PROTOCOL NAME

Short-course antimicrobial therapy for paediatric respiratory infections (SAFER): a multicentre, randomized, controlled, trial designed to determine whether 5 days of high-dose amoxicillin is non-inferior to 10 days of high-dose amoxicillin for the treatment of mild paediatric pneumonia.

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List of Abbreviations

AE	Adverse Event
ARO	Antibiotic-Resistant Organism
CAP	Community-acquired pneumonia
CBC	Complete Blood Count
CHEO	Children's Hospital of Eastern Ontario
CPS	Canadian Paediatric Society
CRF	Case Report Form
CRP	C-reactive protein
DSMB	Data Safety Monitoring Board
ED	Emergency Department
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed Consent form
ICH	International Conference on Harmonisation
ID	Infectious Disease
IDSA	Infectious Disease Society of America
ITT	Intent-to-treat
KT	Knowledge translation
MCH	McMaster Children's Hospital

MRSA	Methicillin-resistant Staphylococcus aureus
NPS	Nasopharyngeal swab
PAE	Pre-intervention event
PCR	Polymerase chain reaction
PERC	Pediatric Emergency Research Canada
PI	Principal Investigator
RA	Research Assistant
RCT	Randomized controlled trial
REB	Research Ethics Board
REDCap	Research Electronic Data Capture
RN	Registered nurse
SAE	Serious Adverse Event
US	United States
WHO	World Health Organization

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Study Summary

Title	Short-course antimicrobial therapy for paediatric respiratory infection: a multicentre, randomized, controlled, non-inferiority trial
Short Title	Short-course antimicrobial therapy for paediatric respiratory infection
Protocol Number	15-237
Phase	3
Methodology	Randomized, double-blind trial Non-inferiority design Control arm – standard therapy (10 days high-dose amoxicillin) Experimental arm – 5 days high-dose amoxicillin
Study Duration	2 years
Study Center(s)	McMaster Children's Hospital Children's Hospital of Eastern Ontario
Objectives	To determine if 5 days of amoxicillin is non-inferior to 10 days of amoxicillin for the treatment of mild community-acquired paediatric pneumonia
Number of Subjects	210
Diagnosis and Main Inclusion Criteria	Community-acquired pneumonia in children aged 6 mos.-10 years, defined as: 1) fever recorded in the ED or at home in the 48h prior to presentation; 2) **any one of**: a. tachypnoea; b. cough; c. increased work of breathing; or d. auscultatory findings consistent with pneumonia; 3) infiltrates on chest radiograph consistent with bacterial CAP; and 4) primary diagnosis CAP Participants must be well enough to be treated as outpatients.
Study Product, Dose, Route, Regimen	Experimental arm: amoxicillin 90 mg/kg/day divided tid x 5 days plus placebo tid x 5 days
Duration of administration	10 days
Reference therapy	Control (standard of care): amoxicillin 90 mg/kg/day divided tid x 10 days

Statistical Methodology	The principal analysis will be per-protocol, as is recommended for noninferiority trials. The crucial statistical comparison will be between the 97.5% (one-sided) CI of the difference between the failure rate of the experimental arm and the standard therapy arm; should the upper bound of this difference be smaller than 7.5%, a conclusion of non-inferiority will be reached.

1 Background Information

1.1 Background and Rationale

1.1.1 Burden of disease

Respiratory infection is the leading cause of death for children worldwide (1,2). Up to 5% of preschoolers in North America and Europe develop community-acquired pneumonia (CAP) every year (3,4). Paediatric hospitalization rates for CAP in the Western world are 1-4 per 1000/year, with pneumonia accounting for up to 20% of all paediatric admissions in some settings (5). It should be noted that morbidity and mortality from lower respiratory tract infections is substantially higher in native and Northern populations in Canada and the United States (6).

1.1.2. Issues relating to the clinical diagnosis of pneumonia

Though physicians commonly diagnose CAP, there are no consensus criteria for its diagnosis. Its most common definition, "inflammation of the parenchyma of the lungs [caused by infection]," (7) is not useful in practice, as there is no way for clinicians to objectively evaluate whether inflammation is present in the lung parenchyma of their patient prior to autopsy. Symptoms and signs of respiratory disease are not specific for pneumonia (8); for example, tachypnoea and increased work of breathing are common presenting symptoms of bronchiolitis, an infectious syndrome involving primarily the small airways caused by viral pathogens. The absence of fever does not rule out pneumonia (9,10); we note that fever was documented in only 18-26% of children admitted to intensive care units because of respiratory failure due to the emerging pathogen enterovirus-D68 in the summer of 2014 (11).

Chest radiography is often assumed to be the 'gold standard' for the diagnosis of pneumonia; however, there are no consensus criteria for the interpretation of chest radiographs, though the World Health Organization (WHO) attempted to establish criteria for pneumonia diagnosis in the context of epidemiologic studies (12). One study enlisted 3 paediatric radiologists at both Boston Children's Hospital and the Children's Hospital of Philadelphia and provided them with a mix of chest radiographs (50 previously read as not having pneumonia, 25 previously read as having an alveolar infiltrate, 25 previously read as having an interstitial infiltrate, and 10 duplicates) taken from patients presenting with potential CAP to the emergency departments of these major children's hospitals (13). Inter-rater reliability was good for alveolar infiltrates (kappa 0.69 95% CI 0.60-0.78) but only slight for interstitial infiltrates (kappa 0.14 95%CI 0.05-0.23), a radiographic finding that is much more commonly found, and stratifying by institution had little effect on these estimates. Intra-rater reliability varied widely between the 6 respondents, with kappa 0.74-1.00 for alveolar infiltrates and kappa 0.21-1.00 for interstitial infiltrates. Please note that these estimates of inter-rater reliability are *between paediatric radiologists;* it has long been known that there are significant differences between the way radiologists and emergency physicians evaluate chest radiographs for pneumonia (14,15). As the decision about whether a particular patient has CAP or not will generally be made by the emergency physician without consulting the radiologist, one might reasonably expect a dramatic decrease in overall inter-rater reliability for most chest radiographs.

Despite all of these issues, observational studies and clinical trials in upper-income countries often use somewhat similar definitions for 'community-acquired pneumonia' using fever, clinical signs of respiratory disease, and chest radiographic criteria, though, as noted

above, none of these are sensitive or specific individually (16-19). Though radiographic criteria have been proposed by the WHO for epidemiologic studies for the diagnosis of pneumonia, no such clinical criteria exist; consequently, most studies have slightly differing case definitions. Though the single most sensitive and specific test for the diagnosis of pneumonia would probably be thoracic CT scan, this diagnostic test involves too much ionizing radiation to use on a routine basis.

1.1.3. Issues relating to the microbiologic diagnosis of pneumonia

It is even more difficult to make a bacteriologic diagnosis than a clinical one. In adults, Gram stain/culture of sputum can be useful in identifying pathogens that may not be treated adequately with typical empiric antimicrobials, as well as permitting de-escalation of broad-spectrum therapy, though the utility of this diagnostic test is balanced by the difficulties inherent in the collection, transport, processing, and interpretation of these specimens (20). Unsurprisingly, it is orders of magnitude more difficult to obtain an adequate sputum specimen from a preschooler than from an adult, essentially rendering this diagnostic test useless in young children. A positive blood culture for a typical pathogen in a child with CAP makes the microbiologic diagnosis, but this occurs so infrequently that current guidelines actively discourage venipuncture in children with mild disease, as harm probably outweighs benefit; an example of typical 'harm' would include hospitalization and initiation of intravenous antibiotic therapy prompted by a 'positive' blood culture for a contaminant pathogen (21).

Urinary pneumococcal antigen testing has been studied extensively in adults and is thought by many clinicians to be helpful in diagnosing CAP in older individuals. Sensitivity of this test was found to be 74.6% in a series of 350 immunocompetent adults with bacteraemic pneumococcal pneumonia (22) and a meta-analysis reported an overall sensitivity of 68.5% (95% credibility interval 62.6-74.2%) and specificity of 84.2% (95% credibility interval 77.5-89.3%) compared to a composite of culture tests as reference standard (23). Unfortunately, this test was found to have much less utility in children owing to high rates of positivity among controls with no significant respiratory symptoms (24,25). A more recent report showed that there might be utility in performing urinary pneumococcal antigen testing in children suspected of having pneumonia who are first found to have elevated C-reactive protein or procalcitonin, but these results can only be called very preliminary due to the small size of the study (24).

Results of different studies examining blood-based polymerase chain reaction (PCR) testing have been mixed, with most investigators finding many cases of culture-positive PCR-negative samples (24,26-28). Culture or PCR of nasopharyngeal swabs (NPS) can readily detect *S. pneumoniae*, but there is little evidence suggesting that these techniques can distinguish between active infection and colonization; the latter is common in young children (25). One group of investigators explored the utility of quantitative PCR for the diagnosis of pneumococcal CAP in human immunodeficiency virus (HIV)-positive adults aged > 18 years admitted to hospital in Soweto, South Africa (29). They defined CAP as requiring either crackles or bronchial breathing on auscultation in the presence of 2 or more of cough, dyspnoea, pleuritic chest pain, or fever, in combination with 'any new radiographic infiltrate'; in their population, a pneumococcal load of >8000 copies/mL had a sensitivity of 82% and specificity of 92% for the diagnosis of CAP. However, as for urinary pneumococcal antigen testing, this assay must be investigated in children prior to making any recommendations for its routine use in paediatrics. Additionally, it should be emphasized that pneumococcus-specific diagnostic tests will always give false-negative results for CAP cases caused by other

pathogens, such as group A *Streptococcus*; these occur much more rarely than pneumococcus-associated CAP but do occur (30).

Mycoplasma pneumoniae, an obligatory intracellular ("atypical") pathogen, is a relatively common cause of CAP in older children (31). In contrast, the role of atypical bacteria has never been well defined in young children. Canadian CAP management guidelines written in 1997 explicitly recommended treatment regimens (i.e. macrolides) for young school-aged children that were active against these pathogens (32). In contrast, newer 2011 Canadian and American guidelines strongly recommend routine usage of antimicrobials that have no activity whatsoever against atypical organisms (21,33), though there have been no recent studies showing a change in the incidence or prevalence of respiratory infection with atypical pathogens in young children. *Mycoplasma* is not considered part of the normal respiratory flora, and so its detection in the nasopharynx via PCR is somewhat suggestive of causation (31). It has been asserted that atypical pneumonia can be diagnosed on clinical and radiographic grounds (20,21); however, a recent Cochrane review found no evidence to suggest that clinical diagnosis is reliable (34), and *Mycoplasma* pneumonia has been shown to produce different radiographic patterns (35). We note that a recent systematic review found that there is "insufficient evidence to support or refute treatment of *Mycoplasma pneumoniae* in [CAP]" (36) and a recent Canadian guideline recommended against prescribing children azithromycin, the agent most often used for *Mycoplasma* treatment in adults (37).

To complicate things further, it had long been presumed that preschoolers commonly develop viral pneumonia (21); a recent large multicentre prospective cohort study verified this assumption, demonstrating that 73% of children admitted to hospital for severe pneumonia in the United States in 2011-12 had a detectable respiratory viral pathogen, compared to only 15% in whom a bacterial pathogen could be found (38). Diagnostics for viral respiratory pathogens are excellent and many centres routinely use multiplexed PCR panels that can detect almost all common important respiratory viruses in NPSs with high sensitivity and specificity (39). However, it should be emphasized that the detection of a respiratory virus in a NPS does not rule out bacterial co-infection, a phenomenon that appears to be relatively common (40). Clinically diagnosed CAP in a preschooler whose NPS is positive for a virus could indicate a primary viral pneumonia or a secondarily-infected bacterial pneumonia. Many clinicians have seen children with positive viral rapid tests who later are found to have positive blood cultures or who later develop features of severe pneumonia consistent with bacterial infection. Given the extreme difficulty in discerning between viral infection and viral and bacterial co-infection, it should not be surprising that radiographic criteria for distinguishing between viral and bacterial pneumonia have never been developed, though many clinicians would presume that a child who had an alveolar infiltrate on chest radiograph would have a bacterial pulmonary infection.

