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Early View

Original research article

The Short *versus* Long antibiotic course for pleural Infection Management (SLIM) randomised controlled open label trial

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Please cite this article as: Hassan M, Gad-Allah M, El-Shaarawy B, *et al*. The Short *versus* Long antibiotic course for pleural Infection Management (SLIM) randomised controlled open label trial. *ERJ Open Res* 2023; in press (https://doi.org/10.1183/23120541.00635-2022).

Title: The Short versus Long antibiotic course for pleural Infection Management (SLIM) randomised controlled open label trial

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Ethics statement: The protocol of the study was approved by the Alexandria University Faculty of Medicine Ethics Committee (ref 0304785). All participants provided written informed consent. The trial was sponsored by Alexandria University. No funding was received for the conduct of the trial.

Acknowledgement: we would like to thank the patients and their families for their involvement in the trial. We would like to thank the resident doctors at Alexandria University Hospitals who helped with screening and other trial activities.

Authors contribution: MH conceived the study idea. MH and ASS wrote the protocol. All authors contributed to data acquisition and interpretation. MH wrote the first manuscript with critical revision from CD and ASS. All authors reviewed and approved the final manuscript.

ABSTRACT

Introduction: Based on expert opinion the length of antibiotic treatment for pleural infection in adults is typically recommended to be a minimum of four weeks. This clinical trial aimed to assess whether shorter antibiotic courses lead to more treatment failures than standard longer courses.

Methods: In an open-label randomised controlled trial adult patients with pleural infection who were medically treated and stabilised within 14 days of admission were randomised to either a short antibiotic course (total course 14-21 days) or a long antibiotic course (total course 28-42 days). Patients were excluded if their baseline RAPID score was >4 (high-risk category). The primary outcome was the incidence of treatment failure by 6 weeks post admission. Secondary outcomes were total length of antibiotic treatment, proportion of patients who resumed normal activity levels within 6 weeks post admission, time from discharge to resuming normal activity levels and the incidence of antibiotic-related adverse reactions.

Results: Between September 2020 and October 2021 50 patients (35 (70%) males, mean age 46±13.7 years), were recruited to the trial and randomly assigned to the short course group (n=25) or the long course group (n=25) with outcome data available for 24 patients in each study group. Treatment failure occurred in 4 (16.7%) patients in the short course group and 3 (12.5%) patients in the long course group. In the intention-to-treat analysis the odds ratio for treatment failure in the long course group was 0.714 (95% CI 0.142-3.600, p=0.683). The median duration of antibiotic treatment in the short course group was 20.5 [18-22.5] days compared to 34.5 [32-38] days in the long course group (p <0.001). There were no statistically significant differences in the other outcomes.

Conclusion: In medically treated adult patients with pleural infection a long course of antimicrobial therapy did not lead to less treatment failures in comparison to a shorter course. These findings need to be confirmed in a larger multi-centre trial.

Trial protocol registration: NCT04615286 (Clinicaltrials.gov)

Keywords: pleural disease, empyema, antibiotic, clinical trial, pleural infection, parapneumonic effusion

INTRODUCTION

Infection of the pleural space is a serious condition associated with substantial morbidity and mortality.[1] The core management involves drainage of the infected fluid and antimicrobial therapy.[2] Based on expert opinion, a minimum of four weeks of antibiotics are used to treat pleural infection, although frequently this is extended to up to 6 weeks in routine clinical practice.[1,3–5]

A key principle of antimicrobial stewardship is administering the minimum effective duration of an antibiotic course - which aims to reduce the risk of antimicrobial resistance and drug toxicity both associated with unnecessarily long courses.[6,7] In lower respiratory tract infections, randomised controlled studies have shown that short courses of antibiotics lead to good clinical outcomes. [8,9] However, in pleural infection there is a paucity of good quality evidence to inform on the optimal duration of antibiotic therapy in adults. A retrospective study of 91 patients with pleural infection reported that antibiotics were prescribed for an average of 4 weeks but were extended to longer durations in some patients. [5] The authors concluded that three weeks of antibiotics were sufficient to treat empyema. The only clinical trial studying the optimum length of antibiotic therapy in pleural infection found that short and long antibiotic regimens had similar risks of treatment failure.[10] However, due to the several exclusion criteria for participation in that trial (which led to exclusion of two thirds of screened patients) the results are not applicable to a substantial proportion of adult patients with pleural infection.

The RAPID score (comprising Renal function, Age, Purulence of pleural fluid, Infection source and Dietary factors) has been validated as a robust tool to predict 3-month mortality in adult patients with pleural infection.[11] The score is stratified into three tiers, with a predicted 3-

month mortality of 3%, 9% and 30% in the low-, intermediate- and high-risk categories respectively.[12] The clinical utility of this score is yet to be determined. However, a robust tool for predicting outcomes is appealing to help identify patients who may be safely treated with shorter antibiotic courses.

This pilot study aimed to investigate whether prescribing shorter courses of antibiotics (2-3 weeks) versus the standard longer courses (4-6 weeks) would lead to difference in rates of treatment failure (defined as the requirement for further management) in adult patients with pleural infection at low-to-intermediate risk of mortality (RAPID score 0–4) who can be safely discharged home within 14 days of hospitalization.

METHODS

Study design

The Short versus Long antibiotic course for pleural Infection Management (SLIM) trial was a pilot open-label pragmatic randomised controlled clinical trial that recruited adult participants admitted with pleural infection to a University Hospital. The protocol of the study was approved by the Alexandria University Faculty of Medicine Ethics Committee (ref 0304785) and was registered on Clinicaltrials.gov (ID NCT04615286). A copy of the protocol is included in the supplementary materials.

