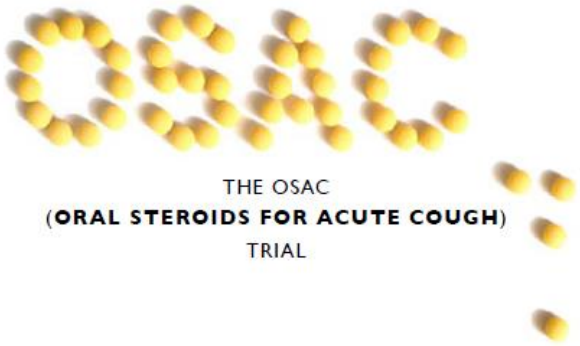

The Oral Steroids for Acute Cough (OSAC) Trial Protocol

Version 1.6 (15 October 2014)

What is the clinical and cost effectiveness of oral steroids in the treatment of acute lower respiratory tract infection (LRTI)? A placebo controlled randomised trial.

Trial Identifiers

EudraCT number: 2012-000851-15

ISRCTN57309858

NHS REC reference: 12/SW/0180

Sponsor reference: 1581

Funder: NIHR School of Primary Care Research

UKCRN Portfolio number: 13751

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Advice on integration with other ongoing primary care research

Professor Stafford Lightman, University of Bristol
Advice on steroid use and effects within the trial

Dr Duncan Dicks
Patient and public representative

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Dr Matthew Fuszard
Patient and public representative

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Advice on asthma / chronic obstructive pulmonary disease (COPD) aspects of the trial

1.7 Trial statistician

Dr Sara Brookes
Senior Lecturer in Medical Statistics, University of Bristol

1.8 Trial Committees

1.8.1 Trial Management Group

The Trial Management Group (TMG) will comprise all investigators, the trial manager, research and administrative staff, with input from patient/public representatives.

Members of the TMG contribute to the trial in the following ways: trial design, trial centre recruitment and trial conduct, trial management, trial logistics and cost management, economic evaluation, trial methods, statistical data analysis, and publication.

The TMG will meet approximately monthly to oversee the day-to-day management of the trial. The TMG will be provided with detailed information by the Centre staff regarding trial progress. Most meetings will be by teleconference, but the TMG will also meet face to face once or twice a year.

1.8.2 Trial Steering Committee

The Trial Steering Committee (TSC) will meet once or twice a year.

The membership will include: independent chairperson Professor Jonathan Mant, University of Cambridge (not involved directly in the trial other than as a member of the TSC); three independent members (Dr Toby Prevost, University of Cambridge; Dr Nick Francis, Cardiff University, and Dr Lindsay Smith, GP); one/two principal investigators; and one or two patient representatives. Trial co-ordinators, statisticians etc will be invited to attend as appropriate. Observers from the NIHR and the sponsor institution (University of Bristol) will be invited to each meeting.

The role of the TSC is to provide overall supervision of the trial on behalf of the NIHR. In particular, the TSC will focus on progress of the trial, adherence to the protocol, patient safety and consideration of new information.

The TSC terms of reference can be found in Appendix 1.

1.8.3 Data Monitoring Committee

The Data Monitoring Committee (DMC) will meet twice a year.

The DMC will review the accruing trial data, unblinded if appropriate, and assess whether there are any safety issues that should be bought to participants' attention or any reasons for the trial not to continue.

The DMC will be independently chaired by Professor Kerry Hood, Cardiff University. In addition there will be 2 other members who are all independent of both the trial and TSC and experts in the field of the research (Dr Kelly Handley, University of Birmingham, and Dr Kathy O'Brien, Cardiff University). The trial statistician may be invited to attend part of the meeting to present the most current data from the trial.

The DMC terms of reference can be found in Appendix 2.

2. Trial Synopsis

Trial title	Oral Steroids for Acute Cough (OSAC)
Phase	Phase II/III
Sponsor	University of Bristol
Chief Investigator	Dr Alastair Hay
ISRCTN	Tbc
EudraCT No.	2012-000851-15
REC reference	12/SW/0180
Medical condition under investigation	Acute lower respiratory tract infection
Purpose of trial	To test whether the use of oral prednisolone 40mg daily for 5 days will reduce the duration of moderately bad or worse cough, and its associated severity, by at least 20% when compared to placebo.
Primary objectives	To investigate in adults ≥18 years presenting to primary care with acute lower respiratory tract infection (LRTI) if the use of oral prednisolone, compared with placebo, reduces: 1. The duration of moderately bad or worse cough by at least 20% and/or 2. The mean of all symptom severity scores on days 2 to 4 (where day 1 is the day of the index consultation).
Secondary objectives	In relation to the use of oral steroids compared with placebo for acute LRTI, we will also: 1. Assess the effects on antibiotic consumption 2. Compare the burden, severity and duration of other symptoms: cough until very little problem; phlegm; shortness of breath; wheeze; blocked / runny nose; chest pain; fever; muscle aching; headache; sleep disturbance; feeling generally unwell; activity disturbance 3. Estimate the cost-effectiveness from the perspectives of the NHS, patients, and society 4. Compare all adverse events including: any new symptoms or worsening of existing symptoms, re-consultations for a documented deterioration in illness and Serious Adverse Events 5. Investigate if response to oral steroids is associated with a clinical diagnosis of asthma at 3 months 6. Assess the patient's satisfaction with treatment and intention to consult for future similar illnesses.
Trial design	A two-arm, individually-randomised, placebo-controlled, blinded superiority trial comparing oral steroids with placebo in patients attending primary care with acute LRTI.
Trial participants	Non-asthmatic adults aged 18 and over
Outcomes	*Primary outcomes:* 1. Duration of moderately bad or worse cough (using a validated[1] web-/paper-based symptom diary) 2. The mean of all symptom severity scores on days 2 to 4 (where day 1 is the day of the index consultation, measured using the symptom diary). *Secondary outcomes:* 1. Antibiotic consumption (symptom diary) 2. Duration of steroid tablet use (symptom diary) 3. Total duration and severity of other symptoms (cough until very little problem; phlegm; shortness of breath; wheeze; blocked / runny nose; chest pain; fever; muscle aching; headache; sleep disturbance; feeling generally unwell; activity disturbance) and abnormal peak flow (symptom diary[1])

	4. Adverse events (see above) including re-consultation for a documented deterioration in illness or hospital admission (symptom diary, weekly telephone call and primary care notes review) 5. Patient satisfaction with treatment and intention to consult for future similar illnesses (symptom diary) 6. Clinical diagnosis of asthma or COPD/ at 3 months (primary care notes review) 7. Quality of life using the EQ-5D (as recommended by NICE[2], web-/paper-based questionnaire administered via weekly telephone call to the patient) 8. NHS treatment and investigation (e.g. chest x-rays, re-consultation) costs (primary care notes review), out-of-pocket patient costs, and societal cost of time off work (symptom diary and/or weekly telephone call).
Sample size	436
IMP, dosage, route of administration	Oral prednisolone (40mg daily) or matched placebo
Duration of treatment of a subject	5 days of treatment with prednisolone or matched placebo, completion of daily symptom diary for up to 28 days (or until patient feels that they have recovered from their illness, whichever is sooner), weekly telephone contact for 28 days (to support symptom diary completion and to collect resource use and quality of life data), or longer if symptoms persist beyond 28 days (weekly telephone interview only) and primary care notes review (conducted after 3 months post-randomisation).

3. Trial Flow Diagram

An appropriate member of the GP practice team identifies eligible adults presenting at the site with acute cough.

→ **PATIENT NOT PRESENTING WITH ACUTE COUGH:** The patient has no further involvement in the trial.

The patient is given a Patient Information Sheet (PIS) explaining what is involved in trial participation. The patient sees the Responsible Clinician as per routine care, who establishes whether the patient's main reason for consulting is acute cough and if they are willing to consider taking part in the OSAC trial. If yes, the patient and Responsible Clinician discuss trial participation. If the patient is willing to participate, the Responsible Clinician will:

- Take verbal consent and record this on the paper Case Report Form (CRF);
- Check the patient's eligibility against the detailed inclusion/exclusion criteria;
- As part of this eligibility check, the Responsible Clinician will check on the GP Practice Information System for any drug interactions which may make the patient ineligible, and record this on the CRF;
- Also as part of this eligibility check, carry out a routine clinical examination, the results of which are recorded on the CRF;
- Complete their routine management, including the discretionary use of a delayed antibiotic prescription (only use after 48 hours if symptoms are worsening or if failing to improve after 7 days).

This consultation will be referred to as the **index consultation**.

→ **PATIENTS DECLINING TO PARTICIPATE OR INELIGIBLE:** Anonymised descriptive data, with Screening ID and reasons for declining to participate or ineligibility, recorded on the site screening log. Declined or ineligible patients have no further involvement in the trial.

If the patient is eligible to participate according to the initial screening process (as above, which includes the check on the practice system for possible drug interactions, and the findings of the clinical examination), the Responsible Clinician will confirm whether the patient wishes to participate in the trial. The Responsible Clinician then books the willing patient into the **baseline recruitment consultation** with a primary care Research/Practice Nurse (from hereafter referred to as the "Recruiting Clinician") who has dedicated time to recruit the patient. The Responsible Clinician then signs the trial prescription (which can only be redeemed by the Recruiting Clinician at the practice) and hands this, and the trial paperwork (the screening form and Responsible Clinician part of the CRF) to the Recruiting Clinician. The patient will then:

(1) Proceed directly to the baseline recruitment consultation allocated by the practice to collect the recruitment data for the patient, or

(2) Arrange another time (on the day of presentation or on the next working day) to attend the baseline recruitment meeting.

→ **PATIENTS DECLINING TO PARTICIPATE:** Anonymised descriptive data, with Screening ID and reasons for declining to participate, recorded on the site screening log. Declined or ineligible patients have no further involvement in the trial.

→ **PARTICIPANTS:** Screening, Trial CRF (clinical examination, and diagnosis sections).

Baseline recruitment meeting: The Recruiting Clinician collects the trial paperwork pertaining to the patient (completed Responsible Clinician part of the CRF, and trial prescription). The Recruiting Clinician gives the patient a full explanation of the trial and obtains written consent. The Recruiting Clinician then:

- Takes his/her next Patient Pack or PP (which includes the pre-randomised (oral steroids or placebo) Medicine Pack) and enters the Patient and Medicine Pack numbers and baseline data onto a web- or paper-based CRF, depending on the Recruiting Clinician's preference (these data will later be entered onto the web-based trial database - electronic CRF (eCRF);
- Attaches Patient ID Number stickers (provided within the PP) to each of the pieces of trial paperwork that have been completed by the Responsible Clinician (completed Responsible Clinician part of the CRF, and trial prescription).
- Completes the remainder of the CRF with the patient. Although it is unlikely, it is possible that during the process of completion of the CRF a further reason for ineligibility may be revealed. If this occurs, the Recruiting Clinician will explain to the patient that they are not eligible after all, and will not issue them with the PP.
- Gives the patient the PP, and teaches them how to: (1) take the trial medicines (as per the trial prescription); (2) return unused trial medicines to the research team (using the pre-paid return envelope provided in the PP); (3) take and record the peak flow readings (using the peak flow meter provided within the PP); (4) complete the symptom diary and return this to the trial centre (using separate pre-paid return packaging).

→ **PATIENTS NOT ELIGIBLE:** Any reasons for ineligibility revealed by the CRF completion process are recorded on the CRF. Ineligible patients have no further involvement in the trial.

→ **PARTICIPANTS:** Trial CRF (symptoms, medical and family history, clinical observations).

Completion of symptom diary for up to 28 days, and weekly telephone contact to collect resource use / QoL data for 28 days (or weekly telephone contact until all symptoms resolve, should the patient's symptoms persist beyond the 28 day period): The trial Research Team supports and encourages patients to complete of the symptom diary (online or paper) through weekly telephone contact (information about resource use and quality of life will also be collected at these points), with additional optional email or text reminders.

