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Effectiveness of a cough management algorithm at the transitional phase from acute to chronic cough in Australian children aged less than 15 years: protocol for a randomised controlled trial

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Title: Effectiveness of a cough management algorithm at the transitional phase from acute to chronic cough in Australian children aged less than 15 years: protocol for a randomised controlled trial

Trial acronym: RICCi Kids Study – Researching Intervention in Chronic Cough in Kids

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Strengths and limitations of this study

- Our study will be the first to assess the clinical and economic impact of an early, evidence-based intervention in the transitional stage from acute to chronic cough in children.
- Conducting the study in primary care facilities addresses the predominant setting in which acute respiratory illnesses are managed
- A limitation of the study is its generalizability to children with acute respiratory illnesses in rural and remote regions.

Abstract

Introduction

Acute respiratory infections (ARI) are leading causes of hospitalisation in Australian children and, if recurrent, are associated with increased risk of chronic pulmonary disorders later in life. Chronic (>4-weeks) cough in children following ARI is associated with decreased quality-of-life scores and increased health and societal economic costs. We will determine whether a validated evidence-based cough algorithm, initiated when chronic cough is first diagnosed after presentation with ARI, improves clinical outcomes in children compared to usual care.

Methods and analysis

A multi-centre, parallel group, open-label, randomised controlled trial, nested within a prospective cohort study in Southeast Queensland, Australia is underway. Seven-hundred-and-fifty children aged less than 15-years will be enrolled and followed weekly for 8-weeks after presenting with an ARI with cough. Two-hundred-and-fourteen children from this cohort with persistent cough at day-28 will be randomised to either early initiation of a cough management algorithm or usual care (107 per group). Randomisation is stratified by reason for presentation, site, and total cough duration at day-28 (<6-weeks and ≥6-weeks). Demographic details, risk factors, clinical histories, examination findings, cost-of-illness data, an anterior nasal swab and parent and child exhaled carbon monoxide levels (when age appropriate) are collected at enrolment. Weekly contacts collect cough status and cost-of-illness data. Additional nasal swabs are collected at days-28 and 56. The primary outcome is time-to-cough resolution. Secondary outcomes include direct and indirect costs of illness and the predictors of chronic cough post-presentation.

Ethics and dissemination

The Children's Health Queensland (HREC/15/QRCH/15) and the Queensland University of Technology University (1500000132) Research Ethics Committees have approved the study. The study will inform best-practice management of cough in children.

Trial registration: Australia and New Zealand Clinical Trials Registry (ANZCTR) number: ACTRN12615000132549. World Health Organization Trial Registration Universal Trial Number: U1111-1166-0388

Study sponsor: The Queensland University of Technology, Victoria Park Ave, Kelvin Grove, Australia

Keywords:

chronic cough, child, Aboriginal and Torres Strait Islander, management, early intervention, randomised controlled trial, cost-effectiveness, respiratory viruses, respiratory bacteria

Introduction

Cough in children is one of the most common reasons for medical encounters in Australia[1] and internationally.[2] In the United Kingdom, 30% of hospital paediatric medical encounters (including Emergency Department (ED) visits) are due to respiratory illnesses, with cough as a symptom accounting for over 8% of all presentations.[3] Cough in children is present in a broad range of respiratory illnesses ranging from mild, self-limiting rhinitis to life-threatening acute and chronic pulmonary disorders.[4] Furthermore, acute illness may bring to medical attention for the first time those with chronic underlying disease. In analyses of our recent cohort study of 664 children aged <15-years presenting with cough to a tertiary paediatric ED,[5] 20% developed chronic (>4-weeks duration) cough after an acute respiratory infection (ARI) and of those, 32% were found at specialist review to have a previously undiagnosed respiratory disorder (unpublished).

Chronic cough in children is an under-recognised, but important cause of morbidity and decreased quality of life (QoL).[6] Although an economic evaluation has never been undertaken, chronic cough likely accounts for substantial direct and indirect economic costs.[7] An Australian study found that >80% of parents had sought five or more medical consultations for their child in the 12-months immediately prior to referral to respiratory specialists for their child's chronic cough.[7] Nevertheless, there are few high quality studies that address the natural history of acute and chronic cough and none completed that have a predominant focus on Australian Indigenous children. Systematic reviews of the natural history of acute cough in children in primary healthcare found wide variation in the design and quality of studies.[8,9] There was large variability in the duration of illnesses evaluated, how outcomes were measured and completeness of follow-up. Importantly, in most studies addressing acute cough in children, validated outcome measures for cough were not used, those with prolonged cough were not reviewed and there was no differentiation between "wet" and "dry" types.[9] Wet cough is important as it implies increased

airway secretions and usually indicates clinically significant lower airway infection and neutrophilic inflammation.[10 11] For example, chronic wet cough is the most common symptom of bronchiectasis[12] and where early diagnosis and treatment improves long-term outcomes.[13 14]

Indigenous people are at high risk of developing chronic pulmonary disorders. Indeed, in nation-wide data for Indigenous Australians, respiratory disorders are: (a) the most common reason for primary healthcare encounters; (b) the second most prevalent self-reported chronic condition; and (c) the second most common cause for hospitalisation.[15] Overall, 27% of Indigenous people report some form of respiratory disease; 19% in those aged <14-years and 38% in those aged >55-yrs. In remote Indigenous children, the rates of hospitalisation for ARI and radiographically-diagnosed pneumonia,[16 17] and the incidence of bronchiectasis,[18] are amongst the highest reported worldwide. Recurrent ARI episodes are common[17] and studies in Indigenous children from central and northern Australia demonstrated associations between these infections and subsequent diagnosis of bronchiectasis.[19 20]

To date, the focus on ARI has been largely on remote Indigenous children, with limited community-based data from those living in urban settings. This is despite socio-economic and health indices being consistently lower for urban Indigenous populations compared to non-Indigenous groups.[15] The lack of data on urban and rural Indigenous populations has been identified as a significant barrier to "Closing the Gap" initiatives.[21] Although over half of the Indigenous population live in urban and regional centres, most research addresses the health and social issues of remote communities and only 11% of all articles about Indigenous health during a 5-year period addressed urban populations.[21] However, preliminary data from our ongoing cohort study of ARI in young urban Indigenous children[22] suggest 20% will develop chronic cough post-ARI, principally from protracted bacterial bronchitis (PBB).

Early detection and appropriate management of the underlying aetiology (eg. bronchiectasis) causing chronic cough in children is important as it results in improved short[23] and medium-term[14] outcomes. Despite the availability of evidence-based cough management guidelines for children in several countries,[24 25] including Australia,[26] the uptake and impact of the guidelines is largely unknown. So far, only one randomised controlled trial (RCT) has evaluated any of these guidelines[27 28] and economic evaluation was absent. This was conducted in five Australian cities where 272 children (mean age 4.5-years, standard deviation 3.7) newly-referred to a paediatric respiratory physician were randomly allocated to either early review and use of a cough algorithm or usual care until review and subsequent use of a pre-defined cough algorithm.[27 28] The study[28] found that children in the "early-arm" group had significantly better clinical outcomes (ie. cough resolution at week-6 post intervention; absolute risk reduction=24.7%, 95% confidence interval (CI) 13-35) and better cough-specific QoL compared to the control group. However, in this study,[28] the median duration of cough at enrolment was 16-weeks (interquartile range 8-32), and investigating earlier intervention is warranted. Furthermore, use of the cough algorithm in 346 children found that approximately 18% had a serious underlying illness. Indigenous children (10/34; 29.4%) were more likely to have bronchiectasis than non-Indigenous children (6.7%; 21/312; odds ratio = 5.78, 95%CI 2.15, 14.5; p<0.001).[29]

Despite the high burden of ARI, there are little published data on interventions for acute and chronic cough, especially for urban and regional Indigenous children. An ARI sometimes unmasks a previously unrecognised chronic respiratory illness, which is a major problem in Indigenous Australians, but one that receives limited attention.[30-32] Early diagnosis and management of chronic respiratory illness in children reduces morbidity and improves QoL. This RCT will therefore

answer the primary question: *"Amongst children aged <15-years with chronic cough post-ARI, does active intervention at 4-weeks improve clinical outcomes?"*

Study objectives

Our primary objective is to determine if children aged <15-years with chronic (>4-weeks) cough post-ARI and managed according to an evidence-based cough algorithm have better clinical outcomes (faster cough resolution) than those receiving standard care.

Our secondary objectives are to:

1. Determine the cost-effectiveness of early intervention in chronic cough following an ARI compared to standard care.
2. Identify the microbiological predictors of chronic cough following an ARI.
3. Characterise the epidemiological, clinical, socio-economic and cultural predictors of chronic cough following an ARI.
4. Establish the epidemiological, clinical, socio-economic and cultural predictors of success or failure of an early intervention in chronic cough following an ARI.

Our study tests the primary hypothesis that amongst children aged <15-years with chronic (>4-weeks) cough post-ARI, initiation of a cough management algorithm at the transition from acute to chronic cough will reduce cough duration.

Methods and analysis

Study design

A nested, open-label RCT (with concealed allocation) within a prospective cohort study of children aged <15-years presenting to 3 primary health care services with an ARI that includes cough as a symptom, and who are followed for 56-days (Figure 1).

Eligibility

Inclusion criteria are:

- Aged <15-years
- At the time of attending the clinic, are diagnosed with an ARI where cough is a symptom
- Provision of written informed consent from parent/guardian and assent from children aged 12 - <15-years
- Siblings are permitted if each meets the above criteria

The exclusion criteria are: known diagnosis of an underlying medical condition, including chronic pulmonary disorders (excluding asthma); immunosuppressive illness, such as primary immunodeficiency, human immunodeficiency virus infection or receiving immunomodulating drugs (except short-course (<2-weeks) oral and ongoing maintenance inhaled corticosteroids) in the 30-days prior to presentation; current or planned participation in another intervention study during the 8-weeks of follow-up; severe ARI requiring hospitalisation, and/or; insufficient English inhibiting provision of written informed consent or workbook completion.

Recruitment

Eligible children are identified when presenting to one of three primary healthcare centres in subtropical, Southeast Queensland, Australia involving metropolitan Brisbane (population 2.2

million), the regional city of Toowoomba (110,000) and the rural town of Warwick (14,000). Parents and their child(ren) will be approached by clinic personnel and informed consent/assent obtained using written and/or pictorial plain language statements.

Data collection, follow-up and intervention (Figure 1)

Children enrolled in each of the three primary healthcare centre cohorts undergo baseline clinical assessments that include demographic details, medical history, risk factors for ARI and cough, presenting features, vital signs, investigations, treatment and cost-of-illness data. Weekly telephone and email contacts collect symptom and cost-of-illness data.

At day-28, any child with a persistent cough (ie. ≤3-day break in cough in the preceding 28-days) is randomised (1:1 allocation) to clinical review and initiation of the cough management algorithm or to continue weekly follow-up. All study participants continue weekly follow-up until day-56 and any child still coughing at that timepoint undergoes clinical review.

The study intervention involves study physician clinical review within 2-weeks of day-28 where the cough management algorithm (Figures 2 and 3) is implemented depending upon whether the child has a specific or non-specific cough. Children in whom the cough has resolved spontaneously between randomisation and physician review, and at that point are deemed by the study physician to require no further management, will not contribute to the primary analysis.

Children in the control group follow a standard care pathway. This reflects what occurs normally in the community for children with cough where the general waiting period for review by a paediatric respiratory physician is on average 6-weeks following referral from a family physician. The parents/guardians of children randomised to the control group are advised to continue follow-

up with instructions that they will be reviewed by a study doctor following day-56 if they are still coughing. They are also counselled to seek advice from their family physician or other healthcare provider if their child is unwell or they are worried, otherwise to continue to self-manage their child's cough as they see fit.

Randomisation, allocation and blinding

An independent biostatistician prepared the randomisation code using a permuted blocking design (block size of 4) to maintain group balance. Randomisation was stratified by reason for presentation (ARI with cough or another reason with an ARI noted incidentally), site and cough duration at day-28 (<6-weeks or ≥6-weeks). Group allocation is concealed in opaque, consecutively numbered envelopes kept in a locked cabinet at the Centre for Children's Health Research, South Brisbane. At randomisation, the child's cough history over the past 28-days and study specific strata are confirmed by the Central Coordinating Site. The Study Coordinator selects the next consecutively numbered opaque sealed envelope from the relevant strata pack, opens the envelope and extracts the randomisation code. Two people check the allocation and the code is assigned to the participant. The Study Coordinator then arranges for the study physician to review within 2-weeks of randomisation those children allocated to the intervention arm. If siblings are also enrolled and each child is still coughing at day-28, randomisation occurs for the first child enrolled (ie, earliest study number) and all siblings are allocated subsequently to the same arm. Differences in strata (eg presentation type and cough duration) will be accounted for in the analysis.

Blinding is not undertaken in this study however parents are not informed at enrolment that their child will be randomised at day-28 to a specific intervention if the child has a persistent cough. Instead they are informed that children who develop persistent cough will be reviewed by a

paediatrician during the study with some children being seen earlier and some later in the 8 week follow-up period. Limited disclosure is permitted under the Australian ethical standards for human research[33] if it is scientifically justifiable and does not present an increased risk of harm to the participant.