1.1.4 Ramifications of these diagnostic uncertainties

To summarize the above: there are no standardized, published, clinical criteria for the diagnosis of paediatric pneumonia, laboratory testing (such as complete blood counts and C-reactive protein measurement) is often unhelpful for the individual patient, observer interpretation of chest radiographs varies widely, and it is often difficult, if not impossible, to establish a microbiologic diagnosis. Antimicrobial treatment for typical bacteria (e.g. *S. pneumoniae*) is quite different than that for atypical pathogens, and there is no specific therapy available for viruses beside influenza; consequently, though the natural history of CAP of *any* aetiology (including pneumococcal) is to spontaneously resolve, the results of a

treatment trial may vary depending on which pathogens are infecting the study participants. There are two potential ways of dealing with this issue: create extremely stringent inclusion criteria, in the hope that the majority of participants have typical bacterial disease, or use more permissive inclusion criteria, enroll many participants, and later analyze subgroups based on the distribution of various covariates postulated to be associated with typical bacterial infection. The first strategy is best suited to individuals with severe disease, of whom the vast majority can be presumed to have bacterial infections; the second is the only way of conducting a clinical trial relevant to children without infection significant enough to warrant hospitalization.

1.1.5. Current recommendations for the duration of treatment of paediatric CAP

In August 2011, comprehensive guidelines for the diagnosis and treatment of paediatric CAP were published independently by the Infectious Disease Society of America (IDSA) (21) and by the Canadian Paediatric Society (CPS) (33). Neither could make definitive recommendations for the optimal duration of therapy due to a paucity of evidence. The IDSA guideline states "Treatment courses of 10 days have been best studied (41), but shorter courses may be just as effective, particularly for more mild disease managed on an outpatient basis." (21) The CPS guideline states (without reference) that courses of 7-10 days are "standard" for mild pneumonia (33). In contrast, in adults there is good evidence that 5 days of therapy is as effective as 7-10 days for CAP (42), and so 5 days of therapy is generally recommended (20,43). A recent survey of Canadian general paediatricians, emergency physicians, and infectious disease specialists showed that few use short courses of antimicrobials to treat paediatric CAP; 50% of all emergency department (ED)-based physicians using β-lactams treat mild pneumonia with 10 or more days of therapy (44).

1.1.6. Current antimicrobial recommendations for the treatment of paediatric CAP

One issue about which there is no debate is the choice of first-line agent for treatment – high-dose amoxicillin. This agent is preferred by both Canadian and American authorities for numerous reasons: it is superior to almost all other oral antimicrobials for the treatment of *Streptococcus pneumoniae,* it is very well tolerated, and it is inexpensive. Note that the original product monograph used in its licensure decades ago by Health Canada and the US FDA recommended a dose of 40 mg/kg/day for children. At that time, this dose was sufficient to adequately kill circulating strains of *S. pneumoniae* causing disease. Unfortunately, by the mid 1990s, increasing *S. pneumoniae* resistance had been recognized, and the potential use of high-dose amoxicillin remarked upon (45). These developments were followed by the explicit recommendation of 80-90 mg/kg/day amoxicillin dosing in guidelines for the treatment of both otitis media and CAP written by the American Academy of Pediatrics (46), the Canadian Paediatric Society (33,47), and the Infectious Disease Society of America (IDSA) (21). Today, all reputable drug reference manuals (Lexi-Comp, MicroMedex, Sanford Guide, etc.) explicitly recommend <u>only</u> 80-90 mg/kg/day amoxicillin for the management of otitis media and CAP, given the potential for treatment failure with 40 mg/kg/day dosing. We note that the monograph for generic amoxicillin included with the comprehensive electronic drug reference published by the Canadian Pharmacists Association lists 80-90 mg/kg/day as the appropriate dose for lower respiratory tract infections (48).

1.1.7 The importance of optimizing the duration of antimicrobial therapy for CAP

Despite the tremendous burden of CAP in children, the optimal duration of antimicrobial use for CAP in children is unknown, as noted above. Antimicrobial selection and duration

should be determined based on clinical evidence, in order to avoid both under- and over-treatment. Infection persistence or recrudescence could result from under-treatment, whereas over-treatment could lead to harms such as increased rates of adverse drug reactions such as anaphylaxis (49), elevated levels of antimicrobial-resistant bacteria circulating in the population (43), and higher drug costs.

1.1.8 Experience with short-course antimicrobial therapy – single trials

Few trials have compared long- (10 day) and short-course (<7 day) therapy for paediatric CAP. Peltola et al. (50) randomized hospitalized children with presumed bacterial infections to 4-day or 7-day courses of parenteral beta-lactam antimicrobials and found no difference between the two groups (short course treatment failure in 1/71, long course treatment failure in 0/50, confidence intervals not provided). Unfortunately, the majority of the study cohort was found to have either a viral infection or a syndrome of undetermined aetiology; it is not surprising that participants not suffering from bacterial infections did not have worse outcomes if they received shorter courses of antibacterials. In 1994-95, Harris et al. randomized 456 paediatric patients with CAP at 23 different US centres to either a 5-day course of azithromycin or to a 10-day regimen of either erythromycin or amoxicillin/clavulanate (51). The 5-day arm was found to have similar rates of success (5-day 94.6% success, 10-day 96.2% success, confidence intervals and noninferiority margin not provided). However, macrolides are no longer the reference standard due to the increased prevalence of macrolide-resistant pneumococci today (52-54) and, as previously noted, the CPS has advocated against the routine use of this agent (37). Moreover, because the half-life of azithromycin is 68 hours, a 5-day course of azithromycin is in effect much longer than a 5-day course of most β-lactams (half life ~ 2 hours), so inferences about the potential success rate of short-course β-lactam therapy cannot be made on the basis of this trial. It should be noted that this trial was not designed as a non-inferiority trial; outcomes in the short- and standard-length antibacterial groups were compared and no statistically significant difference was found, so the results of this trial should properly be called 'indeterminate.' A recent randomized study in Israel compared 3-, 5-, and 10-day amoxicillin therapy for community-acquired pneumonia with alveolar consolidation in preschool children aged 6 – 59 months (55). They found an increased failure rate in the 3-day group but no difference between the 5- and 10-day groups. Note that the investigators had initially estimated requiring a total sample size of over 120 but stopped the study early because they documented 0% failure rates in both 5- and 10-day treatment groups. It should be noted that the noninferiority margin was 10%, a sizable difference between standard and experimental treatments; many clinicians might not think that a short-course therapy for CAP with a potential failure rate of 10% was in fact 'equivalent' to standard therapy with a 0% failure rate. In addition, the results of this single-centre study are not necessarily generalizable to Canadian children today because the population was unvaccinated against *S. pneumoniae*, so the strains causing disease were very likely different, and the majority of participants came from a specific ethnocultural group, the Bedouin, living in the Middle East. This study also provided no information about when the participants were recruited, so it is very possible that many of the strains causing disease in this study were more susceptible to amoxicillin than those circulating today, overestimating the effects of short-course therapy. The overestimation of treatment effects in trials stopped early for benefit has also been well documented (56).

Table 1: Summary of randomized trials of short-course vs. standard-course antibacterials for paediatric bacterial infections in upper-income countries

Publication	Infection type	Experimental arm	Reference arm	Outcome	Comparison
Peltola et al. (50)	inpatients with pneumonia, sepsis, other bacterial infections with increased CRP	4 days antibiotics	7 days antibiotics	clinical recovery by end of treatment	not calculated
Harris et al. (51)	CAP	5 days azithromycin	10 days amoxicillin/ clavulanate (younger) or erythromycin (older)	clinical cure at day 15-19 post-enrolment	outcomes between groups not significant (chi-square p=0.74)
Greenberg et al. (55)	CAP	5 days amoxicillin	10 days amoxicillin	clinical cure by 30 days	ARR = 0%

1.1.9 Systematic reviews of short-course antimicrobial therapy for paediatric CAP

There are few systematic reviews in the literature. A Cochrane review (57) summarized three randomized trials of reasonable quality comparing extremely short-course (3 days) vs. short course (5 days) of antibiotic therapy for paediatric CAP in children aged 2-59 months in India (58), Pakistan (59), and Indonesia/Bangladesh (60). No differences were found in clinical cure rate (RR 0.99; 95% CI 0.97-1.01), treatment failure (RR 1.07; 95% CI 0.92-1.25), or relapse rate (RR 1.09; 95% CI 0.83-1.42). Unfortunately, a meta-analysis showing that 3 days of therapy is non-inferior to 5 days of therapy for CAP is not relevant to Canadian physicians until it is shown that 5 days is non-inferior to 7-10 days, the current standard; it should also be emphasized that patient populations and algorithms for CAP diagnosis are very different in resource-limited settings (61).

1.1.10 Antimicrobial stewardship

Optimizing antimicrobial prescribing, otherwise known as antimicrobial stewardship, has been noted to be the main strategy to deal with escalating antimicrobial resistance and has been called “a fiduciary responsibility for all healthcare institutions across the continuum of care.”(62) The Canadian Paediatric Society has said in a recent statement that “the implementation of antimicrobial stewardship initiatives…is regarded as a key step in reducing *Clostridium difficile* risk [in children].”(63) Many evidence-based guidelines published by Canadian and American authorities in the past ten years have sought to minimize the duration of systemic antimicrobials prescribed to both children and adults for the treatment of common infections such as acute otitis media (47), acute rhinosinusitis (64), acute otitis externa (65), urinary tract infections (66), and intra-abdominal infections (67). Shortening an antimicrobial course by 2-5 days may not seem like much of a difference on an individual patient basis, but when these few days are multiplied by tens of thousands of cases per year, one can begin to appreciate the potential substantial benefits to society in terms of minimizing both population drug resistance and societal health care costs.

Many physicians and laypeople are aware of the links between antimicrobials and the development of resistance; what is not as well known is the association between antibiotics and the development of obesity (68-74) and/or allergy (75,76). We note that a large prospective cohort was recently published which verified that antimicrobial therapy in infancy was associated with a statistically increased risk of obesity by the age of 2 (77). Antibiotic treatment has been observed to directly cause obesity in animal models, which appears in many cases to be mediated through effects on the intestinal microbiome (68-70). Observational data suggest that this same relationship may be present in humans, with a greater magnitude of effect seen in younger age groups, especially with repeated antimicrobial courses (72,73,78). Caregivers may be more receptive to antimicrobial stewardship initiatives to prevent a concrete harm such as obesity rather than to prevent an abstract harm such as "escalating antibiotic resistance".

1.2 Research Question

Our principal research question is: in previously healthy children diagnosed with community-acquired pneumonia in the emergency department who are well enough to be treated as outpatients, does five days of oral high-dose amoxicillin lead to non-inferior rates of clinical cure at 14-21 days post-enrolment compared with the current standard, 10 days of oral high-dose amoxicillin?

This trial will provide key information to all Ontario physicians who treat children with CAP; optimization of management of paediatric CAP will benefit the children affected, their families, and all Canadians. This trial, as the first adequately-powered study investigating the utility of short-course β-lactam therapy for paediatric CAP in upper-income countries, will have a substantial and immediate impact on paediatric medicine.