Consecutive patients admitted with pleural infection were invited to take part in an observational study (the Pleural Infection Cohort Study) and consenting to the SLIM trial occurred at the same time (using the trials within cohorts study design[13]). All patients provided written informed consent for the observational study and the trial, but were only assigned a trial number at the point of discharge (see below).

Participants

The trial included adult participants (≥18 years old) admitted to hospital for treatment of non-tuberculous pleural infection (both parapneumonic and primary pleural infections included). Pleural infection was defined by the presence of at least one of the following: the presence of pus in the pleural space; positive pleural fluid gram stain or culture; or pleural fluid pH < 7.2 or pleural fluid glucose < 40 mg/dL in the setting of acute respiratory infection. Included participants had to have a low to intermediate RAPID score (0-4) at admission and to be fit for discharge within 14 days of admission. Participants were excluded if they needed referral for surgery during admission, if their admission was due to a recurrent ipsilateral pleural

infection within the last three months, or the infected pleural collection was not amenable to drainage at time of diagnosis or large residual collection persisted despite drainage and therefore a prolonged antibiotic course was deemed necessary by the treating clinician.

Randomisation

Eligible participants were recruited to the trial immediately before discharge and randomised in a 1:1 ratio to either the short course or the long course group. Randomisation via permuted blocks with variable sizes was used and was unstratified. The sequence was generated using the online platform Sealedenvelop.com. At the point of randomisation, a member of the study team logged into the website to obtain the treatment allocation after confirmation of eligibility criteria. The allocation was unblinded to participants and team members performing study assessments.

Procedures

The study intervention was the modification of the length of the antibiotic course at the point of discharge from hospital. All other aspects of management were carried out according to standards of care.

Baseline data including patient demographics, admission blood and pleural fluid results, thoracic ultrasound (TUS) and computed tomography findings, and treatments received were recorded on a case reporting form (supplementary material). The initial choice of the antibiotic regimen was based on international guidelines for treating pleural infection [4,14,15], local patterns of microbiology, and known participants' drug allergies. The regimen was subsequently modified according to results of microbiological studies where necessary.

At discharge repeat blood tests and TUS were performed. In the intervention arm (short course antibiotic group) participants were discharged with a minimum of 7 days oral antibiotics and a maximum period of 21 days (total number of antibiotic days 14-21 days, including the intravenous course). In the control arm (long course antibiotic group) participants were prescribed an oral antibiotic course for a minimum of 14 days and up to a maximum period of 42 days (total number of antibiotic days 28-42 days).

Follow up occurred at two visits: 2 weeks post discharge and 6 weeks post admission. While these were encouraged to be face to face, for participants unable to attend both appointments, the first follow up was via telephone. At each visit participants underwent a clinical review for symptom recurrence, treatment adherence was confirmed, and adverse antibiotic reactions were recorded. In addition, during each physical visit, TUS +/- chest radiograph were performed, and blood samples were sent for white cell count and C-reactive protein. The size of residual collection on TUS was quantified using the maximum effusion depth in cm and the height in rib spaces.

Outcomes

The primary outcome was the incidence of treatment failure defined by the requirement of further management (additional antibiotics and/or drainage procedure and/or surgical intervention) within 6 weeks post index admission. Treatment failure was determined by a) clinical deterioration (i.e. worsening or recurrence of symptoms); PLUS either b) biochemical parameters (worsening of WCC [by 2000/mm3] or CRP [by > 20%] from discharge values), or c) radiological parameters (chest radiograph and/or TUS evidence of increasing or new pleural collection).

Secondary outcomes included the total length of antibiotic treatment, proportion of participants who returned to normal activity levels within 6 weeks post admission, time from discharge to resuming normal activity levels and the incidence of antibiotic-related adverse reactions in the study groups. The following outcomes were explored post-hoc: the number of participants with residual pleural collection on thoracic imaging at 6 weeks post admission, and the number of participants with persistent respiratory symptoms 6 weeks post index admission.

Statistics

This was a pilot study and therefore no formal power calculation has been made. A sample size of 50 participants (25 per group) was chosen by the study team to simulate sizes chosen by trials examining outcomes in pleural infection in adult[3] and paediatric[16] populations.

Continuous variables were summarised using the mean and standard deviation (SD) or the median and interquartile range [IQR] according to whether data were normally distributed. Categorical variables were summarised using frequencies and percentages.

The primary outcome was analysed both in the intention to treat (ITT) population (including all participants with known outcome) and the per protocol (PP) population using the chi-squared and Fisher's exact tests. The PP population excluded participants who received antibiotic durations that were discordant with the pre-specified durations for their allocated group. An analysis of the primary outcome adjusted for the RAPID score (low vs. intermediate score), infection source (community- vs. hospital-acquired), the presence of sonographic septations, and whether split sign was seen on the CT scan was carried out using a binary

logistic regression model. The adjusted odds ratio (aOR) with 95% confidence intervals (CI) for treatment failure in the long course group was calculated from the regression model.

For secondary outcomes, continuous variables were compared between the study groups using the Mann Whitney U test. Categorical variables were compared using the chi-squared test or Fisher's exact test as appropriate. A significance level of $< 0{\cdot}05$ was used throughout the analyses.

RESULTS

Between 28th Sept 2020 and 30th Oct 2021, 80 participants were recruited to the observational study. Of these, 50 participants were recruited to the SLIM trial; 25 participants randomised to the short course group and 25 participants randomised to the long course group. Exclusions are summarised in figure 1. The final SLIM study visit was conducted on 9th December 2021 after which the dataset was locked.