Definitions

Definitions used for the clinical management pathway[23 27] are as follows:

• Asthma: recurrent (>2) episodes of wheeze and/or dyspnoea that responds (within minutes) to inhaled beta$_2$ agonist or bronchodilator responsiveness documented on spirometry (≥12% change in the percentage predicted forced expiratory volume in one-second after 400ug of salbutamol).

• Cough resolution: improvement ≥75% or total resolution according to cough diary data for ≥3 consecutive days.[34 35] When cough diary data are unavailable, resolution is defined as total cessation of cough according to parent/guardian verbal report.

• Chest radiograph abnormality: any abnormality (other than peribronchial thickening) identified by a paediatric respiratory physician or radiologist.

Spirometry abnormality: as determined by the American Thoracic Society and European Respiratory Society criteria with Australian predicted values used.[36]

• Primary diagnosis of cough aetiology: diagnosis confirmed by subsequent specific treatment that resulted in cough resolution within 3-weeks.[26 34] The diagnostic criteria are defined *a-priori* following published guidelines:[6]

  • PBB: presence of an isolated chronic wet or productive cough, without signs of another cause and which responds to at least a 2-weeks course of an appropriate antibiotic, such as amoxicillin-clavulanate.

- Recurrent PBB: ≥3 episodes over a 12-month period.

- Reversible airway obstruction: in accordance with American Thoracic Society and European Respiratory Society criteria and adopting Australian predicted values.[36]

• Secondary diagnosis: diagnosis found on objective tests, but where: 1) specific treatment did not lead to resolution or improvement in the cough; or 2) no treatment for this diagnosis was trialled and the cough either resolved spontaneously or with other therapies.[6]

• Specific cough pointers: presence of any of the following: auscultatory abnormality (wheezes, crackles or differential breath sounds), classical cough characteristics, cardiac abnormalities, chest pain, chest wall deformity, daily moist or productive cough for >3-months, digital clubbing, dyspnoea (exertional or at rest), failure to thrive, feeding difficulties (including choking/vomiting), haemoptysis, immune deficiency, neuro-developmental abnormality, recurrent pneumonia, wheeze. These pointers are explained in the Thoracic Society of Australia and New Zealand position statement.[34]

• Tertiary hospital management: that usually requires investigations to be conducted at a paediatric tertiary centre (eg. flexible bronchoscopy with bronchoalveolar lavage, chest high-resolution computed tomographic scan, fluoroscopic swallow screening, etc).

Specimen collection

At recruitment, exhaled carbon monoxide (eCO) measures from the child (if aged ≥ 3 years and can provide an adequate sample) and parent/guardian are collected to provide an objective, non-invasive assessment of cigarette smoking status and exposure[37] using a portable eCO monitor (Smokerlyzer, Bedfont Scientific, England).

All children have bilateral anterior nasal swabs collected at enrolment and at days-28 and 56. Nasal swabs are collected using Virocult® plain cotton tip swabs with viral transport medium (Virocult, MW951, Medical Wire & Equipment, England) inserted 1cm into the nostril and rotated four times on the right side and then on the left side. Swabs are stored locally in -20°C freezers before being transported to the research laboratory where they are stored at -80°C until processing occurs.

Laboratory methods

Swabs are batch-tested for respiratory viruses and bacteria using validated real-time polymerase chain reaction (PCR) assays described previously.[38 39] Virus testing includes rhinoviruses, adenovirus, respiratory syncytial virus, influenza virus types A and B, parainfluenza virus types 1-3, human metapneumovirus, human coronaviruses (OC43, 229E, NL63, HKU1), human bocavirus and human polyomaviruses KI and WU. Bacterial testing includes *Bordetella pertussis*, *Mycoplasma pneumoniae, Streptococcus pneumoniae*, *Staphylococcus aureus, Haemophilus influenzae* (including differentiating between encapsulated and non-encapsulated strains and *H. haemolyticus*) and *Moraxella catarrhalis*.

End points

Participation is completed 56-days (±3-days) following enrolment or, for children in the RCT, when a final diagnosis is determined by the study physician. Other exit points are serious protocol violations and worsening of the child's condition that requires hospitalisation or other active intervention elsewhere. Children meeting the exit criteria will continue to be followed until the end of the study period.

Outcome measures

Primary clinical outcome: Time-to-cough resolution in days

Secondary cost-effectiveness outcomes: Total direct and indirect costs of illness calculated according to the criteria outlined in Table 1.

Secondary microbiological outcomes: Anterior nasal detection by PCR of respiratory viruses and bacteria at days-28 and 56.

Table 1: Cost item, sector allocation and source of cost used in costing acute and chronic cough

Cost item	Sector	Source of cost to be applied
Healthcare service utilisation - *includes costs for diagnostic tests and complementary/alternative therapies* - *distinguishes between public and private, paid and bulk-billed services*	Family Healthcare Health insurers	Manual of resource items and their associated costs[40] National Hospital Costs Data Collection[41] Quarterly Gap Payment &Medical Benefits Statistics[42] Medicare Quarterly Statistics[43] Medicare Benefits Schedule[44] Expert panel or large online provider where required
Medication usage - *includes over-the-counter and prescribed medications*	Family Healthcare	Pharmaceuticals Benefits Scheme (PBS) [45] Online providers when not listed on PBS
Healthcare seeking travel costs - *includes ambulance and community transport services*	Family	Parental Report Private Health Insurance Administration Council[46] Petrol: Average unleaded retail price Translink: average ticket prices
Time spent seeking healthcare	Family	Parental Report

- *Time off work with pay* - *Time off work with pay lost* - *Time off usual activity*	Employers	Average weekly earnings, Australia[47]
Extra time spent caring for child - *Time off work with pay* - *Time off work with pay lost* - *Time off usual activity*	Family Employers	Parental Report Average weekly earnings, Australia[47]
Missed childcare/school	Family	Parental Report
Missed planned activities - *child and others*	Family	Parental Report

Note: Costs will be applied following the completion of data collection ensuring up-to-date cost data

Sample size

Sample sizes for each of the primary healthcare cohorts comprising this study are based on the expected number of eligible children with ARI presenting to each of these services over the study's timeframe and derived from our current studies of chronic cough post ARI in children.[22 48] Between July 2015 and June 2017, we anticipate 750 eligible children will present to the primary healthcare services participating in this study.

Our preliminary data from a cohort study of Indigenous children aged less than 5-years[22] suggest 17% of Indigenous children with an ARI will have chronic cough at day-28. Based on data from the first study of the algorithm[28] for the primary endpoint of cough resolution at day-56, we anticipate a 54% reduction in the proportion of children (54.3% in early arm compared to 29.5% in delayed-arm) with persistent cough at day-56. Hence, 89 children per group with complete evaluable data at day-56 will provide 90% power (α=0.05), to detect this 54% reduction for our primary aim. Assuming a 20% loss to follow-up and spontaneous resolution of cough of between randomisation

and physician review of 5%, we will therefore randomise a minimum of 112 children per group at day-28 across all three sites

Given the entire cohort study will have a 2-year recruitment period, and the natural history and predictors of chronic cough and cost-effectiveness of the intervention are important secondary outcomes, we will not limit recruitment to the RCT arm once 224 children have been randomised. Ongoing enrolment will hence increase study power to address both primary and secondary objectives.

Data Management

Data will be entered into a password protected, custom built, Filemaker Pro Advanced V14 (Filemaker, Inc. Santa Clara, USA) database. The database has been designed to incorporate automatic data checking including logic and inaccurate ranges and maintains a log of any changes to the data. Data fields cannot be left blank and missing data must be coded as such in the database. A specific data management protocol compliant with the Queensland University of Technology's data management policies and principles is in place.

Statistical methods

Data will be presented in accordance with the updated CONSORT criteria.[49] Demographic, clinical, economic, risk factor and microbiological data will be tabulated for the study population overall, by centre and by randomisation group and expressed as proportions and/or means of the selected characteristics by study centre, and presence/absence of chronic cough at day-56 with the corresponding 95%CI. Differences between groups will be assessed using t-tests for comparisons of means and χ^2 test for comparisons of proportions, conditional on test assumptions for each

being satisfied. Non-normally distributed data will be analysed with appropriate non-parametric tests.

Primary objective

Intention-to-treat analyses will be employed. Time-to-cough resolution will be compared between groups using cox proportional hazard methods, adjusting for independent explanatory variables, subject to modelling assumptions being met, particularly proportionality of hazards. All analyses will be performed on the whole cohort and then additional analyses will be performed that account for siblings and type of presentation to the clinic.

Economic objectives

Costing of the intervention will be done according to established methods,[50 51] including detailed sub-analyses of data that account for epidemiological, social, cultural, risk factor and microbiological variables. Cost-effectiveness analysis (CEA) will be modelled using the health sector perspective. Broader societal issues using data from the trial as described above and augmented by the evidence from the literature, especially systematic reviews will also be taken into consideration. CEA approach will involve: identification of resources using the intervention pathway (activities, probabilities and unit costs); measurement of resource use/outcomes; and valuation of costs using unit costs published in the literature and from the trial itself. The time horizon will be specified and current practice (standard care) will be the comparator; and future costs and benefits will be discounted at 3% to present values. Central to this analysis will be the modelling of uncertainty surrounding data quality and gaps using sensitivity analyses, and extension of time horizon, using Treeage software (Treeage Software Inc. Williamstown, MA, USA). The key outcomes will be incremental cost-effectiveness, and cost-savings to the health system due to the interventions.

Other objectives:

Multivariable modelling will be employed to: a) evaluate the microbiological predictors of chronic cough following an ARI as determined at days-28, 42 and 56 post-enrolment; b) evaluate the epidemiological, clinical, socio-economic and cultural predictors of chronic cough at day-28 post-ARI; c) evaluate the epidemiological, clinical, socio-economic and cultural predictors of success or failure of the intervention at day 56; and, d) to compare these predictors between the three study populations. Crude and adjusted relative risks and the respective 95% CIs will be presented, with differences considered statistically significant at $p<0.05$.

Sub-group analyses will be performed for all primary and secondary objectives to examine potential differences by study specific strata. Univariate and multivariate analyses will be performed to evaluate variables independently associated with study endpoints and to assess potential confounding factors in the association between vaccination and disease.

Participant safety

Parents/guardians of all participants will be informed of any new information that arises during the study that may indicate potential harm to the child if he/she were to continue in the study. Any trial-related adverse events will be documented and reported to the relevant Human Research Ethics Committees. Serious adverse events will be reported to the HREC within 24 hours of notification and will be followed until resolution. A decision to withdraw the child following a SAE will be made in consultation with the HREC, investigating team and the child's primary physician. If an adverse event is deemed related to study procedures, the child and his/her family will be eligible for compensation under the Clinical Trial Insurance policies in place for the duration of the study. All participant data will be kept confidential and stored securely in accordance with Australian Privacy Laws. Identifying data will be not be provided to any persons outside of the

study team unless required by Australian law (eg. in the event of the diagnosis of a notifiable disease). Published data will be de-indentified and presented in aggregrate form.

Independent monitoring and quality control

Independent study monitors have been engaged to undertake regular data quality audits, assess compliance with ICH-GCP guidelines and ensure the study is being conducted according to the study protocol and ethical approvals. In-built data quality monitoring and generation of data queries are established within the trial database, with data queries sent to study sites weekly for resolution.

Protocol amendments

All protocol amendments will be submitted to the study's Human Research Ethics Committees (see below) for approval prior to implementation. If any amendments have the potential to affect a family's willingness to continue in the study, all participants will be re-consented to the amended protocol.

Study status

Recruitment began in July 2015.

Ethics and dissemination

The Children's Health Queensland (HREC/15/QRCH/15) and the Queensland University of Technology University (1500000132) Research Ethics Committees have approved the study. The Queensland University of Technology is the trial sponsor.

Participants will be provided with regular study progress reports and a written letter outlining the results of the study. The trial results, including any negative findings, will be published in open-access peer review journals and presented at scientific conferences, paediatric society and general practitioner meetings and other fora. The primary author of the main paper will be the Principal Investigator (KFO). The trial findings are likely to be incorporated into clinical management guidelines. Study data will be held in metadata repositories until the youngest child turns 25 years of age at the Queensland University of Technology. De-identified study data will be made available to external parties on request and, if relevant, with the appropriate Human Research Ethics Committee approvals.

Chronic cough in children is a defining symptom of several chronic pulmonary disorders worldwide. Preventing persistent cough in children may lead to important short and long-term health benefits.

Our proposed intervention[22 26] is similar to the existing Australian guidelines,[52] but also has some differences that were developed following the incorporation of new data unavailable at the time the guidelines were published. Use of guidelines by clinicians depends upon several factors, which include level of evidence, feasibility, degree of implementation and inherent clinician factors.[53] Using an algorithm facilitates clinical guideline implementation by clearly describing pathways of care based upon whether the child presents with a specific or non-specific cough. While this study uses specific study physicians, the overall goal is widespread adoption of the guidelines and management algorithm in the primary healthcare setting. Our extensive data collection, including direct and indirect costs of illness and health care provision, are important in achieving this goal. The study will also provide an avenue for assessing the extent to which these guidelines are being

used currently in different clinical settings given we will collect data on any intervention a child may receive external to our study.

