediately to the parent/carers mobile phone following completion of the e-consent form. The Research Electronic Data Capture application (REDCap; Vanderbilt University, Nashville, TN, US), application is used for e-consent, follow-up surveys, and the case report form.

Data collection procedures

Day 0 survey

Parent-reported surveys sent on day 0 collect information on demographics, relevant comorbidities (e.g., immunodeficiency, chronic heart, and lung disease), history of any previous hospitalisation with severe respiratory infections, household structure (number of children and adults), attendance at out-of-home care/education (playgroup/mothers' group, day-care, kindergarten, preschool or school), symptoms and behaviours observed in the preceding 24 hours (using the Canadian Acute Respiratory Illness and Flu Scale, CARIFS (16)), additional symptoms to better capture lower respiratory involvement (wheezing and difficulty breathing), and antibiotics or antivirals received prior to the ED visit.

Case Report Form (CRF), immunisation data, and biological samples

In additional to parent-completed Day 0 baseline survey, information on a patient electronic CRF is entered by a research nurse, and includes information on demographics (age, sex, postcode, and ethnicity), presentation and ED management (health assessments, support required, investigations required and results, discharge diagnosis, and medications provided). Immunisations registered with the Australian Immunisation Registry are collected independently and linked to the participant using 3 identifiers (name, DOB, Medicare number). The e-consent form also provides the option to consent to the salvage of biological specimens collected during routine care for the ARI episode.

Follow-up

Patient-reported outcome and patient-reported outcome measures are recommended as a way of capturing the true impact of disease on children and families over time. Parents receive weekly follow up surveys every 7 days from day 7 until symptom recovery, or day 28 (whichever occurs earlier), sent to parents' smart phones via automated messaging. Parents are also asked to report on the presence and severity of several respiratory, behavioural, and activity-based outcomes (using CARIFS) and additional symptoms (wheezing and difficulty breathing) to capture lower respiratory involvement. Additional outcomes, developed in collaboration with consumers, are requested at each time point. These include parents answering "yes" or "no" to the question: "Is your child still sick?". In addition, two summary questions are asked: a) "Has your child returned to playgroup/mothers' group, day-care, kindergarten, preschool or school in last 7 days?", if yes,

"when"); and b) "Is your child as active as usual today?", if yes, "When did your child return to their usual level of activity?" Parents are also asked if their child has received additional medical care or prescription medication.

If the parent completing a follow-up survey on Day 7, 14, 21 or 28 reports that their child is "still sick", they will be provided with the option to access a link to downloadable supportive information sheet "*Respiratory Tract Infection – General Home Care Advice*". This resource has been developed in consultation with clinicians and parent groups. The instructions are written at a level of readability appropriate for the general population with accompanying pictograms. Emphasis has also been placed on making the information accessible for all parents including those with low health literacy. The information sheet outlines how to provide supportive care for a child with an ARI, provides links to further resources as well as contact phone numbers for further health advice.

Outcome measures

Primary Outcome

The primary endpoint for the registry will be the return to pre-morbid health state, as assessed by parents, by day 7. This will be determined by the parental survey response on day 7.

Secondary Outcomes

The secondary endpoints for the registry are: (i) time to full recovery of ARI symptoms (in days, (ii) time to return to normal childhood activities (in days; defined as: sufficient improvement to return to day-care; school; playgroups or other social outings), (iii) proportion of children who have returned to their pre-morbid health state by day 7, 14, 21 and 28, (iv) proportion of children who are free from cough by day 7, 14, 21 and 28, (v) proportion of children who are free from fever by day 7, 14, 21 and 28, (vi) proportion of children with clinical failure (defined as: repeat emergency presentation or hospitalisation; general practice re-presentation; modification or unplanned prolongation of antibiotic therapy) by day 7, 14, 21, 28, (vii) proportion of children

intolerant to therapy. These endpoints will be assessed using data from the parental surveys and/or any post enrolment return presentation to the ED.