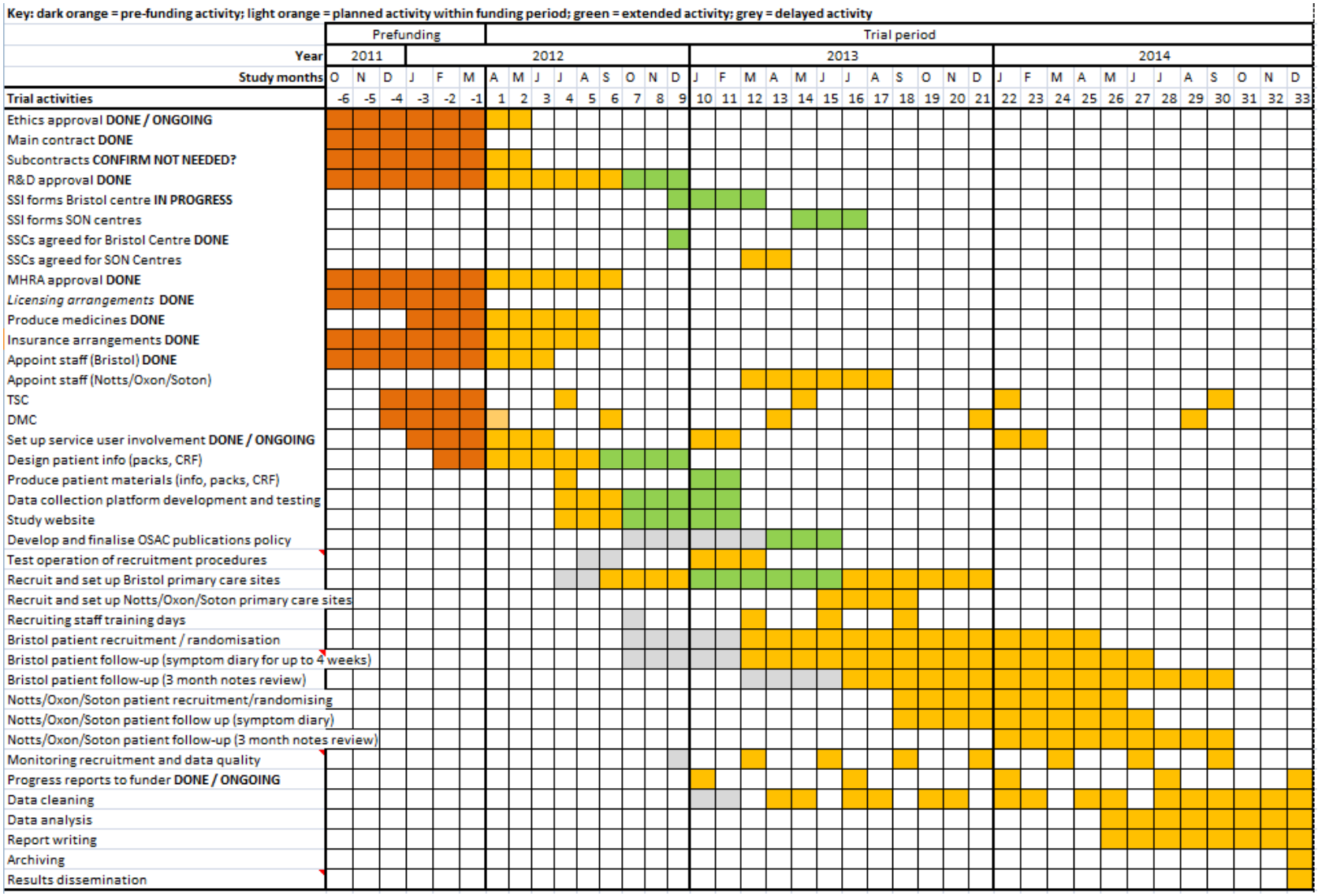
→ **PARTICIPANTS:** Symptom diary, patient resource use / costs, QoL measures.

Medical notes review: The trial Research Nurse or the primary care site completes a form designed to extract information from the primary care patient notes regarding: (i) the number of NHS contacts (with reasons), investigations, prescriptions and referrals in the month following recruitment and (ii) clinical diagnoses of asthma, COPD, whooping cough (pertussis) and/or lung cancer in the 3 months following recruitment.

→ **PARTICIPANTS:** NHS contacts, referrals, antibiotic prescription, adverse events.

4. Timetable and Milestones

4.1 Trial activities



OSAC Gantt chart updated 21 February 2013

4.2 Trial staff

Year	2011			2012											2013												2014											
Study months	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
Trial staff	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Trial Manager Bristol																																							
Trial Administrator Bristol 1 (1 FTE)																																							
Trial Administrator Soton (0.2 FTE)																																							
Trial Administrator Oxford (0.2 FTE)																																							
Trial Administrator Nottingham (0.2 FTE)																																							
Research Nurse Bristol (1.0 FTE)																																							
Research Associate Soton (0.4 FTE)																																							
Research Associate Oxford (0.4 FTE)																																							
Research Associate Nottingham (0.4 FTE)																																							
Research Associate Health Econ (0.4 - 0.6 FTE)																																							
Research Associate Statistician (0.5 FTE)																																							
Trials Unit Research Mngr (BRTC) (0.2 - 0.05 FTE)																																							
Database Manager Oxford (0.5 to 0.25 FTE)																																							

OSAC Gantt chart updated 12 September 2012

5. Glossary of Terms

Baseline recruitment consultation	A separate meeting following the index (or routine) consultation, in which the GCP-trained primary care clinician responsible for recruiting the patient to the trial (the Recruiting Clinician) provides a full explanation of trial participation, takes consent, completes the trial Case Report Form and provides the patient with the patient pack (including the trial medications). This appointment should be on the same working day as the routine consultation, or on the next working day.
BRTC	Bristol Randomised Trials Collaboration
Centre	One of the four cities (Bristol, Nottingham and Oxford and Southampton), each with a PI, from which Sites will be recruited and co-ordinated.
Code-break	Record held by UHBristol of allocation of active vs. placebo (and Medicine ID number) to Patient ID number.
CRF	Case Report Form
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product, also referred to as the "Trial Medicine". This is either prednisolone or matched placebo.
Index consultation	The routine consultation between the patient and the GCP-trained primary care clinician responsible for the patient's routine care, in which the patient's Responsible Clinician checks that the patient is presenting with acute cough as the main concern, introduces the trial, takes verbal consent and carries out a detailed check of eligibility including checking for potential drug interactions on the GP practice information system. The Responsible Clinician also arranges a separate, subsequent baseline recruitment consultation with another GCP-trained primary care clinician responsible for recruiting the patient (the Recruiting Clinician), taking written consent, collecting baseline recruitment data and issuing the patient pack or PP (including the trial medications).
LRTI	Lower respiratory tract infection
Medicine ID number	The unique number assigned to the IMP at manufacture (by the IMP manufacturer using the randomisation data provided by BRTC) and assigned, with the Patient Pack, to the Patient ID number according to the randomisation schedule provided to UH Bristol by the BRTC.
Medicine pack	The packaging containing the IMP uniquely identified by the Medicine ID number.
Patient ID number	The unique number already allocated to the PP which is assigned to the recruited patient by the Recruiting Clinician following informed written consent during the baseline recruitment interview.
Patient pack (PP)	The plastic wallet containing all the materials necessary for patient recruitment. All items will be labelled with the Patient ID Number and will include a: Consent Form, PIS, CRF, Symptom Diary, pre-paid return envelope (for returning the completed symptom diary should the patient wish to complete this on paper), pre-paid return packaging (for returning any unused trial medicines to the research team), uniquely identified Trial Medicine Pack (containing either prednisolone or matched placebo), Peak Flow Meter and plastic Mouthpiece, Trial Participation Card, Patient ID stickers, an OSAC pen and a £5 High Street Voucher as a token of thanks for the patient's time in undertaking to participate in the trial.
PIS	The Patient Information Sheet, which is given to the patient on arrival at the primary care site, or by the Responsible Clinician, and also included in the patient pack. All patients will be provided with the full PIS and a summary

	PIS (which has been ethically approved).
Randomisation data	A list of random numbers generated by BRTC in line with the requirements of the trial sponsor and of the medicine supplier (Piramal) and provided to Piramal (in a manner which maintains the complete blinding of the trial team) for their use in numbering the medicine packs which are provided to UH Bristol Pharmacy. The random numbers will form the identifiers on the open code break document sent with each delivery of medication packs to UH Bristol.
Randomisation schedule	Instructions provided by BRTC to UH Bristol Pharmacy regarding active vs. placebo medicine allocation to Patient Packs.
Recruiting Clinician	The GCP-trained primary care clinician who takes responsibility for consenting and recruiting the patient according to the OSAC trial protocol.
Responsible Clinician	The GCP-trained primary care clinician who takes responsibility for the clinical management of the patient's LRTI at presentation, for confirming the patient's eligibility to take part in the trial, for checking for possible drug interactions on the GP practice information system, for conducting the clinical examination and for signing the trial prescription (for steroids or placebo) and passing this to the Recruiting Clinician.
Screening ID	The unique number assigned to the trial Case Report Form sections 1 and 2 prior to confirming patient eligibility for recruitment into the trial during the index consultation. This number will be entered onto the trial screening log to allow for tracking of ineligible patients.
Site	GP practice
Source data	For the OSAC trial, the source data will be defined as follows: **Case Report Forms:** for CRF sections 1, 2 and 4 the source data will be the electronic data entered by clinicians onto OpenClinica at the GP site within 24 hours of recruitment, transcribed at the site from the paper forms. For CRF3, the source data will be considered to be the paper copy of the form returned by clinicians to the trial centre. **Patient symptom diary:** the source data for patients completing the diary online will be the electronic data they enter that is uploaded into OpenClinica. For patients completing paper symptom diaries, the source data will be considered to be the data recorded on the paper diary IF this is more complete than the shadow diary data collected by the trial research team in the weekly follow-up telephone calls. For patients whose paper diaries are not returned, or where the data returned in the paper diary are less complete than the shadow data, the shadow data collected on the phone will be considered as the source data. **Review of primary care medical notes:** the source data will be considered to be the electronic data entered onto OpenClinica at the GP practice.
Trial Participation Card	Trial participants will be requested to carry this with them while participating in the trial. It will record the Medicine and Patient ID numbers to be used for emergency unblinding.
Trial Prescription	If the patient is eligible to participate in the trial (following completion of the detailed eligibility check, including checking for interactions on the GP practice information system, and the clinical examination) the Responsible Clinician will authorise a trial prescription, to be passed by the practice to the Recruiting Clinician at the baseline recruitment meeting, and on receiving which the Recruiting Clinician will be authorised to provide the consented patient with a trial PP.

6. Lay summary

Most people get at least one chest infection every year and a high proportion present to health services (annual NHS cost for consultations and antibiotics £190M) and need to take time off work/other responsibilities. Symptoms are frequently prolonged (lasting 3 to 4 weeks) and no treatment (including antibiotics) has been shown to reduce either symptom severity or duration. Despite this, and strong evidence that inappropriate antibiotic prescribing fuels the development of the antibiotic-resistant bacterial strains (including MRSA), around 75% of adults presenting to GPs are still prescribed antibiotics.

Many of the symptoms of chest infections (cough, phlegm, shortness of breath and wheeze) overlap with those of asthma attacks. While there is good evidence that steroids help patients with asthma, very little research has been conducted to assess if steroids can have the same beneficial effects in non-asthmatic patients suffering from chest infections. More evidence is needed to help doctors to understand if a high dose of steroids (given by tablets) are better than, and could help doctors and patients to rely less on, antibiotics. A high dose has been selected to maximise the chances of the trial detecting an effect. If effects are found, lower doses will be tested in the future.

To carry out this research 436 non-asthmatic adults will be recruited from GP practices. People who are very unwell will be excluded, and those suffering from chronic health conditions. The main marker of success will be if oral steroids shorten the duration of the most severe symptoms by at least 20%. The ability of steroids to help reduce antibiotic consumption, help doctors identify previously unrecognised asthma and reduce costs to the NHS, will also be investigated.

Only patients who give valid, written consent will take part in the trial. They will be randomly given either (i) a 5 day course of (active) steroid tablets or; (ii) a 5 day course of placebo (inactive) tablets that look, feel and taste identical to the active treatment. They will be asked to complete a daily symptom diary (either on-line, or a paper-based version) for at least 7 and up to 28 days (or until they feel they have recovered from their illness, whichever is sooner), and must be available to receive a weekly telephone call from the trial team, for 4 weeks, to record data on their healthcare costs and quality of life. Should the patient's symptoms persist beyond the 28 day period, we will seek their permission to continue to make weekly telephone contact in order to collect data on the duration of their symptoms. Participation will not affect patients' access to all other aspects of usual care, and in an emergency, their doctor will be able to find out which treatment they were given.

If the use of steroids was to reduce the annual cost of treating chest infections by as little as 1%, then the NHS would recoup the cost of the trial in one year. The research will be carried out by a multi-disciplinary team who have a successful track record of collaborative working that has delivered a number of large, NIHR- and MRC-funded clinical trials and other studies (see Section 25).