Study site selection was based upon several factors, including existing relationships, feasibility and as they incorporated geographically and demographically different Indigenous communities. Studies evaluating ARI and chronic cough have had differing study designs, objectives and endpoints between populations. Australian data suggest cough burden is independent of age and aetiology, but dependent upon clinical setting.[29] In Australia, there are clear risk and burden distinctions between children from urban and remote areas and between Indigenous and non-Indigenous children.[54] Indigenous children in urban areas have received much less attention than those in remote centres. Failure to account for these differences may lead to inappropriate interventions or implementation of management guidelines that may not be applicable across all settings.

The economic data and analyses in this study will be the first to describe the cost of ARI and its outcomes in Indigenous children in Australia, and one of the few worldwide. Further, the cost-effectiveness analyses of the intervention will provide data critical to clinical and public policy decisions with respect to incorporation of the intervention into routine care at both the primary and tertiary health care levels. Such decisions will be enhanced by our incorporation of direct and indirect costs to the family, community and health care sector,[55] particularly given the focus on resource allocation in Indigenous health in Australia[56] and the different mechanisms for delivery of primary health care services compared to mainstream Australia.[57]

We have incorporated microbiological components into the RCT as the role of infectious agents in the transition from ARI to chronic wet cough remains largely unknown. Whether persistent

shedding, new acquisition and/or virus-bacteria interactions are associated with the development of chronic cough post-ARI is a clinical and research gap needing to be addressed. A study of 170 children aged 5-16 years presenting to their family physician with a cough lasting >14-days detected *M. pneumoniae* and *B. pertussis* in 12.9% and 36.6% respectively.[58] Cough duration was shorter in *M. pneumoniae* than *B. pertussis* cases and co-detection with respiratory viruses was not associated with cough duration.[58] Important limitations of this study[58] were how cough was reported (weekly rather than daily) and that data were not collected from the time of ARI onset. Other studies[59] have also tested for bacteria and viruses in nasopharyngeal specimens, but to date none have followed children from ARI onset and examined the association with developing chronic cough. Our Brisbane-based lower airway studies of children with chronic cough from PBB found intense neutrophilic airway inflammation and evidence of innate immune activation, suggesting PBB may follow a single ARI episode with impaired pathogen clearance from the airways, either permanently or temporarily leading to a cycle of chronic inflammation.[60] Small case series from the late 1990s have reported chronic pulmonary sequelae following influenza infection in young children[61] and a relationship between adenovirus infection and bronchiectasis.[62]

The major threats to the validity of our proposal are loss to follow-up and potential for contamination of the control group based on the type of standard care they may receive. In our current ARI study in urban Indigenous children, loss to follow-up at the 4-week time point post-ARI is 23%. Procedures to minimise this loss include: home visiting by Indigenous research personnel, regular text and email messaging, and personal letters to families. Analysis plans will include measures to account for missing data and sensitivity analyses to assess the extent of bias.

Although contamination of the control group is possible, based on a multicentre RCT conducted in five major Australian cities,[29] it is unlikely that a child in standard care will receive treatment

similar to the intervention arm. In another of our studies, just 27% of children seek further medical advice for cough in the 4-weeks following presentation to an ED for an illness with cough as a symptom. Furthermore, of the 20% receiving antibiotics during this 4-week period, most are prescribed antibiotics at the time of the original ED presentation. Hence, it is unlikely this will influence the validity of our RCT for several reasons: (i) We can assess any intervention either group receives outside of the RCT since our weekly follow-up data collection captures these events. (ii) In the possible, but unlikely event of a change in treatment in the control group, the effect size of the intervention will be smaller requiring a larger sample size. The *a-priori* sample size is conservative with 90% power and a smaller effect size will still be detectable within the available study population (e.g. a 35% difference with power of 80% requires 114 per group). (iii) To ensure robustness, an independent person will recalculate the sample size when 50% of children have completed the RCT component.

In summary, our RCT will be the first to examine the impact of a cough management algorithm implemented at the transitional stage from acute to chronic cough in Indigenous children. Clinical effectiveness will be evaluated concurrently with detailed epidemiological, clinical, microbiological and economic determinants of ARI and cough persistence in this population. If successful, the study may provide the data necessary to facilitate the uptake and implementation of cough management guidelines in the primary healthcare setting, potentially reducing the long-term burden of disease on the child, family, community and healthcare sector.

Protocol version

Version 4 dated 9 June 2016

List of abbreviations

ARI = acute respiratory infection; CEA = cost-effectiveness analysis; CI confidence interval; eCO = exhaled carbon monoxide; ED = Emergency Department; PBB = protracted bacterial bronchitis; PCR = polymerase chain reaction; QoL = quality of life; RCT = randomised controlled trial.

Authors' contributions

KOG conceived the study, devised the study protocol and oversees study implementation nationally and was the primary author of the manuscript. KG contributed to study conception, the grant application and will play a leading role in the interpretation of the microbiological data. MT contributed to study conception, grant application, community consultation and implementation of the study. TS and DW contributed to study conception and the grant application and are responsible for the microbiological components of the study and interpretation of the laboratory data. MO contributed to study conception and the grant application and is responsible for the economic components of the study. SR is the National Study Coordinator with major input into data instruments, standard operating procedures and GCP compliance. HB, ACM, DA and MkO are responsible for the clinical implementation of the intervention and evaluation of study diagnostic outcomes. PJT contributed to study conception and will play a role in knowledge translation and implementation of study findings into clinical guidelines. ABC played a major role in study conception, grant application, protocol development and implementation and helped draft the manuscript. All authors read and approved the final manuscript.

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Role of study sponsor and funding agencies

The study sponsor and funding agency have had, and will not have, any role in study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication.

Competing interests

No authors have any competing interests to declare.

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References

1. Britt H, Miller G, C. , Charles J, et al. General practice activity in Australia 2009–10. General practice series no. 27. Canberra: AIHW, 2010.

2. Irwin RS, Gutterman DD. American College of Chest Physicians' cough guidelines. Lancet 2006;**367**(9515):981.

3. Whitburn S, Costelloe C, Montgomery AA, et al. The frequency distribution of presenting symptoms in children aged six months to six years to primary care. Prim Health Care Res Dev 2011;**12**(2):123-34.

4. Chang AB. Cough: are children really different to adults? Cough 2005;**1**:7.

5. Drescher BJ, Chang AB, Phillips N, et al. Chronic cough following acute respiratory illness in children. In: ESPID, ed. 31st Annual Meeting of the European Society for Paediatric Infectious Diseases. Milan, Italy, 2013.

6. Marchant JM, Masters IB, Taylor SM, et al. Evaluation and outcome of young children with chronic cough. Chest 2006;**129**(5):1132-41.

7. Marchant JM, Newcombe PA, Juniper EF, et al. What is the burden of chronic cough for families? Chest 2008;**134**(2):303-9.

8. Thompson M, Vodicka TA, Blair PS, et al. Duration of symptoms of respiratory tract infections in children: systematic review. BMJ 2013;**347**:f7027.

9. Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. Br J Gen Pract 2002;**52**(478):401-9.

10. Chang AB, Faoagali J, Cox NC, et al. A bronchoscopic scoring system for airway secretions--airway cellularity and microbiological validation. Pediatr Pulmonol 2006;**41**(9):887-92.

11. Douros K, Alexopoulou E, Nicopoulou A, et al. Bronchoscopic and high-resolution CT scan findings in children with chronic wet cough. Chest 2011;**140**(2):317-23.

12. Chang AB, Redding GJ, Everard ML. Chronic wet cough: Protracted bronchitis, chronic suppurative lung disease and bronchiectasis. Pediatr Pulmonol 2008;**43**(6):519-31.

13. Bastardo CM, Sonnappa S, Stanojevic S, et al. Non-cystic fibrosis bronchiectasis in childhood: longitudinal growth and lung function. Thorax 2009;**64**(3):246-51.

14. Kapur N, Masters IB, Chang AB. Longitudinal growth and lung function in pediatric non-cystic fibrosis bronchiectasis: what influences lung function stability? Chest 2010;**138**(1):158-64.

15. Pink B, Allbon P. The Health and Welfare of Australia's Aboriginal and Torres Strait Islander Peoples: 2008. Canberra: Australian Bureau of Statistics and Australian Institute of Health & Welfare., 2008.

16. O'Grady KA, Taylor-Thomson DM, Chang AB, et al. Rates of radiologically confirmed pneumonia as defined by the World Health Organization in Northern Territory Indigenous children. Med J Aust 2010;**192**(10):592-5.

17. O'Grady KA, Torzillo PJ, Chang AB. Hospitalisation of Indigenous children in the Northern Territory for lower respiratory illness in the first year of life. Med J Aust 2010;**192**(10):586-90.

18. Chang AB, Grimwood K, Mulholland EK, et al. Bronchiectasis in indigenous children in remote Australian communities. Med J Aust 2002;**177**(4):200-4.

19. Valery PC, Torzillo PJ, Mulholland K, et al. Hospital-based case-control study of bronchiectasis in indigenous children in Central Australia. Pediatr Infect Dis J 2004;**23**(10):902-8.

20. Singleton RJ, Valery PC, Morris P, et al. Indigenous children from three countries with non-cystic fibrosis chronic suppurative lung disease/bronchiectasis. Pediatr Pulmonol 2014;**49**(2):189-200.

21. Eades SJ, Taylor B, Bailey S, et al. The health of urban Aboriginal people: insufficient data to close the gap. Med J Aust 2010;**193**(9):521-4.

22. Hall KK, Chang AB, Sloots TP, et al. The respiratory health of urban indigenous children aged less than 5 years: study protocol for a prospective cohort study. BMC Pediatr 2015;**15**:56.

23. Chang AB, Robertson CF, van Asperen PP, et al. A cough algorithm for chronic cough in children: a multicenter, randomized controlled study. Pediatrics 2013;**131**(5):e1576-83.

24. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest 2006;**129**(1 Suppl):1S-23S.

25. Keeley D. Cough in children: new guidelines from the British Thoracic Society. Postgrad Med J 2008;**84**(995):449.

26. Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest 2006;**129**(1 Suppl):260S-83S.

27. Chang AB, Robertson CF, van Asperen PP, et al. Can a management pathway for chronic cough in children improve clinical outcomes: protocol for a multicentre evaluation. Trials 2010;**11**:103.

28. Chang AB, Robertson CFPP, van Asperen PP, et al. A cough algorithm on chronic cough in children: A multicentre randomized controlled study. Pediatrics 2012;**131:** e1576-83.

29. Chang AB, Robertson CF, Van APP, et al. A multi-centre study on chronic cough in children: burden and etiologies based on a standardized management pathway. Chest 2012;**142**(4):943-50.

30. O'Grady KF, Revell A, Maguire GP, et al. Lung health care for Aboriginal and Torres Strait Islander Queenslanders: breathing easy is not so easy. Aust Health Rev 2011;**35**(4):512-9.

31. O'Grady KF, Revell A, Maguire G, et al. Lung Health Services for Aboriginal and Torres Strait Islander Peoples in Queensland. Brisbane: Queensland Government, 2010.

32. Chang AB, Marsh RL, Upham JW, et al. Toward making inroads in reducing the disparity of lung health in Australian indigenous and new zealand maori children. Frontiers in Pediatrics 2015;**3**:9.

33. Australian National Health and Medical Research Council. National Statement on Ethical Conduct in Human Research (2007): Canberra: Australian Government, 2007.

34. Chang AB, Landau LI, Van Asperen PP, et al. Cough in children: definitions and clinical evaluation - Position statement of the Thoracic Society of Australia and New Zealand. Med J Australia 2006;**184**(8):398-403.

35. Marchant JM, Masters IB, Taylor SM, et al. Utility of signs and symptoms of chronic cough in predicting specific cause in children. Thorax 2006;**61**(8):694-8.

36. Hibbert ME, Lannigan A, Landau LI, et al. Lung function values from a longitudinal study of healthy children and adolescents. Pediatr Pulmonol 1989;**7**(2):101-9.

37. Sandberg A, Skold CM, Grunewald J, et al. Assessing recent smoking status by measuring exhaled carbon monoxide levels. PLoS One 2011;**6**(12):e28864.

38. O'Grady KA, Torzillo PJ, Rockett RJ, et al. Successful application of a simple specimen transport method for the conduct of respiratory virus surveillance in remote Indigenous communities in Australia. Trop Med Int Health 2011;**16**(6):766-72.

39. O'Grady KA, Whiley DM, Torzillo PJ, et al. Mailed versus frozen transport of nasal swabs for surveillance of respiratory bacteria in remote Indigenous communities in Australia. BMC Infect Dis 2013;**13**:543.

40. Department of Health and Ageing. Manual of resource items and their associated costs for use in submissions to the Pharmaceutical Benefits Advisory Committee involving economic evaluation Canberra: Australian Government; 2015 [cited 2015 01 April 2015]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/content/health-pbs-general-pubs-manual-content.htm.

41. Department of Health and Ageing. National Hospital Cost Data Collection (NHCDC) Report Canberra: Australian Government; [Available from: http://www.health.gov.au/internet/main/publishing.nsf/content/health-casemix-data-collections-NHCDCReports.

42. Private Health Insurance Administration Council. Quarterly Gap Payment & Medical Benefits Statistics Canberra: Australian Government; 2012 [Available from: http://phiac.gov.au/wp-content/uploads/2012/11/Gap-Sep12.pdf.

43. Department of Health and Ageing. Quarterly Medicare Statistics Canberra: Australian Government; [Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/Quarterly-Medicare-Statistics.

44. Department of Health and Ageing. Medicare Benefits Schedule Canberra: Australian Government; [Available from: http://www.mbsonline.gov.au.