Data management

Registry data derived from parental surveys, parental instruction sheet information, case report forms, laboratory and pharmacy records, and imaging results will be directly entered into a web-based database (REDCap). To ensure all data is stored safely in confidential conditions, each participant record will be referred to by a unique study-specific identifier and accessible only by study personnel. Paper materials linking the participant to medical data or any other database material will be maintained on site in a secure location.

Data analysis plan

Proportion reaching the primary outcome and the median time to reach secondary outcomes, as determined by parental surveys, will be assessed in the PATRIC Clinical Registry. Subgroup analysis, by age group, risk factors and treatments prescribed will be performed. Severe outcomes, including hospital representation, will be cross-checked against the medical record. The proportion lost to follow up prior to return to their premorbid state will also be reported.

Summarised descriptive statistics for individual demographics, risk factors, concurrent medications, allergies, immunisation status, ARI diagnosis and clinical markers of severity (temperature, respiratory rate, oxygen saturations on air) will be reported for all enrolled participants. Subgroup analysis will be stratified by age groups (infants: <12 months; young children: 13-59 months; older children: ≥60 months), antibiotic exposure (before presentation to hospital, prescribed during their hospital stay or by other healthcare provider during follow-up period), laboratory-confirmed viral and bacterial ARI and risk factors (e.g., immunocompromising conditions).

Proportions for categorical variables will be summarised as frequency and percent proportion, with 95% confidence intervals. Frequencies below five will be reported as "<5" to ensure confidentiality. Summaries of continuous variables will be reported as mean and standard

deviation for symmetric distributions and median and interquartile range for asymmetric distributions.

Use of the platform for nested clinical trials

The PATRIC Clinical Registry provides a framework for intervention studies, randomising participants to specific diagnostic approaches and treatments. PATRIC trials share similar data and use the same clinical outcomes. Data from the registry will continue to inform trial simulations and provided baselines for standard of care. A pilot clinical trial, assessing the optimal duration of amoxycillin duration in physician-diagnosed community-acquired pneumonia is underway (ACTRN12621000967886).

Ethics and dissemination

The PATRIC platform and embedded registry is conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (CPMP/ICH/13595). Platform materials, including protocols and amendments are submitted to an appropriate human research ethics committee (HREC), and host institution for written approval as required. Written consent is obtained from parents during recruitment. PATRIC staff ensure the participants' anonymity is maintained through de-identifying data and using a participant identifier for analysis. All data is collected, stored, and removed in compliance with data protection laws. Study results will be communicated by presentation and journal publication.

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Authors contributions

RP, MUB, MLB, TLS and CCB designed the registry and trial platform. Expert advice was provided by AM and PCR. RP and CCB wrote the protocol, sought ethics approval and funding. MUB developed the database and MAJ assisted with statistical advice and simulations for nested clinical trials. RP, SD, MLB and CCB designed electronic consent and registry materials. RP and DO led the writing of this manuscript. All authors have read and approved the final version of this manuscript.

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Competing interest's statement

The authors have no competing interests to disclose.