7. Expert Summary

- Acute lower respiratory tract infection (LRTI), defined as an acute cough with at least one of: sputum, chest pain, shortness of breath and/pr wheeze, is one of the most common conditions managed by health services internationally.
- LRTI is costly to both health services (consultations and antibiotic use) and patients (lost time from work, reduced quality of life).
- Despite good evidence that antibiotics do not reduce the duration or severity of LRTI symptoms, they continue to be widely prescribed leading to unnecessary bacterial resistance to antibiotics.
- Many of the symptoms observed in LRTI are mediated by inflammation, and are also seen in patients with exacerbations of asthma, for which systemic corticosteroids ("steroids") are highly effective.

- European evidence suggests that clinicians are already using steroids for LRTI, even though there is very limited evidence to support their use for this condition.
- The trial hypothesis is that oral steroids at 40mg daily for 5 days (vs. placebo) will reduce the duration of moderately bad (or worse) symptoms associated with LRTI by at least 20% in adults ≥18 years presenting to primary care.
- This relatively high dose of steroids has been selected in order to maximise the probability of detecting a treatment effect, i.e. an 'efficacy' dose has been selected such that a negative result cannot be criticised for being due to an inadequate dose. However, in the event of a positive result, the widespread use of high-dose steroids for all patients with LRTI would not necessarily be advocated, but rather, that further research using lower dose oral as well as inhaled steroids should be conducted.
- An individually-randomised, controlled, blinded trial design will be used in which patients are given either (i) 2 x 20mg oral prednisolone tablets daily for 5 days; or (ii) 2 x placebo tablets for 5 days.
- Duration of moderately bad or worse cough and/ or the severity of all its associated symptoms on days 2 to 4 (the primary outcomes) will be assessed using a validated symptom diary. Secondary outcomes will include: antibiotic consumption; duration of tablet use; total duration and severity of cough (and other) symptoms; adverse events or clinical diagnoses of asthma at 3 months, patient satisfaction with treatment and intention to consult for future similar illnesses; quality of life, costs and time off work; and the number of primary and secondary care NHS contacts up to and including 1 month, including investigations, e.g. chest x-rays.
- With an alpha of 0.05 and a beta of 0.9, and conservatively allowing for attrition of 0.2, the trial will need to randomise 218 patients to each arm (total = 436).
- For the primary analysis, descriptive statistics will be obtained for the two treatment groups to characterise patients and assess baseline comparability. In accordance with CONSORT guidelines, all comparative analyses will be conducted on an intention-to-treat basis. The primary comparison will be the steroid versus placebo therapy.
- The cost-effectiveness of the steroids will be assessed by comparing the patient benefit observed with the cost to the NHS, to patients and to society in general.
- Results from this trial will increase knowledge regarding the specific clinical and cost-effectiveness of steroids for LRTI (and so give clinicians a treatment option that could substantially improve health), but also contribute to a growing body of research investigating the effects of steroids on the undesirable inflammatory symptoms associated with infection.
- The trial will be conducted by an internationally-recognised group with expertise in the clinical area and the proposed scientific methods, as well as a track record of successful collaboration to deliver complex, multicentre studies.

8. Introduction

8.1 Background

Epidemiology, costs and current management of acute LRTI

LRTI, defined as an acute cough with at least one of: sputum, chest pain, shortness of breath and/or wheeze,[3] is the one of the most commonly condition managed in primary care in the UK and internationally.[4] Assuming 75% of patients are prescribed antibiotics[5] and a 20% re-consultation rate (within the same illness episode),[3] using conservative national morbidity survey estimates,[4] acute cough costs the UK National Health Service at least £190 million annually.[6] Patient costs have also been shown to be significant[7] and absenteeism from work is common.

Despite very good evidence that antibiotics do not reduce the duration or severity of LRTI symptoms,[8] they continue to be widely prescribed[5] leading to unnecessary bacterial resistance to antibiotics.[9] This constitutes an increasing and serious threat to public health.[10]

Rationale for testing the effectiveness of corticosteroids in LRTI

Symptoms of LRTI include cough, wheeze and shortness of breath which are similar to the symptoms of exacerbated asthma.[11 12] The moderately bad (or worse) symptoms associated with LRTI may be expected to last up to 1 week,[6] while complete symptom resolution may take 3 to 4 weeks. These prolonged symptoms are thought to be due to a transient bronchial hyper-responsiveness.[13 14] Experimental evidence suggests similar changes to bronchial epithelium in people with and without asthma during a respiratory tract infection, with a significant reduction in FEV_1 seen in both groups,[11] as well as bronchial hyper-responsiveness and airways inflammation.

Oral and inhaled corticosteroids ("steroids") are widely prescribed for the treatment of, respectively, acute and chronic asthma and work by exerting an array of anti-inflammatory effects.[15] There is increasing interest in the potential role of steroids in modifying the undesirable effects of infection-associated inflammation. Benefits have been demonstrated for children with acute croup[16] and community-acquired pneumonia (if also given β agonists);[17] adults hospitalised with community-acquired pneumonia;[18] adults with post-infectious persistent cough;[19] and adults with acute tonsillitis.[20] The trial team is aware of further trials being planned or currently recruiting, e.g. oral steroids for children with deafness associated with otitis media plus effusion (personal communication Dr Nick Francis, March 2011) and steroids for acute sinusitis (personal communication, Professor Theo Verheij, October 2011). Research and anecdotal evidence suggests that, respectively, European and UK clinicians have started prescribing steroids for LRTI (in the absence of chronic obstructive pulmonary disease or COPD),[21] even though there is limited evidence to support them for this condition.

Long-term steroid use is known to be associated with an array of unwanted systemic side effects.[22] However, in the absence of specific contraindications,[22 23] a short (up to 1 week) course of high dose steroids is considered to be safe and associated with few side effects.[24] One trial found that there was no difference in rates of adrenal suppression between 40mg of prednisolone given for 8 days and either tapered off or abruptly stopped.[25] Furthermore, any adrenal suppression that does occur with a short term course is minimal and likely to dissipate within 1-2 weeks.[23]

On 15 March 2011, Medline, Embase and Cochrane were searched for systematic reviews or RCTs using the terms: ["Chest infection.mp" or "acute bronchitis.mp" or "lower respiratory tract infection.mp" or "lower respiratory tract illness.mp" or "acute cough.mp"] combined with ["Randomi*"] and ["steroids.mp" or corticosteroids.mp"] and found one relevant trial.[26] This tested the effects of very high dose fluticasone (1mg twice daily, equivalent to 2mg twice daily of beclometasone, for 2 weeks) in non-asthmatic adults presenting to Dutch primary care with cough >2 weeks. The inhaled corticosteroids were effective in reducing the mean cough frequency score among non-smokers, but interpreting the clinical importance of a reduced cough score is difficult for clinicians and patients, the effects of oral steroids were not tested and there was no economic evaluation. The International Controlled Trials Register (see http://www.controlled-trials.com/isrctn/) has also been searched to confirm there are no similar trials being currently conducted or planned.

Since there is good evidence of oral steroid effectiveness for acute asthma; the symptoms of LRTI overlap with those of acute asthma; prednisolone tablets at a dose of 40mg daily for 5 to 7 days is the most commonly used oral steroid for acute asthma; there is pharmacokinetic evidence to suggest a minimum dose of 20mg daily is required for non-asthmatic patients,[27] and it is important that the first trial of its kind uses an adequate (anti-inflammatory) dose; a placebo-controlled, randomised trial is proposed to test the effectiveness of oral steroids at 40mg daily for 5 days for adults presenting to primary care with acute LRTI.

8.2 Justification for trial design

This translational research will provide definitive information to help primary care clinicians improve the management of LRTI, for which there is currently no effective intervention. A blinded, maximum dose, design has been chosen since: (a) the primary outcome is subjective and; (b) treatment with this agent for this clinical problem is novel making a trial on the efficacy end of the spectrum important.

The primary outcomes of 'duration of moderately bad or worse symptoms' and 'mean severity of all symptoms between days 2 and 4' (where day 1 is the day of the index consultation) have been selected since the

hypothesis is that the anti-inflammatory effects of steroids will relieve both the duration and severity of the unwanted bronchospasm and other unwanted inflammatory side effects of infection. The timing of the severity outcome between 2 and 4 days has been selected as this is when symptoms are rated as the worst problem by patients.[6]

The OSAC trial will use the same, validated symptom diary that has been used in a number of similar previous trials.[6] [28] The diary records the severity of the following symptoms: cough; phlegm; shortness of breath; wheeze; blocked / runny nose; chest pain; fever; muscle aching; headache; sleep disturbance; feeling generally unwell; activity disturbance.

Each symptom was scored from 0 to 6 (0 = no problem, 1 = very little problem, 2 = slight problem, 3 = moderately bad, 4 = bad, 5 = very bad and 6 = as bad as it could be). The diary has previously been validated,[1] is sensitive to change and internally reliable (Cronbach's alpha 0.75 i.e. in optimal range).[6]

The EQ-5D has been shown to be moderately responsive in patients with acute cough/LRTI, and is a suitable measure for use in economic evaluation studies of acute cough/LRTI.[29]

If a clinically important treatment effect is demonstrated, then it will not be concluded that high-dose steroids should be routinely used for patients with acute LRTI (though of course this remains a clinical decision). Rather, further trials of lower-dose oral/ inhaled steroids would be conducted. If no treatment effect is found, it is unlikely that further, lower-dose steroid research would be warranted for acute LRTI.

9. Trial Objectives and Design

9.1 Trial Hypothesis

The use of oral prednisolone 40mg daily for 5 days (NHS cost = £2.18) will reduce the duration of moderately bad or worse cough and/ or the severity of all symptoms on days 2 to 4 by at least 20% when compared to placebo treatment in adults ≥18 years presenting to primary care with acute LRTI.

9.2 Trial Design

The trial will be a two-arm, individually-randomised, placebo-controlled, superiority trial comparing oral steroids with placebo in patients attending primary care with acute LRTI.

9.3 Primary Research Questions

Does the use of oral prednisolone reduce the duration of moderately bad or worse cough and/ or the severity of all its associated symptoms on days 2 to 4 by at least 20% when compared to placebo treatment in adults ≥18 years presenting to primary care with acute LRTI?

9.4 Secondary Research Questions

In relation to the use of oral steroids compared with placebo treatment for acute LRTI, we will also:

1. Assess the effects on antibiotic consumption;
2. Estimate the cost-effectiveness from the perspectives of the NHS, patients, and society;
3. Compare the burden, severity and duration of abnormal peak flow and the following symptoms: cough until 'very little problem'; phlegm; shortness of breath; wheeze; blocked / runny nose; chest pain; fever; muscle aching; headache; sleep disturbance; feeling generally unwell; activity disturbance
7. Compare adverse events including: any new symptoms or worsening of existing symptoms, re-consultations for a documented deterioration in illness and Serious Adverse Events.
8. Investigate if patients' subjective or objective response to oral steroids is associated with a clinical diagnosis of asthma or COPD;
4. Assess patients' satisfaction with treatment and intention to consult for future similar illnesses.

9.5 Population

Adults (≥18 years) presenting to primary care with cough as the main symptom and with at least 1 symptom or sign localizing to the lower respiratory tract (sputum, chest pain, shortness of breath and/or wheeze). These eligibility criteria are accepted in the field and are the same as used in previous studies of LRTI.[3 6]

9.6 Intervention and placebo

Patients will be randomly assigned to one of two treatments: (i) 2 x 20mg oral prednisolone tablets daily for 5 days or; (ii) 2 x 20mg oral placebo tablets daily for 5 days (patients may stop taking the trial medication earlier than this if they feel completely better). Patients, clinicians, outcome assessors and the trial team will be blinded to allocation through the use of placebo tablets. At the discretion of the responsible clinician, and in line with NICE guidance,[2] all patients will be offered either no antibiotic or a delayed (rescue) antibiotic (of the clinician's choice) prescription, which will be post-dated for at least one working day after the recruitment interview. Clinicians will not be restricted in their prescribing of β agonist inhalers (e.g. salbutamol).

9.7 Outcomes

Primary outcomes:

1. Duration of moderately bad or worse cough (using a validated[1] web/paper based symptom diary);
2. The mean of all symptom severity scores on days 2 to 4 (where day 1 is the day of the index consultation, measured using the symptom diary).

Secondary outcomes:

1. Antibiotic consumption (symptom diary);
2. Duration of steroid tablet use (symptom diary);
3. Total duration and severity of other symptoms (cough until 'very little problem'; phlegm; shortness of breath; wheeze; blocked / runny nose; chest pain; fever; muscle aching; headache; sleep disturbance; feeling generally unwell; activity disturbance) and abnormal peak flow (symptom diary[1]);
4. Adverse events (see above) including re-consultation for a documented illness deterioration (symptom diary and primary care notes review);
5. Patient satisfaction with treatment and intention to consult for future similar illnesses (symptom diary);
6. Clinical diagnosis of asthma or COPD at 3 months (primary care notes review);
7. Quality of life using the EQ-5D (as recommended by NICE[2], questionnaire administered via weekly telephone call);
8. NHS treatment and investigation (e.g. chest x-rays, re-consultation) costs (primary care notes review), out-of-pocket patient costs, and societal cost of time off work (symptom diary / weekly telephone call).