45. Department of Health and Ageing. Pharmaceutical Benefits Scheme Canberra: Australian Government; [Available from: http://www.pbs.gov.au/pbs.

46. Private Health Insurance Administration Counci. Private Health Insurance Administration Council Queensland Reports Canberra: Australian Government; [Available from: http://phiac.gov.au/industry/industry-statistics.

47. Australian Bureau of Statistics. Average weekly earnings, Australia Canberra: Australian Government; [Available from: http://www.abs.gov.au/austats.

48. Drescher BJ, Chang AB, Phillips N, et al. The development of chronic cough in children following presentation to a tertiary paediatric emergency department with acute respiratory illness: study protocol for a prospective cohort study. BMC Pediatr 2013;**13**:125.

49. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Trials 2010;**11**:32.

50. Drummond MF, Sculpher MJ, Torrance GW. *Methods for the Economic Evaluation of Health Care Programs*. Oxford: Oxford University Press, 2005.

51. Gold MR, editor. *Cost Effectiveness in Health and Medicine*. Oxford: Oxford University Press, 1996.

52. Gibson PG, Chang AB, Glasgow NJ, et al. CICADA: Cough in Children and Adults: Diagnosis and Assessment. Australian cough guidelines summary statement. Med J Aust 2010;**192**(5):265-71.

53. Chang AB, Landau LI, Van Asperen PP, et al. Cough in children: definitions and clinical evaluation. Med J Aust 2006;**184**(8):398-403.

54. O'Grady KA, Chang AB. Lower respiratory infections in Australian Indigenous children. J Paediatr Child Health 2010;**46**(9):461-5.

55. Ungar WJ, Coyte PC, Pharmacy Medication Monitoring Program Advisory B. Prospective study of the patient-level cost of asthma care in children. Pediatr Pulmonol 2001;**32**(2):101-8.

56. Peiris D, Brown A, Howard M, et al. Building better systems of care for Aboriginal and Torres Strait Islander people: findings from the Kanyini health systems assessment. BMC Health Serv Res 2012;**12**:369.

57. Ong KS, Carter R, Kelaher M, et al. Differences in primary health care delivery to Australia's Indigenous population: a template for use in economic evaluations. BMC Health Serv Res 2012;**12**:307.

58. Wang K, Chalker V, Bermingham A, et al. Mycoplasma pneumoniae and respiratory virus infections in children with persistent cough in England: a retrospective analysis. Pediatr Infect Dis J 2011;**30**(12):1047-51.

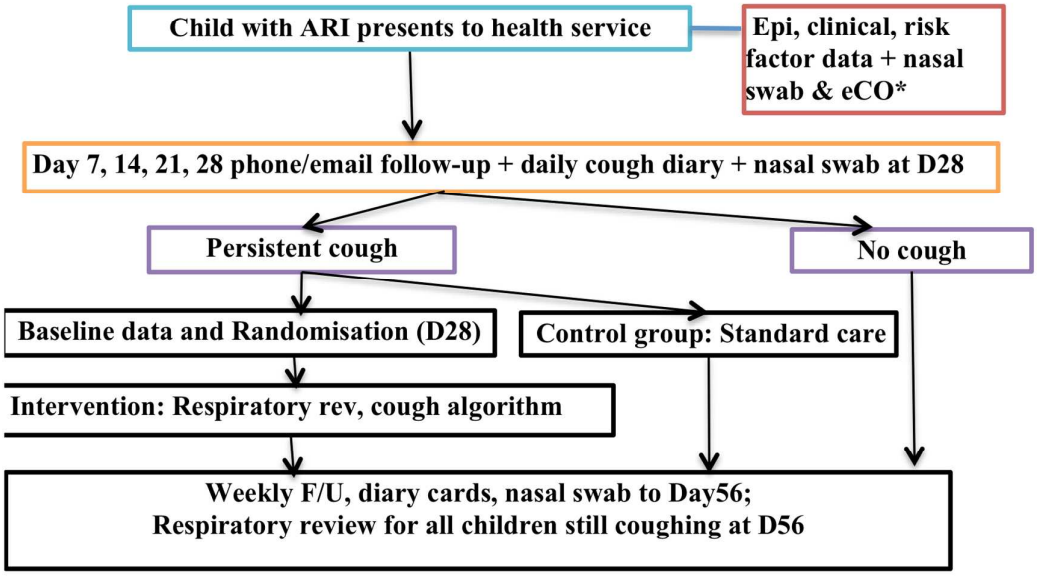
59. Bisgaard H, Hermansen MN, Bonnelykke K, et al. Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. Bmj 2010;**341**:c4978.

60. Marchant JM, Gibson PG, Grissell TV, et al. Prospective assessment of protracted bacterial bronchitis: airway inflammation and innate immune activation. Pediatr Pulmonol 2008;**43**(11):1092-9.

61. Laraya-Cuasay LR, DeForest A, Huff D, et al. Chronic pulmonary complications of early influenza virus infection in children. Am Rev Respir Dis 1977;**116**(4):617-25.

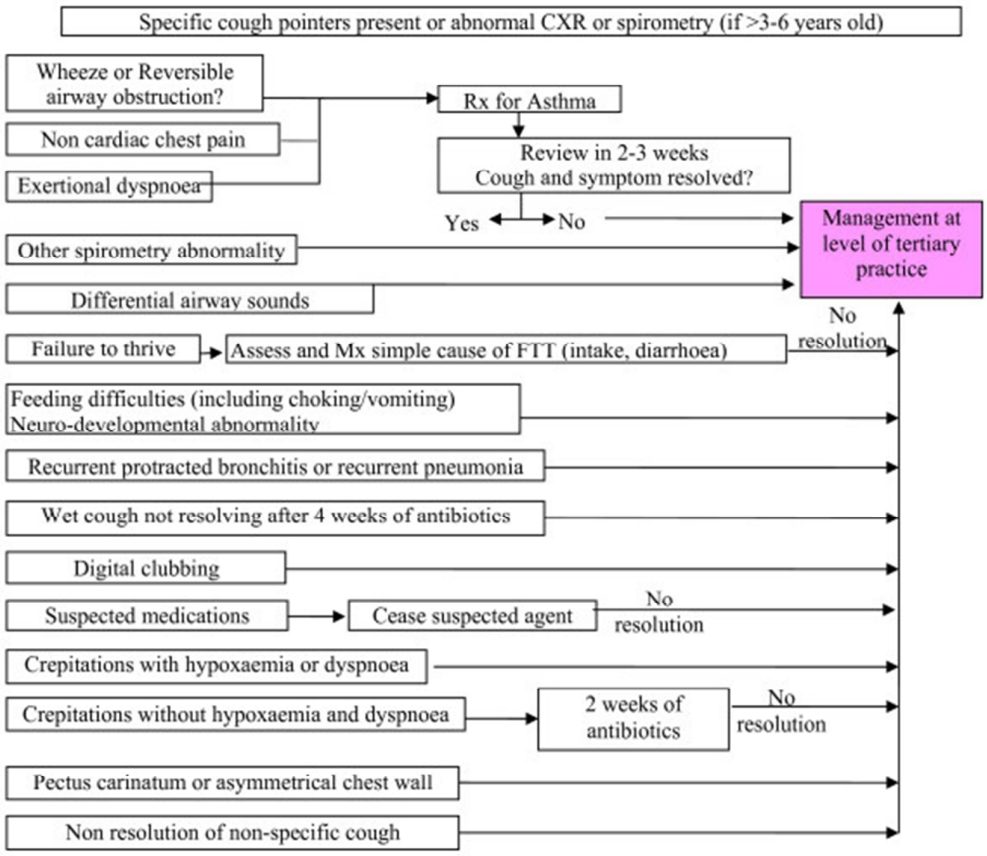
62. Bateman ED, Hayashi S, Kuwano K, et al. Latent adenoviral infection in follicular bronchiectasis. Am J Respir Crit Care Med 1995;**151**(1):170-6.

Figure 1: Overview of study design



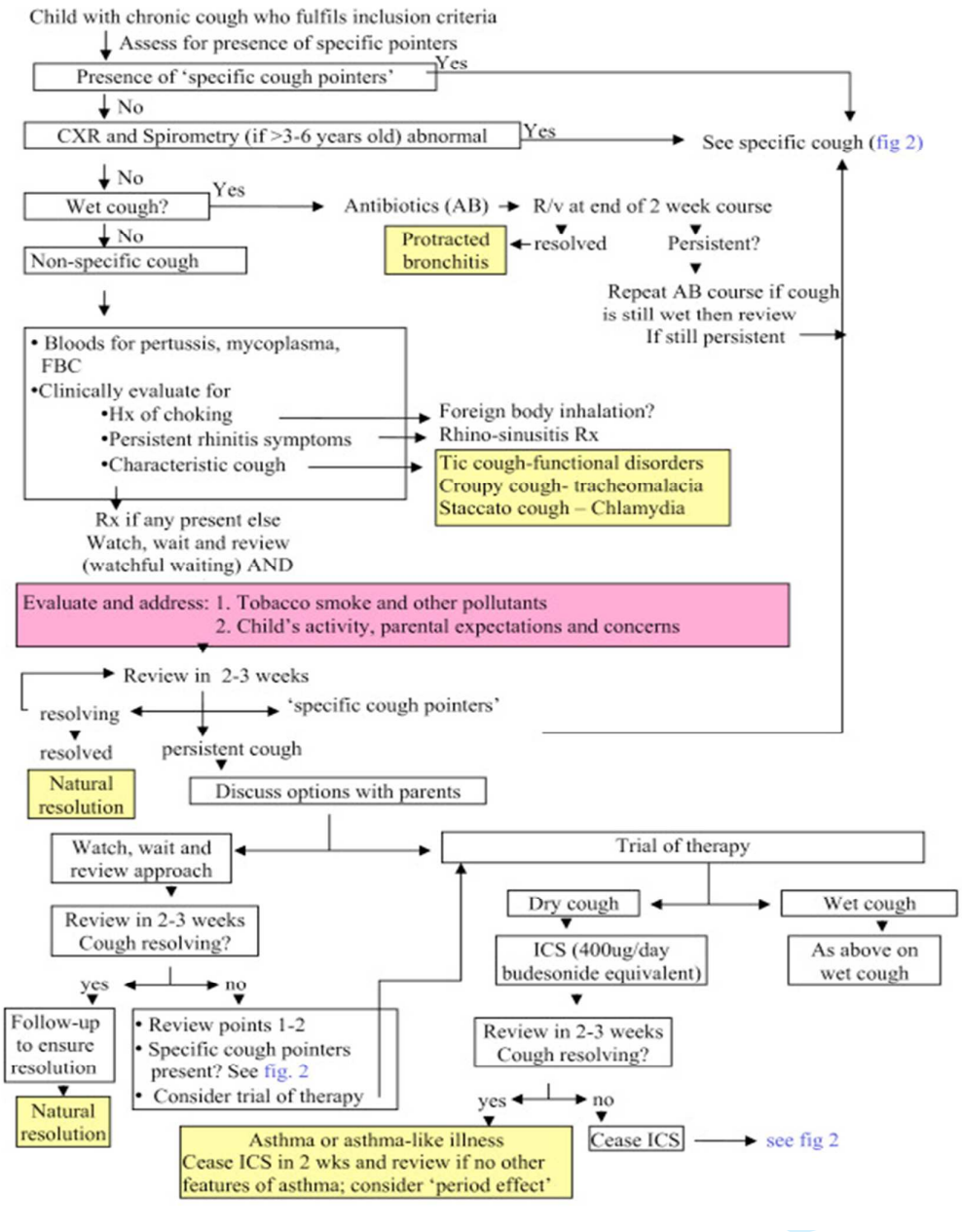
* Exhaled carbon monoxide

Figure 2. Specific cough pathway



CXR – chest radiograph; FTT – Failure to thrive; Rx – Treatment; Mx - management

Figure 3. Non-specific cough pathway



AB – antibiotic; CXR – chest radiograph; FBC – full blood count; Hx – history; ICS – Inhaled corticosteroid; Mx – management; R/v – review; Rx – Treatment;

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	24
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 a 25
	5b	Name and contact information for the trial sponsor	4
	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	25
	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)	-

Introduction

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	5-7
	6b	Explanation for choice of comparators	~~7-8~~
Objectives	7	Specific objectives or hypotheses	7-8
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)	9

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	9, 21
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)	9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	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)	10, 14.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	23
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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	15
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)	Figure 1

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	16.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	23
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	11
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	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	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	10
	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	14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17.
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	17-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-19
	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)	17-19.
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	
	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	N/A
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	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
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)	20

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	19
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	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
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	20
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	19
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	~~20~~ 21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	~~20~~ 21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	~~15~~ Suppl.
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	13-14

*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

Effectiveness of a cough management algorithm at the transitional phase from acute to chronic cough in Australian children aged less than 15 years: protocol for a randomised controlled trial

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Paediatrics, Evidence based practice
Keywords:	chronic cough, children, intervention, randomised controlled trial, cost effectiveness

Title: Effectiveness of a cough management algorithm at the transitional phase from acute to chronic cough in Australian children aged less than 15 years: protocol for a randomised controlled trial

Trial acronym: RICCi Kids Study – Researching Intervention in Chronic Cough in Kids

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Strengths and limitations of this study

- Our study will be the first to assess the clinical and economic impact of an early, evidence-based intervention in the transitional stage from acute to chronic cough in children.
- Conducting the study in primary care facilities addresses the predominant setting in which acute respiratory illnesses are managed
- A limitation of the study is its generalisability to children with acute respiratory illnesses in rural and remote regions.