Figure 1: Flowchart of PATRIC registry design surveys, and the case report form

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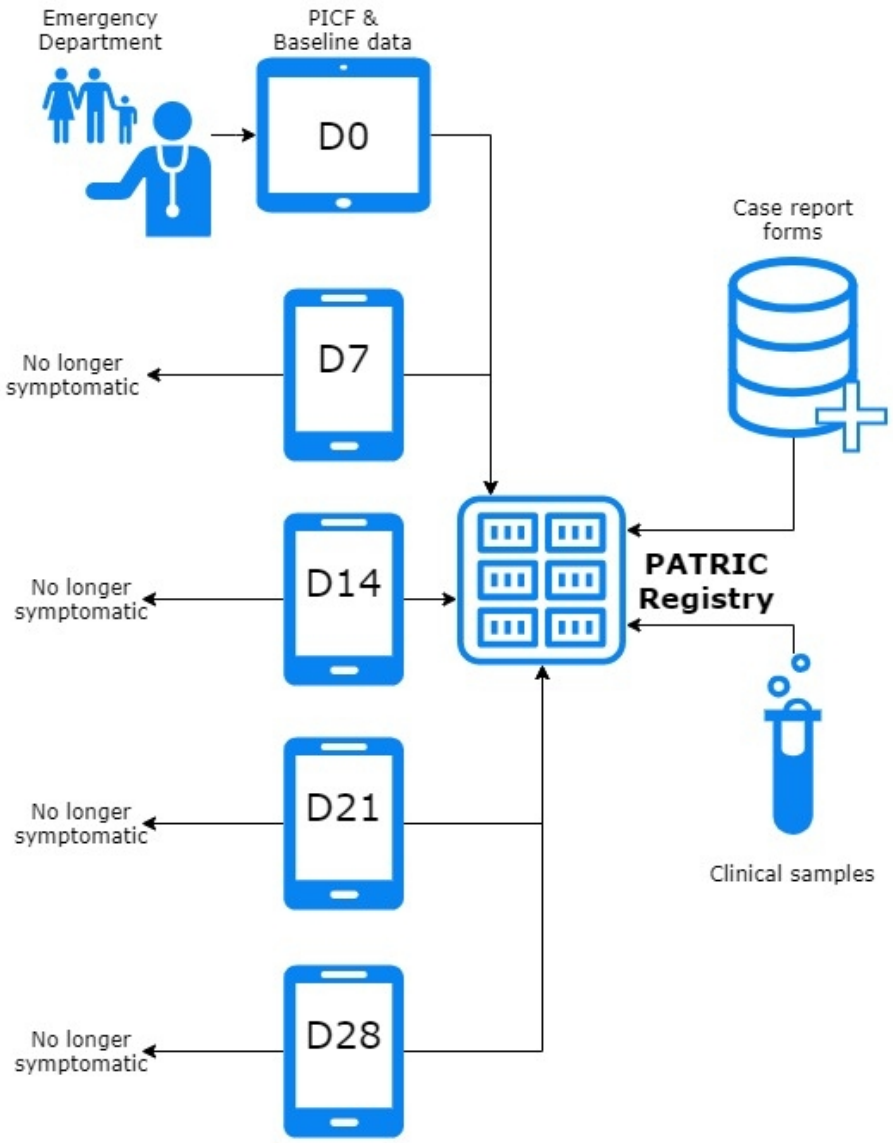

Figure 1: Flowchart of PATRIC registry design surveys, and the case report form

195x245mm (72 x 72 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number addressing item
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1
	2b	All items from the World Health Organization Trial Registration Data Set	Page 1
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	Page 12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1, 11
	5b	Name and contact information for the trial sponsor	Page 12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Investigator led, Page 12.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introductio			

n			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3-4
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	Page 4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 7-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	N/A
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 7-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 7-10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double	Page 9-10

		data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be	N/A

		independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 5
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via	Page 11

		publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) Clinical Registry Protocol

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The Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) Clinical Registry Protocol

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Abstract

Introduction

Acute Respiratory Infections (ARI) are the most common cause of paediatric hospitalisation. There is an urgent need to address ongoing critical knowledge gaps in ARI management. The Pragmatic Adaptive Trial for Respiratory Infections in Children (PATRIC) Clinical Registry will evaluate current treatments and outcomes for ARI in a variety of paediatric patient groups. The registry will provide a platform and data to inform a number of PATRIC clinical trials, testing various interventions in ARI treatment and management to optimise paediatric ARI care.

Methods and analysis

The PATRIC Clinical Registry is a single centre, prospective observational registry recruiting from a tertiary paediatric Emergency Department in Western Australia. Through characterising demographic, clinical, treatment and outcome data, the PATRIC Clinical Registry will improve our understanding of antibiotic utilisation and ARI outcomes in children.

Ethics and dissemination

The PATRIC Clinical Registry is conducted in accordance with the Declaration of Helsinki, and the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (CPMP/ICH/13595) July 1996. Approval is provided by the Child and Adolescent Health Service (CAHS) Human Research Ethics Committee (HREC). Study results will be communicated by presentation and publication (HREC: RGS0000003078.)

Trial registration number: Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12619000903189**.** UTN: U1111-1231-3365.