9.8 Expected Duration of Trial

The overall trial duration will run from 1st April 2012 to 31st December 2014, with patient recruitment taking place from the end of October 2012 (pending all approvals in place) to 27 October 2014. Recruitment will take place in the Bristol centre in the first recruiting season (2012-13), and all four centres (Bristol, Oxford, Nottingham and Southampton) will recruit during the second season (from September 2013 to October 2014).

Each patient will be involved in the trial for up to 28 days. Patients will be asked to measure and record their peak flow, and complete a daily symptom diary for no less than 7 days and up to 28 days (or sooner if all of their symptoms are resolved for two days running); to record any potential side effects of the trial medication for the first 7 days; and to answer four sets of weekly questions about their use of healthcare resources and their quality of life (on days 7, 14, 21 and 28, and, for consenting patients whose symptoms

persist beyond the 28 day period, weekly telephone calls will continue to be made until all symptoms have resolved, to collect data on symptom duration). Patients' medical notes will also be reviewed by the research team or by the primary care site after three months from randomisation.

9.9 End of Trial

The end of the trial will occur when the data analysis has been completed.

10. Selection of Subjects

10.1 Inclusion Criteria (all must apply)

1. Aged 18 years or over
2. Consulting for an acute (≤ 28 days) cough as the main presenting symptom
3. In the past 24 hours, the patient has had at least one of the screening symptoms listed below (a-d), localizing to the lower respiratory tract and suggestive of an acute lower respiratory tract infection (RTI):
   a) Phlegm (sputum)
   b) Chest pain
   c) Shortness of breath
   d) Wheeze
4. Patient and practice have sufficient time for consent and randomisation into the trial by the end of today
5. Patient able and willing to give informed consent themselves
6. Patient able and willing to complete the daily symptom diary themselves
7. Patient able, willing and available to receive weekly telephone calls from the trial team.

10.2 Exclusion Criteria (presence of any warrants exclusion)

1. Known lung cancer or chronic lung disease (e.g. cystic fibrosis, COPD, bronchiectasis)
2. Has an 'active' diagnosis of asthma (for which any treatment has been given in the past 5 years)
3. The patient's RTI warrants same day hospital admission or immediate antibiotics (NB: use of delayed prescription (post-dated by at least one working day after the recruitment interview) does not preclude OSAC trial participation):

   According to NICE guidelines, the patient warrants immediate antibiotic treatment by virtue of ONE OR MORE of the following:

   A. Is clinically very unwell or has symptoms and signs suggestive of pneumonia, *e.g. tachypnoea (>20bpm), unilateral chest signs or consolidation, or hypoxia (oxygen saturation <94%)* or other systemic infection, *e.g. suspected bacteraemia* OR

   B. Is at high risk of complications, including patients with chronic heart, chronic lung (e.g. COPD, bronchiectasis and cystic fibrosis), chronic renal, chronic liver or neuromuscular disease or immunosuppression; or with complications from previous episodes of lower respiratory tract infection, e.g. hospital admission for pneumonia OR

   C. AGED OVER 65 years with at least TWO of the following criteria, or AGED OVER 80 years with at least ONE of the following criteria:

      I. Unplanned hospitalisation within the previous year

      II. Type 1 or Type 2 diabetes

      III. History of cardiac failure
4. Requires an oral or systemic antibiotic today to treat another infection unrelated to their acute cough, e.g. a co-existing cellulitis (NB: use of topical antibiotics does not preclude OSAC trial participation)
5. Recently (≤1 month) used inhaled corticosteroids
6. Recently (≤1 month) used short (up to 2 weeks) course systemic corticosteroids
7. Currently using, or has previously (≤12 months) used systemic steroids for a cumulative period greater than 2 weeks, i.e. "long-term" use

8. Known to be pregnant, is trying to conceive or is at risk of pregnancy (e.g. unwilling to take a reliable form of contraception) in the next month
9. Currently breast-feeding
10. This is not the patient's usual practice, i.e. patient is visiting or is not intending to stay with the practice for the 3 month trial follow up period
11. Previously randomised in the OSAC trial
12. Has been involved in another medicinal trial within the **last 90** days or any other clinical research study within the **last 30** days
13. Is unable to give informed consent or complete the trial paperwork (including the symptom diary) through mental incapacity, e.g. major current psychiatric illness, learning difficulties and dementia
14. Known immune-deficiency, e.g. chemotherapy causing immunosuppression, asplenia or splenic dysfunction, advanced cancer or HIV infection
15. **(For winter 2014/2015 only)** patient is **aged 70, 78 or 79** and due to receive the shingles vaccine in conjunction with the influenza vaccine
16. Has any of the following (A – P) known contra-indications or cautions to oral steroids

Current OR previous history of:

A. Peptic ulcer disease

B. Previous TB

C. NO previous chickenpox AND known recent (≤28 days) history of close personal contact with chickenpox OR herpes zoster

D. Known allergy to prednisolone or other OSAC trial tablet ingredients (potato starch, lactose monohydrate, colloidal silicon dioxide, sodium starch glycolate, magnesium stearate), galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption

E. Osteoporosis

F. Glaucoma

G. Suspected ocular herpes simplex

H. Cushing's disease

I. Epilepsy

J. Severe affective disorders, e.g. manic depression, previous steroid psychosis

K. Previous steroid myopathy

L. Intention to use a live vaccine in the next 8 weeks **or** has received a live vaccine in the previous 2 weeks (NB: assess live vaccine status by cross-checking with BNF)

Current history only:

M. Uncontrolled diabetes (HbA1C > 8%)

N. Uncontrolled hypertension (NB: as per Responsible Clinician's routine clinical judgement)

O. Taking other interacting medication (e.g. phenytoin and anti-coagulants)

P. ANY OTHER BNF listed contra-indication or caution (NB: as per Responsible Clinician's routine clinical judgement)

17. Is unable to swallow tablets

Clinicians will be asked to use the British National Formulary (BNF) and their clinical prescribing systems to check for significant interactions for all patients. A SOP will be produced to describe the checking process.

10.3 Selection of Participants

The trial aims to recruit 436 patients, attending primary care with acute LRTI, into the trial. On arrival at the site every potential participant will be given a Patient Information Sheet (PIS) by the primary care site inviting them to participate in the trial. Participating sites will also be provided with PDF copies of the PIS so that they can be e-mailed to patients who make initial contact with the practice by telephone, to enable the patient to become familiar with the aims of the research before they visit the practice. A summary PIS developed to complement the full PIS has been ethically approved.

Verbal consent will be sought before a full eligibility check is performed. Subject to meeting the inclusion and exclusion criteria, a subject will be asked to give written informed consent prior to receiving the trial medications. Participant involvement in the trial is detailed further in Section 11.

10.4 Selection of Sites

The Primary Care Research Network (PCRN) will assist with the identification of GCP-trained, research-experienced primary care sites (GP practices). It is a legal requirement that anyone involved with recruitment and the taking of informed consent in a clinical trial must have completed a GCP training course. The OSAC trial team will ensure that these requirements are met through liaising closely with the local PCRN to identify sites with GCP-trained clinicians and by including the requirement for any clinician taking consent for OSAC to have attended appropriate GCP training in line with local practice, but within the last 5 years.

The University of Bristol will follow its Green Light (monitoring) Process, in line with MHRA requirements, in order for the trial sponsor / monitor to document the preparedness of the other collaborating centres (Oxford, Southampton and Nottingham) to conduct recruitment locally.

Following training from, and with the support of, their local centres, these sites will recruit autonomously using methods similar to those successfully employed in previous studies (https://www.grace-LRTI.org and http://www.dutystudy.org.uk/).[6] Web-based data collection (Oxford) and randomisation system (BRTC) will mean no geographical restriction to site participation other than local research governance approval, and sites will be reimbursed for the cost of recruiting and conducting notes reviews through NHS Service Support Costs.

We anticipate that around 15 actively recruiting sites will be needed per centre to complete recruitment over 2 winter recruitment seasons (2 seasons for the Bristol centre, and 1 season for each of the other 3 centres). Following the first recruiting season (2012-13) at the Bristol centre, a formal review of all trial procedures will be conducted in order to inform the start of the second recruitment season (2013-14) which will involve all trial centres.

We are anticipating that the clinical research networks will also assist with site visits and induction to the trial.

10.5 Piloting recruitment

The trial procedures will be piloted through an iterative process where the trial team will liaise closely with a number of independent primary care clinicians to conduct detailed reviews of the paper and electronic CRF, the recruitment procedures and to discuss potential challenges to recruitment to the trial. Recruitment will be initiated in one or two selected GP practices who will conduct internal piloting, i.e. establishing the efficacy of the planned recruitment procedures and materials with real patients. These patients' data will be included in the trial dataset. Once recruitment has been proven to be effective and feasible within the initial 'piloting' sites, and any changes made in response to issues identified during this initial stage, the trial will be opened up to a wider range of participating sites.

10.6 Training for recruiting sites

Each GP practice recruiting to the trial will receive training in all trial recruitment and baseline data collection procedures prior to the start of recruitment. This training will be provided to Bristol centre sites by the Trial Research Nurse, with the assistance of other members of the trial team as appropriate. A training log will be maintained within the Trial Master File. Training will be provided to Oxford, Nottingham and Southampton centre sites by the local trial team with assistance from the Bristol trial centre as required.

All clinicians involved in assessing eligibility, prescribing trial medications and taking consent for the trial will be required to have recently (within 5 years) attended GCP training, evidence of which will be requested and stored in the Trial Master File. The trial team will provide support to recruiting sites in identifying locally available GCP training and in liaising with local PCRN staff to ensure that this is made available to site-based recruiters.

10.7 Randomisation Procedure and Code-break

Randomisation will be stratified by centre (Bristol, Nottingham, Oxford and Southampton) using a variable block size. The four centres will be provided with identical, sealed, sequentially numbered Patient Packs to distribute to the participating recruitment sites (GP practices). The number on the Patient Pack will be that from the randomisation schedule provided by BRTC. After an eligible patient has consented to participate, their details will be entered onto a secure, web-based data collection platform (hosted by Oxford) along with the Patient ID number and the Medicine ID number of the Patient Pack that has been allocated to them.

The patient ID number will be different to the Medicine ID number to enable flexibility in the numbers recruited at each centre, allowing medicine packs to be combined with patient packs as needed at the UH Bristol pharmacy (see Drug Accountability table in section 12.4). This will thus allow for temporary differential fluctuations in recruitment rates between centres.

The UH Bristol pharmacy will hold the randomisation schedule and a log of which Medicine Pack was put into which Patient Pack (hereafter referred to as the Code-break) and provide a 24 hour emergency unblinding service. During working hours (Monday to Friday, 9am to 5pm), concerned clinicians should contact the UH Bristol pharmacy clinical trials unit on 0117 342 4175. Out-of-hours, the Trust on-call Emergency Duty Pharmacist is available via the Trust switchboard 0117 923 0000. Each participant will be given a Trial Participation Card with details of who their Responsible Clinician should contact in the event of an emergency. The Trial Manager and Centre Co-ordinators will also hold these cards.

A standardised procedure for breaking the code will be available (UH Bristol CT 5 01 Emergency Code Breaking). When necessary, the code for a particular participant can be broken at any moment during the trial. The codes will only be broken in case of a medical emergency, if unblinding will influence the patient's treatment, or the patient has suffered an unexpected serious adverse event (e.g. anaphylaxis; admission to hospital with life threatening illness (e.g. septicaemia; meningitis; severe pneumonia requiring ITU admission; death)).

The Code-break will only be released to the investigative team once written confirmation has been received that primary outcome data analysis is complete. The UH Bristol Pharmacy will also record a list of all participants and their treatment allocation and file this in the pharmacy trial file and provide a copy to the Trial Manager at the end of the trial. Formal SOPs will be developed to describe each of these procedures in detail.

11. Trial Procedures

11.1 Baseline assessment

The receptionist or responsible primary care clinician at the primary care site will give adults presenting with LRTI a Patient Information Sheet (PIS) which details what is involved in trial participation, for them to read and consider prior to receiving a full explanation from a GCP-trained primary care clinician. If the patient has made initial contact with the practice by telephone and is able to receive e-mail, participating sites may e-mail a PDF copy of the PIS to the patient so that the patient can become familiar with the aims of the study prior to attending the practice. During the routine consultation (referred to from here on as the 'index consultation') the GCP-trained primary care clinician (referred to from now onwards as the "Responsible Clinician") will raise the possibility of trial participation with patients who are presenting with acute cough as the main concern, and obtain verbal consent following a brief explanation of the trial. The Responsible Clinician will enter a screening ID number onto the first two sections of the CRF prior to checking the patient's eligibility. The Responsible Clinician will then carry out a detailed check of the inclusion/exclusion criteria, including checking on the GP practice information system for any possible drug interactions, and carry out a routine clinical examination of which the results, and the clinician's diagnosis, will be recorded on the CRF. Any patient who is not eligible to participate or declines to participate will be recorded, using the Screening ID to allow for tracking, on the screening form with reasons for ineligibility or declining and have no further involvement in the trial.