Baseline and discharge data are summarised in Table 1. The median [IQR] age of participants of the short course group was 43 [34-49] years while the median age in the long course group was 52 [39-59] years (p=0.153). Seventy-two percent of the short course group participants and 68% of the long course group participants were males. More participants in the short course group (68%) were in the low RAPID score category than in the long course group (40%). In addition, sonographic evidence of septations were more common in the long course group (77.7%) than in the short course group (28.6%). Participants in the long course group received more days of intravenous antibiotics (mean difference 2 days, 95% CI 0.3-3.8 days).

One participant in the long course group was lost to follow up and one participant from the short course group died from a malignancy-related pulmonary embolism before attending the first follow up visit. Therefore, outcome data were available for 24 participants for each study group. There were 4 instances of protocol deviation, all in the short course group, where participants received antibiotic courses ranging between 24 and 30 days.

<u>Outcomes</u>

All participants attended physically for the first follow up visit. The second follow up visit was attended physically by 93% of the participants and the remaining undertook the visit via telephone. The primary outcome, treatment failure, occurred in 4 (16.7%) participants in the short course group and 3 (12.5%) participants in the long course group (table 2). In the ITT

population, the odds ratio for treatment failure in the long course group was 0.714 (95% CI 0.142-3.600, p=0.683). After adjusting for other covariates, the aOR was 0.542 (95% CI 0.070 – 4.227, p=0.559). The difference in treatment failure was not statistically significant in the analysis of the PP population (table 2).

Treatment failure was diagnosed at the first follow up visit in all 4 participants in the short course group. In the long course group treatment failure was diagnosed at the first follow up visit in 1participant while the 2 other treatment failures were diagnosed at the second follow up visit. Of those with treatment failure, 2 participants from the short course group required another chest tube insertion, while 2 participants of the short course group and all those in long course group with treatment failure were referred to surgery.

Table 2 summarises the results of the secondary outcomes. The median duration of antibiotic treatment in the short course group was 20.5 [18-22.5] days compared to 34.5 [32-38] days in the long course group, p <0.001 (figure 2). There were no statistically significant differences in other outcomes. Notably, in the 41 participants with treatment success at 6 weeks post admission, 20 (48.8%) participants had at least one persistent respiratory symptom; 9 (45%) participants from the short course group and 11 (52.4%) participants in the long course group.

DISCUSSION

The results of this pilot randomised trial confirm the feasibility of randomising adult patients with low-to-intermediate risk pleural infection to shorter courses of antibiotic. There was no statistically significant difference in short-term outcomes between short and long courses of antibiotics, but a larger study power is needed to definitively rule out the superiority of longer antibiotic courses. Despite an antibiotic course that was on average reduced by 14 days, there was no significant difference in time to return to their normal levels of activity, nor the rate of persistent respiratory symptoms by 6 weeks from diagnosis.

There has been a paucity of evidence for the optimum length for antimicrobial therapy for adult pleural infection to inform guidelines which is highlighted in the recent ERS/ESTS statement on pleural infection[17]. This study is an attempt to tackle this gab in evidence and the results support the feasibility of prescribing a 3-week treatment course. It is noteworthy that the study excluded patients who required hospital admission for a duration of more than 14 days (20% of screened patients). Therefore, the results of the study are not applicable to those with longer

Shorter durations of antimicrobials are associated with lower future risk of infection by antibiotic-resistant organisms, a problem that was responsible for 1.27 million deaths globally in 2019.[18] Avoiding longer durations of antimicrobial therapy has been shown to improve mortality in severe community-acquired pneumonia.[19] Another implication of a shorter antibiotic course in treating pleural infection is to prevent the delay in declaring failure of medical treatment and referral for definitive management. In two of the three participants who failed medical therapy in the long course group in this study, the decision to refer to surgery was delayed until the completed more than 4 weeks of antibiotics.

This study utilised the RAPID score to stratify participants according to the severity of infection, to exclude participants at high-risk of mortality, who may be more vulnerable to complications with a shorter antimicrobial treatment course. Unlike predictive scores in community-acquired pneumonia, such as the CURB65 which is used to inform the site of care[20] and the choice of empirical antibiotic therapy,[21] the RAPID score has not been studied as a tool to guide management. To our knowledge, this is the first study to suggest a clinically meaningful use for the RAPID score, where patients with low-to-intermediate scores can be given shorter outpatient antimicrobial courses. Future studies looking into other clinical/biochemical factors to guide the intensity and length of antimicrobial therapy in pleural infection would be useful. Indeed, in other respiratory infections guidance by sputum bacterial load[22] of serum biomarkers[23] have been successfully used to guide antimicrobial therapy with improved outcomes.

The results of this trial are in agreement with the only published randomised trial studying antibiotic duration in adult pleural infection. The trial included 55 participants with community-acquired parapneumonic pleural infection and no excess treatment failure with a 3-week versus a 2-week antibiotic course was observed.[10] However, in that trial all patients were treated with co-amoxiclav, and therefore patients who were penicillin-allergic were excluded. In our trial, the choice of any suitable antibiotic regimen was modifiable according to microbiological results and informed by patients' drug intolerances, to make the study more pragmatic and the results more generalizable. Additionally, and unlike the aforementioned trial, our study included patients with both community and hospital acquired pleural infections and both parapneumonic and primary pleural infections. Our results also agree with a retrospective study of predominantly surgically treated patients,[5] where it was found that three weeks of antibiotics were sufficient to treat empyema.