Keywords: Respiratory Tract Infections, Registries, Pediatrics, Pragmatic Clinical Trials

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1

Strengths and limitations of this study:

- This clinical registry provides a mechanism to optimise acute respiratory infection (ARI) care and a platform for future ARI intervention trials.
- Patient-reported outcomes and use of parents' hand-held devices enables a more flexible approach to registry data collection.
- Emergency department recruitment may result in the enrolment of children with more severe ARI.
- Follow-up is dependent on parental recall and timely data entry by parents.
- Current study materials may not be culturally appropriate for all patient groups (i.e., Aboriginal and Torres Strait Islander populations, who experience an increased burden of ARI).

Introduction

Acute respiratory infections (ARI), inclusive of both upper and lower respiratory tract infections (URTI, LRTI), are common in children. While URTI is mostly mild and self-limiting, LRTIs including pneumonia and bronchiolitis are frequent causes of paediatric hospital admissions. Outside the neonatal period, ARI remains the leading cause of childhood mortality (1) with global data (2019) estimating that LRTI resulted in 671,927 deaths, and 59.2 million disability-adjusted life years for children under 5 years (2). In Australia, ARI-associated mortality is rare, but the morbidity and economic burden of paediatric ARI remains substantial. It is estimated that, on average, Australian children experience thirteen ARI episodes in their first two years of life (3). In Western Australia (WA), ARI is the most common reason for childhood presentation to an emergency department and hospitalisation (4), with at least one in four Aboriginal children and one in fifteen non-Aboriginal children in WA hospitalised for a chest infection before their fifth birthday (5).

Most ARI episodes are secondary to respiratory viruses (6, 7). A recent case-control study investigating the viral and bacterial burden of pneumonia in WA children found that one or more respiratory virus was identified in 56% of cases versus 29% of controls (6). The population-

attributable fraction for pneumonia by Respiratory Syncytial Virus (RSV), human metapneumovirus (HMPV), influenza, and adenovirus was estimated to 20%, 10%, 6% and 4% respectively. This is compared with the most frequently detected bacterial species, *Mycoplasma pneumoniae* (attributable fraction; 7%). *Streptococcus pneumonia*e, *Haemophilus influenzae* and *Streptococcus pyogenes* are important bacterial causes of ARI.

Many of the current treatment recommendations for paediatric ARI have not been tested through clinical trials. Antibiotics are frequently prescribed for management of childhood pneumonia and many other ARIs (6, 8). However, given the substantial contribution of respiratory viruses to paediatric ARI, antibiotics may have little or no benefit in most ARI cases. Antimicrobial resistance (AMR) has been identified by the World Health Organization as a serious global threat. Injudicious use of antibiotics for ARI care contributes to the global concern of AMR (9). Well-designed antimicrobial trials for ARI management, conducted in the era of conjugate pneumococcal and HiB vaccination are few in number (10) and supportive care trials have been infrequently performed (11).

More than a decade ago, the Infectious Disease Society of America (IDSA) recommended robust time-to-event analyses in ARI trial design (12). However, despite numerous professional societies noting the limited trial data (10, 13), there has been slow progress towards evidence-based antimicrobial use in ARI management. Traditional randomised controlled trials have inherent design limitations, including increased expense, reduced generalisability, and delays in research translation. Provided the ongoing uncertainty about optimal ARI management strategies, the increasing threat of AMR and new therapeutic options expected; barriers to conducting clinical trials for ARI in paediatric populations must be overcome.

To drive and inform evidence-based ARI care, we have established a prospective clinical registry recruiting children with ARI presenting for urgent care at the emergency department (ED). This has been developed to document risk factors, symptoms, severity and duration of illness, microbiology (when obtained), treatment adherence and disease outcomes and to explore factors associated with rapid symptom resolution. The Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) Clinical Registry serves as a research platform, generating critical baseline

data for future clinical trials in ARI, focusing on time-to-event endpoints. Commencing in a single centre, the registry has been designed to expand into a multicentre registry and adaptive clinical trial platform.