The Responsible Clinician completes their routine management, and may give the patient a discretionary delayed antibiotic prescription, post-dated by at least one working day after the recruitment interview (to be used if the patient's condition deteriorates after 48 hours or if failing to improve after 7 days) and the discretionary use of a β agonist. If the patient has given verbal consent, the Responsible Clinician will book them into a 'baseline recruitment' meeting with a GCP-trained primary care clinician allocated by the practice to recruit patients (referred to from now onwards as the "Recruiting Clinician"). The Responsible Clinician will sign and issue a trial prescription (which will be passed directly to the Recruiting Clinician and can only be redeemed against a Patient Pack which will be given to the patient by the Recruiting Clinician). The baseline recruitment meeting must take place on the same day as the index consultation, except in the three situations described below.

Same-day recruitment
Same-day recruitment is preferred because it will be more efficient for many patients, who may want to return to routine activities rather than make another visit to the recruiting site the following day. Same-day recruitment will also help to ensure the validity of antibiotic consumption as one of the secondary outcome measures: many patients will want to start a treatment for their chest infections the day that they see the Responsible Clinician. In the absence of receiving a trial treatment, these patients would be more likely to start taking antibiotics (assuming they have been provided with a delayed prescription or if they visit another healthcare services provider to obtain antibiotics) if they wait until the following day to be recruited.

Patient triaged into an appointment on a subsequent day
If a patient phones up requesting an appointment and is triaged (but not treated with any antibiotics) into an appointment for the following day, this patient could be recruited on the day of their appointment. NB if the patient's cough is managed, i.e. treated with antibiotics, and there is no expectation that they would need to be seen again, they should not be brought back to the practice or visited at home by a Research Nurse with the sole purpose of being recruited into the trial.

Patient or site does not have time for the recruitment interview on the same day as the routine consultation
If the site or patient do not have time for the recruitment interview on the same day as the routine consultation, e.g. if the patient sees the Responsible Clinician at the end of the working day, and if patients requiring a delayed antibiotic prescription are given a post-dated script, the patient can be recruited on the following working day as long as:

1. The recruitment interview is not deferred to the Monday following a weekend;
2. Any delayed prescription should be post-dated by at least one working day after the recruitment interview.

This is to ensure that the patient has the opportunity to take the first dose of their trial medication prior to collecting their delayed antibiotic prescription. The prescription should be kept within the practice and given to the patient when they return for their recruitment interview.

Prior to the baseline recruitment meeting the Recruiting Clinician will have been given the trial paperwork that has been completed by the Responsible Clinician within the index consultation (Eligibility Check CRF, Clinical Examination and Diagnosis CRF, and signed trial prescription). A full trial explanation, and an opportunity to ask questions, is given to the patient by the Recruiting Clinician, and the patient's written consent obtained.

As instructed by the trial prescription, the Recruiting Clinician will issue the patient with a uniquely numbered Patient Pack (including trial medicines, Patient Information Sheet, symptom diary, peak flow meter, trial participation card, prepaid return envelope (in which to return the completed symptom diary to the trial team), prepaid return packaging (in which to return any unused trial medications to the research team), patient ID (PID) stickers, an OSAC pen and £5 High Street Voucher). The Recruiting Clinician will affix the PID stickers onto the CRF and trial prescription paperwork. The Recruiting Clinician will access the secure, web-based data collection platform (hosted by the University of Oxford) to enter the patient's baseline data using

a standard computer within the GP practice. Online data entry will take place either at the recruitment meeting or later, depending on the clinician's preference to use the online or paper data collection forms.

Patients will be recruited in line with the trial recruitment Standard Operating Procedure. This will include checking the first and second parts of the CRF (completed by the Responsible Clinician) for completeness, collecting the remaining baseline recruitment data on the remaining CRF sections, explaining how to take the trial medications, how to measure and record peak flow, how to complete the symptom diary and how to return any unused trial medicines and the empty medicine packaging.

The Recruiting Clinician will note (during the consenting process) and record on the participant registration section of the CRF (paper version only) the following information:

(i) The most suitable day, times and telephone number(s) on which the patient would prefer the research team to make the weekly telephone contact to ask about the patient's resource use and quality of life;
(ii) Whether the patient wishes to complete the symptom diary on paper or on-line;
(iii) How the patient wishes to be further supported in their completion of the symptom diary: i.e. by automated email and/ or daily automated texts in addition to the weekly telephone calls.

To enable the recruitment process to be adapted to suit the site's routine way of working, the CRF will be divided into four sections:

1. Eligibility Check (to be completed by the Responsible Clinician)
2. Clinical Examination and Diagnosis (to be completed by the Responsible Clinician)
3. Participant Registration (to be completed by the Recruiting Clinician)
4. Symptoms, Signs and Medical History (to be completed by the Recruiting Clinician)

Baseline CRF data items to be collected will include:

Socio-demographic factors to include:

- Age
- Gender
- Postcode (in order to assign deprivation index)
- Smoking history

Past medical history to include:

- Medications (acute and chronic)
- Respiratory history (e.g. past history of asthma)

Symptoms will include:

- Duration of cough
- Shortness of breath
- Wheeze
- History of fever
- Diarrhoea

We will also include short, validated questionnaires, to identify clinically unrecognised asthma[31] and chronic obstructive pulmonary disease (COPD).[32]

Signs (to be assessed by the Responsible or Recruiting Clinician) to include

- Peak flow (with a comment regarding peak flow technique: good/reasonable or poor; to be measured using the EU Scale Mini Wright Adult Standard peak flow meter)
- Weight (to estimate the mg/kg steroid dose achieved using 40mg daily)
- Height (to estimate predicted peak flow)
- Temperature
- Respiratory rate

- Oxygen saturations
- Chest examination findings

Each randomised subject will be provided with a Trial Participation Card detailing emergency contact numbers, to include how concerned clinicians may contact the (24/7) on-call pharmacist at the University Hospitals Bristol NHS Foundation Trust (UH Bristol) if requiring emergency unblinding. Subjects will be requested to carry this card with them at all times whilst participating in the trial and to present it to their Responsible Clinician in the event of an emergency.

Following the baseline recruitment meeting, the Recruiting Clinician will enter all of the baseline recruitment data onto the web-based trial database, except for consent and participant registration data. Consent and participant registration data forms will be sent by secure fax to the local trial centre by the end of the day and then returned by post using a pre-paid return envelope within 24 hours; this data will be entered onto the trial management database by the trial centre team. The remaining baseline CRF data will be entered by the Recruiting Clinician by the end of the working day.

Where possible the Recruiting Clinician will recruit the patient at the GP practice. However, if it would be more convenient for the patient, or more convenient for the practice (for example, if a clinical room was not available for the recruitment interview), and if the patient has been confirmed as eligible to take part by the Responsible Clinician at the GP surgery (completion of CRF1 and CRF2, authorisation of trial prescription and confirmation of eligibility by a qualified doctor), the Recruiting Clinician may offer to visit the participant later that same day or on the following day (if the next day recruitment option is chosen) at the patient's home.

Prior to any home recruitment visit, the patient will be asked to sign a form consenting for their contact details to be passed to the Recruiting Clinician face to face, by telephone or fax so that the Recruiting Clinician can subsequently contact the patient. These contact details will be destroyed as soon as the patient has been contacted.

Any home recruitment visits will be carried out in line with the GP practice's normal home visiting procedures, and will require the Recruiting Clinician to bring to the patient's home a set of calibrated standard weighing scales normally used at the GP practice, and any other equipment needed to complete the clinical observations in Section 4.1 of the CRF. The Recruiting Clinician will also ensure that they have access to the relevant information from the patient's medical record in order to complete Sections 4.3 and 4.4 of the CRF.

11.2 Patient follow-up / subsequent assessments

Patients will complete a symptom diary every day for at least 7 days and up to 28 days or until symptoms have been completely resolved for two days running (whichever is soonest), on-line or on paper. As well as recording the severity of their symptoms, completing the symptom diary includes taking and recording peak flow measurements. The patient will also keep a record (within the symptom diary) of potential side effects for the first 7 days of participation. Patients who choose to complete the symptom diary online will be able to provide information about NHS resource use, out-of-pocket expenditure and time off work online, while patients who have opted to complete the symptom diary on paper will be asked these questions over the telephone. All patients will be telephoned weekly (with additional optional e-mail / text support, depending on the contact preferences stated during the giving of informed consent) to support symptom diary completion, and to collect the weekly data on resource use and quality of life measures (EQ-5D). These methods and measures are validated, and similar to those successfully used (with <20% attrition) in previous[6] [33] [34] as well as ongoing (see https://www.grace-LRTI.org/) studies. All follow-up will be managed by a member of the trial Research Team at the Bristol centre. Follow-up will continue for 28 days from the index consultation.

Should any of the patient's symptoms persist beyond the 28 day period, we will seek their permission to continue to make weekly telephone calls in order to collect data on the duration of their symptoms. We will not ask the patient to complete any further trial paperwork after the completed 28 day symptom diary.

Three £5 vouchers will be given to the patient, the first at the baseline recruitment assessment as a thank-you token for joining the trial, the second by post after completion of the second week's questions (including the weekly telephone call questions) and the third by post after the completed symptom diary has been received by the trial team or (for patients completing the diary online) the electronic symptom diary has been completed. There is systematic review evidence that the use of small monetary tokens increases response rates.[35]

A review of the primary care notes will be undertaken by either the research team or the recruiting primary care site, after three months post-randomisation, to record: (i) in the month after recruitment the number of NHS contacts (with reasons, including deterioration of illness), prescriptions and referrals (the lapse of a further two months before collecting these data will allow sufficient time for the inclusion of secondary care hospitalisation reports in the patient's primary care notes) and (ii) clinical diagnoses of asthma/ COPD/ whooping cough (pertussis)/ lung cancer in the 3 months post-randomisation.

11.3 Withdrawal of Subjects

11.3.1 Withdrawal from the trial

Participants have the right to withdraw from the trial at any time for any reason, without their medical care being affected. Where possible, data already collected will continue to be used in the trial and patients who withdraw from the trial will be asked if they are still willing to provide follow-up data via the symptom diary. If a patient withdraws, the reason for and type of withdrawal will be documented in the CRF. For example, type of withdrawal may include:

1. Trial use of baseline (CRF) data
2. Use of trial medication
3. Completing symptom diary
4. Receiving telephone calls, letters, email or texts to support symptom diary completion
5. Review of their primary care record
6. Any combination or all of the above

The Principal Investigators also have the right to withdraw patients from the trial drug in the event of inter-current illness, Adverse Events (AEs), Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), protocol violations, administrative reasons or other reasons. The reason for withdrawal will be documented in the CRF. If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised. It is understood by all concerned that an excessive rate of withdrawals can render the trial un-interpretable, therefore unnecessary withdrawal of patients will be avoided.

We will establish a staggered process such that if a patient discovers that they are pregnant within the first 5 days of the trial, they will be instructed to stop their trial medications immediately, though they will be able to continue to participate in as many other aspects of the trial as they wish. If pregnancy is discovered after the first 5 days, the patient will still be able to participate in as many aspects of the trial as they wish. A longer monitoring period will be put in place to establish the safe delivery of a healthy infant.

We will request return of the trial Medicine Packs from patients who withdraw. Recruitment will continue until the required number of symptom diaries and day 7, 14, 21 and 28 resource use / quality of life data are received, thereby replacing any participants who have withdrawn before symptom diary outcomes are collected.

A formal SOP will be developed to describe the withdrawal process.

12. Trial Medication

12.1 Investigational Medicinal Product and comparator

The Investigational Medicinal Product (IMP) for this trial will be prednisolone (2 x 20 mg oral tablets per day for 5 days, or until all symptoms have resolved, whichever is soonest), supplied by Piramal. Placebo tablets will be manufactured by Piramal to exactly match the prednisolone tablets in dimensions and appearance, such that allocation concealment and blinding of the trial is maintained.