1.3 Potential Risk and Benefits

Both arms of the trial will be given high-dose amoxicillin, the standard of care for the treatment of paediatric CAP. The main theoretical risk to those in the short-course group will be relapse due to potential under-treatment, which will be minimized by maintaining close contact with all participants. As discussed above, although the CPS guideline states that 7-10 days of antibiotic therapy for paediatric CAP is 'standard' for uncomplicated pneumonia (33), the IDSA guidelines explicitly say that it is likely that shorter courses will be just as effective and that further studies are needed (21). These studies have already been done in adults, in whom the standard is now five days of therapy for uncomplicated pneumonia (42); additionally, the previously-noted study done in Israel documented no increased relapse rate in those children given 5 days of antimicrobials, though the non-inferiority margin was overly wide and the trial was stopped early for benefit (55). It is for these reasons that it is critical to conduct a study such as this, in an effort to optimize the way we care for children through evidence-based antimicrobial stewardship initiatives. Close monitoring should mitigate any of the possible risks of short-course therapy. For example, the research assistant, at the time of the first contact 3-5 days after enrollment, will ensure that the participant has defervesced; should this not be the case, the participant will be continued on a 10-day course of (open-label) amoxicillin. We will also ensure that caregivers have detailed instructions outlining which medical professionals at McMaster Children's Hospital (MCH) and the Children's Hospital of Eastern Ontario (CHEO) to contact in the event of a clinical deterioration during the study period at all hours to facilitate re-evaluation of the participant and appropriate medical management. Overall, given that

study participants will likely have much closer follow-up than non-participants, that medications will be provided free of charge, and that they will be guaranteed to receive first-line antimicrobial therapy (i.e. high-dose amoxicillin), study participants stand to directly benefit from participating in the study.

2 Study Objectives

Primary

To determine, in children diagnosed with mild community-acquired pneumonia in the paediatric ED, whether 5 days of high-dose amoxicillin leads to non-inferior rates of early clinical cure, compared to the reference standard of 10 days of high-dose amoxicillin.

Secondary

Our secondary objectives are to evaluate the following epidemiological features in children diagnosed with mild CAP in the current era of universal vaccination with the 13-valent pneumococcal vaccine (PCV13) and include:

1. To establish the distribution of saliva C-reactive protein (CRP) values in a cohort of children meeting study criteria for CAP.
2. To determine what proportion of study participants have *Streptococcus pneumoniae* high-level colonization or *Mycoplasma pneumoniae* detected in nasopharyngeal swab (NPS) specimens.
3. To determine what proportion of study participants with alveolar consolidation documented on chest radiograph have NPS specimens positive for at least one virus.
4. To investigate whether the results of (2) and (3) differ substantially when stratified by age group (6-59 months vs. 5-10 years of age).
5. To explore whether any of the above factors appear to be more common in children who do not achieve early clinical cure.
6. To determine whether there are significant differences in the intestinal microbiome of children treated with 5 days of high-dose amoxicillin as compared to 10 days of high-dose amoxicillin.

3 Eligibility Criteria

3.1 Inclusion Criteria

Children aged 6 months to 10 years presenting with CAP will be eligible. Similar to other trials (16-19), CAP will be defined if all of the **four** following numeric criteria are met:

1) fever (>37.5 C axillary, > 37.7 C oral, or >38 C rectal) recorded in the ED or at home in the 48h prior to presentation;
2) **any one of**:
    a. tachypnoea on exam (>60 bpm for age <1 y, >50 bpm for 1-2 y of age, >40 bpm for 2-4 y of age, and >30 bpm for >4 y of age);
    b. cough on exam or by history;
    c. increased work of breathing on exam; or

d. auscultatory findings (focal crackles, bronchial breathing, etc.) consistent with pneumonia;
3) infiltrates on chest radiograph consistent with bacterial CAP as judged by the ED physician; and
4) the attending ED physician diagnoses the child with primary CAP. (Children treated with systemic steroids in the ED will be presumed to have primary asthma exacerbation with possible infection and therefore will not meet inclusion criteria.)

This definition is almost identical to the 'reference standard' in a recent study designed to investigate the accuracy of ICD-9-CM billing codes (16) and very similar to those used in other clinical trials (17-19). Many other studies of pneumonia simply use clinician diagnosis as a definition (79-81); as detailed earlier, this approach is fraught with inaccuracies. The inclusion of fever as a necessary criterion will diminish the probability of recruiting participants with pertussis (which is much less likely to be associated with fever (6)) or noninfectious conditions, neither of which would be expected to respond to amoxicillin. The necessity for participants to display a respiratory symptom or sign will diminish the probability of recruiting those with infections of other organ systems who are erroneously diagnosed with pneumonia. The requirement for participants to have a chest radiograph displaying a pneumonic infiltrate will likely increase the probability that they have an infection caused by a bacterial pathogen. Finally – since the aim of this pragmatic trial is to answer a real-world question asked by emergency physicians – it is important that all study participants are actually diagnosed with CAP.

To be included, participants must be well enough to be treated as outpatients (adequate volume status, able to tolerate oral medication, oxygen saturation >90%, no evidence of impending respiratory failure); obviously, if a child is ill enough to be admitted to hospital, it would be unwise to attempt short-course therapy. Additionally eligible participants must have no evidence of empyaema or necrotizing pneumonia, as routine management of these conditions would require parenteral antibacterials (and admission to hospital).

3.2 Exclusion Criteria

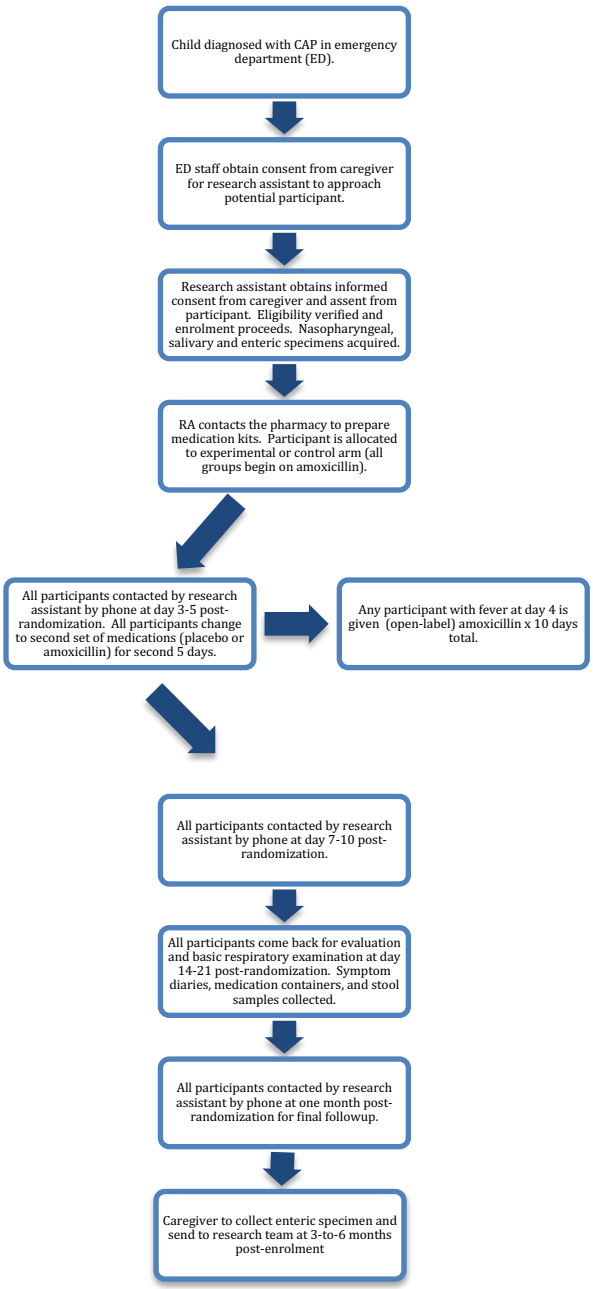
Children will be excluded if they have any of the following: cystic fibrosis, anatomic lung disease, bronchiectasis, congenital heart disease, history of repeated aspiration or velopharyngeal incompetence, malignancy, conditions requiring treatment with immune suppressants, primary immunodeficiency, advanced HIV infection, ongoing anticoagulant therapy, renal dysfunction, suspected infectious mononucleosis, prolonged admissions (>48 h) to hospital within the past 2 months, pneumonia previously diagnosed within the past month, lung abscess diagnosed within the past six months, ongoing therapy with tetracycline-type antibiotics, receipt of > 24 hours of beta-lactam antibiotic therapy already received at presentation to the ED, receipt of at least a 5 day course of amoxicillin < 72h prior to presenting to the ED, receipt of an intravenous cephalosporin or azithromycin in the ED, or suspected allergy to penicillin. Children will not be eligible to participate more than once.

4 Study Design

4.1 Description

A multicentre, randomized, controlled, double-blind, trial. Previously well children aged 6 months - 10 years presenting to the EDs of McMaster Children's Hospital (MCH) and the Children's Hospital of Eastern Ontario (CHEO) with presumed CAP will be randomized to a 10-day course of high-dose amoxicillin, or a 5-day course of amoxicillin plus 5 days placebo.

Figure 1. Study Flowchart.



As noted above, participants will be recruited and enrolled in the ED at the time of their presentation with CAP. They will then be contacted by the research assistant (RA) by telephone at days 3-5 and 7-10 post-enrolment to verify clinical stability and to investigate any possible problems. Participants will return to the hospital at day 14-21 for a basic respiratory physical examination and to permit delivery of the caregiver daily diaries and medication containers from the second five days, as well as the collection of a stool sample. A final stool sample will be collected by the child's caregiver at three-to-six months after randomization and will be returned to the research team.

The study aims to randomize 210 patients in total, 1:1 ratio to experimental (5 days amoxicillin) and control (10 days amoxicillin) arms. Treatment allocation will be assigned using a randomization scheme generated by the Pharmacy Research Support Services unit of Hamilton Health Sciences. The RA will assign a study ID after informed consent by the participant's caregiver has been granted and eligibility has been confirmed. The details of all randomization activities – the identity of the RA contacting the pharmacy, and the time and date of randomization– are recorded in the source documentation. The RA will convey the study ID code to the study pharmacist. The study pharmacist will have a master list of treatment assignment numbers and the corresponding treatment arms, which will enable them to deliver the appropriate medications to the study participant.

There are three scenarios that may lead to unblinding of treatment assignment:

1) Clinical deterioration in the patient on day 6 or later after randomization possibly consistent with worsening CAP, or
2) The occurrence of a clinically significant adverse event plausibly related to amoxicillin administration on day 6 or later after randomization.
3) Caregiver-initiated withdrawal of the participant from the study at day 6 or later up until the clinical evaluation at day 14-21 (if requested by the caregiver).

Obviously, clinical deterioration or potential drug adverse events at time points up to day 6 will not require unblinding of treatment assignment, as all participants will be on open-label amoxicillin up to this time. Clinical deterioration after day 6 may not require unblinding; for example, should a child develop new fever and oral lesions consistent with gingivostomatitis at day 7 (a not uncommon clearly viral infection), this would clearly have no association whatsoever with the study medication nor with the pre-existing respiratory infection and would not lead to unblinding or any change in the study procedures (though the event would be recorded).

When the RA is made aware of participant difficulties consistent with scenario 1 or 2, the RA will inform the local Principal Investigator (PI) or delegate who may recommend participant re-evaluation, either in the ED or in a hospital clinic where another study physician can evaluate the participant properly. If unblinding is required, this information can be provided to the physician evaluating the study participant 24 hours a day, 7 days a week following authorization by the local PI or their delegate. All of this information – the description of the clinical deterioration/possible drug adverse reaction, the treatment assignment, and the evaluation of the ED or clinic physician – will be recorded in the participant's source documents. Any study unblinding events at external sites (ie. CHEO) will be reported to the study sponsor within 24 hours. This reporting should be initiated by phone or fax with a written narrative to follow within 48 hours.

4.2 Study Endpoints

4.2.1 Primary Outcome

The primary outcome, early clinical cure, will be defined by meeting all of the following criteria:

1) significant improvement in dyspnoea and increased work of breathing, and no recorded tachypnoea, at the day 14-21 follow-up visit;
2) no more than 1 fever spike (as defined above) as a result of bacterial respiratory illness from day 4 up to and including the day 14-21 follow-up visit; and
3) lack of a requirement for additional antibacterials or admission to hospital because of persistent/progressive lower respiratory illness during the 2 weeks after enrollment.

This definition of clinical cure is similar to that used in other studies of 5-day CAP therapy in children (51) and adults (42).