Despite randomization in this trial, between study groups there were baseline differences in the number of participants in each RAPID score category and in the proportion of participants with sonographic septations. However, these imbalances were subsequently adjusted for in the analysis of the primary outcome. Further, it remains unclear whether higher RAPID scores or the presence of septations on ultrasound are predictors of treatment failure.[11,24] The median age of the subjects included was relatively younger than commonly reported in pleural infection. However, this partially reflects different patient demographics where the trial recruited and inclusion of a lower risk tier of the RAPID score spectrum. It is worth noting that imaging findings suggestive of evolving fibrosis (split pleura sign, multi-loculation and volume loss) were not different between study groups.

Important limitations of this study are that the study was conducted in a single centre and the sample size was relatively small. This small size may have not provided enough study power to detect significant change in the primary outcome between the study groups. The findings will need to be replicated in a larger multi-centre study. Another limitation of the study was the open label design, however ensuring generalizability with a pragmatic flexible choice of antibiotic regimens did not make blinding possible. The short course group had a number of protocol deviations in terms of antibiotic course length. Finally, the study did not collect long-term data, such as one-year mortality, which is another limitation of the study.

CONCLUSIONS

This single-centre pilot randomised controlled trial showed that there was no statistically significant difference between long and short courses of antimicrobial therapy in terms of incidence of treatment failure in medically-treated adult patients with pleural infection who are stabilised within 14 days of admission and who have a low to intermediate risk of mortality

per the RAPID score. Due to the pilot nature of this trial, a larger multicentre study is needed to confirm these findings. Further studies are needed to identify clinical and/or biochemical factors to help triage suitable patients to ambulatory or less invasive management with shorter antimicrobial courses.

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Tables

Table 1: Admission and in-hospital data of study participants

	Short course group (n=25)		**Long course Group (n=25)**	
	Participants with available data	**Result**	**Participants with available data**	**Result**
Age	25	43 [34-49]	25	52 [39-59]
Sex, male	25	18 (72%)	25	17 (68%)
Symptom duration before admission, days	24	17 [9.25-39.00]	24	16.5 [10-27.5]
Any comorbidity or risk factor*	25	23 (92%)	25	24 (96%)
Poor dentition		13 (52%)		11 (44%)
Intravenous drug user		6 (24%)		5 (20%)
Cardiovascular disease		4 (16%)		4 (16%)
Diabetes		5 (20%)		7 (28%)
Respiratory		4 (16%)		3 (12%)
Septations on ultrasound	14	4 (28.6%)	18	14 (77.7%)
CT signs				
Split sign	22	18 (81.1%)	24	17 (70.8%)
Volume loss	22	3 (13.6%)	24	2 (8.3%)
Multi-loculated	25	10 (40%)	24	10 (41.7%)
Infection source	25		25	
Community-acquired		20 (80%)		22 (88%)

Hospital-acquired		5 (20%)		3 (12%)
Infection type Primary pleural Parapneumonic	23	 19 (82.6%) 4 (17.4%)	25	 18 (72%) 7 (28%)
Purulent pleural fluid	25	20 (80%)	25	16 (64%)
RAPID category Low Intermediate	25	 17 (68%) 8 (32%)	25	 10 (40%) 15 (60%)
Admission blood tests Albumin, mg/dL	25	3.01+0.58	25	2.71+0.61
WBC, $X10^9$/L	24	12.3 [8.77-17.23]	25	12.8 [10.2-18.85]
Haemoglobin, g/dL	24	11.19+1.99	25	10.66+2.15
Platelet, cells/mm^3	24	328.5 [213.25-444]	25	376 [312-484]
CRP, mg/L	20	158.68+94.95	15	163.60+92.64
Drain Size <18 Fr 18 Fr or larger	20	 9 (45%) 11 (55%)	21	 12 (57%) 9 (43%)
Duration of drainage, days	18	9 [6-12]	18	7 [4-11]
Discharge blood tests WBC, $X10^9$/L	24	9.09+3.44	25	9.68+3.93
Platelet, cells/mm^3	24	362 [276-486.25]	25	508 [287-596]
CRP, mg/L	23	32 [15.9-44.7]	24	21.9 [16.5-32.7]
Length of intravenous antibiotic course, days	25	9.12+3.56	25	11.20+2.51

Length of stay, days	25	10.52+3.28	25	11.63+2.58
Status at discharge	25		25	
No residual collection		11 (44%)		11 (44%)
Residual collection		14 (56%)		13 (52%)
Outpatient drainage		0 (0%)		1 (4%)
Inpatient antibiotics	25		25	
Ampicillin-sulbactam/metronidazole		15 (60%)		14 (56%)
Cephalosporin/metro		3 (12%)		3 (12%)
Other		7 (28%)		8 (32%)
Outpatient antibiotics	25		25	
Co-amoxiclav/metronidazole		6 (24%)		10 (40%)
Moxifloxacin		6 (24%)		6 (24%)
Moxifloxacin/metro		7 (28%)		0 (0%)
Co-amoxiclav		0 (0%)		4 (24%)

Data are presented as mean ± standard deviation or median [interquartile range] for continuous variables, and as frequency (percentage) for categorical variables