12.2 Packaging, labelling and dispensing

The labelling of medication packs will be MHRA-approved and conform to Annexe 13 (GMP) and Article 13.3 of Directive 2001/20/EC. A template label will be approved by UH Bristol and provided to Piramal by the Chief Investigator. Each Medication Pack will have a Medicine ID number, randomly generated to ensure prednisolone and placebo medicine packs are indistinguishable (e.g. avoid all placebo packs being assigned an odd number) and thus maintain allocation concealment. This random number will be generated by the Bristol Randomised Trials Collaboration and provided to the manufacturer who will use it to form the identifier and include it with the open code break document sent with each delivery of medication packs to UH Bristol.

The medicines will be received from Piramal and stored by the pharmacy at University Hospitals Bristol NHS Foundation Trust (UH Bristol). A randomisation schedule will be provided to UH Bristol pharmacy by the Bristol Randomised Trials Collaboration (BRTC) assigning active vs. placebo treatment to each Patient ID number. The Patient ID number will have two digits to identify the Centre followed by three patient number digits (e.g. XXYYY). All Patient Packs will be pre-labelled with the Patient ID number and will contain the relevant items of trial paperwork (consent form, trial participation card and symptom diary, all with pre-printed Patient ID numbers). The Bristol centre will make up the patient packs and provide them to UH Bristol. UH Bristol will add either placebo or active tablets to the Patient Packs according to the randomisation schedule provided by BRTC. UH Bristol will keep a log of which Medicine Pack is put into which Patient Pack. Complete Patient Packs will be stored by UH Bristol pharmacy until instruction is received from the Bristol research team to send packs to a Trial Centre (Bristol, Southampton, Oxford or Nottingham).

Complete Patient Packs will be released by a pharmacist at UH Bristol and dispensed to the trial centres (Bristol, Southampton, Oxford or Nottingham) in batches of 32, via same-day courier service in line with all applicable regulations. This will be arranged by the Bristol trial centre (which will be the single point of contact for UH Bristol for the purposes of the trial). UH Bristol will keep a log of which Patient Packs are sent to which Centre. The trial Centres will be responsible for supplying the Patient Packs to the GP practices in their area, 4 Patient Packs at any one time, such that clinicians can draw from their allocation as recruitment proceeds. Trial centres will keep a log of Patient Packs sent to a GP practice, with all Patient Packs signed for on receipt at the GP practice and an email sent to the trial Centre detailing the Patient ID numbers received. Sites will liaise with their local Centre when more packs are required, and the local centre will then make a request for additional packs to the Bristol Centre, which will liaise with UH Bristol to send a further batch to the local Centre. GP practices will store the medicines up to 25°C as stated in the Summary of medicinal Product Characteristics (Prednisolone Galen 20 mg, 07 February 2012) and protect them from light and excessive humidity.

We intend to transport the medicines in line with standard clinical shipping practice in the country of manufacture of the 20mg prednisolone tablets (Germany). The manufacturer has confirmed that their prednisolone is shipped under ambient conditions and that ICH stability data states that the 20mg prednisolone tablets (Galen) can be stored at a temperature of up to 40°C and a relative humidity of 75% for 6 months, therefore short-term deviation from the normal storage temperature (15-25°C) is not critical and thus short-term storage of up to 30°C is possible without any loss of quality. The storage environment will be secure (i.e. a locked cabinet or room) with access limited to members of the practice team recorded as being involved in the trial. If sites have medication storage which is temperature monitored the trial medicines should be stored there. Otherwise, the trial centre will ensure GP sites have minimum/maximum thermometers available to monitor the temperature. The GP sites will check the temperature weekly and prior

to issuing medicines to recruited patients, recording the temperature on the temperature log and notifying the trial centre if the temperature has exceeded 25°C. On completion of the baseline questionnaire (CRF) online the clinician will enter both the Patient ID number and Medicine ID number as requested.

A formal trial risk assessment will be produced and a SOP will be developed to describe each of these procedures in detail.

12.3 Dosing Regimen

According to the randomisation schedule a participant will receive either prednisolone or placebo. The allocation will be unknown to the clinician and participant. Regardless of allocation each participant will be asked to take 2 x 20mg oral tablets per day for 5 days or until all their symptoms have resolved (whichever is soonest). There are no special dietary requirements to be imposed.

12.4 Drug accountability

A formal SOP will be developed to detail the paperwork associated with each step.

Activity	Responsibility
QP release of medicine	Piramal
Put together Patient Packs minus the trial medicines, and supply to UH Bristol	Bristol Centre
Receive medicine from Piramal	UH Bristol
Addition of medicine to Patient Packs as per randomisation schedule	UH Bristol
Send Patient Packs (in batches of 32) to trial centres via same-day courier service organised by Bristol trial centre	UH Bristol
Receive Patient Packs from UH Bristol and store appropriately	Trial Centres
Send Patient Packs to sites	Trial centres
Receive Patient Packs from trial Centres and store appropriately	Sites
Prescribe and dispense to trial participant, and maintain dispensing log	Sites
Order more supplies	Sites from trial Centres Trial Centres from Bristol Centre. Bristol Centre from UH Bristol
Return of unused medicines	Patient will return unused medicine to Bristol centre in a stamped addressed envelope. Bristol centre will deliver to UH Bristol
Destruction of unused medication	UH Bristol
Unblinding	UH Bristol

12.5 Subject compliance

Patients will record the medication that they take in their daily symptom diary. It will be requested that empty packaging and unused medicines are returned to the Bristol centre for safe disposal (using prepaid return packaging provided in the patient pack). Any leftover medication will be counted by Bristol Centre to check consistency with the participant diary. All dosing errors and discrepancies will be recorded. No invasive monitoring of adherence will be undertaken.

12.6 Concomitant Medication

See exclusion criteria, section 11.

At the discretion of the responsible clinician, and in line with NICE guidance, all patients will be offered either no antibiotic or a delayed (rescue) antibiotic prescription (of the clinician's choice), post-dated by at least one

working day after the recruitment interview, and clinicians will be free to prescribe a β agonist inhaler, e.g. salbutamol. Patients will continue medication for other acute and chronic conditions as advised by their GP.

12.7 Known side effects
Please refer to the Summary of medicinal Product Characteristics and the British National Formulary, and to section 14.3 below.

12.8 Return and destruction of medicines
Any medicine that is returned will be passed to UH Bristol for destruction in line with the UH Bristol pharmacy medication disposal SOP.

13. Assessment of Effectiveness

Primary outcomes:
1. Duration of moderately bad or worse cough (using a validated[1] web/paper-based symptom diary).
2. The mean of all symptom severity scores on days 2 to 4 (where day 1 is the day of the index consultation and baseline recruitment meeting, measured using the symptom diary).

Secondary outcomes:
1. Antibiotic consumption (symptom diary).
2. Duration of steroid tablet use (symptom diary).
3. Total duration and severity of other symptoms (cough until 'very little problem'; phlegm; wheeze; fever; chest pain; shortness of breath; sleep disturbance; activity disturbance; and feeling unwell) and abnormal peak flow (symptom diary[1]).
4. All adverse events including: any new symptoms or worsening of existing symptoms, re-consultations for a documented deterioration in illness and Serious Adverse Events.
5. Patient satisfaction with treatment and intention to re-consult for future similar illnesses (symptom diary).
6. Clinical diagnosis of asthma or COPD at 3 months (primary care notes review).
7. Quality of life using the EQ-5D (as recommended by NICE2, weekly telephone call).
8. NHS treatment and investigation (e.g. chest x-rays, re-consultation) costs (primary care notes review), out-of-pocket patient costs, and societal cost of time off work (symptom diary / weekly telephone call).

14. Assessment of Safety

14.1 Definitions

14.1.1 Adverse Event (AE)
AEs are defined as any untoward medical occurrence in a clinical trial participant. An AE does not necessarily have to have a causal relationship with the trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (International Conference on Harmonisation [ICH] definition). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

All AEs will be recorded in the Case Report Form (CRF) for the duration of the participant's direct involvement in the trial (28 days).

14.1.2 Serious Adverse Event (SAE)
A SAE is defined by ICH as any untoward medical occurrence that at any dose of the trial medication meets any of the following conditions:

1. **Results in the death of the participant**
2. **Is life-threatening**
   The term "life-threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
3. **Requires in-patient hospitalisation or prolongation of existing hospitalisation**
   For any event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of these outcomes, the CI should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to UH Bristol (who acts on behalf of the Sponsor in these instances).
4. **Results in persistent or significant disability / incapacity**
   Any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.
5. **Is a congenital anomaly / birth defect**
   Exposure to the trial drug before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.
6. **Other medical events**
   Medical events that may jeopardise the subject or may require an intervention to prevent a characteristic or consequence of a SAE. Such events are referred to as 'important medical events' and are also considered as 'serious' in accordance with the definition of a SAE.

14.1.3 Adverse Event Associated With the Use of the Drug

An AE is considered to be associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed below:

- **Not related:** An AE that is not related to the use of the drug.
- **Doubtful:** An AE for which an alternative explanation is more likely, e.g. concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
- **Possible**: An AE that might be due to the use of the drug and for which an alternative explanation, e.g. concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable and therefore, the causal relationship cannot be excluded.
- **Probable***:* An AE that might be due to the use of the drug. The relationship in time is suggestive. e.g. confirmed by IMP withdrawal. An alternative explanation is less likely, e.g. concomitant drug(s), concomitant disease(s).
- **Very likely:** An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive, e.g. it is confirmed by IMP withdrawal and re-introduction.

14.2 Procedure for reporting

All adverse event reporting will be in accordance with the UH Bristol 'Research Related Adverse Event Reporting Policy' (see Appendix 3). A formal SOP and flowchart will be developed to describe the reporting procedure in detail.

14.2.1 All Adverse Events

All AEs will be reported by the Chief Investigator from the time a signed and dated informed consent form is obtained until completion of the patient follow-up at 28 days following trial entry. If a Responsible Clinician believes a trial-related SAE has occurred beyond 28 days, they will be able to report those to the Investigator. Those occurrences meeting the definition of SAEs must be reported using the Serious Adverse Event Form (see Appendix 3*)*, including any related SAE which a Responsible Clinician believes has occurred beyond the 28 days following trial entry). UH Bristol, on behalf of the Sponsor, will evaluate any safety information that is spontaneously reported by a CI beyond the timeframe specified in the protocol.

All AEs, regardless of seriousness, severity, or presumed relationship to trial drug, must be recorded in the source document and the CRF, together with any measures taken. All Centre PIs must record in the CRF their opinion concerning the relationship of the adverse event to trial therapy. UH Bristol, on behalf of the Sponsor, assumes responsibility for appropriate reporting of adverse events to the regulatory authorities.

14.2.2 Serious Adverse Events (SAEs)

All SAEs must be reported to the UH Bristol contact (0117 342 0233) and Centre PI by a delegated member of the research team within 24 hours of their knowledge of the event. The Chief Investigator and Sponsor should also be informed.

All SAEs that have not resolved by the end of the trial (i.e. by the end of the primary care notes review follow-up period), or that have not resolved upon discontinuation of the participant's participation in the trial, must be followed until any of the following occurs:

- the event resolves
- the event stabilises
- the event returns to baseline, if a baseline value is available
- the event can be attributed to agents other than the trial drug or to factors unrelated to trial conduct
- when it becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The death of a participant is considered an SAE, as is any event requiring hospitalisation (or prolongation of hospitalisation) that occurs during the course of a participant's participation. Exceptions to this are hospitalisations for:

- social reasons in absence of an adverse event
- in-clinic protocol measures
- surgery or procedure planned before entry into the trial (must be documented in the CRF)

14.2.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

All relevant information about a SUSAR which occurs during the course of the trial and is fatal or life-threatening will be reported within 7 days to the MHRA and the relevant ethics committee by UH Bristol, on behalf of the Sponsor. The expectedness of an adverse event will be determined by whether or not it is listed in the Summary of Product Characteristics, the British National Formulary and study protocol.

All relevant information about a non-fatal or life-threatening SUSAR which occurs during the course of the study will be reported within 15 days to the MHRA and the relevant ethics committee by UH Bristol, on behalf of the Sponsor. The expectedness of an adverse event will be determined by whether or not it is listed in the Summary of Product Characteristics, the British National Formulary and study protocol.