Our definition was created using explicit criteria to ensure transparency and maximize the generalizability of the results. However, to optimize the appropriateness of the definition, the criteria are somewhat complex; this is to ensure that 'failure' in the trial would be associated with a clinical scenario that would merit a change in overall management, even if that change was as little as a requirement for additional follow-up by the treating clinician.

The first criterion of the definition states 'significant improvement' in respiratory symptoms; this will be assumed to be present if the participant's caregiver opines that the child has no functional limitation resulting from any residual dyspnoea/increased work of breathing. The second criterion notes that more than a single spike of fever is required for 'failure' to avoid erroneous conclusions resulting from an errant thermometer reading. Fevers of unknown aetiology will be presumed to be associated with bacterial respiratory illness, but participants with fevers due to other discernible causes, whether viral (new respiratory illness documented by a nasopharyngeal specimen positive for a virus not present at the time of initial enrolment, clinical croup, stomatitis/herpangina, hand-foot-mouth disease, gastroenteritis with positive stool results, conjunctivitis, meningoencephalitis, viral hip synovitis, peri-or myocarditis, hepatitis) or bacterial (cellulitis and other soft tissue infections, septic arthritis/osteomyelitis, meningitis, urinary tract infection with positive urinalysis, or cholecystitis) would be considered to have met clinical cure criteria. Clearly, admission to hospital – even if antimicrobial treatment does not need to be changed – is not conducive to short-course therapy and merits a decision of treatment 'failure.'

For the measurement of the primary outcome, a physician or nurse, blinded to treatment allocation, will assess temperature, respiratory rate, and evident increased work of breathing in person using standardized protocols; these physical examination findings are the most important when assessing response to therapy. Lack of fever at home will be verified through assessment of the symptom diaries. Medical visits for persistent respiratory illness will be assessed by directly asking the participant's caregiver; though caregiver report is not an entirely reliable modality, we believe that the sensitivity and specificity of the question 'Did your child see another health professional because of a concern about respiratory illness within the past ten days?' should be adequate.

4.2.2. Secondary outcomes

Secondary outcomes will include:

1) the number of days the participant is absent from school;
2) the total number of caregiver-days that their work is disrupted to care for the child;

3) the number of days of mild drug adverse reactions;
4) the incidence of severe drug adverse reactions (including anaphylaxis);
5) participant adherence to the study medications
6) recurrence of respiratory illness after the day 14-21 visit that leads to an ED visit or another antimicrobial course; and
7) development of new Antibiotic-Resistant Organism (ARO) colonization, and the degree of perturbation of the intestinal microbiome at day 14-21 post-enrolment and 3-to-6 months post-enrolment

We feel that these outcomes are important to children and their caregivers, especially for mild illness with an excellent prognosis. These will all be participant- or caregiver-report measures, and will be measured through participant documentation in the diaries; there will also be secondary verification by the research assistant at telephone contact on days 3-5 and 7-10 after enrollment. The symptom diary will include the following: temperature, dyspnoea (older participants), increased work of breathing, school attendance, caregiver absenteeism, days of mild diarrhoea, abdominal discomfort, rash) and severe (anaphylaxis) drug adverse reactions, and the number of missed medication doses. The caregivers will be instructed how to take their child's temperature and assess increased work of breathing.

5 Expected Duration of Subject Participation

Attempted recruitment will be triggered in the ED as soon as a child of the appropriate age is diagnosed by the ED MD with CAP during study hours. After consent is given for study staff to approach, the RA will explain to the caregiver and participant the nature of the trial, which will take approximately 30 minutes. If consent is granted, the participant will be provided the appropriate medications and nasopharyngeal, salivary and rectal specimens will be collected; at McMaster, nasopharyngeal swabs will have previously been collected as standard of care, but at CHEO, these will be collected after consent. The enteric specimens may be collected following the index visit and returned to the site. The caregiver will be given the study materials prior to discharge home from the ED.

The RA will phone the caregiver once at day 3-5 and once at day 7-10 to verify clinical stability of the participant. These phone calls should take less than five minutes, unless there is an issue that the caregiver wishes to discuss.

The participant will return to the hospital at day 14-21. At this visit, the RA will collect the study diaries, ask whether the participant developed new fever or required additional antimicrobials, and will have a physician or nurse perform a brief physical examination (temperature, respiratory rate, and assessment of increased work of breathing). An enteric (stool sample or rectal swab or both) sample will also be requested. This sample may be collected prior to the visit, produced at the visit, or returned to the site following the visit. The visit should take less than ten minutes.

The RA will phone the caregiver one month after enrolment. This phone call will also take less than five minutes.

Finally, caregivers will be asked to collect a final set of enteric samples for intestinal microbiome analysis and ARO colonization measurement 3-to-6 months post-enrolment.

6 Study Medication/Intervention

6.1 Study Medication Description

All study participants will begin the study receiving high-dose amoxicillin divided three times daily to be given orally for five days. Ideal dosing would be 90 mg/kg/day but the Canadian Paediatric Society guidelines indicate that 75-100 mg/kg/day is appropriate, and so doses will vary over this range within weight strata to simplify medication administration and reduce potential dosing errors. Participants will be given standard dosing based on their weight as detailed in the table below:

AMOXICILLIN STANDARDIZED DOSING *(maximum dose: 1000mg)*		
Weight range (kg)	**Amoxicillin (mg) / DOSE**	**Volume (mL) / DOSE** **based on 50mg/mL liquid*
7.5 - 10	250	5
10.1 – 13	350	7
13.1 – 15	400	8
15.1 – 17	500	10
17.1 – 20	550	11
20.1 – 25	650	13
25.1 – 30	800	16
$\geq$ 30.1	1000	20

After the first five days of amoxicillin, half of the participants will take a second five days of amoxicillin dosed identically to the first five days (using a different product with different colour). Half of the participants will be given five days of placebo (see 6.2).

Amoxicillin is probably the most-prescribed antibacterial prescribed to children in North America for a variety of infections, the most common of which are probably streptococcal pharyngitis and acute otitis media. It is generally very well tolerated by otherwise healthy children. Candidiasis been found to be more common with amoxicillin administration than with placebo in a meta-analysis (82); anecdotally, subsequent to amoxicillin prescription, many physicians have observed the occurrence of diarrhoea, abdominal discomfort, and rash (both type I hypersensitivity-mediated [i.e. urticarial] and others [e.g. morbilliform]). Anaphylaxis and other manifestations of type I mediated hypersensitivity reactions are rare but serious and so we will be actively monitoring for them.

No dose adjustments will be made. Should a study participant develop recrudescent respiratory illness they will be evaluated by a physician at the ED or an in-hospital clinic; should that physician decide that antimicrobial therapy needs to be changed, the physician will prescribe further open-label therapy. Should a study participant develop a potentially drug-related AE, the local PI will decide if that participant requires follow-up at the ED or an in-hospital clinic; if so, the physician who evaluates the study participant , as well as the local PI or delegate, will decide if the study drug requires unblinding and/or discontinuation.

6.2 Control Product Description

As noted above, half the study participants will receive a placebo medication during days 6-10 (inclusive) post-randomization. This placebo will be Ora-Plus (NDC0574-0303-16) by Perrigo distributed by Medisca, mixed with banana flavouring, and sugar. We do not expect any significant side-effects associated with placebo administration.

6.3 Formulation, Packaging, and Labeling

For Open-label Day 1 – 5 of study: Amoxicillin oral powder for reconstitution 250mg/5mL mixed berry flavoured (NOVAMOXIN® DIN #00452130) manufactured by TEVA-Canada Ltd. Study drug will be packaged by pharmacy as kits. Each kit will contain 1 bottle of 100mL of NOVAMOXIN oral powder for reconstitution 250mg/5mL and 1 x 60mL of distilled water.

Labeling of the study drug kit at the MCH site will be as follows:

```
    HAMILTON HEALTH SCIENCES - MCMASTER SITE
  1200 MAIN ST W HAM ON 905-521-2100 EXT: 73447
    SAFER STUDY  REB: 15-237 DR. J. PERNICA
PATIENT NAME:          STUDY#: 01-
DATE DISPENSED:          BOTTLE# 1
SHAKE WELL AND GIVE   MG/  ML THREE TIMES DAILY
FOR 15 DOSES THEN STOP AND TAKE FROM BOTTLE# 2
NOVAMOXIN 50 MG/ML SUSPENSION X 100 ML
EXPIRY:
SHAKE WELL AND REFRIGERATE
  *** TO BE USED BY QUALIFIED INVESTIGATOR ***
```

or

```
   HAMILTON HEALTH SCIENCES - MCMASTER SITE
 1200 MAIN ST W HAM ON 905-521-2100 EXT: 73447
   SAFER STUDY   REB: 15-237   DR. J. PERNICA
PATIENT NAME:_____ STUDY#: 01_______
DATE DISPENSED:_____ BOTTLE# 1
SHAKE WELL AND GIVE____MG/____ML THREE TIMES DAILY
FOR 15 DOSES THEN STOP AND TAKE FROM BOTTLE# 2
NOVAMOXIN 50 MG/ML SUSPENSION X 100ML
EXPIRY:_____
SHAKE WELL AND REFRIGERATE
  *** TO BE USED BY QUALIFIED INVESTIGATOR ***
  *** RETURN ANY UNUSED MEDICATION TO CLINIC ***
```

Labeling of the study drug kit at the CHEO site will be as follows:

Etude SAFER
Dr. J. Pernica REB# 15-237
(Jour 1 – 5)
KIT # xx, expiration yyyy-mm-dd
Contenu:
Teva (Novo) Amoxicillin 50mg/ml – 100mls
Directions:
Remplir le blancs sur la bouteille (le dose). Conserver au refrigerateur entre 2 et 8C.

Commenditaire: Hamilton Health Sciences McMaster Children's Hospital
1200 Main St W Ham ON 905-521-2100 x 73447
A etre utilise seulement par un Investigateur qualifie
Retourner les bouteilles a retour a l'hopital

SAFER Study
Dr. J. Pernica REB# 15-237
(Day 1 – 5 Open-Label)
KIT # xx, expiry yyyy-mm-dd
Contents:
Teva (Novo) Amoxicillin 50mg/ml – 100mls
Directions:
Complete blanks on amoxicillin bottle (dose). Store refrigerated between 2 and 8C.

Sponsor: Hamilton Health Sciences McMaster Children's Hospital
1200 Main St W Ham ON 905-521-2100 x 73447
To be used only by Qualified Investigator
Return used/unused bottles to next visit

For Double-blinded Day 6 - 10 of study:
Active arm: Amoxicillin oral powder for reconstitution 250mg/5mL (APO-AMOXI® DIN#00628158) manufactured by APOTEX, to be mixed with distilled water by the pharmacy.
Placebo arm: Ora-Plus mixed with banana flavouring and sugar.

Study drug (Active or Placebo) will be dispensed in identical amber bottles to maintain the blind. Study medication for days 6-10 will be obtained directly from the pharmacy at the McMaster site. Labels at the McMaster site will be as follows:

HAMILTON HEALTH SCIENCES - MCMASTER SITE
1200 MAIN ST W HAM ON 905-521-2100 EXT: 73447
SAFER STUDY REB: 15-237 DR. J. PERNICA
PATIENT NAME: STUDY #: 01-
DATE DISPENSED: BOTTLE# 2
START TAKING AFTER 15 DOSES FROM BOTTLE# 1
SHAKE WELL AND GIVE MG/ ML THREE TIMES DAILY
FOR 15 DOSES
APO-AMOXI 50 MG/ML SUSPENSION OR PLACEBO X 100 ML
EXPIRY:
SHAKE WELL AND REFRIGERATE
*** TO BE USED BY QUALIFIED INVESTIGATOR ***

Study kits for the double-blinded Day 6-10 medication at the CHEO site will be labeled as follows:

SAFER study
Dr. J. Pernica REB# 15-237
(Day 6 – 10 BLINDED)
KIT # xx, expiry yyyy-mm-dd
Contents:
EITHER Amoxicillin (APO-AMOXI) 50mg/ml – 100mls
OR PLACEBO liquid
For unblinding contact research team
Complete blanks on amoxicillin bottle (dose). Store refrigerated between 2 and 8C.