Primary objective

The PATRIC Clinical Registry aims to: (i) accurately and efficiently characterise demographic, clinical, treatment, and outcome data from eligible participants in order to optimise the care of children with ARI and, (ii) provide the underlying preliminary evidence and platform for a pragmatic adaptive clinical trial on childhood ARI, a critical step towards evidence-based ARI care.

Secondary objectives

Secondary objectives are to: (i) demonstrate the willingness of parents and/or guardians (hereafter referred to as parents) to enrol their children in an electronic prospective ARI registry; (ii) estimate the distribution of treatment response under alternative management options within different ARI patient subgroups; (iii) optimise parent-reported outcomes and refine patient-reported outcome measures for ARI treatment and (iv) provide surveillance data to characterise seasonal trends in ARI and real-time data for ARI epidemics as they arise.

Methods and analysis

Study design

The PATRIC Clinical Registry is an observational, prospective cohort of children who present to an emergency department with an ARI. Information including demographic, symptoms, vaccination history, medical history, treatment, and follow-up responses are collected.

The PATRIC Clinical Registry provides the foundation for the PATRIC platform, collecting baseline data to inform the design of and providing tools and mechanism to recruit to ARI intervention trials nested within the platform. While this manuscript describes the methodology for the PATRIC Clinical Registry, each individual trial to be conducted within the PATRIC platform will have an independent protocol, with unique objectives and outcomes. Each PATRIC trial will also have individual ethics and regulatory approvals as required. It is proposed that trials may involve antimicrobial, immunomodulatory, and supportive care interventions.

Patient and community involvement

The objectives of the PATRIC Clinical Registry have been discussed with, and supported by, the *Wesfarmers Centre of Vaccines and Infectious Diseases (WCVID) Consumer Reference Group* to ensure the study objectives and procedures are relevant and acceptable for the ARI patient community. An information video, participant information sheet, e-consent forms, e-survey, and supportive information sheets were co-designed with input from consumers and tested for usability and acceptance with a pilot group of parents of young children (14). Intervention in the future PATRIC trials will also be guided by discussions and the priorities of the WCVID consumer reference group as well as other consumer groups.

Study setting

Participants are enrolled from children presenting with physician-diagnosed ARI to the emergency department. At time of writing, recruitment is underway at Perth Children's Hospital (PCH), Western Australia (WA). The PCH is the only tertiary paediatric hospital for the state of WA (population: 2.6 million (15)). It is intended that the PATRIC Clinical Registry will be implemented across multiple sites in Australia, initially focusing on paediatric emergency departments. Recruitment started in February 2020 and is ongoing. The PATRIC Clinical Registry is designed to prospectively collect data on eligible participants.

Eligibility criteria, sample size and recruitment procedures

Inclusion Criteria

Children and adolescents who meet the following criteria are eligible for registry enrolment:

(i) aged ≥ 1 months and <18 years AND

(ii) symptoms and signs of ARI: a documented fever ≥37.5^{0}C or history of fever in the past 96 hours AND cough, and/or shortness of breath and/or influenza-like symptoms such as sore throat or fatigue AND

(iii) total duration of symptoms <21 days at time of enrolment.

Exclusion criteria

A potentially eligible child who meets any of the following criteria will be excluded from participation:

(i) children < 1 months old or 18 years and older OR

(ii) previous participation in PATRIC within the last 3 months OR

(iii) parents whose English is insufficient to understand study materials, OR

(iv) parents do not complete the baseline survey, OR

(v) parents not willing or able to provide consent.

Patient recruitment and consent

The registry does not have a fixed sample size. ED research nurses will identify and approach parents whose children meet the eligibility criteria. Parents are then presented a departmental electronic tablet to view the 3min participant information video, information form and electronic consent form. They are also able to access these materials on their own hand-held device using a QR code. Upon completion of the electronic consent, a copy of the participant information sheet, and signed electronic consent is sent to the parents' email address. As shown in Figure 1, The Day 0 baseline survey is then sent immediately to the parent/carers mobile phone following completion of the e-consent form. The Research Electronic Data Capture application (REDCap; Vanderbilt University, Nashville, TN, US), application is used for e-consent, follow-up surveys, and the case report form.