CRP: C-reactive protein; CT: computed tomography; WBC: white cell count

* Some participants had more than one comorbidity or risk factor

Table 2: Primary and secondary outcomes for the study groups

	Short course group (n=24)		Long Group (n=24)		P value
	Participants with available data	**Result**	**Participant with available data**	**Result**	
Treatment failure, ITT	24	4 (16.7%)	24	3 (12.5%)	Chi^2 0.167 (p=0.683) Fisher's Exact p=1
Treatment failure, PP	20	4 (20%)	24	3 (12.5%)	Chi^2 0.459 (p=498), Fisher's exact p=0.684
Total antibiotic duration, days	24	20.5 [18-22.5]	24	34.5 [32-38]	<0.001
Returned to ADL	20	11 (55%)	21	9 (42.9%)	0.436
Time to return to ADL from admission	11	10 [4.5-18]	9	13 [6-18]	0.970
Antibiotic-related adverse events	21	0 (0%)	24	2 (8.3%)	Fisher's exact p=0.488
Residual pleural collection	20	4 (20%)	21	2 (9.5%)	Fisher exact p=0.409
Persistent Symptoms at 6 weeks post admission	20	9 (45%)	21	11 (52.4%)	Chi^2 0.382 (p=0.537)

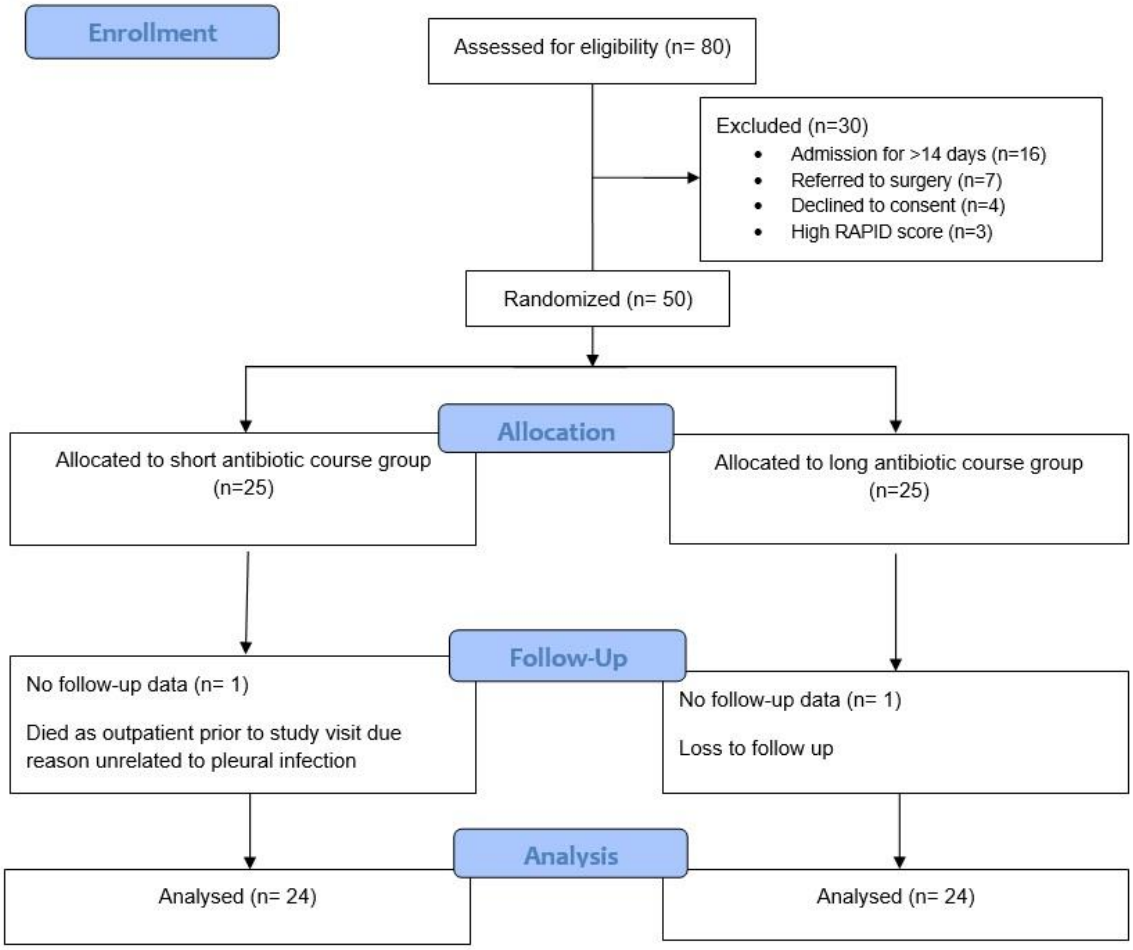
ADL: activities of daily living; ITT: intention to treat; PP: per protocol