Hamilton Health Sciences McMaster Children's Hospital
1200 Main St W Ham ON 905-521-2100 x 73447
To be used only by Qualified Investigator
Return used/unused bottles to next visit

Etude SAFER
Dr. J. Pernica REB# 15-237
(Day 6 – 10 AVEUGLE)
KIT # xx, expiry yyyy-mm-dd
Contenu:
SOIT Amoxicillin (APO-AMOXI) 50mg/ml – 100mls
OU PLACEBO liquid
Pour retirer l'etat d'aveugle, contacter l'Investigateur
Remplir le blancs sur la bouteille (le dose). Conserver au refrigerateur entre 2 et 8C.

Hamilton Health Sciences McMaster Children's Hospital
1200 Main St W Ham ON 905-521-2100 x 73447
A etre utilise seulement par un Investigateur qualifie
Retourner les bouteilles a retour a l'hopital

6.4 Accountability Procedures and Storage

Prior to dispensing, amoxicillin, in powder form, and ORA-PLUS will be kept at room temperature in study area of pharmacy or segregated within the medication room of the ED. Daily temperature logs are kept in the pharmacy to ensure that temperature is within the 15 to 30^{o} C range. All study medications will be purchased and received by Pharmacy Research Coordinator or designate per acquisition standard procedure. Accountability logs for each study drug will be kept. Standard operating procedure for receiving, storing and accounting for clinical trial medications and supplies for Pharmacy Research Support Services will be followed to ensure compliance with good clinical practices and the applicable regulatory requirements.

After a patient consents, the RA will assign a study ID. The RA will contact the study pharmacy and communicate this code so that the study pharmacist can allocate the appropriate kit containing the appropriate study drug for day 6-10 (either amoxicillin or placebo). All participants will receive amoxicillin for the first five days post-randomization. The RA will obtain the study medications from the ED or study pharmacy and transfer to the participant's caregiver, indicating that all must be kept refrigerated at all times. At MCH, if the participant is enrolled after PReSS hours, the RA will use an after-hours open-label kit to provide medication for the first five days of the study to the caregiver and will communicate the enrolled participant's Study ID to the pharmacy and request that the 6-10 day medications be prepared for the participant. When the participant and caregiver return to the hospital for the measurement of the primary outcome at Visit 1, they will bring all medication bottles back. Residual volume will be measured and destroyed according to standard pharmacy procedure.

6.5 Subject Compliance with Study Medication/Intervention(s)

Measuring adherence in a trial setting is not a simple matter. There are direct and indirect methods of assessing adherence; of these, direct methods are much more accurate. These include directly observed therapy or measurement of drug levels in blood, both of which are impractical for a study such as this, and would likely cause substantial inconvenience and/or pain to the study participants. Indirect methods include patient (or caregiver) (self-) report; pill counts; patient diaries; electronic medication monitors; rates of prescription refills; assessment of the patient's clinical response; and measurement of physiologic markers (83).

Of these seven, we plan to use the first three, and the last four are not appropriate for the study (monitors are expensive, no refills are needed, and, in this case, neither patient assessment nor measurement of physiologic markers will inform adherence). Some investigators state that patient self-report is "simple, inexpensive, and the most useful method in the clinical setting," though they note that the results are "easily distorted by the patient"; these same authors note that pill counts are "objective, quantifiable, and easy to perform," again noting that participants can dump medication to conceal nonadherence (83). In the proposed trial, adherence with medications will be assessed from the diaries but will also be measured by checking the (returned) medication containers; any left-over medication will be weighed. Individuals who do not successfully take 75% of the prescribed medication doses will be judged to have been 'nonadherent' for the purposes of the per-protocol analysis.

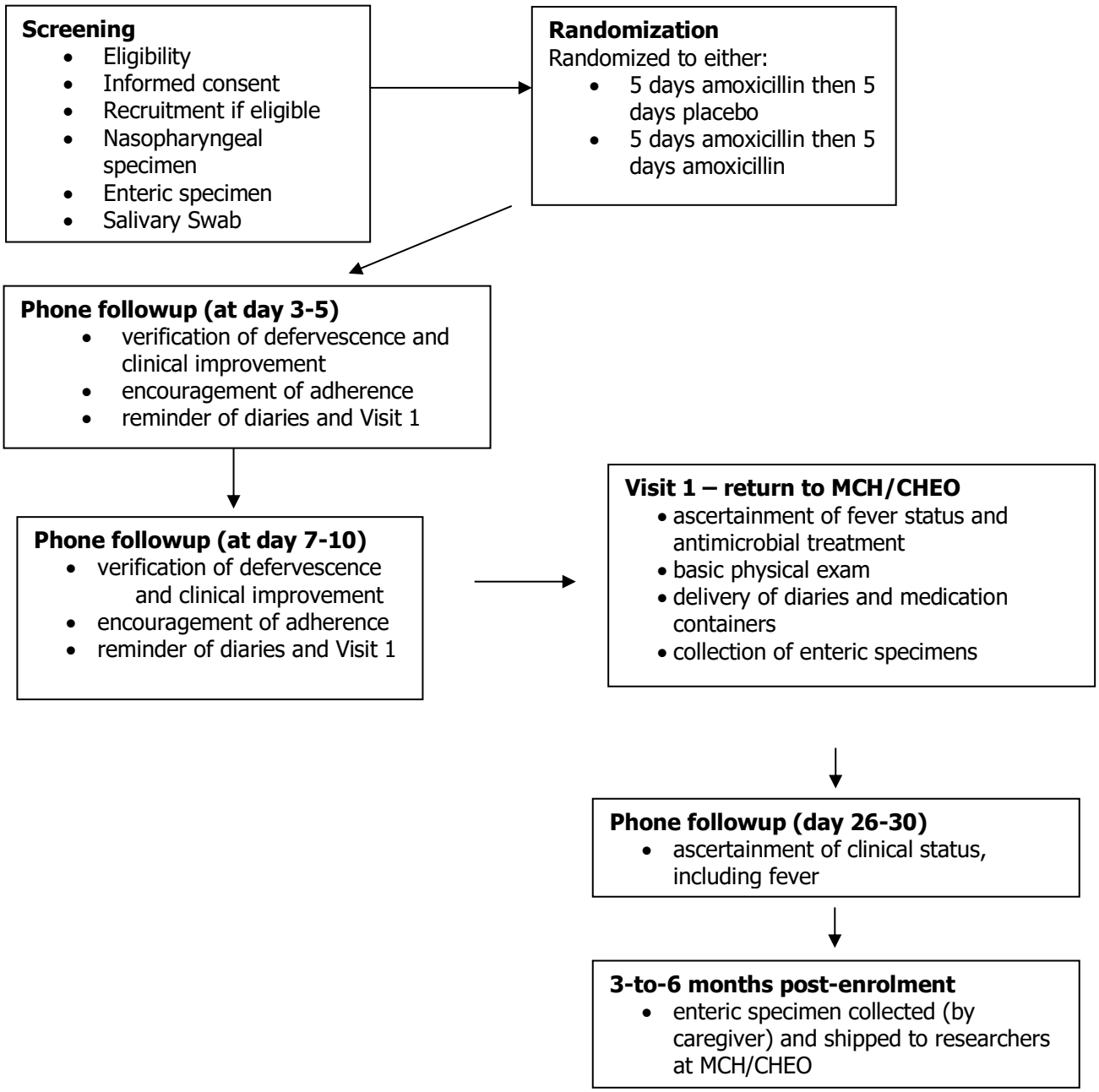
It should be emphasized that this is a pragmatic trial, and so extraordinary measures to ensure adherence would actually be counter-productive. The caregivers of the participants in this trial will be reminded far more frequently of the need to administer medications than caregivers outside of a trial scenario, via RA reminders and study diaries; consequently, lapses in adherence can be reasonably estimated to be much smaller than they would be in routine clinical care.

6.6 Concomitant Medications and Prohibited Meds

As noted in the Exclusion Criteria, children taking anticoagulants or tetracycline-type antibiotics will not be permitted to take part in the trial because of potential interactions with amoxicillin.

7 Study Procedures/Evaluations

7.1 Schematic of Study Design



7.2 Screening, Baseline Visit, and Randomization

Education will be provided to ED staff (MDs, RNs, trainees) to inform them of the rationale and objectives of the study. These ED staff will then notify the RAs when a child is diagnosed with CAP; at CHEO, an organized network of volunteers will also participate in

ED surveillance. Gift cards ($5) will be given to ED healthcare providers that notify study staff of potential study participants in order to incentivize notification; this strategy has worked well in the pilot at McMaster. The RAs will proceed to the ED to attempt to recruit the participant where informed consent (and assent for participants aged > 7 y) will take place. Contact with the potential participant will occur soon (i.e. less than 60 minutes) after the diagnosis of CAP is made by the ED physician. At MCH, if a potential participant is diagnosed at a time where an RA is not available, ED staff will obtain consent to approach and the RA will contact the caregiver within 24 hours of ED discharge to attempt to recruit and enroll the participant.

For those participants for whom consent is provided, eligibility will be verified using the Screening Form, basic demographics (age and gender) will be recorded, and triage respiratory rate and weight will be abstracted from the patient chart. This form will take approximately five minutes to complete. At MCH, it is standard of care for all children diagnosed with CAP to have nasopharyngeal sampling to detect respiratory viruses, so this will have been done prior to enrolment. At CHEO, some participants may not have had this performed, so consent to collect this specimen will be requested and collection [by a registered nurse (RN)] for those who consent will commence after the Enrolment Form is completed. Finally, consent will be sought to collect enteric specimens (either rectal swab or bulk stool sample or both), which will be done by the RA, RN or the caregiver (following the RA or RN's direction). Enteric samples will be requested to establish baseline intestinal microbiome composition and to assess colonization with antibiotic resistant organisms (AROs), namely ampicillin-resistant E. coli and enterobacteriaceae with extended-spectrum beta-lactamase (ESBL) production. Enteric samples can be collected up to 24 hours post-visit, as necessary.. If blood work was ordered previously by the attending ED MD, the results will be noted (and C-reactive protein will be added on, if possible) but no additional blood draws will occur as part of the study activities. For those participants who did not have serum CRP measured, an optional salivary sample will be requested for salivary C-reactive protein measurement; this is accomplished using a small sponge (Salimetrics Children's Sponge) placed in the buccal mucosa or beneath the tongue (for 60-90 seconds) and is not invasive. At MCH, nasopharyngeal specimens will be processed by the virology laboratory as part of routine care. These will be tested for the following:

1. 11 different respiratory viral pathogens (influenza A, influenza B, RSV A/B, parainfluenza virus I-III, rhinovirus, enterovirus, adenovirus, and human metapneumovirus) using the multiplex PCR platform in clinical use at McMaster
2. 3 different atypical respiratory pathogens (*Legionella pneumophila, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae*) using a multiplex LAMP platform, and
3. *S. pneumoniae* incidence density using a *lytA* target.

At MCH, nasopharyngeal, rectal swab specimens, and saliva specimens will be stored in Dr. Smieja's laboratory. At CHEO, nasopharyngeal and enteric specimens as well as saliva samples will be stored in Dr. Slinger's laboratory. All CHEO nasopharyngeal and enteric specimens will be sent to Hamilton for testing at McMaster at the end of the study. All salivary specimens will be processed by Kim Hall in the McMaster Clinical Trials Laboratory.

Participants judged to be eligible to continue will be assigned a study ID. Randomization of the participants will be completed using a randomization scheme generated by the study pharmacy at McMaster University and will pre-assign kit contents to a given Study ID. The RA will notify the study pharmacy at MCH or CHEO, and will communicate the Study ID to

the pharmacist, at which point the appropriate medications will be prepared. If a participant is enrolled outside of PReSS operational hours at MCH, the RA will dispense an open-label after-hours kit to the caregiver and contact the pharmacy with the Study ID so that the blinded kit of medication can be prepared and provided to the caregiver at a later date (prior to Day 6). All participants will be given an initial 5 days of amoxicillin to begin. For potential participants at the McMaster site who present at a time when an RA is not available, the attending ED physician will prescribe amoxicillin at the study dose (i.e. the standard of care) and obtain consent for subsequent RA contact and potential enrolment within 24 hours after ED discharge. Recruitment at CHEO will only proceed between 10 am and 10 pm daily.