Data collection procedures

Day 0 survey

Parent-reported surveys sent on day 0 collect information on demographics, relevant comorbidities (e.g., immunodeficiency, chronic heart, and lung disease), history of any previous hospitalisation with acute respiratory infections, household structure (number of children and adults), attendance at out-of-home care/education (playgroup/mothers' group, day-care, kindergarten, preschool or school), symptoms and behaviours observed in the preceding 24 hours (using the Canadian Acute Respiratory Illness and Flu Scale, CARIFS (16)), additional symptoms to better capture lower respiratory involvement (wheezing and difficulty breathing), and antibiotics or antivirals received prior to the ED visit.

Case Report Form (CRF), immunisation data, and biological samples

In additional to parent-completed Day 0 baseline survey, information on a patient electronic CRF is entered by a research nurse, and includes information on demographics (age, sex, postcode, and ethnicity), presentation and ED management (health assessments, support required, investigations required and results, discharge diagnosis, and medications provided). Immunisations registered with the Australian Immunisation Registry are collected independently and linked to the participant using 3 identifiers (name, DOB, Medicare number). The e-consent form also provides the option to consent to the salvage of biological specimens collected during routine care for the ARI episode.

Follow-up

Patient-reported outcome and patient-reported outcome measures are recommended as a way of capturing the true impact of disease on children and families over time. Parents receive weekly follow-up surveys every 7 days from day 7 until symptom recovery, or day 28 (whichever occurs earlier), sent to parents' smart phones via automated messaging. The 7-day follow-up was chosen in an attempt to maximise retention, minimise loss to follow up and ensure the generalisability of results. Parents are also asked to report on the presence and severity of several respiratory,

behavioural, and activity-based outcomes (using CARIFS) and additional symptoms (wheezing and difficulty breathing) to capture lower respiratory involvement.

Additional outcomes, developed in collaboration with consumers, are also requested at each time point. These include parents answering "yes" or "no" to the question: "Is your child still sick?". In addition, two summary questions are asked: a) "Has your child returned to playgroup/mothers' group, day-care, kindergarten, preschool or school in last 7 days?", if yes, "when"); and b) "Is your child as active as usual today?", if yes, "When did your child return to their usual level of activity?" These questions are used to determine time dependent outcomes (see secondary outcomes). Parents are also asked if their child has received additional medical care or prescription medication.

If the parent completing a follow-up survey on Day 7, 14, 21 or 28 reports that their child is "still sick", they will be provided with the option to access a link to downloadable supportive information sheet "*Respiratory Tract Infection – General Home Care Advice*". This resource has been developed in consultation with clinicians and parent groups. The instructions are written at a level of readability appropriate for the general population with accompanying pictograms. Emphasis has also been placed on making the information accessible for all parents including those with low health literacy. The information sheet outlines how to provide supportive care for a child with an ARI, provides links to further resources as well as contact phone numbers for further health advice.

Outcome measures

Primary Outcome

The primary endpoint for the registry will be the return to pre-morbid health state, as assessed by parents, by day 7. This will be determined by the parental survey response on day 7.

Secondary Outcomes

The secondary endpoints for the registry are: (i) time to full recovery of ARI symptoms (in days, (ii) time to return to normal childhood activities (in days; defined as: sufficient improvement to return to day-care; school; playgroups or other social outings), (iii) proportion of children who have returned to their pre-morbid health state by day 7, 14, 21 and 28, (iv) proportion of children who are free from cough by day 7, 14, 21 and 28, (v) proportion of children who are free from fever by day 7, 14, 21 and 28, (vi) proportion of children with clinical failure (defined as: repeat emergency presentation or hospitalisation; general practice re-presentation; modification or unplanned prolongation of antibiotic therapy) by day 7, 14, 21, 28, (vii) proportion of children intolerant to therapy. These endpoints will be assessed using data from the parental surveys and/or any post enrolment return presentation to the ED.