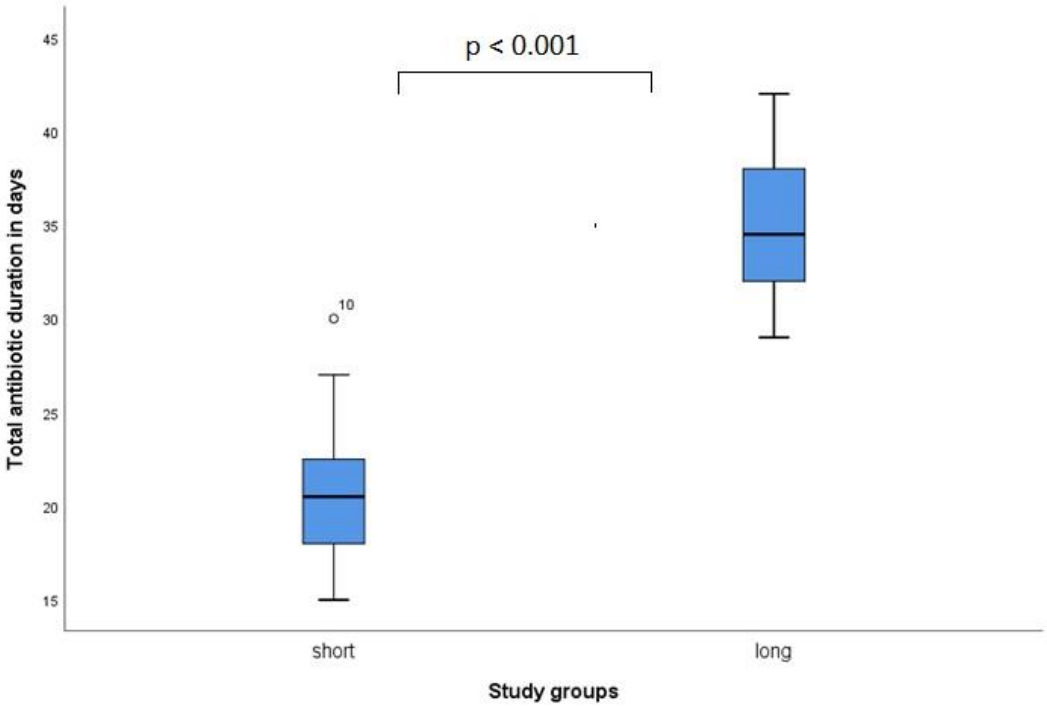
Figure legends

Figure 1: Flow of the participants through the trial

Figure 2: The difference of antibiotic duration between the study groups. Please note that the mark above the left boxplot refers to trial participant number 10 who was randomised to the short course group but received 30 days of antibiotic therapy (a trial deviation).

CONSORT 2010 Flow Diagram




p < 0.001
Total antibiotic duration in days
45
40
35
30
25
20
15
10
short
long
Study groups

The Short versus Long antibiotic course for pleural Infection Management (SLIM) randomised controlled open label trial

Supplementary Material

Contents

1- Trial Protocol

Title: Short versus Long antibiotic course for pleural Infection Management (SLIM trial): protocol of a randomized controlled open label trial

Version and date: Version 1.4 – 14th Nov 2020

Sponsor:

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Ethics approval: the protocol of the study was approved by the Alexandria University Faculty of Medicine Ethics Committee (ref 0304785)

Registration: NCT04615286 (Clinicaltrial.gov)

Introduction

Infection of the pleural space is serious condition that requires hospitalization, invasive interventions and long courses of antibiotics[1]. Treatment of pleural infection requires long hospital admission with a median of 19 days[2] and medical treatments fails requiring surgical intervention in up to 30% of cases[3]. The mortality from pleural infection is around 10% at 3 months[4].

Besides drainage of the infected fluid, antibiotics are a core component of management of pleural infection[5] and are typically given intravenously in the first few days of treatment until the condition is stabilized at which stage patients are shifted to oral antibiotics of equivalent spectrum. In almost half of the cases of pleural infection, the choice of antibiotics is entirely empirical due to low yield of microbiological tests on pleural fluid in these cases[6]. International guidelines cite a minimum length of antibiotic course of pleural infection of four weeks[5,7] with antibiotic courses typically lasting six weeks[8]. However, these recommendations are based on expert opinion with no robust evidence to support such durations. A recent trial compared a two-week versus a three-week antibiotic course for parapneumonic pleural infections. The trial that concluded prematurely due to inability to recruit to target sample size and found that the two regimens were equivalent in terms of risk of failure of medical treatment[9]. Besides being an underpowered study, the results are only applicable to parapneumonic effusions but not primary pleural infections.

The RAPID score has recently been validated as a robust tool to predict 3-month mortality of patients with pleural infection based on demographic and laboratory data (table 1)[4]. A low score (0-2) is associated with 2-3% mortality, medium score (3-4) 9% mortality and high score (5-7) 30% mortality at three months[10]. The utility for this score in clinical management is yet to be determined and this study will attempt using this score to stratify lengths of antibiotic treatment based on proposed risk of adverse outcomes as stipulated by the RAPID score. A shorter antibiotic course that is as effective as the standard long course is desirable given the common occurrence of side effects with antibiotic treatment. The presence of a robust predictive score of outcome seems as an attractive tool to help stratify patients who can be safely treated with shorter antibiotic courses.

The aim of this study is to investigate the feasibility and safety of prescribing shorter courses of antibiotics (2-3 weeks) versus the standard longer courses (4-6 weeks) in medically-treated patients with pleural infection at lower risk of mortality (RAPID score 0–4) who can be safely discharged home within 14 days of hospitalization and how this impacts success of medical treatment.

Table 1: Components of the RAPID score[4]

Parameter	Value	Score
Renal function (blood urea nitrogen)	<14 mg/dL 14-23 mg/dL >23 mg/dL	0 1 2
Age	< 50 years 50 – 70 years > 70 years	0 1 2
Purulence of pleural fluid	Purulent Non-purulent	0 1
Infection Source	Community-acquired Hospital-acquired	0 1
Dietary factors (serum albumin)	≥2.7 g/dL <2.7 g/dL	0 1

Methods

This protocol is written in accordance with the guidance of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[11].

Trial design and study setting

SLIM is an open label randomized controlled clinical trial that will recruit patients admitted with pleural infection to a University Hospital. Consecutive patients admitted with pleural infection will be invited to take part in an observational study (the Pleural Infection Cohort Study) and consenting to SLIM will occur at the same time of consenting to the cohort study. This design is termed trials within cohorts.[12]

Inclusion of other hospitals as recruiting sites is not planned but will be considered if recruitment is deemed slow.