14.3 'Expected' Adverse Events and Reactions

A previous trial[36] suggests the following side effects (listed below with the frequency with which they occurred in the prednisolone and placebo arms of the trial respectively) should be measured and should not be regarded as 'unexpected':

Side effects	% Adverse Events in prednisolone arm (n = 127)	% AEs in placebo arm (n = 122)	Difference
Dizziness	3.9%	3.3%	0.7%
Dyspepsia	1.6%	2.5%	-0.9%
Nausea	0.8%	2.5%	-1.7%
Constipation	2.4%	0.8%	1.5%
Hunger	0.8%	0.0%	0.8%

Side effects	% Adverse Events in prednisolone arm (n = 127)	% AEs in placebo arm (n = 122)	Difference
Vomiting	0.0%	0.8%	-0.8%
Insomnia	0.8%	0.8%	0.0%
Night sweats	1.6%	0.0%	1.6%
Rash	0.0%	0.0%	0.0%
Hot flushes	0.8%	0.0%	0.8%
Depression	0.0%	0.0%	0.0%
Thirst	0.0%	0.8%	-0.8%
Anorexia	0.0%	0.0%	0.0%
Diarrhoea	0.0%	0.0%	0.0%
Drowsiness	0.0%	0.8%	-0.8%
Pruritus	0.0%	0.0%	0.0%
Combinations of minor symptoms	6.3%	2.5%	3.8%

In terms of more serious side effects, these are recognised but are thought to be to be rare. For example, a literature search (Medline 1950 to present) conducted 9 July 2012 to quantify the incidence of steroid-induced psychosis found two studies, concluding that mild and reversible mood and cognitive changes appear common during steroid treatment, but that more studies are needed to determine the incidence of steroid-induced psychosis.[37 38] Regarding diabetic ketoacidosis, we found one Danish study estimating the annual incidence of diabetic ketoacidosis at 12.9 per 100,000.[39] No data were presented regarding steroids precipitating an episode of diabetic ketoacidosis. Finally, we searched for evidence of harm to the unborn child from steroids. No studies were found, but the BNF states that "the benefits of treatment with corticosteroids during pregnancy and breastfeeding outweighs the risk" and that "88% of prednisolone is inactivated as it crosses the placenta.

In addition, any symptom, side effect or adverse event listed in the Summary of Product Characteristics and the British National Formulary will not be regarded as unexpected.

14.4 Treatment Stopping Rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator, Regulatory Authority or Funder on the basis of new safety information or for other reasons given by the Data Monitoring Committee / Trial Steering Committee regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the Trial Steering Committee, who will advise on whether to continue or discontinue the trial and make a recommendation to the Sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected.

15. Statistics

15.1 Sample size

Since the distribution of the 'moderately bad or worse cough' duration outcome variable is positively skewed, sample size calculations are based on the log-normal distribution. The mean (SD) duration of bad or moderately worse cough was taken from one of our studies examining the effectiveness of prescribed antibiotics for acute LRTI,[6] and were estimated as 5.8 (4.1) days. Using standard formulae for the mean and standard deviation of a lognormal distribution, this corresponds to geometric mean (GM) 4.74 days, and mean (SD) 1.555 (0.637) log days. Sample size was calculated based on a 20% reduction in the duration of cough, corresponding to GM 3.79 days (mean 1.333 log days). Allowing (conservatively) for 20% attrition, an alpha 0.05 and 90% power, 218 participants will need to be randomised per arm, requiring a total sample size of 436.

The mean (SD) symptom severity score between days 2-4 taken from the same trial,[6] were estimated as 2.3 (1.1). Since the distribution of symptom severity scores is positively skewed power calculations were based on the log-normal distribution. A mean (SD) of 2.3 (1.1) therefore corresponds to GM 2.075 and mean (SD) 0.73 (0.454) log score. Given a final achieved sample size, after 20% attrition, of 174 participants in each arm the trial will give over 95% power to detect a difference a reduction in geometric mean symptom severity score, between days 2-4, of at least 20%.

Assuming a conservative year round average of 0.1 eligible patients presenting per site per day and an invitation: randomisation ratio of 7:1, then if the 4 centres each maintain around 15 active recruiting sites, recruitment will take 388 days, or around 18 months (2 recruiting seasons) for one centre and 9 months (1 recruiting season) for the remaining three centres, after taking account of days when recruiting staff are on annual/sick leave. This equates to just under 10 patients randomised per month per centre. An 18-month recruitment period starting in October 2012 (see Gantt chart, section 4) will also ensure recruitment over two winters when presentations are most frequent. Bristol will be the only centre recruiting in the first winter season, with all four centres recruiting in the second.

15.2 Randomisation

Randomisation will be stratified by centre (Bristol, Nottingham, Oxford and Southampton) using a variable block size. The four centres will be provided with identical, sealed, sequentially numbered Patient Packs to distribute to the participating sites. Once the eligibility of a potential participant is confirmed and written informed consent obtained, the patient will be given the next available sequentially numbered Patient Pack. This will then determine their Patient ID number and Medicine Pack number, both of which will be entered onto the web-based data collection platform (hosted by the University of Oxford) when prompted as part of the online registration process.

15.3 Minimising bias

Selection bias will be minimised by encouraging recruiting practices to invite consecutive eligible patients, where this is possible, and measured by asking them to record, on the initial screening form, the characteristics of patients/reasons for declining where this is not possible. Recruiting staff (see further details below) will enrol or randomise patients only after their eligibility has been confirmed by the Responsible Clinician. Randomisation will be concealed using identical Patient Packs for both active and placebo treatments. Within these Patient Packs, Medicine Packs will be labelled with a unique Medicine ID number to ensure allocation concealment (as described in section 12.2). Placebo effects and observer bias will be minimised through patient, clinician and trial personnel blinding to treatment allocation. However, some patients, especially those who have used oral steroids before and patients with diabetes who test their BMs regularly may notice a change if taking active drug or no change if taking placebo, thereby undermining blinding. Symptom diary attrition will be minimised through weekly telephone contacts made by a member of the research team to the patient at a time convenient to the patient, supplemented by optional e-mail and/or text reminders (as per the patient's stated preference) successfully employed in previous studies with outcomes, for which follow-up rates of 80% (see https://www.grace-LRTI.org/) and 90% were achieved.[40 41]

15.4 Data Analysis

A statistical analysis plan will be developed. All data will be analysed using Stata. For the primary analyses, descriptive statistics will be obtained for the two randomisation groups to characterise recruited patients and assess baseline comparability to ascertain any marked imbalance between the two arms. In accordance with CONSORT guidelines,[42] all estimates of relative effect will be as per the strategy of an intention-to-treat basis (White et al 2011). The primary comparisons will be the steroid therapy versus placebo group. All comparisons will be conducted using linear or logistic regression, according to whether the outcome variable is continuous or binary, adjusted for centre as the stratification variable and prior duration of the illness. If appropriate, we will use NNT and NNHs to summarise the treatment effect estimates. Any outcomes not normally distributed will be appropriately addressed and any transformations documented and justified in the final trial report. Sensitivity analyses will be conducted to investigate the potential effects of missing data. Estimated effects of the intervention on each primary outcome will be reported with equal prominence.

Secondary analyses will include repeating the primary analyses, adjusting for any variables exhibiting marked imbalance at baseline, to examine whether this influences the findings. Finally, appropriate interaction terms will be entered into the primary regression analyses in order to conduct pre-planned sub-group analyses of any differential effects of the active therapy versus placebo across the following patient factors: age, prior duration of illness, presence of wheeze on auscultation, antibiotic consumption, β agonist consumption[43] , smoking[26] and self-reported personal history of hay fever and/or allergic rhinitis and/or eczema. Since the trial is designed to detect overall differences between the groups, rather than interactions of this kind, the results of these subgroup analyses will be presented using confidence intervals as well as overall p-values, and interpreted with due caution.

Since we will have data regarding patients' adherence to medication (recorded on the symptom diary and when they return any unused medicines) we will conduct analysis accounting for compliance by repeating the primary analysis amongst those who adhere to the medication.

Adverse events will be compared using descriptive statistics.

We do not plan to conduct any interim analyses.

15.5 Economic Evaluation

The aim of the economic evaluation is to compare the costs and benefits of caring for patients in each treatment group.

Identification of resource use

The cost of treating patients with oral steroids in addition to usual care will be compared with the cost of usual care alone. The analysis will consider costs associated with the delivery of care from the perspective of the NHS, direct costs incurred by families, and time off work and usual activities. Resource use will be measured, weekly, from the point of randomisation until the final follow-up at 28 days. The analysis will include all healthcare costs unless clearly unrelated to LTRI.

The costs identified as being of relevance in this analysis are:

- Healthcare sector (NHS): cost of intervention (oral steroids); all primary care consultations by professional (GP, Nurse Practitioner, Practice Nurse, Health Care Assistant) and by location (at the surgery, telephone, home visit); other primary care contacts e.g. NHS Direct, Walk-in Centres, out-of hours contacts; out-patient appointments/clinic visits; in-patient stays; investigations; and prescribed medication.
- Patient costs: travel, over-the-counter medication, expenditure on prescriptions, loss of earnings, child care and domestic help.
- Costs associated with lost production: time off work and usual activities.

Measurement of resource use

NHS primary care resource use data will be collected by primary care notes review using methods successfully employed in previous studies (see http://www.descarte.co.uk/). In addition, use of other NHS resources, including secondary and community care, and patient costs will be collected using a specially designed questionnaire administered weekly, by telephone, by a member of the research team. These methods have led to near-complete data in previous studies.[7] [34] Quantity of oral steroids used will be collected from the symptom diary.

Valuation of resource use

- Intervention: we will cost the oral steroids using the British National Formulary (BNF).
- Healthcare: primary care consultations costed using Curtis;[44] National evaluations will be used to value consultations with NHS Direct,[45] Walk-in Centres; DH reference costs for all secondary care costs;[46] BNF for prescribed medication.

- Patient costs: as reported and Automobile Association schedule for valuing mileage in the case of car use.
- Time off work: we will use the human capital approach to value time off work and explore different ways of using the information about how work absence was handled by the employer, collected from the symptom diary, to inform a friction cost approach. This information will be collected from the symptom diary / weekly telephone contact.

Cost consequences
These will relate the costs of each strategy from each perspective to duration of symptoms, Quality Adjusted Life Years (QALYs) derived from the weekly EQ-5D scores, antibiotic consumption, and patient satisfaction.

Cost-effectiveness analysis
Will relate the extra cost to the NHS of using oral steroids in addition to usual care with the extra benefit gained in terms of number of patients reducing their symptom duration by at least 20% and QALYs.

Uncertainty
The effect of uncertainty in unit cost estimates or assumptions about resource use will be addressed in sensitivity analyses. Uncertainty in the cost-effectiveness/utility ratios resulting from patient variation in resource use and effectiveness will be captured by estimating confidence intervals around the net benefit statistic and estimating cost-effectiveness acceptability curves.

Population effects
If treatment with oral steroids is at least as effective as placebo, we will model the population cost and benefit of implementation using prevalence data from the National Morbidity Survey[4] or from the NSPCR database group, if they have investigated prevalence of steroid use for LRTI.

16. Quality Assurance

The stages of quality assurance for the OSAC trial will be as follows:

(i) The person completing the eCRF checks their data entry is accurate.
The trial case report form (CRF) is the primary data collection instrument for the trial. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be inserted. If the item is not applicable to the individual case, "N/A" will be inserted. Electronic data entry will be the preferred method of data capture, and for any paper forms used (including consent forms) clinicians will be requested to complete them legibly in black ink. If any entry errors are made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialled and dated.

(ii) A random sample of 20% of CRFs and (where available) paper symptom diaries will be checked, by the trial Research Team, against entries within the web-based database for quality purposes.
The percentage checked will be increased if a significant error rate is found. In addition, the first five sets of recruitment data collected from a new site will be scrutinized.

(iii) Recruiting sites will be asked to perform a self-audit on all entries and provide a return to the Bristol trial centre (who will report to the Trial Sponsor).

(iv) A 10% sample audit will be conducted by the UH Bristol monitoring team, in line with the Service Level Agreement.

The structure of these audits will be agreed with the Sponsor and with the UH Bristol monitoring team.
The content of the database will be validated at two stages:

1. At data entry stage, validation rules will be set to run on submission of data in order to direct clinicians to fields which require completion, should any essential fields have been missed, and to flag up anomalous or incomplete entries so that clinicians can correct data prior to final submission of the electronic CRF;
2. Management information regarding data quality and completeness at centre, site and patient level generated from data within the trial database and used by the Trial Manager to inform the implementation and monitoring of the trial.

SOPs will be developed to address each aspect of quality control and quality assurance procedures.

17. Data Handling

Custodian: Head of School, Social and Community Medicine, University of Bristol.

The database and randomisation system will be designed so as to protect patient information in line with the Data Protection Act 1998. Trial staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at the trial centres. The participants will be identified only by a patient ID number on the CRF (both on the paper and web-based forms). All documents will be stored securely and made accessible only to trial staff and authorised personnel. The trial will comply with the Data Protection Act 1998 which requires data to be anonymised as soon as it is practical to do so.

Formal SOPs will be developed to detail each element of the data handling procedure.