Abstract

Introduction

Acute respiratory infections (ARI) are leading causes of hospitalisation in Australian children and, if recurrent, are associated with increased risk of chronic pulmonary disorders later in life. Chronic (>4-weeks) cough in children following ARI is associated with decreased quality-of-life scores and increased health and societal economic costs. We will determine whether a validated evidence-based cough algorithm, initiated when chronic cough is first diagnosed after presentation with ARI, improves clinical outcomes in children compared to usual care.

Methods and analysis

A multi-centre, parallel group, open-label, randomised controlled trial, nested within a prospective cohort study in Southeast Queensland, Australia is underway. Seven-hundred-and-fifty children aged less than 15-years will be enrolled and followed weekly for 8-weeks after presenting with an ARI with cough. Two-hundred-and-fourteen children from this cohort with persistent cough at day-28 will be randomised to either early initiation of a cough management algorithm or usual care (107 per group). Randomisation is stratified by reason for presentation, site, and total cough duration at day-28 (<6-weeks and ≥6-weeks). Demographic details, risk factors, clinical histories, examination findings, cost-of-illness data, an anterior nasal swab and parent and child exhaled carbon monoxide levels (when age appropriate) are collected at enrolment. Weekly contacts collect cough status and cost-of-illness data. Additional nasal swabs are collected at days-28 and 56. The primary outcome is time-to-cough resolution. Secondary outcomes include direct and indirect costs of illness and the predictors of chronic cough post-presentation.

Ethics and dissemination

The Children's Health Queensland (HREC/15/QRCH/15) and the Queensland University of Technology University (1500000132) Research Ethics Committees have approved the study. The study will inform best-practice management of cough in children.

Trial registration: Australia and New Zealand Clinical Trials Registry (ANZCTR) number: ACTRN12615000132549. World Health Organization Trial Registration Universal Trial Number: U1111-1166-0388

Study sponsor: The Queensland University of Technology, Victoria Park Ave, Kelvin Grove, Australia

Keywords:

chronic cough, child, Aboriginal and Torres Strait Islander, management, early intervention, randomised controlled trial, cost-effectiveness, respiratory viruses, respiratory bacteria

Introduction

Cough in children is one of the most common reasons for medical encounters in Australia[1] and internationally.[2] In the United Kingdom, 30% of hospital paediatric medical encounters (including Emergency Department (ED) visits) are due to respiratory illnesses, with cough as a symptom accounting for over 8% of all presentations.[3] Cough in children is present in a broad range of respiratory illnesses ranging from mild, self-limiting rhinitis to life-threatening acute and chronic pulmonary disorders.[4] Furthermore, acute illness may bring to medical attention for the first time those with chronic underlying disease. In analyses of our recent cohort study of 817 children (96% non-Indigenous) aged <15-years presenting with cough to a tertiary paediatric ED,[5] 20% (95% confidence interval (CI) 17.2, 22.7) developed chronic (>4-weeks duration) cough after an acute respiratory infection (ARI). Of those, 42% were diagnosed at specialist review with protracted bacterial bronchitis and 32% were found to have a previously undiagnosed respiratory disorder, including asthma, large airway lesions (such as tracheomalacia), obstructive sleep apnoea and bronchiectasis (unpublished).

Chronic cough in children is an under-recognised, but important cause of morbidity and decreased quality of life (QoL).[6] Although an economic evaluation has never been undertaken, chronic cough likely accounts for substantial direct and indirect economic costs.[7] An Australian study found that >80% of parents had sought five or more medical consultations for their child in the 12-months immediately prior to referral to respiratory specialists for their child's chronic cough.[7] Nevertheless, there are few high quality studies that address the natural history of acute and chronic cough and none completed that have a predominant focus on Australian Indigenous children. Systematic reviews of the natural history of acute cough in children in primary healthcare found wide variation in the design and quality of studies.[8,9] There was large variability in the duration of illnesses evaluated, how outcomes were measured and completeness of follow-up.

Importantly, in most studies addressing acute cough in children, validated outcome measures for cough were not used, those with prolonged cough were not reviewed and there was no differentiation between “wet" and “dry” types.[9] Wet cough is important as it implies increased airway secretions and usually indicates clinically significant lower airway infection and neutrophilic inflammation.[10] [11] For example, chronic wet cough is the most common symptom of bronchiectasis[12] and early diagnosis and treatment improves long-term outcomes.[13] [14]

Indigenous people are at high risk of developing chronic pulmonary disorders. Indeed, in nation-wide data for Indigenous Australians, respiratory disorders are: (a) the most common reason for primary healthcare encounters; (b) the second most prevalent self-reported chronic condition; and (c) the second most common cause for hospitalisation.[15] Overall, 27% of Indigenous people report some form of respiratory disease; 19% in those aged <14-years and 38% in those aged >55-yrs. In remote Indigenous children, the rates of hospitalisation for ARI and radiographically-diagnosed pneumonia,[16] [17] and the incidence of bronchiectasis,[18] are amongst the highest reported worldwide. Recurrent ARI episodes are common[17] and studies in Indigenous children from central and northern Australia demonstrated associations between these infections and subsequent diagnosis of bronchiectasis.[19] [20]

To date, the focus on ARI has been largely on remote Indigenous children, with limited community-based data from those living in urban settings. This is despite socio-economic and health indices being consistently lower for urban Indigenous populations compared to non-Indigenous groups.[15] The lack of data on urban and rural Indigenous populations has been identified as a significant barrier to “Closing the Gap” initiatives.[21] Although over half of the Indigenous population live in urban and regional centres, most research addresses the health and social issues of remote communities and only 11% of all articles about Indigenous health during a

5-year period addressed urban populations.[21] However, preliminary data from our ongoing cohort study of ARI in young urban Indigenous children[22] suggest 20% will develop chronic cough post-ARI, principally from protracted bacterial bronchitis (PBB).

Early detection and appropriate management of the underlying aetiology (eg. bronchiectasis) causing chronic cough in children is important as it results in improved short[23] and medium-term[14] outcomes. Despite the availability of evidence-based cough management guidelines for children in several countries,[24 25] including Australia,[26] the uptake and impact of the guidelines is largely unknown. So far, only one randomised controlled trial (RCT) has evaluated any of these guidelines[27 28] and economic evaluation was absent. This was conducted in five Australian cities where 272 children (mean age 4.5-years, standard deviation 3.7) newly-referred to a paediatric respiratory physician were randomly allocated to either early review and use of a cough algorithm or usual care until review and subsequent use of a pre-defined cough algorithm.[27 28] The study[28] found that children in the "early-arm" group had significantly better clinical outcomes (ie. cough resolution at week-6 post intervention; absolute risk reduction=24.7%, 95% confidence interval (CI) 13-35) and better cough-specific QoL compared to the control group. However, in this study,[28] the median duration of cough at enrolment was 16-weeks (interquartile range 8-32), and investigating earlier intervention is warranted. Furthermore, use of the cough algorithm in 346 children found that approximately 18% had a serious underlying illness. Indigenous children (10/34; 29.4%) were more likely to have bronchiectasis than non-Indigenous children (6.7%; 21/312; odds ratio = 5.78, 95%CI 2.15, 14.5; p<0.001).[29]

Despite the high burden of ARI, there are little published data on interventions for acute and chronic cough, especially for urban and regional Indigenous children. An ARI sometimes unmasks a previously unrecognised chronic respiratory illness, which is a major problem in Indigenous

Australians, but one that receives limited attention.[30-32] Early diagnosis and management of chronic respiratory illness in children reduces morbidity and improves QoL. This RCT will therefore answer the primary question: *"Amongst children aged <15-years with chronic cough post-ARI, does active intervention at 4-weeks improve clinical outcomes?"*

Study objectives

Our primary objective is to determine if children aged <15-years with chronic (>4-weeks) cough post-ARI and managed according to an evidence-based cough algorithm have better clinical outcomes (faster cough resolution) than those receiving standard care.

Our secondary objectives are to:

1. Determine the cost-effectiveness of early intervention in chronic cough following an ARI compared to standard care.
2. Identify the microbiological predictors of chronic cough following an ARI.
3. Characterise the epidemiological, clinical, socio-economic and cultural predictors of chronic cough following an ARI.
4. Establish the epidemiological, clinical, socio-economic and cultural predictors of success or failure of an early intervention in chronic cough following an ARI.

Our study tests the primary hypothesis that amongst children aged <15-years with chronic (>4-weeks) cough post-ARI, initiation of a cough management algorithm at the transition from acute to chronic cough will reduce cough duration.

Methods and analysis

Study design

A nested, open-label RCT (with concealed allocation) within a prospective cohort study of children aged <15-years presenting to 3 primary health care services with an ARI that includes cough as a symptom, and who are followed for 56-days (Figure 1).

Eligibility

Inclusion criteria are:

- Aged <15-years
- At the time of attending the clinic, the child is identified as having a possible respiratory illness (including those reported to have fever or viral/bacterial illness) that has parent reported cough as a symptom
- Provision of written informed consent from parent/guardian and assent from children aged 12 - <15-years
- Siblings are permitted if each meets the above criteria

The exclusion criteria are: known diagnosis of an underlying medical condition, including chronic pulmonary disorders (excluding asthma); immunosuppressive illness, such as primary immunodeficiency, human immunodeficiency virus infection or receiving immunomodulating drugs (except short-course (<2-weeks) oral and ongoing maintenance inhaled corticosteroids) in the 30-days prior to presentation; current or planned participation in another intervention study during the 8-weeks of follow-up; severe ARI requiring hospitalisation, and/or; insufficient English inhibiting provision of written informed consent or completion of participant interviews.

Recruitment

Eligible children are identified when presenting to one of three primary healthcare centres in subtropical, Southeast Queensland, Australia involving metropolitan Brisbane (population 2.2 million), the regional city of Toowoomba (110,000) and the rural town of Warwick (14,000). Parents and their child(ren) will be approached by clinic personnel and informed consent/assent obtained using written and/or pictorial plain language statements.

Data collection, follow-up and intervention (Figure 1)

Children enrolled in each of the three primary healthcare centre cohorts undergo baseline clinical assessments that include demographic details, medical history, risk factors for ARI and cough, presenting features, vital signs, investigations, treatment and cost-of-illness data. Weekly telephone and/or email and/or face-to-face contacts collect cough status, type (ie wet, dry variable) and cough score,[33] medication (including over-the-counter remedies) and health service provider use for the cough and cost-of-illness data. Wet and dry cough are classified as per parent/carer reports, which were found previously to be accurate (compared to respiratory physician and bronchoscopy) in a study of children with chronic cough.[34] The cost-of-illness data are collected at each parent/carer contact, specialist review and from examining medical records. A minimum of three contact attempts are made at each weekly time-point. We did not employ daily diary cards as planned originally, since although their use in chronic cough studies was reliable, we found that in children with acute cough diary completion and return rates were low during preliminary work undertaken for this study. We also could not use smartphone apps as the ownership of smart phones in the target communities is low. Thus, instead we relied upon weekly parent recall of acute child illness, which has been shown to introduce minimal bias (<10%) in prevalence studies.[35]

At day-28, any child with a persistent cough (ie. ≤3-day break in cough in the preceding 28-days) is randomised (1:1 allocation) to clinical review and initiation of the cough management algorithm or to continue weekly follow-up. All study participants continue weekly follow-up until day-56 and any child still coughing at that timepoint undergoes clinical review until a definitive diagnosis is established or the child exits the protocol. The decision to follow children until day-56 was based on data from our ED cough study suggesting 42% of children with persistent cough at day-28 will be diagnosed with PBB (manuscript in preparation) that resolves with a 14-day course of amoxycillin-clavulanic acid. Children requiring ongoing care beyond two study physician reviews are referred to a tertiary paediatric respiratory medicine service.

The study intervention involves study physician clinical review within 2-weeks of day-28 where the cough management algorithm (Figures 2 and 3) is implemented depending upon whether the child has a specific or non-specific cough. Children in whom the cough has resolved spontaneously between randomisation and physician review, and at that point are deemed by the study physician to require no further management, will not contribute to the primary analysis.

Children in the control group follow a standard care pathway. This reflects what occurs normally in the community for children with cough where the general waiting period for review by a paediatric respiratory physician is on average 6-weeks following referral from a family physician. The parents/guardians of children randomised to the control group are advised to continue follow-up with instructions that they will be reviewed by a study doctor following day-56 if they are still coughing. They are also counselled to seek advice from their family physician or other healthcare provider if their child becomes unwell or they are worried, otherwise to continue to self-manage their child's cough as they see fit.

Randomisation, allocation and blinding

An independent biostatistician prepared the randomisation code using a permuted blocking design (block size of 4) to maintain group balance. Randomisation was stratified by reason for presentation (ARI with cough or another reason with an ARI noted incidentally), site and cough duration at day-28 (<6-weeks or ≥6-weeks). Group allocation is concealed in opaque, consecutively numbered envelopes kept in a locked cabinet at the Centre for Children's Health Research, South Brisbane. At randomisation, the child's cough history over the past 28-days and study specific strata are confirmed by the Central Coordinating Site. The Study Coordinator selects the next consecutively numbered opaque sealed envelope from the relevant strata pack, opens the envelope and extracts the randomisation code. Two people check the allocation and the code is assigned to the participant. The Study Coordinator then arranges for the study physician to review within 2-weeks of randomisation those children allocated to the intervention arm. If siblings are also enrolled and each child is still coughing at day-28, randomisation occurs for the first child enrolled (ie, earliest study number) and all siblings are allocated subsequently to the same arm. Differences in strata (eg presentation type and cough duration) will be accounted for in the analysis.