Data management

Registry data derived from parental surveys (provided at enrolment and at regular intervals thereafter) and case report forms (collected by a research nursing and capturing discharge diagnosis, laboratory, radiology, and pharmacy data). All data are directly entered into a web-based database (REDCap). To ensure all data is stored safely in confidential conditions, each participant record will be referred to by a unique study-specific identifier and accessible only by study personnel. Paper materials linking the participant to medical data or any other database material will be maintained on site in a secure location.

Data analysis plan

Proportion reaching the primary outcome and the median time to reach secondary outcomes, as determined by parental surveys, will be assessed in the PATRIC Clinical Registry. Subgroup analysis, by age group, risk factors and treatments prescribed will be performed and compared. Severe outcomes, including hospital representation, will be cross-checked against the medical record. The proportion lost to follow up prior to return to their premorbid state will also be reported.

Summarised descriptive statistics for individual demographics, risk factors, concurrent medications, allergies, immunisation status, ARI diagnosis and clinical markers of severity (temperature, respiratory rate, oxygen saturations on air) will be reported for all enrolled participants. Subgroup analysis will be stratified by age groups (infants: <12 months; young children: 13-59 months; older children: ≥60 months), antibiotic exposure (before presentation to hospital, prescribed during their hospital stay or by other healthcare provider during follow-up period), laboratory-confirmed viral and bacterial ARI and risk factors (e.g., immunocompromising conditions).

Proportions for categorical variables will be summarised as frequency and percent proportion, with 95% confidence intervals. Frequencies below five will be reported as "<5" to ensure confidentiality. Summaries of continuous variables will be reported as mean and standard deviation for symmetric distributions and median and interquartile range for asymmetric distributions.

Associations between specific covariates of interest and the primary or secondary outcomes will be explored using prediction models. Logistic and cox proportional hazards regression models will be primarily used with random effects models considered if clustering by site is observed post multisite expansion. The adjusted odds of returning to a pre-morbid health state 7 days after presentation (or hazards if time-dependent secondary outcomes are assessed) can be determined by demographics and risk factors (such as age, ethnicity, and previous infection), clinical presentation (such as symptoms, oxygen saturation, and respiratory rate), investigations ordered (such as chest x-ray, and nasopharyngeal swabs), and discharge diagnosis.

Use of the platform for nested clinical trials

The PATRIC Clinical Registry provides a framework for intervention studies, randomising participants to specific diagnostic approaches and treatments. PATRIC trials share similar data and use the same clinical outcomes. Data from the registry will continue to inform trial simulations and provided baselines for standard of care.

A pilot clinical trial, assessing the optimal duration of amoxycillin duration in physician-diagnosed community-acquired pneumonia is underway (ACTRN12621000967886). This open label trial

aims to identify a minimum non-inferior dose of antibiotics to the current standard of care, where the interventions include various lengths of amoxycillin therapy and the primary outcome is the proportion returning to a pre-morbid health state 7 days after presentation. In addition to existing registry surveys, families will receive additional monitoring surveys on days 2, 4, and 10 after presentation to ensure sufficient resolution to compare different durations of therapy. Analysis will be undertaken on an intention to treat basis primarily involving estimating dose response. Statistical inference will be computed under a Bayesian framework using Markov chain Monte Carlo methods. Prior distributions for the trial framework will be learned from accumulated evidence in the registry.

Ethics and dissemination

The PATRIC platform and embedded registry is conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (CPMP/ICH/13595). Platform materials, including protocols and amendments are submitted to an appropriate human research ethics committee (HREC), and host institution for written approval as required. Written consent is obtained from parents during recruitment. PATRIC staff ensure the participants' anonymity is maintained through de-identifying data and using a participant identifier for analysis. All data is collected, stored, and removed in compliance with data protection laws. Study results will be communicated by presentation and journal publication.

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Authors contributions

RP, MUB, MLB, SO, TLS and CCB designed the registry and trial platform. Expert advice was provided by AM and PCR. RP and CCB wrote the protocol, sought ethics approval and funding. MUB developed the database and MAJ assisted with statistical advice and simulations for nested clinical trials. RP, SD, MLB and CCB designed electronic consent and registry materials. RP and DO led the writing of this manuscript. All authors have read and approved the final version of this manuscript.