Eligibility criteria

Inclusion

- Adult patients (≥18 years old)
- Willing to provide informed consent
- Admitted to hospital for treatment of pleural infection (both parapneumonic and primary pleural infections included). Pleural infection will be defined by the presence of one of the following:
  a) the presence of pus in the pleural space;
  b) positive pleural fluid gram stain or culture; or
  c) pleural fluid pH < 7.2 or pleural fluid glucose < 40 mg/dL in the setting of acute respiratory infection.
- RAPID low or intermediate score (0-4)
- Fit for discharge within 14th day of admission

Exclusion:

- Failure of medical treatment within 14 days of admission and need for surgical referral
- Need for hospital admission beyond 14 days due to medical reasons
- Admission to recurrent ipsilateral pleural infection within the last three months
- RAPID high score (5 or more)
- Pleural infection not amenable to drainage at time of diagnosis and therefore upfront decision to treat with prolonged antibiotics
- Residual pleural collection (despite attempted drainage) that the managing clinician indicated is for prolonged oral suppressive therapy (i.e. six weeks of oral antibiotics).

Patients will only be randomised to one of the study arms of SLIM if found eligible, and for ineligible patients, their data collection will follow the protocol of the cohort study with no change in their care.

Interventions

The study intervention is the modification of the length of the antibiotic course at the point of discharge from hospital. All other aspects of care will be carried out according to recognised clinical standards. The choice of the antibiotics will rely on results of microbiological studies, and if non-informative will follow international guidelines for treating pleural infection and local patterns of microbiology[1,6]. A separate document will be prepared to provide guidance for outpatient antibiotics in the absence of culture results.

In the active arm, patients who are ready for discharge will be prescribed an oral antibiotic course for a minimum period of 7 days and a maximum period that makes the overall length of antibiotic administration 21 days (total number of antibiotic days 14-21 days). In the control arm, at the point of discharge, patients will be prescribed an oral antibiotic course for a minimum of 14 days and a maximum period that makes the overall length of antibiotic administration 42 days (total number of antibiotic days 28-42 days). Treatment duration allocation will be open label.

Baseline data

Besides patient demographics and infection source, the following data will be collected at the points of admission and discharge as appropriate:

- Date of diagnosis confirmation

- Vital signs

-Blood investigations (minimum: urea and electrolytes, full blood count, C-reactive protein, and serum albumin)

- Pleural fluid parameters (macroscopic appearance, biochemistry, cultures (blood and pleural fluid), pH)

- Chest X-ray at baseline and at discharge

- Thoracic ultrasound (TUS) images at baseline (effusion size and extent of septations)

- Chest computed tomography images at baseline (presence of pleural split sign, lung consolidation or microbubbles)

- Treatments received as inpatient (chest tube size and time till removal, volume of effusion drained, intravenous and oral antibiotics given)

- Total length of hospital admission

Participant timeline:

Participants admitted to hospital for treatment of pleural infection will be approached to take part in both the observational and interventional studies. For patients who sign an informed consent to both, and upon confirmation of their eligibility to the trial, they will be randomised to a study arm once a decision is made about fitness for discharge from hospital which is within 14 days from admission.

Upon discharge, two face-to-face follow up visits will be planned to coincide with clinical practice of following up patients post admission for pleural infection.

a- Two weeks post discharge (+/- 7 days)

A clinical review to ascertain adherence to treatment and ensure no symptoms of recurrence are present (fever, night sweats, haemoptysis or purulent expectoration, chest pain). Any adverse events related to antibiotic treatment will be recorded. During this visit thoracic US (TUS) +/- chest X-ray will be performed. If a participant is not willing or able to attend in person, a remote review will be performed (via telephone).

b- Six weeks from initial admission (+/- 7 days)

During this visit the following will be performed:

Clinical review of symptoms (relating to infection recurrence or adverse events due to antibiotic treatment)

Check adherence to study treatment. Participants will be asked to bring back the used empty antibiotic packs.

Blood to be sent for white cell count and C-reactive protein

Chest X-ray

c- Unscheduled Visits - Besides the two planned visits, participants will be allowed to contact the study team between the time points if they develop any of the symptoms of recurrence mentioned above. A study clinician will determine whether a clinical review is required and will arrange accordingly

Outcomes

Primary outcome:

Incidence of failure of treatment as judged by trial clinician requiring further antibiotics and/or tube drainage and/or surgical intervention by six weeks post initial admission. Failure will be determined based on the one or more of the following parameter: clinical (recurrence of symptoms), biochemical (worsening of WCC [by 2000/mm^3] or CRP [by $\geq$ 20%] from discharge values) and radiological (chest X-ray +/- TUS evidence of increasing or new pleural collection).

Secondary outcomes:

- Total length of antibiotic treatment (in days) in the study arms
- Number of participants with worsening in the 6-week chest X-ray as compared to discharge chest X-ray in the study arms. Chest X-ray pairs (discharge vs 6-week) will be read by a respiratory physician blinded to treatment allocation who will judge whether there is worsening (versus stability or improvement)
- Time (in days) to return to normal daily activities in participants of the study arms

- Readmission within 30 days from discharge

Sample Size:

A sample size of 50 participants (25 per arm) was chosen by the study team simulating sizes chosen by trials examining outcomes in pleural infection in adult[8] and paediatric[13] populations.

Randomisation and treatment allocation

Patients will be randomised 1:1 to the active or the control arm. Randomisation using permuted blocks with variables sizes will be used and the sequence will be generated using the online platform Sealedenvelop.com. At the point of randomisation, a member of the study team will log into the website and obtain the treatment allocation after confirmation of eligibility criteria. Being an open label study, allocation will be known to the patient and the study team performing assessments of study visits.

Data management

Data will be collected directly into paper case report forms that will bear the study number of the participants but no other identifiable information. No data sources (e.g. lab results, etc.) will be stored within the trial files to maintain confidentiality of patients' medical data.