Blinding is not undertaken in this study, however parents are not informed at enrolment that their child will be randomised at day-28 to a specific intervention if the child has a persistent cough. Instead they are informed that children who develop persistent cough will be reviewed by a paediatrician during the study with some children being seen earlier and some later in the 8-week follow-up period. Limited disclosure is permitted under the Australian ethical standards for human research[36] if it is scientifically justifiable and does not present an increased risk of harm to the participant.

Definitions

Definitions used for the clinical management pathway[23 27] are as follows:

• Asthma: recurrent (>2) episodes of wheeze and/or dyspnoea that responds (within minutes) to inhaled beta$_2$ agonist or demonstrates bronchodilator responsiveness documented on spirometry (≥12% change in the percentage predicted forced expiratory volume in one-second after 400ug of salbutamol).

• Cough resolution: improvement ≥75% or total resolution according to cough diary data for ≥3 consecutive days.[37 38] When cough diary data are unavailable, resolution is defined as total cessation of cough according to parent/guardian verbal report.

• Chest radiograph abnormality: any abnormality (other than peribronchial thickening) identified by a paediatric respiratory physician or radiologist.

Spirometry abnormality: as determined by the American Thoracic Society and European Respiratory Society criteria with Australian predicted values used.[39]

• Primary diagnosis of cough aetiology: diagnosis confirmed by subsequent specific treatment that resulted in cough resolution within 3-weeks.[26 37] The diagnostic criteria are defined *a-priori* following published guidelines:[6]

  • PBB: presence of an isolated chronic wet or productive cough, without signs of another cause and which responds to at least a 2-weeks course of an appropriate antibiotic, such as amoxicillin-clavulanate.

  • Recurrent PBB: ≥3 episodes over a 12-month period.

- Reversible airway obstruction: in accordance with American Thoracic Society and European Respiratory Society criteria and adopting Australian predicted values.[39]

• Secondary diagnosis: diagnosis found on objective tests, but where: 1) specific treatment did not lead to resolution or improvement in the cough; or 2) no treatment for this diagnosis was trialled and the cough either resolved spontaneously or with other therapies.[6]

• Specific cough pointers: presence of any of the following: auscultatory abnormality (wheezes, crackles or differential breath sounds), classical cough characteristics, cardiac abnormalities, chest pain, chest wall deformity, daily moist or productive cough for >3-months, digital clubbing, dyspnoea (exertional or at rest), failure to thrive, feeding difficulties (including choking/vomiting), haemoptysis, immune deficiency, neuro-developmental abnormality, recurrent pneumonia, wheeze. These pointers are explained in the Thoracic Society of Australia and New Zealand position statement.[37]

• Tertiary hospital management: that usually requires investigations to be conducted at a paediatric tertiary centre (eg. flexible bronchoscopy with bronchoalveolar lavage, chest high-resolution computed tomographic scan, fluoroscopic swallow screening, etc).

Specimen collection

At recruitment, exhaled carbon monoxide (eCO) measures from the child (if aged ≥ 3 years and can provide an adequate sample) and parent/guardian are collected to provide an objective, non-invasive assessment of cigarette smoking status and exposure[40] using a portable eCO monitor (Smokerlyzer, Bedfont Scientific, England).

All children have bilateral anterior nasal swabs collected at enrolment and at days-28 and 56. Anterior nasal swabs rather than nasopharyngeal swabs are being used as: a) they are more acceptable to children; b) in our experience have comparable sensitivity to nasopharyngeal specimens[41] and, besides, any loss in sensitivity is considered acceptable when the purpose of the specimen is epidemiological rather than for a clinical diagnosis,[42] and; c) they permit more extensive swabbing of the nares. Nasal swabs are collected using Virocult® plain cotton tip swabs with viral transport medium (Virocult, MW951, Medical Wire & Equipment, England) inserted 1cm into the nostril and rotated four times on the right side and then on the left side. Swabs are stored locally in -20°C freezers before being transported to the research laboratory where they are stored at -80°C until processing occurs.

Laboratory methods

Swabs are batch-tested for respiratory viruses and bacteria using validated real-time polymerase chain reaction (PCR) assays described previously.[42] [43] Virus testing includes rhinoviruses, adenovirus, respiratory syncytial virus, influenza virus types A and B, parainfluenza virus types 1-3, human metapneumovirus, human coronaviruses (OC43, 229E, NL63, HKU1), human bocavirus and human polyomaviruses KI and WU. Bacterial testing includes *Bordetella pertussis*, *Mycoplasma pneumoniae, Streptococcus pneumoniae*, *Staphylococcus aureus, Haemophilus influenzae* (including differentiating between encapsulated and non-encapsulated strains and *H. haemolyticus*) and *Moraxella catarrhalis*.

End points

Participation is completed 56-days (±3-days) following enrolment or, for children in the RCT, when a final diagnosis is determined by the study physician. Other exit points are serious protocol violations and worsening of the child's condition that requires hospitalisation or other active

intervention elsewhere. Children meeting the exit criteria will continue to be followed until the end of the study period.

Outcome measures

Primary clinical outcome: Time-to-cough resolution in days

Secondary cost-effectiveness outcomes: Total direct and indirect costs of illness calculated according to the criteria outlined in Table 1.

Secondary microbiological outcomes: Anterior nasal detection by PCR of respiratory viruses and bacteria at days-28 and 56.

Table 1: Cost item, sector allocation and source of cost used in costing acute and chronic cough

Cost item	Sector	Source of cost to be applied
Healthcare service utilisation - *includes costs for diagnostic tests and complementary/alternative therapies* - *distinguishes between public and private, paid and bulk-billed services*	Family Healthcare Health insurers	Manual of resource items and their associated costs[44] National Hospital Costs Data Collection[45] Quarterly Gap Payment &Medical Benefits Statistics[46] Medicare Quarterly Statistics[47] Medicare Benefits Schedule[48] Expert panel or large online provider where required
Medication usage - *includes over-the-counter and prescribed medications*	Family Healthcare	Pharmaceuticals Benefits Scheme (PBS) [49] Online providers when not listed on PBS
Healthcare seeking travel costs	Family	Parental Report Private Health Insurance

- includes ambulance and community transport services		Administration Council[50] Petrol: Average unleaded retail price Translink: average ticket prices
Time spent seeking healthcare *- Time off work with pay* *- Time off work with pay lost* *- Time off usual activity*	Family Employers	Parental Report Average weekly earnings, Australia[51]
Extra time spent caring for child *- Time off work with pay* *- Time off work with pay lost* *- Time off usual activity*	Family Employers	Parental Report Average weekly earnings, Australia[51]
Missed childcare/school	Family	Parental Report
Missed planned activities *- child and others*	Family	Parental Report

Note: Costs will be applied following the completion of data collection ensuring up-to-date cost data

Sample size

Sample sizes for each of the primary healthcare cohorts comprising this study are based on the expected number of eligible children with ARI presenting to each of these services over the study's timeframe and derived from our current studies of chronic cough post-ARI in children.[22 52] Between July 2015 and June 2017, we anticipate 750 eligible children will present to the primary healthcare services participating in this study.

Our preliminary data from a cohort study of Indigenous children aged less than 5-years[22] suggest 20% of Indigenous children with an ARI will have chronic cough at day-28. Based on data from the first study of the algorithm[28] for the primary endpoint of cough resolution at day-56, we anticipate

a 54% reduction in the proportion of children (54.3% in early arm compared to 29.5% in delayed-arm) with persistent cough at day-56. Hence, 89 children per group with complete evaluable data at day-56 will provide 90% power (α=0.05), to detect this 54% reduction for our primary aim. Assuming a 20% loss to follow-up and spontaneous resolution of cough of between randomisation and physician review of 5%, we will therefore randomise a minimum of 112 children per group at day-28 across all three sites.

Given the entire cohort study will have a 2-year recruitment period, and the natural history and predictors of chronic cough and cost-effectiveness of the intervention are important secondary outcomes, we will not limit recruitment to the RCT arm once 224 children have been randomised. Ongoing enrolment will hence increase study power to address both primary and secondary objectives. This approach has approval from the all relevant human research ethics committees (HREC).

Data Management

Data will be entered into a password protected, custom built, Filemaker Pro Advanced V14 (Filemaker, Inc. Santa Clara, USA) database. The database has been designed to incorporate automatic data checking including logic and inaccurate ranges and maintains a log of any changes to the data. Data fields cannot be left blank and missing data must be coded as such in the database. A specific data management protocol compliant with the Queensland University of Technology's data management policies and principles is in place.

Statistical methods

Data will be presented in accordance with the updated CONSORT criteria.[53] Demographic, clinical, economic, risk factor and microbiological data will be tabulated for the study population overall, by centre and by randomisation group and expressed as proportions and/or means of the selected

characteristics by study centre, and presence/absence of chronic cough at day-56 with the corresponding 95%CI. Differences between groups will be assessed using t-tests for comparisons of means and χ^2 test for comparisons of proportions, conditional on test assumptions for each being satisfied. Non-normally distributed data will be analysed with appropriate non-parametric tests.

Primary objective

Intention-to-treat analyses will be employed. Time-to-cough resolution will be compared between groups using cox proportional hazard methods, adjusting for independent explanatory variables, subject to modelling assumptions being met, particularly proportionality of hazards. All analyses will be performed on the whole cohort and then additional analyses will be performed utilising frailty models[54] that account for the clustering effects of siblings and site of recruitment.

Economic objectives

Costing of the intervention will be done according to established methods,[55 56] including detailed sub-analyses of data that account for epidemiological, social, cultural, risk factor and microbiological variables. Cost-effectiveness analysis (CEA) will be modelled using the health sector perspective. Broader societal issues using data from the trial as described above and augmented by the evidence from the literature, especially systematic reviews will also be taken into consideration. The CEA approach will involve: identification of resources using the intervention pathway (activities, probabilities and unit costs); measurement of resource use/outcomes; and valuation of costs using unit costs published in the literature and from the trial itself. The time horizon will be specified and current practice (standard care) will be the comparator; and future costs and benefits will be discounted at 3% to present values. Central to this analysis will be the modelling of uncertainty surrounding data quality and gaps using

sensitivity analyses, and extension of time horizon, using Treeage software (Treeage Software Inc. Williamstown, MA, USA). The key outcomes will be incremental cost-effectiveness, and cost-savings to the health system due to the interventions.

Other objectives:

Multivariable modelling will be employed to: a) evaluate the microbiological predictors of chronic cough following an ARI as determined at days-28, 42 and 56 post-enrolment; b) evaluate the epidemiological, clinical, socio-economic and cultural predictors of chronic cough at day-28 post-ARI; c) evaluate the epidemiological, clinical, socio-economic and cultural predictors of success or failure of the intervention at day 56; and, d) to compare these predictors between the three study populations. Crude and adjusted relative risks and the respective 95% CIs will be presented, with differences considered statistically significant at $p<0.05$.

Sub-group analyses will be performed for all primary and secondary objectives to examine potential differences by study specific strata. Univariate and multivariate analyses will be performed to evaluate variables independently associated with study endpoints and to assess potential confounding factors in the association between vaccination and disease. Multiple imputation models will be used to evaluate the effect of missing data. Additional analyses will be undertaken to assess the effect of multiplicity in the assessment of microbial associations with cough outcomes.

Participant safety

Parents/guardians of all participants will be informed of any new information that arises during the study that may indicate potential harm to the child if he/she were to continue in the study. Any trial-related adverse events will be documented and reported to the relevant HREC. Serious adverse events will be reported to the HREC within 24-hours of notification and will be followed until resolution. A decision to withdraw the child following a serious adverse event will be made in consultation with the HREC, investigating team and the child's primary physician. If an adverse event is deemed related to study procedures, the child and his/her family will be eligible for compensation under the Clinical Trial Insurance policies in place for the duration of the study. All participant data will be kept confidential and stored securely in accordance with Australian Privacy Laws. Identifying data will be not be provided to any persons outside of the study team unless required by Australian law (eg. in the event of the diagnosis of a notifiable disease). Published data will be de-indentified and presented in aggregrate form.

Independent monitoring and quality control

Independent study monitors have been engaged to undertake regular data quality audits, assess compliance with Good Clinical Practice guidelines and ensure the study is being conducted according to the study protocol and ethical approvals. In-built data quality monitoring and generation of data queries are established within the trial database, with data queries sent to study sites weekly for resolution.

Protocol amendments

All protocol amendments will be submitted to the study's HREC (see below) for approval prior to implementation. If any amendments have the potential to affect a family's willingness to continue in the study, all participants will be re-consented to the amended protocol.

Study status

Recruitment began in July 2015.

Ethics and dissemination

The Children's Health Queensland (HREC/15/QRCH/15) and the Queensland University of Technology University (1500000132) HREC have approved the study. The Queensland University of Technology is the trial sponsor.