The process of contacting the participant, completing informed consent, filling out the Enrolment Form, randomization, and providing study medications will take less than 45 minutes. For those participants at CHEO who did not have a nasopharyngeal specimen acquired as part of routine clinical care, this will take an additional five minutes.

7.3 Phone call 1

The RA will call the caregiver at day 3-5 post randomization. The RA will inquire as to whether the participant's fever has continued and/or there has been any worsening of the child's condition that worries the caregiver (see Followup Call form). Any child with ongoing fever or worsening respiratory symptoms will not be eligible to transition to the second series of medications (either 5 days of placebo or 5 days of amoxicillin, depending on treatment assignment) and will be given a further five days of open-label amoxicillin. The RA will investigate whether the caregiver has had any problems filling out the patient diary and will encourage adherence to the study medications. Any caregiver worries will be explored by the RA and will be conveyed to the local study PI. The local PI will determine whether children with ongoing fever or new/worsening symptoms will require an impromptu visit to either the ED or a hospital clinic.

This phone call will take less than five minutes, unless there is a particular caregiver concern that needs to be explored more thoroughly.

7.4 Phone call 2

The RA will call the caregiver at day 7-10 post randomization. The RA will inquire as to whether the participant's fever has returned and/or there has been any worsening of the child's condition that worries the caregiver (see Followup Call form). Any child with more than a single spike of recurrent fever, worsening respiratory symptoms, or new symptoms not previously present will require an additional visit to either the ED or a hospital clinic, where a more thorough evaluation can take place by a physician. The local PI will liaise with the physician doing this evaluation and determine whether unblinding and/or study withdrawal is required. For example, a child who developed a generalized urticarial rash at day 7 would absolutely require unblinding and study withdrawal, whereas a child who developed fever and a large Methicillin-resistant Staphylococcus aureus (MRSA) abscess requiring incision and debridement at day 7 would not require unblinding nor study withdrawal; the difference in these two vignettes is that it is quite plausible in the former that the amoxicillin was responsible for the event, while in the latter there is clearly no plausible association between the two clinical scenarios.

The RA will also investigate whether the caregiver has had any problems filling out the patient diary and will encourage adherence to the study medications. Any caregiver worries

will be explored by the RA and will be conveyed to the local study PI to determine if an impromptu visit needs to be made to either the ED or a hospital clinic.

This phone call will take less than five minutes, unless there is a particular caregiver concern that needs to be explored more thoroughly.

7.5 Visit 1

The participant and caregiver will return to the hospital at day 14-21. At this time, the RA will complete the Primary Outcome Assessment form. This involves asking the caregiver if the child had any further episodes of fever, was prescribed any additional antimicrobials by any provider, and doing a basic physical exam of the child. The exam will be completed by a nurse or a physician in either the ED or a hospital clinic and will include a temperature reading, a respiratory rate, and a visual inspection of the child's work of breathing. This assessment should take 5-10 minutes.

At this visit, participants will also deliver symptom diaries and medication containers. A further enteric specimen for intestinal microbiome analysis and ARO colonization measurement will be requested. Enteric samples from this visit can be collected up to 24 hours pre- or post-visit, if necessary.

7.6 Phone call 3

The RA will call the caregiver at one month post-randomization. The RA will inquire as to whether the participant had additional episodes of fever, was prescribed additional antibiotics, or had recrudescence of pneumonia symptoms subsequent to the primary outcome assessment at Visit 1. The RA will also remind caregivers who have consented to enteric specimen collection to submit an optional enteric sample at 3-to-6 months post-enrollment. This phone call should take no more than five minutes, though this will vary depending on how many questions the caregiver has.

7.7 Caregiver-initiated withdrawal

Caregivers are free to withdraw their consent for their child's participation at any time during this clinical trial, with or without a stated reason. Caregivers will be provided contact information for the RA and local PI to facilitate withdrawal procedures. At the time of withdrawal, the RA and/or local PI will offer participant clinical review at MCH or CHEO and solicit a history of adverse events but will not insist on this. Participants who withdraw will be offered open-label high-dose amoxicillin for all days remaining until the tenth day post-recruitment. Caregivers who wish their child to cease taking the blinded study medication (on day 6-10 post-recruitment) and switch to open-label amoxicillin for the remainder of the 10 days post-recruitment but who would like their child to still be evaluated clinically (Visit 1, at day 14-21) will be given that option; the participant will thus remain in the study and be eligible for the intention-to-treat analysis but the protocol violation will be noted (and therefore the participant will not be eligible for the per-protocol analysis).

8 Statistical Plan

8.1 Sample Size Determination

We estimate the baseline failure rate of standard therapy to be ~5%; this estimate is consistent with previous studies in children (51), is less than that found in similar adult studies (42), and was the approximate rate seen in the pilot study. We will use a noninferiority margin of an additional 7.5%. As this is a non-inferiority trial, the crucial statistical comparison will be between the 97.5% (one-sided) CI of the difference between the failure rate of the experimental arm and the standard therapy arm; should the upper bound of this difference be smaller than 7.5%, a conclusion of non-inferiority will be reached. As the maximum baseline failure rate in the reference arm is probably 5%, the maximum failure rate in the experimental arm that would still be felt to be 'non-inferior' would be 12.5%; the margin of 7.5% was selected to make the maximum failure rate in the experimental arm less than 13.5%, the median acceptable failure rate in treatment of community-acquired pneumonia found in a 2008 survey of infectious disease physicians (84). Setting α at 5%, with 80% power, 135 participants in each arm will be required for this trial (PASS software package, NCSS LLC, Kayesville, UT); as we will have accrued ~ 60 subjects in the pilot to be 'rolled-over', an additional 210 participants will be required.

The pilot had very low rates of loss to follow-up (2/61, 3%) presumably due to the acute nature of the problem and the fact that many caregivers appreciate the clinical service provided. We anticipate enrolling ~60 participants per year at McMaster Children's Hospital, based on the pilot results. As CHEO has many more children presenting to their ED, we predict conservatively that we will be able to enroll at least 75 per year at that site. All estimates below are based on data from CHEO ED census Mar 2011 – Apr 2013.

Children (aged 6 mos. – 10 y) with CAP to CHEO ED:	1442/year
As above, restricted to those arriving 10 am – 10 pm:	986/year
Projected enrolment with MCH ineligibility/success rates:	124/year

Detailed review of 50 randomly selected charts of children aged 6 months – 10 years diagnosed with CAP at the CHEO ED in 2013 demonstrated that 22 (44%) met all inclusion and exclusion criteria. Assuming McMaster rates of missing/refusal of approach/refusal of consent, estimated enrolment would be 986*0.44*(55/(55+56+38+9)) = 151 participants/year.

Overall, it is very likely that we will be able to recruit 50-75 participants/year at McMaster Children's and 75-100 participants/year at the Children's Hospital of Eastern Ontario.

8.2 Statistical Methods

We will adopt CONSORT criteria in reporting the trial. The principal analysis will be per-protocol, as is recommended for noninferiority trials (85-87). The principal analysis is not intention-to-treat (ITT) simply because the effect of ITT analysis is to reduce the difference seen between treatment groups; in a superiority trial, this functions to buttress a conclusion of superiority, but in a non-inferiority trial, ITT analysis could lead to a false conclusion of non-inferiority by masking a true difference between treatment arms.

The baseline characteristics will be analyzed using descriptive statistics reported as mean (standard deviation) or median (first quartile, third quartile) for continuous variables depending on the distribution and count (percent) for categorical variables. As the primary outcome is binary, the chi-square test will be used; secondary outcomes will be analysed using chi-square or t-test depending on the distribution of the outcome variable. As this is a non-inferiority trial, the crucial statistical comparison will be between the 95%CI of the difference between the failure rate of the experimental arm and the standard therapy arm; should the upper bound of this difference be smaller than 7.5%, a conclusion of non-inferiority will be reached. Descriptive analyses will be used to compare rates of viral and atypical co-infections in the entire study population and between groups, stratified by age. We will use the t-test or chi-squared test to analyze secondary outcomes as appropriate (former for continuous variables, latter for dichotomous variables). These analyses will be exploratory. The following sensitivity analyses are planned: 1) intention-to-treat analysis; 2) strict per-protocol analysis including only those participants adherent to their medications and whose radiographs were reported by a radiologist to have alveolar infiltrates; 3) per-protocol analysis stratified by whether the saliva CRP was greater than the 75%ile; and 4) per-protocol analysis stratified by whether a virus, an atypical pathogen, or high-level *S. pneumoniae* colonization was found in the NPS. If evidence is found of effect modification or confounding related to the above parameters additional analyses will be undertaken. The results of all analyses will be reported as estimate of effect, corresponding 95% confidence interval and associated p-values. All p-values will be reported to three decimal places with those less than 0.001 reported as $p<0.001$. The criterion for statistical significance will be set at alpha = 0.05.

8.3 Interim Analyses

The Data Safety Monitoring Board (DSMB) will oversee a single interim analysis of the study data halfway through enrollment (i.e. after 100 participants have been enrolled). Rates of early clinical failure (the primary outcome) will be calculated for each arm of the study and the study will be prematurely terminated if the proportion of treatment failures in the experimental arm is statistically significantly greater ($p<0.0001$) than 7.5% *more* than the proportion of treatment failures in the control arm. Should one of the arms of the trial be found to be this much greater than the other, the DSMB will order unblinding, and should the increased failure rate be in the control arm, the trial will continue, as this would certainly be due to chance. The trial will not be stopped early for benefit simply because trials stopped early for benefit have been shown to consistently overestimate treatment effects (56), and, if short-course therapy is truly non-inferior to standard therapy, participants in the trial would be at overall decreased risk compared with non-participants due to the surveillance measures built into the trial.

8.4 Role of the Data Safety Monitoring Board

The DSMB, comprised of two clinical experts and a biostatistician, guided by a charter to be created, will be responsible for safety oversight of the study, including monitoring of adverse reactions. The DSMB will be responsible for making recommendations on safety issues, premature trial termination, and unblinding of study groups. The DSMB, which will be blinded to study group, will compare rates of early clinical failure in treatment arms once, halfway through enrollment (see section 8.3 above). Additionally, the DSMB will review

safety data on a biannual basis for each arm of the study; specific items that will be monitored include:

1. the number of participants in each arm that clinically worsen on or after day 6 post-recruitment and require a change in antimicrobial therapy
2. the number of participants in each arm that develop a serious adverse event (SAE)
3. the number of participants in each arm that clinically worsen after the primary outcome measurement and require institution of antimicrobial therapy

If safety concerns arise, more frequent meetings will be initiated, and the trial may be terminated. The DSMB will receive immediate notification and reports of serious adverse reactions.

9 Safety and Adverse Events

The investigators will report adverse events (AEs) as per standard procedure of the Hamilton Integrated Research Ethics Board (REB), the CHEO REB, and Health Canada.

9.1 Definitions

Adverse Event (AE)

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. An AE can therefore be any new, or worsening of an existing, unfavorable and unintended sign, symptom, laboratory finding outside of normal range with associated clinical symptoms or suspected latent clinical symptoms in the opinion of the investigator, physical examination finding, or disease temporally associated with the use of the study drug, whether or not the event is considered related to the study drug. Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned). Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Pre-intervention Event (PAE)

A pre-intervention event is any AE that occurs subsequent to randomization and prior to starting the day 6-10 medication series, i.e. while on the first five days of high-dose amoxicillin (the reference standard for the treatment of paediatric CAP).

Serious Adverse Event (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is defined in GCP guidelines (88) as “any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity."