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Competing interest's statement

The authors have no competing interests to disclose.

Figure 1: Flowchart of PATRIC registry design surveys, and the case report form

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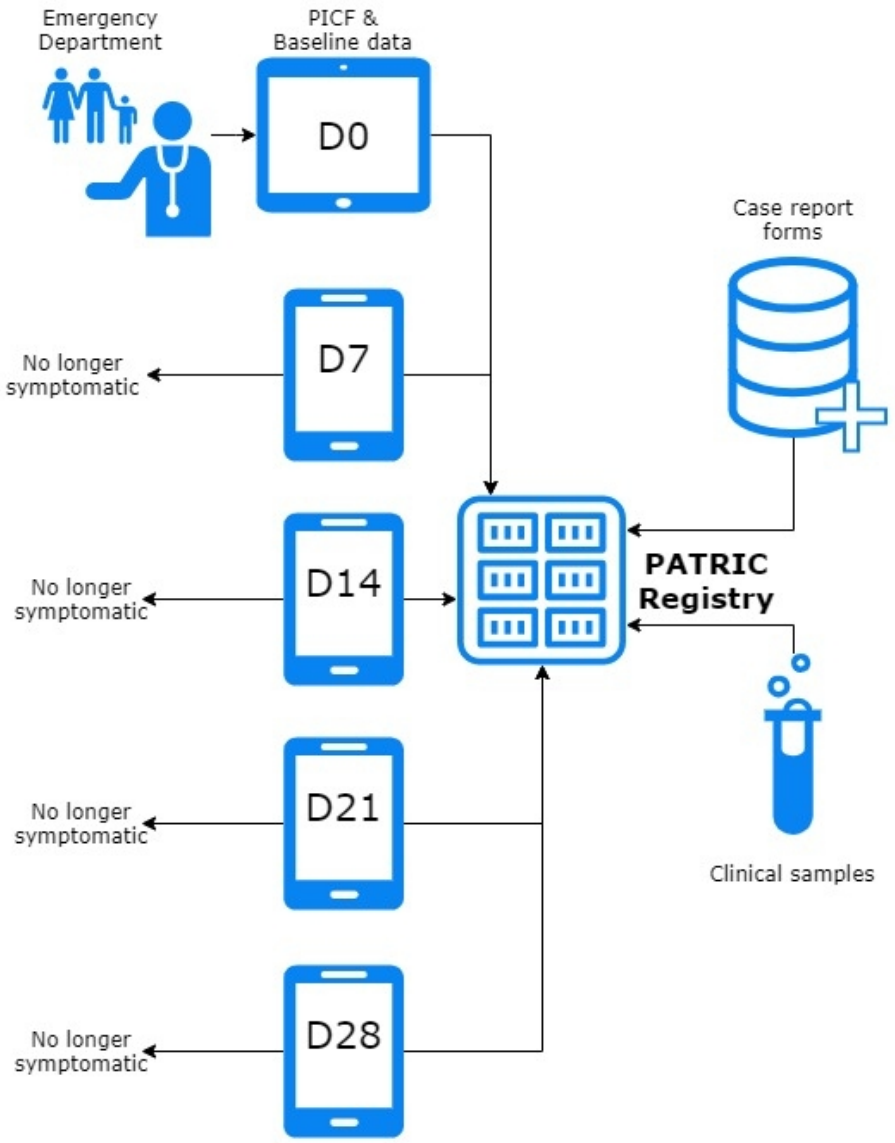

Figure 1: Flowchart of PATRIC registry design surveys, and the case report form

195x245mm (72 x 72 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number addressing item
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1
	2b	All items from the World Health Organization Trial Registration Data Set	Page 1
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	Page 12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1, 11
	5b	Name and contact information for the trial sponsor	Page 12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Investigator led, Page 12.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introductio			

n			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3-4
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	Page 4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 7-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	N/A
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 7-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 7-10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double	Page 9-10

		data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be	N/A

		independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 5
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via	Page 11

		publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.