Participants will be provided with regular study progress reports and a written letter outlining the results of the study. The trial results, including any negative findings, will be published in open-access peer reviewed journals and presented at scientific conferences, paediatric society and general practitioner meetings and other fora. The primary author of the main paper will be the Principal Investigator (KFO). The trial findings are likely to be incorporated into clinical management guidelines. Study data will be held in metadata repositories until the youngest child turns 25 years of age at the Queensland University of Technology. De-identified study data will be made available to external parties on request and, if relevant, with the appropriate HREC approvals.

Discussion

Chronic cough in children is a defining symptom of several chronic pulmonary disorders worldwide. Preventing persistent cough in children may lead to important short and long-term health benefits. Our proposed intervention[22 26] is similar to the existing Australian guidelines,[57] but also has some differences that were developed following the incorporation of new data unavailable at the time the guidelines were published. Use of guidelines by clinicians depends

upon several factors, which include level of evidence, feasibility, degree of implementation and inherent clinician factors.[58] Using an algorithm facilitates clinical guideline implementation by clearly describing pathways of care based upon whether the child presents with a specific or non-specific cough. While this study uses specific study physicians, the overall goal is widespread adoption of the guidelines and management algorithm in the primary healthcare setting. Our extensive data collection, including direct and indirect costs of illness and health care provision, are important in achieving this goal. The study will also provide an avenue for assessing the extent to which these guidelines are being used currently in different clinical settings given we will collect data on any intervention a child may receive external to our study.

Study site selection was based upon several factors, including existing relationships, feasibility and how they incorporated geographically and demographically different Indigenous communities. Studies evaluating ARI and chronic cough have had differing study designs, objectives and endpoints between populations. Australian data suggest cough burden is independent of age and aetiology, but dependent upon clinical setting.[29] In Australia, there are clear risk and burden distinctions between children from urban and remote areas and between Indigenous and non-Indigenous children.[59] Indigenous children in urban areas have received much less attention than those in remote centres. Failure to account for these differences may lead to inappropriate interventions or implementation of management guidelines that may not be applicable across all settings.

The economic data and analyses in this study will be the first to describe the cost of ARI and its outcomes in Indigenous children in Australia, and one of the few worldwide. Further, the CEA of the intervention will provide data critical to clinical and public policy decisions with respect to incorporation of the intervention into routine care at both the primary and tertiary health care

levels. Such decisions will be enhanced by our incorporation of direct and indirect costs to the family, the community and health care sector,[60] particularly given the focus on resource allocation in Indigenous health in Australia,[61] and the different mechanisms for delivery of primary health care services compared to mainstream Australia.[62]

We have incorporated microbiological components into the RCT as the role of infectious agents in the transition from ARI to chronic wet cough remains largely unknown. Whether persistent shedding, new acquisition and/or virus-bacteria interactions are associated with the development of chronic cough post-ARI is a clinical and research gap needing to be addressed. A study of 170 children aged 5-16 years presenting to their family physician with a cough lasting >14-days detected *M. pneumoniae* and *B. pertussis* in 12.9% and 36.6% respectively.[63] Cough duration was shorter in *M. pneumoniae* than *B. pertussis* cases and co-detection with respiratory viruses was not associated with cough duration.[63] An important limitations of this study[63] was that data were not collected from the time of ARI onset. Other studies[64] have also tested for bacteria and viruses in nasopharyngeal specimens, but to date none have followed children from ARI onset and examined the association with developing chronic cough. In the analyses of microbiological data collected in our study of children attending an ED with cough, *M. cattarhalis* detected by PCR in anterior nasal swabs collected at time presentation was the only organism independently associated with persistent cough at 4-weeks after controlling for age, gender and the presence of any viruses.[5] Our Brisbane-based lower airway studies of children with chronic cough from PBB found intense neutrophilic airway inflammation and evidence of innate immune activation, suggesting PBB may follow a single ARI episode with impaired pathogen clearance from the airways, either permanently or temporarily leading to a cycle of chronic inflammation.[65] Small case series from the late 1990s have reported chronic pulmonary sequelae following influenza

infection in young children[66] and a relationship between adenovirus infection and bronchiectasis.[67]

The major threats to the validity of our proposal are loss to follow-up and potential for contamination of the control group based on the type of standard care they may receive. In our current ARI study in urban Indigenous children, loss to follow-up at the 4-week time point post-ARI is 23%. Procedures to minimise this loss include: home visiting by Indigenous research personnel, regular text and email messaging, and personal letters to families. Analysis plans will include measures to account for missing data and sensitivity analyses to assess the extent of bias.

Although contamination of the control group is possible, based on a multicentre RCT conducted in five major Australian cities,[29] it is unlikely that a child in standard care will receive treatment similar to the intervention arm. In another of our studies,[52] just 27% of children sought further medical advice for cough in the 4-weeks following presentation to an ED for an illness with cough as a symptom (unpublished data). Furthermore, of the 9.7% receiving antibiotics during this 4-week period,[5] most were prescribed antibiotics at the time of the original ED presentation. Hence, it is unlikely this will influence the validity of our RCT for several reasons: (i) We can assess any intervention either group receives outside of the RCT since our weekly follow-up data collection captures these events. (ii) In the possible, but unlikely event of a change in treatment in the control group, the effect size of the intervention will be smaller requiring a larger sample size. The *a-priori* sample size is conservative with 90% power and a smaller effect size will still be detectable within the available study population (e.g. a 35% difference with power of 80% requires 114 per group). (iii) To ensure robustness, an independent person will recalculate the sample size when 50% of children have completed the RCT component.

In summary, our RCT will be the first to examine the impact of a cough management algorithm implemented at the transitional stage from acute to chronic cough in Indigenous children. Clinical effectiveness will be evaluated concurrently with detailed epidemiological, clinical, microbiological and economic determinants of ARI and cough persistence in this population. If successful, the study may provide the data necessary to facilitate the uptake and implementation of cough management guidelines in the primary healthcare setting, potentially reducing the long-term burden of disease on the child, family, community and healthcare sector.

Protocol version

Version 4 dated 9 June 2016

List of abbreviations

ARI = acute respiratory infection; CEA = cost-effectiveness analysis; CI confidence interval; eCO = exhaled carbon monoxide; ED = Emergency Department; HREC = Human Research Ethics Committees; PBB = protracted bacterial bronchitis; PCR = polymerase chain reaction; QoL = quality of life; RCT = randomised controlled trial.

Authors' contributions

KOG conceived the study, devised the study protocol and oversees study implementation nationally and was the primary author of the manuscript. KG contributed to study conception, the grant application and will play a leading role in the interpretation of the microbiological data. MT contributed to study conception, grant application, community consultation and implementation of the study. TS and DW contributed to study conception and the grant application and are responsible for the microbiological components of the study and interpretation of the laboratory data. MO contributed to study conception and the grant application and is responsible for the

economic components of the study. SR is the National Study Coordinator with major input into data instruments, standard operating procedures and GCP compliance. HB, ACM, DA and MkO are responsible for the clinical implementation of the intervention and evaluation of study diagnostic outcomes. PJT contributed to study conception and will play a role in knowledge translation and implementation of study findings into clinical guidelines. ABC played a major role in study conception, grant application, protocol development and implementation and helped draft the manuscript. All authors read and approved the final manuscript.

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Role of study sponsor and funding agencies

The study sponsor and funding agency have had, and will not have, any role in study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication.

Competing interests

No authors have any competing interests to declare.

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References

1. Britt H, Miller G, C. , Charles J, et al. General practice activity in Australia 2009–10. General Practice Series no. 27. Canberra: AIHW, 2010.

2. Irwin RS, Gutterman DD. American College of Chest Physicians' cough guidelines. Lancet 2006;**367**(9515):981.

3. Whitburn S, Costelloe C, Montgomery AA, et al. The frequency distribution of presenting symptoms in children aged six months to six years to primary care. Prim Health Care Res Dev 2011;**12**(2):123-34.

4. Chang AB. Cough: are children really different to adults? Cough 2005;**1**:7.

5. O'Grady KF, Grimwood K, Sloots TP, et al. Upper airway viruses and bacteria and clinical outcomes in children with cough. Pediatr Pulmonol 2016. DOI: 10.1002/ppul.23527

6. Marchant JM, Masters IB, Taylor SM, et al. Evaluation and outcome of young children with chronic cough. Chest 2006;**129**(5):1132-41.

7. Marchant JM, Newcombe PA, Juniper EF, et al. What is the burden of chronic cough for families? Chest 2008;**134**(2):303-9.

8. Thompson M, Vodicka TA, Blair PS, et al. Duration of symptoms of respiratory tract infections in children: systematic review. BMJ 2013;**347**:f7027.

9. Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. Br J Gen Pract 2002;**52**(478):401-9.

10. Chang AB, Faoagali J, Cox NC, et al. A bronchoscopic scoring system for airway secretions--airway cellularity and microbiological validation. Pediatr Pulmonol 2006;**41**(9):887-92.

11. Douros K, Alexopoulou E, Nicopoulou A, et al. Bronchoscopic and high-resolution CT scan findings in children with chronic wet cough. Chest 2011;**140**(2):317-23.

12. Chang AB, Redding GJ, Everard ML. Chronic wet cough: Protracted bronchitis, chronic suppurative lung disease and bronchiectasis. Pediatr Pulmonol 2008;**43**(6):519-31.

13. Bastardo CM, Sonnappa S, Stanojevic S, et al. Non-cystic fibrosis bronchiectasis in childhood: longitudinal growth and lung function. Thorax 2009;**64**(3):246-51.

14. Kapur N, Masters IB, Chang AB. Longitudinal growth and lung function in pediatric non-cystic fibrosis bronchiectasis: what influences lung function stability? Chest 2010;**138**(1):158-64.

15. Pink B, Allbon P. The Health and Welfare of Australia's Aboriginal and Torres Strait Islander Peoples: 2008. Canberra: Australian Bureau of Statistics and Australian Institute of Health & Welfare. 2008.

16. O'Grady KA, Taylor-Thomson DM, Chang AB, et al. Rates of radiologically confirmed pneumonia as defined by the World Health Organization in Northern Territory Indigenous children. Med J Aust 2010;**192**(10):592-5.

17. O'Grady KA, Torzillo PJ, Chang AB. Hospitalisation of Indigenous children in the Northern Territory for lower respiratory illness in the first year of life. Med J Aust 2010;**192**(10):586-90.

18. Chang AB, Grimwood K, Mulholland EK, et al. Bronchiectasis in indigenous children in remote Australian communities. Med J Aust 2002;**177**(4):200-4.

19. Valery PC, Torzillo PJ, Mulholland K, et al. Hospital-based case-control study of bronchiectasis in indigenous children in Central Australia. Pediatr Infect Dis J 2004;**23**(10):902-8.

20. Singleton RJ, Valery PC, Morris P, et al. Indigenous children from three countries with non-cystic fibrosis chronic suppurative lung disease/bronchiectasis. Pediatr Pulmonol 2014;**49**(2):189-200.

21. Eades SJ, Taylor B, Bailey S, et al. The health of urban Aboriginal people: insufficient data to close the gap. Med J Aust 2010;**193**(9):521-4.

22. Hall KK, Chang AB, Sloots TP, et al. The respiratory health of urban indigenous children aged less than 5 years: study protocol for a prospective cohort study. BMC Pediatr 2015;**15**:56.

23. Chang AB, Robertson CF, van Asperen PP, et al. A cough algorithm for chronic cough in children: a multicenter, randomized controlled study. Pediatrics 2013;**131**(5):e1576-83.

24. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest 2006;**129**(1 Suppl):1S-23S.

25. Keeley D. Cough in children: new guidelines from the British Thoracic Society. Postgrad Med J 2008;**84**(995):449.

26. Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest 2006;**129**(1 Suppl):260S-83S.

27. Chang AB, Robertson CF, van Asperen PP, et al. Can a management pathway for chronic cough in children improve clinical outcomes: protocol for a multicentre evaluation. Trials 2010;**11**:103.

28. Chang AB, Robertson CFPP, van Asperen PP, et al. Effect of a cough algorithm on chronic cough in children: A multicentre randomized controlled study. Pediatrics 2013; 131:e1576-83

29. Chang AB, Robertson CF, Van APP, et al. A multi-centre study on chronic cough in children: burden and etiologies based on a standardized management pathway. Chest 2012;**142**(4):943-50.

30. O'Grady KA, Revell A, Maguire GP, et al. Lung health care for Aboriginal and Torres Strait Islander Queenslanders: breathing easy is not so easy. Aust Health Rev 2011;**35**(4):512-9.

31. O'Grady KF, Revell A, Maguire G, et al. Lung Health Services for Aboriginal and Torres Strait Islander Peoples in Queensland. Brisbane: Queensland Government, 2010.

32. Chang AB, Marsh RL, Upham JW, et al. Toward making inroads in reducing the disparity of lung health in Australian indigenous and new zealand maori children. Frontiers in Pediatrics 2015;**3**:9.

33. Chang AB, Newman RG, Carlin JB, et al. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. Eur Respir J 1998;**11**(2):462-6.

34. Chang AB, Gaffney JT, Eastburn MM, et al. Cough quality in children: a comparison of subjective vs. bronchoscopic findings. Respir Res 2005;**6**:3.

35. Arnold BF, Galiani S, Ram PK, et al. Optimal recall period for caregiver-reported illness in risk factor and intervention studies: a multicountry study. Am J Epidemiol 2013;**177**(4):361-70.