Important medical events are AEs that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

The term severe is used to describe the intensity of a specific event (as in mild, moderate, or severe); the event itself, however, may be of minor medical significance (such as severe headache). This is not the same as serious, which is based on outcome of the event, as described above. Seriousness, not intensity, serves as a guide for defining regulatory reporting obligations.

9.2 Assigning Attribution of Adverse Events

The investigator **must** attempt to determine the cause of each event. To ensure consistency of AE/SAE causality assessments, the following guideline will be applied:

Related: There is an association between the event and *either* the administration of amoxicillin or its premature discontinuation, a plausible mechanism for the event to be related to the amoxicillin or its premature discontinuation, and causes other than the investigational study drug have been ruled out.

Possibly Related: There is an association between the event and *either* the administration of amoxicillin or its premature discontinuation, and there is a plausible mechanism for the event to be related to the amoxicillin or its premature discontinuation, but there may also be an alternative etiology, such as an intercurrent illness.

Unlikely Related:

The event is related to an etiology other than amoxicillin or its premature discontinuation (the alternative etiology must be documented in the study subject's medical record) and/or there is no plausible mechanism for the event to be caused by amoxicillin or its premature discontinuation.

Though we do not expect any adverse events related to the only other study procedure – nasopharyngeal and/or rectal specimen acquisition – should an AE be thought to be 'related' or 'possibly related' to these study activities, this will be documented in the participant's record.

9.3 Documentation, Monitoring, and Reporting of Adverse Events

Specific adverse events that have a higher likelihood of being caused by amoxicillin administration include rash, diarrhoea, candidiasis, and anaphylaxis. Nausea and vomiting are commonly reported in association with amoxicillin use, though a recent meta-analysis did not find their occurrence to be any more common with amoxicillin use as compared to placebo (82). As rash, diarrhoea, nausea, and vomiting can also be caused by intercurrent infection, each participant reporting an AE will have to have their case reviewed by an investigator. Parents will be informed that any development of anaphylaxis requires immediate evaluation at the appropriate ED; should this happen while the participant is

taking the second set of medications or shortly thereafter (i.e. day 6 to day 14) the participant's treatment assignment will be unblinded if deemed necessary per the attending physician and local PI/delegate. Anaphylaxis that occurs more than 24 hours after cessation of amoxicillin (or placebo) is highly unlikely to be related to that product.

We note that adverse events associated with antimicrobials are likely to be fewer in study participants than in children whose caregivers do not agree to participate in the study; furthermore, the AEs that occur are likely to be handled more promptly. This is because the study drug we are using is the standard of care for paediatric CAP and the entire aim of the study is to verify that shorter courses of amoxicillin are non-inferior to amoxicillin given for the standard longer duration. As noted previously, we will be actively seeking out drug AEs during the phone calls at day 3-5 and 7-10 and will be asking parents to fill out a daily symptom diary where potential AEs will be asked about.

Specific adverse events that have a higher likelihood of being caused by short durations of antimicrobials for CAP include recrudescence of CAP and symptoms associated with this, including fever, cough, difficulty breathing, tachypnoea, abdominal pain, and malaise. Having said that, it is also not uncommon for children to experience these symptoms when contracting a new (intercurrent) respiratory viral infection. We will be actively seeking evidence of potentially recrudescent infection when contacting caregivers at day 3-5 and day 7-10; additionally, we will ask caregivers to contact us if these symptoms develop. Any participant with new or worsening respiratory symptoms will be asked to come back to hospital for evaluation at the ED or an in-hospital clinic by a physician; should this physician feel that the participant might have inadequately treated bacterial CAP, and the PI concurs that unblinding will be beneficial to patient management, the participant's treatment assignment will be unblinded.

We do not expect any AEs associated with study-related specimen collection. Nasopharyngeal swabs are done routinely at MCH as part of the work-up of children judged to have CAP given that the majority of these infections, especially in children younger than 6, are caused by viruses. Nasopharyngeal aspirates may not always be done at CHEO as part of the routine work-up for CAP by the attending ED MD but are extremely low-risk procedures and are routinely done at CHEO for all children with a respiratory syndrome (pneumonia, bronchiolitis, whooping cough, etc.) admitted to hospital. Rectal swabs are similarly very low-risk interventions; the procedure for obtaining a rectal specimen is similar to that involved in taking a rectal temperature (the reference standard for temperature measurement in young children); however, obtaining a rectal swab specimen takes much less time than rectal temperature measurement. As part of our gastroenteritis research, we have now obtained rectal swabs on over one thousand preschoolers with no adverse reactions to date; we note as well that rectal swabs are routinely acquired from all inpatients (children and adults) at Hamilton Health Sciences hospitals for the determination of colonization status with MRSA or other antibiotic-resistant organisms. Any AE that occurs between the times a study participant signs the informed consent form and the time s/he departs the study at the end of the final follow-up visit (or at the time of early discontinuation of the subject from the study for any reason) will be captured and recorded. AEs will be described as 'preintervention', 'related', and 'serious' as applicable, but all will be recorded. AEs that are diagnosed by a physician as a particular syndrome (e.g. 'cellulitis') will have that diagnosis recorded.

All SAEs that are both unexpected and related to the study product will be reported to Health Canada, and those related to the study product or procedures will be reported to the appropriate REB as soon as possible, but no later than 15 calendar days (7 days if fatal or

life-threatening) after first knowledge of the event. Further information and significant new information on ongoing reported serious adverse events will be provided to the sponsor, the REB and Health Canada, as applicable. Copies of all information about the SAE will be kept in the Regulatory binder.

All caregivers will be asked to complete a Symptom Diary form each day post-randomization until the tenth post-randomization day; on this form, clinical features of persistent or worsening respiratory disease will be asked about (e.g. fever, difficulty breathing, overall clinical status) in addition to common (e.g. diarrhoea) and serious (e.g. anaphylaxis) AEs known to be associated with amoxicillin administration. In addition, the RA will specifically ask about symptoms and signs consistent with respiratory deterioration or amoxicillin-associated AEs. This will also be done at the time of Visit 1, when the participants return to be clinically evaluated at day 14-21 post-randomization.

The SAE most likely to occur is hospitalization in the first few days post-recruitment due to worsening respiratory status. Though the majority of children with mild CAP do well on oral antimicrobials, a small percentage will worsen and require admission to hospital because of progressive oxygenation failure and/or the need for operative drainage of pleural-based collections. These AEs would be classified as pre-intervention SAEs; these SAEs would not be related to any trial procedures, as all study participants will be receiving the first-line antimicrobial of choice (high-dose amoxicillin) for the first five days post-enrolment. (They will, of course, be reported as any other SAE.) We note that the risk of harm to trial participants will likely be less than those of non-participants, because study staff will be contacting all study participants at intervals to verify clinical stability. As detailed above, the RAs will contact all study participants once at day 3-5 post-recruitment and once at day 7-10 post-recruitment and will be actively questioned about symptoms indicative of worsening respiratory status. Furthermore, all participants that are persistently febrile at day 4 post-recruitment will complete 10 days of open-label high-dose amoxicillin.

9.4 Adverse Event Follow-up

The follow-up plan for AEs in this trial has been designed with the following important points in mind: first, that amoxicillin given at 90 mg/kg/day, though technically 'off-label', is the standard of care for children with community-acquired pneumonia, and second, that the 'experimental' arm in this trial involves using a shorter course of amoxicillin than the standard, which could logically never increase the rate of drug-related adverse events. We will outline various scenarios that may occur and the follow-up plan associated with those.

1. Clinical worsening of respiratory-type symptoms in the first five days post-randomization felt to be progression of CAP

Should the RA discover that the participant's symptoms appear to be worsening, they will recommend going back to the local ED for re-evaluation and/or report this to the local PI or delegate, who may recommend going back to the local ED. Should this be confirmed by the attending physician, they may change the antimicrobial regimen or recommend hospitalization for intravenous antimicrobials. This participant will be judged to not have achieved 'early clinical cure' (i.e. treatment failure) and Health Canada will be informed of the SAE if hospitalization is required. The plan for official clinical follow-up will be made by the attending ED physician or the inpatient most-responsible paediatrician, as per routine

clinical care. Of course, the participant's caregiver will be offered the choice of continuing with the regularly scheduled follow-up study phone calls and visits, should they wish to do so. Should the RA discover that the participant has ongoing fever, but the caregiver feels the child is improving, the RA will contact the PI or delegate for additional guidance and potential further follow-up with the caregiver. The participant will need to be moved to open-label amoxicillin, but the PI or delegate can decide on whether the participant needs to be re-assessed in the ED or in the ID clinic.

2. Clinical worsening of respiratory-type symptoms on day 6 or later post-randomization up until Visit 1 (day 14-21) felt to be progression of CAP

Should the RA discover that the participant's symptoms appear to be worsening, or if the participant develops recurrent fever that might be associated with pneumonia, they will notify the local PI or designate who may recommend going back to the local ED or ID clinic for re-evaluation. Should the attending physician feel that the participant's clinical status is in fact in line with worsening CAP, they may change the antimicrobial regimen or recommend hospitalization for intravenous antimicrobials. This participant will be judged to not have achieved 'early clinical cure' (i.e. treatment failure) and Health Canada will be informed of the SAE as required. The plan for official clinical follow-up will be made by the attending ED physician or the inpatient most-responsible paediatrician, as per routine clinical care. Should the attending ED physician or the inpatient most-responsible paediatrician be unsure of the most appropriate course of action, they will be offered the opportunity to consult with a paediatric infectious disease specialist (Dr. Pernica at MCH, Dr. Slinger at CHEO) either over the phone or in clinic; if this occurs, appropriate followup with the Paediatric Infectious Disease service will be arranged, as per routine clinical care. Of course, the participant's caregiver will be offered the choice of continuing with the regularly scheduled follow-up study phone calls and visits, should they wish to do so.

3. Ongoing fever or respiratory-type symptoms found at the clinical assessment at Visit 1 (day 14-21)

In the event that physical examination is not normal, the RA will notify the local PI or designate, who will decide if additional clinical followup in ID clinic or ED is required. The clinician doing the physical examination will use their clinical judgment to determine if the participant is unwell enough to require assessment from a physician before going home. If the participant does indeed require urgent assessment, the clinician will either page the on-call Infectious Diseases physician or recommend going to the ED.

4. Clinical worsening of respiratory-type symptoms after Visit 1 (day 14-21) felt to be new/worsening CAP

The only scheduled followup after Visit 1 is the phone followup at approximately one month after enrolment. Should the RA discover that the caregiver is concerned with respiratory symptoms at that point – or should the caregiver contact the RA before or after then – the RA will notify the local PI or designate who may recommend followup either at the local ED (for caregivers that are concerned about their child being acutely unwell) or with the child's family physician. Development of new/worsening respiratory symptoms more than two weeks subsequent to the discontinuation of antimicrobials (even in children who might only have received five days of amoxicillin) are unlikely to be caused by a recrudescence of the initial bacterial illness, given the natural history of CAP in children (not to mention the fact that the majority of these episodes are caused by viral pathogens). The RA will contact the

caregiver after the planned physician visit and repeatedly until the caregiver thinks the child's respiratory status has stabilized; should the child's status worsen, the RA will recommend further followup by the child's family physician or in the ED. Should the child require hospitalization, this SAE will be noted and Health Canada notified as required.

5. Development of symptoms possibly representing adverse amoxicillin reactions up until Visit 1

Should the RA discover that the child has developed symptoms suggestive of a severe generalized allergic reaction (facial swelling, wheezing/difficulty breathing, itchy red wheals, severe vomiting immediately after medication administration, etc.) at the time of one of the phone visits – or if they are contacted by the caregiver independently about these types of symptoms – they will recommend immediate ED evaluation and inform the PI immediately. (Note that caregivers will be educated re: signs and symptoms of generalized severe allergic reactions at recruitment and will be told to seek medical assistance immediately should this occur.) The RA or study nurse will contact the caregiver again after this visit; should the diagnosis of generalized allergic reaction have been given, the SAE will be noted and Health Canada notified. The management of a participant subsequent to a severe allergic reaction judged to be secondary to amoxicillin will be entirely at the discretion of the ED physician that assesses the participant. Of course, the participant's caregiver will be offered the choice of continuing with the regularly scheduled follow-up study phone calls and visits, should they wish to do so.