A screening log will be kept electronically on a spreadsheet that is password protected on a secure computer. This log will have the name and demographics of patients approached for the study as well as study number and treatment allocation for randomised patients.

At completion of study assessments for the last recruited patients, data will be transferred from paper CRFs to electronic form (spreadsheets) to allow statistical analysis. These spreadsheets will be stored securely after trial conclusion with the principal investigator and will be accessible to other members of the study team. Request to access study data by other teams will be expected via email and access will be granted by the principal investigator if the request is deemed reasonable.

Statistics

A per protocol analysis will be carried out for all outcomes. Given that this is a feasibility study, no replacement for participants lost to follow up will be attempted. Continuous variables will be compared between the study arms using t-test or Mann Whitney test according to the normality of the study data. Categorical variables (including primary outcome measure) will be compared using the Chi squared test or Fisher exact test as appropriate. A binary logistic regression model will be used to predict treatment failure (dependent variable) adjusting for RAPID score and whether infection was primary or parapneumonic (independent variables).

Safety monitoring reporting

The study intervention (shorter antibiotic course) is envisaged to cause less adverse events due to less exposure to antibiotics. All treatment-related adverse events will be collected routinely as part of the study. As a safety measure, an interim analysis will be planned when half the recruitment target is reached to ensure that the study intervention does not impose unacceptable risks to subjects randomised to this arm.

Ethics and dissemination

Approval will be sought from the Ethics Committee of Alexandria Faculty of Medicine and the protocol will be registered in an open-access trials database before the recruitment of the first patient. All participants will be required to sign an informed consent form prior to enrolment in the study. A scientific report with the results of the study will be prepared once the recruitment finishes.

References

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11. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Ann Intern Med 2013;158(3):200.

12. Kim SY, Flory J, Relton C. Ethics and practice of Trials within Cohorts: An emerging pragmatic trial design. Clinical Trials 2018;15(1):9–16.

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2- Trial Case Report Forms

3- Age		Date of admission	dd/mm/yy
Gender		Date of consent	dd/mm/yy
Symptoms at admission (circle all that applies)	Cough Fever Sputum Night sweats Chest Pain Weight Loss Dyspnoea	Duration of symptoms before admission	days
		Pre-admission antibiotics	Y / N
Risk factors / comorbidities (circle all that applies)	Poor dentition IVDU Cardiovascular Diseases DM Liver Disease	Renal Disease Neurological disease Active cancer Immune suppression Other (specify):	Respiratory Smoker: PYI:
Radiology			
Ultrasound	Depth: cm	Height: spaces	Echogenic Septated Complex septated
CXR	Loculated: y / n	Consolidation: y / n	
CT	Split sign: y / n Consolidation: y / n	Microbubbles: y / n Volume loss: y / n	Air-fluid level: y / n
Community Acquired		Y / N	
Vital signs on admission: BP:		Temp:	
Pleural Fluid			
Physical	Pus/turbid/straw	pH	
LDH		Glucose	
Protein		ADA	
Neutrophils		Lymphocytes	
C&S		AFB	
Blood culture		Other microbiology	
Blood tests on admission			
BUN:	Creatinine:	Na:	K:
Albumin:	Hb:	Platelets:	WBC:
Neutrophils:	Lymphocytes:	CRP:	
RAPID Score*	Low (0-1)	Intermediate (2-4)	High (5-7)
Initial treatments			
Chest tube	Size: F Date inserted:	Volume drained initial 24 hours	ml
Antibiotics			
Anticoagulation			

*RAPID score: BUN: <14, 14-23, >23; Age: <50, 50-70, >70 year; Purulence: purulent, non-purulent; Infection source: community, hospital-acquired; Albumin: $\geq$2.7 gm, <2.7 gm

Date of discharge	dd/mm/yy
LOS	days
Status at discharge (tick what applies)	No tube, suppressive antibiotics Tube out, good drainage, oral antibiotics Tube out, residual collection, oral antibiotics Tube out, full antibiotic course completed inpatient Ongoing outpatient drainage, oral antibiotics Referred to surgery Other (specify)
RAPID score	
Eligible for SLIM	Y / N
Randomisation group	
Antibiotics	
Date of IV to oral shift	
N0. of days of IVs	
No. of days of oral antibiotics prescribed	
Vitals	
Temp	
Bloods	
Creatinine	
CRP	
WBC	
Neutrophils	
Platelets	
Discharge antibiotics Duration prescribed	
Radiology	
US (residual effusion)	Height: Depth:
CXR	
Date tube out	
No. of days tube in situ	
SLIM Follow-up visit 1 date	
SLIM Follow-up visit 2 date	

Visit number	FU 1 / FU 2 / unscheduled	
Visit format	Face-to-face / telephone	
Date	dd/mm/yy	
Time since admission	Days	
Time since discharge	Days	
Respiratory symptoms (tick all that applies)	Chest pain Fever Cough Night sweats Sputum Dyspnoea	
Duration of symptoms		
Study arm	Short course - Long course	
Antibiotics		
No. of days of oral completed		
Adherence confirmed	Y / n	
Remaining days of oral antibiotic		
Time from discharge to return to work/normal activity	Days	
Bloods/radiology		
WBC		
CRP		
Platelets		
US Residual effusion	Depth: Height	
Lung consoildation	Y / n	
Pleural thickening	mm	
CXR evidence of new/worsened collection	Y / n	
Treatment Failure (tick if any applies)	Hospital re-admission Further antibiotics Insertion of chest drain Referral to surgery	Date IV/Oral Date Date Date
Details		

3- CONSORT checklist

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	7-9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9-10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.