36. Council NHMR. National Statement on Ethical Conduct in Human Research (2007): Canberra: Australian Government, 2007.

37. Chang AB, Landau LI, Van Asperen PP, et al. Cough in children: definitions and clinical evaluation - Position statement of the Thoracic Society of Australia and New Zealand. Med J Australia 2006;**184**(8):398-403.

38. Marchant JM, Masters IB, Taylor SM, et al. Utility of signs and symptoms of chronic cough in predicting specific cause in children. Thorax 2006;**61**(8):694-8.

39. Hibbert ME, Lannigan A, Landau LI, et al. Lung function values from a longitudinal study of healthy children and adolescents. Pediatr Pulmonol 1989;**7**(2):101-9.

40. Sandberg A, Skold CM, Grunewald J, et al. Assessing recent smoking status by measuring exhaled carbon monoxide levels. PLoS One 2011;**6**(12):e28864.

41. Lambert SB, Whiley DM, O'Neill NT, et al. Comparing nose-throat swabs and nasopharyngeal aspirates collected from children with symptoms for respiratory virus identification using real-time polymerase chain reaction. Pediatrics 2008;**122**(3):e615-20.

42. O'Grady KA, Torzillo PJ, Rockett RJ, et al. Successful application of a simple specimen transport method for the conduct of respiratory virus surveillance in remote Indigenous communities in Australia. Trop Med Int Health 2011;**16**(6):766-72.

43. O'Grady KA, Whiley DM, Torzillo PJ, et al. Mailed versus frozen transport of nasal swabs for surveillance of respiratory bacteria in remote Indigenous communities in Australia. BMC Infect Dis 2013;**13**:543.

44. Department of Health & Ageing. Manual of resource items and their associated costs for use in submissions to the Pharmaceutical Benefits Advisory Committee involving economic evaluation Canberra: Australian Government; 2015 [cited 2015 01 April 2015]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/content/health-pbs-general-pubs-manual-content.htm.

45. Department of Health & Ageing. National Hospital Cost Data Collection (NHCDC) Report Canberra: Australian Government; [Available from: http://www.health.gov.au/internet/main/publishing.nsf/content/health-casemix-data-collections-NHCDCReports.

46. Private Health Insurance Administration Council. Quarterly Gap Payment & Medical Benefits Statistics Canberra: Australian Government; 2012 [Available from: http://phiac.gov.au/wp-content/uploads/2012/11/Gap-Sep12.pdf.

47. Department of Health & Ageing. Quarterly Medicare Statistics Canberra: Australian Government; [Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/Quarterly-Medicare-Statistics.

48. Department of Health & Ageing. Medicare Benefits Schedule Canberra: Australian Government; [Available from: http://www.mbsonline.gov.au/.

49. Department of Health & Ageing Pharmaceutical Benefits Scheme Canberra: Australian Government; [Available from: http://www.pbs.gov.au/pbs.

50. Private Health Insurance Administration Council. Private Health Insurance Administration Council Queensland Reports Canberra: Australian Government; [Available from: http://phiac.gov.au/industry/industry-statistics.

51. Australian Bureau of Statistics. Average weekly earnings, Australia Canberra: Australian Government; [Available from: http://www.abs.gov.au/austats.

52. Drescher BJ, Chang AB, Phillips N, et al. The development of chronic cough in children following presentation to a tertiary paediatric emergency department with acute respiratory illness: study protocol for a prospective cohort study. BMC Pediatr 2013;**13**:125.

53. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Trials 2010;**11**:32.

54. Hougaard P. Frailty models for survival data. Lifetime Data Anal 1995;**1**(3):255-73.

55. Drummond MF, Sculpher MJ, Torrance GW. *Methods for the Economic Evaluation of Health Care Programs*. Oxford: Oxford University Press, 2005.

56. Gold MR, editor. *Cost Effectiveness in Health and Medicine*. Oxford: Oxford University Press, 1996.

57. Gibson PG, Chang AB, Glasgow NJ, et al. CICADA: Cough in Children and Adults: Diagnosis and Assessment. Australian cough guidelines summary statement. Med J Aust 2010;**192**(5):265-71.

58. Chang AB, Landau LI, Van Asperen PP, et al. Cough in children: definitions and clinical evaluation. Med J Aust 2006;**184**(8):398-403.

59. O'Grady KA, Chang AB. Lower respiratory infections in Australian Indigenous children. J Paediatr Child Health 2010;**46**(9):461-5.

60. Ungar WJ, Coyte PC, Pharmacy Medication Monitoring Program Advisory B. Prospective study of the patient-level cost of asthma care in children. Pediatr Pulmonol 2001;**32**(2):101-8.

61. Peiris D, Brown A, Howard M, et al. Building better systems of care for Aboriginal and Torres Strait Islander people: findings from the Kanyini health systems assessment. BMC Health Serv Res 2012;**12**:369.

62. Ong KS, Carter R, Kelaher M, et al. Differences in primary health care delivery to Australia's Indigenous population: a template for use in economic evaluations. BMC Health Serv Res 2012;**12**:307.

63. Wang K, Chalker V, Bermingham A, et al. Mycoplasma pneumoniae and respiratory virus infections in children with persistent cough in England: a retrospective analysis. Pediatr Infect Dis J 2011;**30**(12):1047-51.

64. Bisgaard H, Hermansen MN, Bonnelykke K, et al. Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. Bmj 2010;**341**:c4978.

65. Marchant JM, Gibson PG, Grissell TV, et al. Prospective assessment of protracted bacterial bronchitis: airway inflammation and innate immune activation. Pediatr Pulmonol 2008;**43**(11):1092-9.

66. Laraya-Cuasay LR, DeForest A, Huff D, et al. Chronic pulmonary complications of early influenza virus infection in children. Am Rev Respir Dis 1977;**116**(4):617-25.

67. Bateman ED, Hayashi S, Kuwano K, et al. Latent adenoviral infection in follicular bronchiectasis. Am J Respir Crit Care Med 1995;**151**(1):170-6.

Figure 1. Overview of Study Design

Figure 2. Specific cough pathway

Figure 3. Non-specific cough pathway

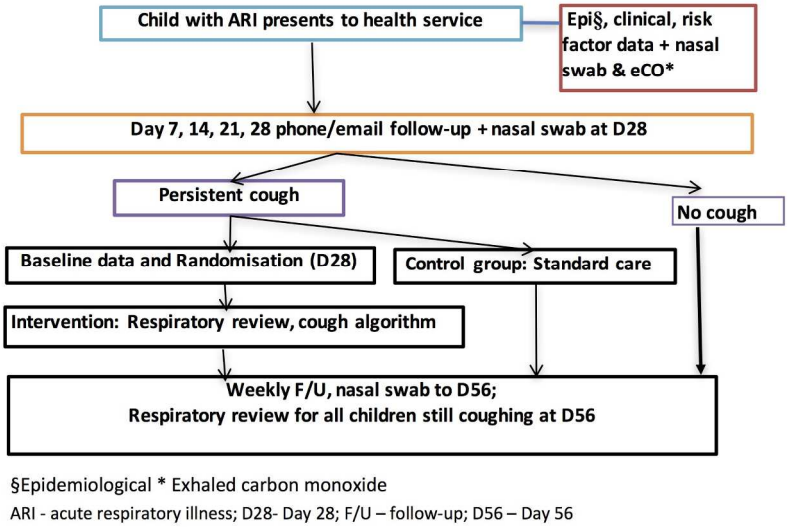

Figure 1. Overview of Study Design

206x118mm (300 x 300 DPI)

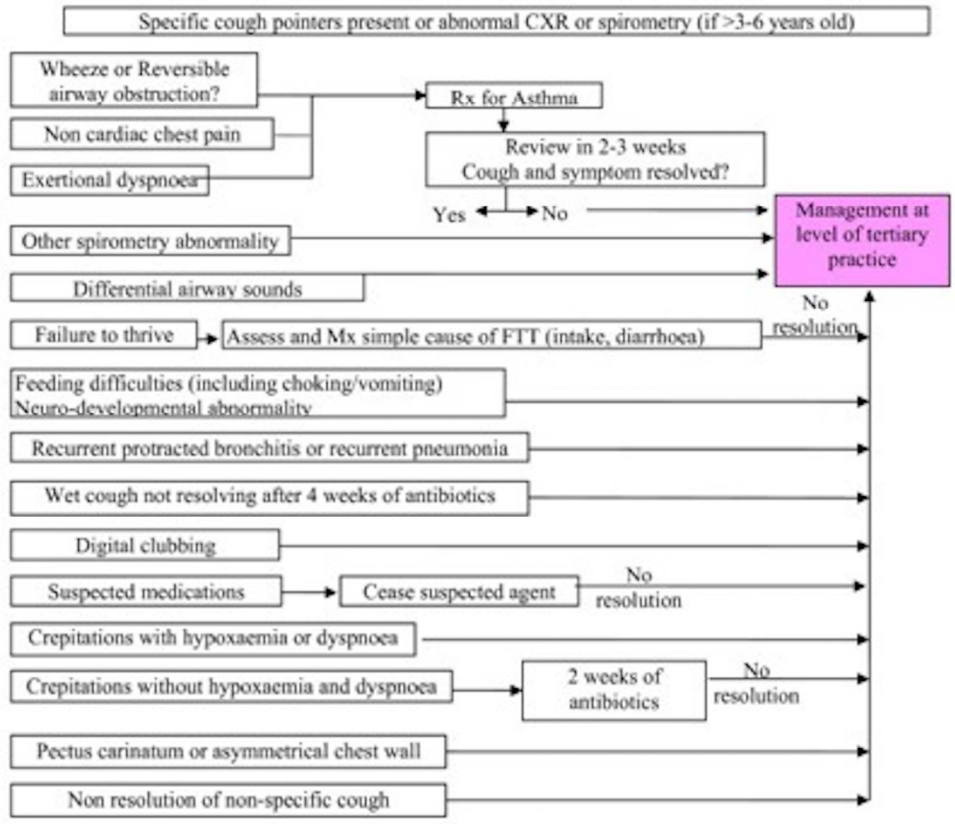

Figure 2. Specific cough pathway

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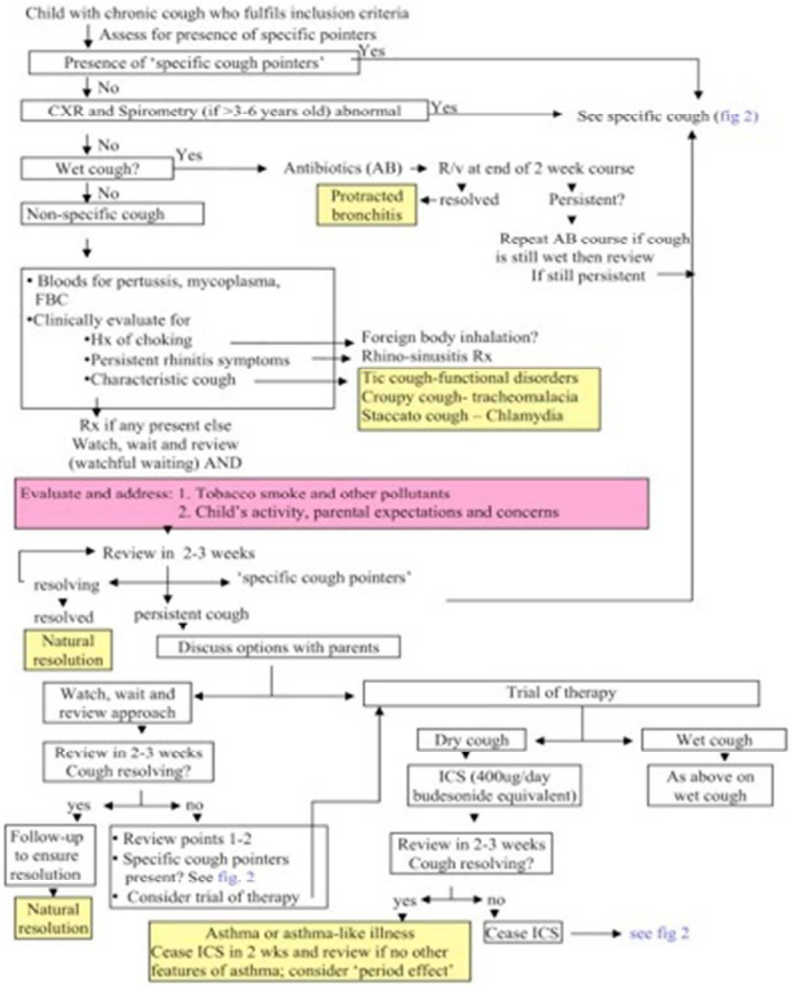

Figure 3. Non-specific cough pathway

146x179mm (72 x 72 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	24
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 a 25
	5b	Name and contact information for the trial sponsor	4
	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	25
	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)	-

Introduction

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	5-7
	6b	Explanation for choice of comparators	~~7-8~~
Objectives	7	Specific objectives or hypotheses	7-8
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)	9

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	9, 21
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)	9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	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)	10, 14.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	23
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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	15
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)	Figure 1

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	16.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	23
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	11
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	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	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	10
	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	14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17.
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	17-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-19
	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)	17-19.
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	
	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	N/A
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	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
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)	20

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	19
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	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
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	20
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	19
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	~~20~~ 21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	~~20~~ 21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	~~15~~ Suppl.
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	13-14

*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.