If this type of reaction (potentially severe generalized allergic reaction) occurs on day 6-11 post-randomization, the study medication will be halted, and presumably the ED physician will prescribe an antibiotic of an alternate class to finish CAP therapy (though this is not mandatory). The SAE will be noted and Health Canada notified as required. If this occurs on day 12 or later, it is unlikely to be related to the study medication (type I hypersensitivity reactions typically occur within 4 hours and almost never occur more than 24 hours after administration of the offending agent). In either of these scenarios, unblinding of treatment assignment will be done after measurement of the primary outcome at Visit 1, as earlier unblinding would not lead to any change in patient management in this time period. Of course, the participant's caregiver will be offered the choice of continuing with the regularly scheduled follow-up study phone calls and visits, should they wish to do so.

Should the RA discover that the child has developed symptoms potentially related to amoxicillin (rash, diarrhoea, abdominal pain, etc.) they will liaise with the local PI or designate, who will decide whether the participant needs to be re-assessed clinically, and if so, in the ID clinic or in the ED. If the participant requires assessment, and if the reaction is found to be severe and likely related to amoxicillin administration, the plan for follow-up will be similar to that noted above for acute severe generalized allergic reactions, though non-anaphylaxis drug reactions are not likely to be categorized as SAEs and so Health Canada will not be notified.

If the local PI or designate feels that the symptoms may be related to amoxicillin, but are not serious or severe, they will make a clinical decision as to whether study medication requires discontinuation or not. (Mild tolerable diarrhoea is an example of a very common symptom caused by amoxicillin that would not be an indication for a change. Participants with mild symptomatology not requiring discontinuation of study medications will continue with the regular schedule of follow-up and the AE will be noted. Mild drug reactions should resolve after completion of the course of therapy; this will be verified by the RA at Visit 1

and at the 1-month telephone followup and this information will be relayed to the local PI or designate who will make the clinical decision as to whether further followup is required (and by whom).

6. Development of symptoms possibly representing adverse amoxicillin reactions after Visit 1

Should the caregiver report the development of symptoms concerning to the caregiver after visit 1, the RA will notify the local PI or designate to determine what sort of clinical followup is required, if any. Note that symptoms that develop in this time interval are unlikely to be related to amoxicillin, though it is possible for delayed reactions to present within this timeframe. The management plan for the symptomatology will be as directed by the clinician who assesses the participant. If it is judged that the symptoms are an AE related to study medications or procedures, the local PI or designate will follow up with the participant routinely either by telephone or in clinic until the AE resolves or has stabilized in the opinion of a physician following the child. If a SAE develops, it will be reported to Health Canada as soon as possible, if the SAE is unexpected and related to study drug.

7. Development of other symptoms or AEs

Should the participant develop symptoms that are not likely to be those associated with amoxicillin treatment and/or do not appear to be indicative of worsening respiratory status, the RA will notify the local PI or designate, who may recommend followup with the family physician or the ED. The RA will also facilitate unblinding of treatment assignment if this is requested by the attending physician in order to optimize clinical care and will contact the caregiver by phone subsequent to the MD assessment. Should the symptom/AE not be thought to be related to the participant's underlying CAP or amoxicillin therapy, in the opinion of the attending MD and the local PI or designate, study followups will continue as planned; should the AE not have resolved or stabilized by the time of the one-month followup, the local PI or designate will continue to follow-up with the caregiver until that time. Should the symptom/AE be a manifestation of worsening respiratory illness, or thought to be related to amoxicillin, followup will proceed as described earlier.

9.5 Treatment Discontinuation

The criteria for permanent discontinuation of further study product/interventions for an individual subject are as follows:

- Failure to defervesce by day 4 post-enrolment (see section 7)
- Requirement for hospitalization because of worsening respiratory illness
- Severe reaction potentially associated with amoxicillin such as a generalized allergic reaction (urticarial rash, bronchospasm, angioedema, hypotension, etc.) (see 9.3 and 9.4)
- Requirement for prohibited concomitant medications
- Completion of treatment/intervention as defined by the protocol

- Clinical reasons believed to be life-threatening by the physician, even if not addressed in the toxicity section of the protocol

The subject will continue to be followed with the subject's permission if the study treatment/intervention is discontinued. There will be no changes to the follow-up visit schedule, and the data/specimens collected at the time of those visits, except no study treatment/intervention will be administered.

9.6 Premature Study Discontinuation for an Individual Subject

The criteria for permanent discontinuation from the study for an individual subject are as follows:

- Request of the subject to withdraw from the trial
- Any clinical adverse event, laboratory abnormality, intercurrent illness, other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The subject is judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the trial results.

In the event that the subject is withdrawn from the study due to an AE, this must be recorded on the case report form (CRF). The subject should be followed and treated by the investigator or designate until the abnormal parameter or symptom has resolved or stabilized. It is up to the clinician to determine that the AE is either resolved or that it has reached a stable state, after which no further follow-up is necessary. There should also be source documentation to support this determination.

9.7 Protocol Violations/Deviations

In this pragmatic randomized controlled trial (RCT), there are no protocol deviations that will result in the discontinuation of study medications or followup. As noted previously, adherence will be monitored; failure to successfully take 75% of medications will be judged 'nonadherent' and those individuals will not be included in the per-protocol analysis.

10 Data Handling and Record Keeping

10.1 Data Management Responsibilities

Data collection is the responsibility of the research staff at the site under the supervision of the Principal Investigator. During the study the investigator must maintain complete and accurate documentation for the study. The RAs will, after informed consent is obtained, recruit the participant and complete the relevant documentation (CRFs, follow-up phone calls, etc.) either on paper or directly into the study database using a tablet device. (Paper forms will need to be digitized by the research staff later on.) The local PI will review all data at their site to ensure clarity and accuracy. Paper forms will be kept on-site in a locked cabinet in a locked room to which only the study staff have access. Adverse events must be graded, assessed by severity and causality and reviewed by the site investigator or designee.

The study database has been created using REDCap (Research Electronic Data Capture) software. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are securely housed in an on-site limited access data center managed by the Department of Pediatrics at McMaster University. All web-based information transmission is encrypted. The data is all stored on a private, firewall protected network. All users are given individual user ids and passwords and their access is restricted on a role-specific basis. REDCap was developed specifically around Health Insurance Portability and Accountability Act (HIPAA)-Security guidelines and is implemented and maintained according to McMaster University guidelines. REDCap currently supports > 500 academic/non-profit consortium partners on six continents and 38,800 research end-users.

10.2 Confidentiality

All subject related information including Case Report Forms, laboratory specimens, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Subjects will be identified only by means of a coded number specific to each subject. As noted above, the REDCap study database is securely protected and encrypted. All computerized databases will identify subjects by numeric codes only. Upon request, subject records will be made available to the study sponsor, monitoring groups representative of the study sponsor, and Health Canada.

10.3 Record Retention

All research records will be retained for a minimum of 25 years after closure. Paper copies will be destroyed after 5 years and the digital records will be maintained thereafter in the encrypted, password-protected database.

11 Quality Control and Quality Assurance

The trial will be conducted in accordance with the latest version of the Declaration of Helsinki, Good Clinical Practice (GCP), International Conference on Harmonization (ICH) regulatory guidelines, and Division 5 of Health Canada Food and Drug regulations and requirements regarding ethical committee review, informed consent, and other statutes and regulations regarding the protection of the rights and welfare participants participating in the study.

The protocol, including the informed consent document and all recruiting materials, will be submitted to the Research Ethics Boards for review and approval. No changes will be made to the protocol without REB approval, except where necessary to eliminate apparent immediate hazards to participants. The caregiver will be able to withdraw their consent to participate at any time without prejudice. Additionally, the investigators may withdraw an infant if, in the investigator's clinical judgment, it is in the best interest of the infant.

Data will be collected using REDCap electronic data capture. This system will be used to

generate reports. There is also an audit trail function which is compliant with current Canadian regulations.

11.1 Study Monitoring Plan

On-site monitoring of remote sites will be conducted by qualified research personnel as required. Monitoring will be conducted through personal visits with the local PI and site staff (every 3-6 months or as needed based on enrolment and participant study visits) as well as any appropriate communications by mail, fax, e-mail, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. The Essential Documents in the Investigator Regulatory Files will be monitored and checked for accuracy and completeness. The monitor will identify any items missing from the Regulatory Binder. Site personnel are responsible for maintenance of the Regulatory Binder. The consent document will be reviewed for content to ensure it contains the required (and additional, as applicable) regulatory elements. The consent document will be compared to the protocol and site specific REB procedures for informed consent documentation to ensure agreement between the two documents. Consent forms monitoring will be documented in the monitoring time point report.

11.2 Ethical Considerations

This study will be conducted according to Canadian and international standards of Good Clinical Practice for all studies. Applicable government regulations and HiREB and CHEO research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the HiREB and CHEO REB for formal approval to conduct the study. The decision of the REBs concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form and assent form if applicable, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent and assent form will be submitted with the protocol for review and approval by the appropriate REB. The formal consent of a subject, using the REB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Budget & Finance

The study will be funded from the following sources: Physicians' Services Incorporated Foundation Health Research Grant, Hamilton Health Sciences Early Career Award, and Dr. Pernica's start-up funds from the Department of Pediatrics of McMaster University.

13 Knowledge Translation Plan

The nature of the proposed trial is strongly toward the pragmatic end of the clinical trial spectrum (89); consequently, the results of the trial will be positioned for rapid integration

into clinical practice by Canadian physicians. To that end, both integrated and end-of-grant knowledge translation (KT) methods will be employed to facilitate communication of study results to healthcare practitioners – the main knowledge users for this study. The principal KT goal of the project will be, subsequent to the determination of whether short-course antimicrobial therapy is noninferior to the standard of care, to facilitate integration of trial results into current Canadian CAP guidelines and disseminate the information to the healthcare community. To do this, research team members will collaborate with established networks of clinicians experienced in the dissemination of clinical guidelines to healthcare practitioners, i.e. the Canadian Paediatric Society, Association of Medical Microbiology and Infectious Disease Canada, Infectious Disease Society of America, Canadian Association of Emergency Physicians, and Pediatric Emergency Research Canada (PERC). Given that PERC, a highly successful research network involving 15 children's hospitals, represents a key group of knowledge users for this study, the executive was invited to the table in the design phase to ensure that the study objectives were relevant to Canadian emergency physicians and the study protocol was structured in such a way to optimize both internal and external validity. PERC has since unanimously endorsed the proposed study as one deserving of its support; furthermore, the study protocol was presented to the wider PERC community for more feedback at its annual meeting in 2014. The above-noted collaborations will be stimulated though presentation at major Canadian and American meetings (Pediatric Academic Societies, Canadian Paediatric Society, etc.); healthcare decision makers will be provided a one page synopsis of the results and invited to meet with study team members to discuss the implications. The end-of-grant KT strategy will also focus on publication of results in a peer-reviewed open-source journal (preferably a general paediatric journal because of the broad audience), oral and poster presentation at local and national meetings, and leveraging dissemination through the diverse professional networks of the research team members (the applicant and co-investigators are trained in disciplines including paediatric infectious disease, adult infectious disease, medical microbiology, clinical epidemiology, and paediatric emergency). In all cases, messages will be tailored to ensure relevance to the target audience.

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Appendix A: Schedule of Procedures/Evaluations

Evaluation	Recruitment day 0	Phone call day 3-5	Phone call day 7-10	Visit 1 day 14-21	Phone call day 26-30	3-to-6 months post-enrolment
Consent	X					
Screening for eligibility	X					
Nasopharyngeal specimen	X					
Salivary or Serum CRP	X					
Enteric specimen	X			X		
Screening for clinical deterioration (including fever)		X	X	X	X	
Targeted physical exam	X			X		
Return of antimicrobial containers				X		
Enteric specimen (by caregiver)						X