A summary of the overall trial results will be made available to those participants who have confirmed that they wish to receive them. Verbal consent will be obtained from each participant at the final 28 day telephone call to allow their GP practice to be informed which trial medication (prednisolone or placebo) the patient had been allocated, once data analysis has been completed.

18. Data Management

Data collection and management will be conducted using a secure, web-based system (OpenClinica) which will be developed, validated, hosted and supported by the University of Oxford. The system will maximise access (from any primary care site in England) whilst also minimising risk of data loss, duplication and security issues with laptops and portable media. The system will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance.

All patients will be consented using paper consent forms, pre-numbered with the Patient ID number, and provided in the Patient Pack. The Patient ID Number will include a check digit to reduce data entry errors onto the online system. Consent forms will be scanned and linked to the patient's database entry by Centre staff. All paper consent forms and participant registration details will be sent by secure fax to the Bristol centre on the day of recruitment and then returned to the Bristol Centre by pre-paid return addressed envelopes enclosed within the Patient Packs.

Entry of data into the on-line database will be the default method of data capture however paper-based alternatives will be provided in order to accommodate GPs who prefer this option and to enable recruitment to continue in the event of the website being inaccessible. As soon as the website is accessible, the data will be entered onto the database by the Site Recruiting Clinician, except participant registration details, which will be entered by Centre staff onto the off-line trial management database in Bristol. All paperwork related to patients' inclusion in the trial (except consent forms and registration details), once data are added to the web-based trial database, will be stored in the GP Practice until the complete Patient Recruitment folders are collected by courier and returned to the Bristol Centre.

Unique Patient ID numbers will be sequentially generated, from the randomisation process performed prior to recruitment by BRTC, and these will be used on pre-printed consent forms, of which paper records will be held at the trial centres and archived in Bristol at the end of the trial. Patient identifiers will be kept on a separate system from the clinical data and data protection requirements will be further enforced by best practice trial management procedures.

Following the end of the trial, the database will be cleaned and locked. SOPs will be developed to describe these processes.

At the outset of the trial an archiving plan will be developed. At the conclusion of the trial and after the database has been locked, all data will be archived for 15 years in accordance with the Sponsor's guidance and NIHR guidance. This will be in a secure location and available on request for audit and inspection by regulatory bodies. The Chief Investigator is responsible for authorising retrieval and disposal of archived material.

The location of the trial medicines will be tracked using the web-based database by all responsible personnel (see 12.4).

Formal SOPs will be developed for each aspect of trial data management and entry.

19. Publication Policy

An OSAC publication policy will be developed in line with University of Bristol guidance within the first 12 months of the trial, and trial publications will be subjected to an independent quality assurance procedure (as per University of Bristol protocols).

20. Auditing and Inspection

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical trial data are credible. This research trial will be run in accordance with GCP.

20.1 Direct Access to Source Data / Documents

The Centre PIs and trial sites will allow monitors (from UH Bristol on behalf of the Sponsor), persons responsible for the audit, representatives of the Ethics Committee and of the Regulatory Authorities to have direct access to source data / documents. This is reflected in the Participant Information Sheet (PIS). Trial monitoring will be undertaken on behalf of the Sponsor by UH Bristol using their monitoring standard operating procedure http://www.uhbristol.nhs.uk/files/nhs-ubht/IS11-Monitoring_v3.5_15.09.2010.pdf]

20.2 Trial Monitoring

20.2.1 Before the Trial

The Centre PIs and trial sites will allow the monitor to visit the site and facilities where the trial will take place in order to ensure compliance with the protocol requirements. The University of Bristol's Green Light procedure will be implemented in each of the other collaborating centres (Oxford, Southampton and Nottingham) in order to document preparedness to conduct recruitment locally. A monitoring plan will be agreed prior to commencement of the trial.

20.2.2 During the Trial

The Centre PIs will allow the monitor and/or the Sponsor to:

- Inspect the site, the facilities and the material used for the trial;

- Meet all members of his/her team involved in the trial;
- Consult all of the documents relevant to the trial;
- Check that the CRFs have been filled out correctly;
- Directly access source documents for comparison of data therein with the data in the CRFs;
- Verify that the trial is carried out in compliance with the protocol and local regulatory requirements;
- Carry out trial monitoring at regular intervals, depending on the recruitment rate, and arranged between the CI and monitor;

All information dealt with during these visits will be treated as strictly confidential.

21. Ethics and Regulatory Approvals and Reporting

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to Central Bristol Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

Any subsequent protocol amendments will be submitted to the REC and MHRA, on the agreement of the Sponsor.

Annual progress reports will be submitted to the main REC. The first report will be submitted 12 months after the date on which the favourable opinion was given, and thereafter until the end of the trial. Progress reports will also be submitted to the funder in line with NSPCR / NIHR reporting requirements. Copies of these reports will be sent to the Sponsor prior to submission. Copies of all relevant reports will be made available to the DMC and TSC as appropriate.

Annual safety reports will be provided on the anniversary of the granting of CTA for the trial and sent to the MHRA and the main REC within 60 days of this date. A copy will be sent to the Sponsor prior to submission.

An end of study declaration will be submitted to the REC and MHRA within 90 days of the end of the trial. A final report at conclusion of the trial will be submitted to the NSPCR/NIHR, the Sponsor, the REC and the MHRA within one year of the end of the trial.

22. Insurance / Indemnity

The insurance arranged by the University is in respect of serious injury to a research participant arising from participation in the trial; injury would include serious mental injury. It is however not possible to arrange insurance that would cover injuries to non-trial participants in the remote eventuality that steroid psychosis caused a participant to injure someone else. The University's Public Liability insurance would cover the University of Bristol should it be held legally liable for such an eventuality but the normal rules of negligence (causation/forseeability) would apply.

23. Financial Aspects

This trial is funded by the NIHR School of Primary Care Research.

24. Patient and Public Involvement

Our three collaborating patient/public representatives have already given comment regarding the trial treatments and design. These have included requests for reassurance that treatment will be at least as good as if patients do not participate; giving a clear understanding regarding how much time trial participation will take; and a full explanation regarding treatment side effects. We have included costs to facilitate the Patient Representatives' agreement to sit on our Trial Steering Committee and Trial Management Group. They have agreed to help with: refining the trial protocol and paperwork (e.g. patient information sheets, symptom diary); optimising strategies for maximising recruitment and for minimising loss to patient follow-up, and determining the type and content of trial outputs, especially those external to the academic community. In addition, they will provide ongoing advice and input to the implementation and management of the trial.

25. Investigative team expertise

Dr Alastair Hay is a senior academic GP and experienced primary care trialist (e.g. HTA funded Paracetamol and Ibuprofen for the Treatment of CHildhood fever (PITCH) trial). He is currently leading a number of other multicentre observational studies.

Dr Sara Brookes is a senior lecturer in medical statistics at the University of Bristol.

Dr Sandra Hollinghurst is a senior lecturer in health economics and has considerable experience in designing, conducting and analysing economic evaluations alongside trials, particularly in a primary care setting. Recent studies include the economic evaluation of the PITCH trial.

Dr Anthony Harnden is a senior academic GP with extensive experience in the design, conduct and management of observational studies and clinical trials.

Dr Kay Wang is a GP and NIHR Doctoral Research Fellow with an interest in persistent cough and acute respiratory tract infections in children. She has experience of setting up observational research and trials in primary care.

Professor Denise Kendrick is an experienced trialist with a Masters in medical statistics. She has extensive experience of designing, conducting and recruiting participants to RCTs in primary care and community settings.

Dr Elizabeth Orton is a Lecturer and Specialty Registrar in Public Health, University of Nottingham.

Dr Michael Moore is a GP partner and experienced researcher with experience of setting up and running pragmatic trials in primary care. He has strategic links with the primary care networks as hub network clinical lead of PCRNSW - the top performing primary care network - and will provide advice regarding promoting the trial within the PCRN.

Professor Paul Little is an internationally recognised senior academic GP with a very strong track record of designing and delivering primary care trials.

Dr Matthew Thompson is a senior academic GP with experience in leading observational diagnostic studies of children with acute infections in primary and secondary care.

Harriet Downing is an experienced multi-centre study manager who, as part of a multidisciplinary team, has overseen the successful recruitment and retention of over 5,000 children to the NIHR HTA funded DUTY study.

26. Signatures

_____ _____

Chief Investigator Date

Print name

_____ _____

Sponsor Date

Print name

27. Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of change	Details of changes made
Pre-approval re-submission	**1.1**	**1 October 2012**	**Harriet Downing**	1) The trial statistician has changed from Professor Jonathan Sterne to Dr Sara Brookes (p5). 2) The membership of the TSC and DMC has been updated (p6). 3) The terms of reference of the TSC and DMC have been updated in line with agreement reached at the inaugural meeting of the OSAC Trial TSC and DMC on 5 July 2012 (Appendices 1 and 2). 4) The statement that the efficacy of prednisolone will be compared to "standard care" has been updated in all instances to comparison with placebo (whole document). 5) The list of symptoms that will be followed up as secondary objectives has been updated (p7; p16-18). 6) Inclusion of our intention to look for clinical diagnoses of lung cancer after 3 months from recruitment, in addition to clinical diagnoses of asthma and COPD (throughout) 7) We wish to extend the scope of the weekly telephone follow-up beyond 28 days should the patient's symptoms persist before this time. We propose to contact the patient weekly, by telephone, for as long as their symptoms persist, to collect data on the duration of their symptoms. The patient will not be required to continue to complete the symptom diary or any other trial paperwork beyond the 28 day period (throughout) 8) The trial Gantt charts have been updated (p10-11) 9) The exclusion criteria have been refined and rationalised to increase the clarity of presentation (p19) 10) Clarification of the definition of an adverse event as any new symptoms or worsening of existing symptoms that either (i) meet the trial definition of a Serious Adverse Event as per section 14, or (ii) are not stated in the Summary of medicinal Product Characteristics for Prednisolone (Galen 20mg, 07 Feb 2012) (throughout). 11) Updated the section on the transport and storage of medicines to reflect new information that temperature-controlled conditions are not necessary for prednisolone 20mg (Galen), as supported by ICH stability data (p26). 12) Addition of clear definitions of randomisation data, randomisation schedule and source data (p13). 13) Addition of further information about serious side-effects from steroids (steroid-induced psychosis and diabetic ketoacidosis) and about the evidence of harm to the unborn child (p31). 14) Addition of description of the strategy for training OSAC recruiters, including the provision and legal importance of GCP training (p21). 15) Addition of statement that following the first season of recruitment (Bristol centre only), a formal

Amendment No.	Protocol Version No.	Date issued	Author(s) of change	Details of changes made
				review of all trial procedures will be held to inform the start of the second recruitment season (all four trial centres) (p21). 16) Addition of piloting plans (p21). 17) Clarification of the University of Bristol's legal position on non-negligent harm to third parties as a result of participation in this research (p39).
1	**1.2**	**13/12/2012**	**Sue Harris**	1) The removal of Melissa Spears, junior statistician from the list of collaborators (p5). 2) Insertion of REC reference number in Trial Synopsis (p7). 3) Spelling correction of "Steroids" in trial title (throughout). 4) Secondary outcomes numbering reformatted to restart at 1 in Trial Synopsis (p7). 5) Deletion of "lung cancer" from Secondary Outcomes clinical diagnoses at 3 months as we are not hypothesising that we will identify more lung cancer in patients treated with steroids (throughout). 6) Insertion of "Screening ID and…" into Trial Flow Diagram (p9) 7) Inclusion of clinical diagnosis of whooping cough (pertussis) after 3 months from recruitment in addition to asthma, COPD and lung cancer as possible underlying causes of acute coughs (p9 and 26). 8) Addition of "an OSAC pen" in the Patient Pack (PP) in Glossary of Terms (p12) and in Section 11.1 (p23). 9) Amended wording following ethical approval of Summary PIS in Glossary of Terms (p12/13) and throughout. 10) Addition and explanation of Screening ID in Glossary of Terms (p13) to allow for tracking of ineligible patients on trial screening log. 11) Amendment of "consent" to "permission" re: weekly telephone calls post-28 days as consent already obtained (p15 and 26). 12) Deletion of "crepitations" as one of inclusion criteria symptoms for LRTI (throughout). 13) Deletion of "and report lung cancer as a baseline characteristic" (p18) as we are not hypothesising that we will identify more lung cancer in patients treated with steroids. 14) Deletion of "<u>and Withdrawal…" from heading for Section 10, Selection (p19), as Withdrawal is covered in Section 11.</u> 15) Updated inclusion criteria (Section 10.1, p19) to accurately reflect changes and clarifications to eligibility criteria on Case Report Form: a) deletion of "Patient's first time in the OSAC trial" – this is covered in exclusion criteria; b) deletion of "…or within 24 hours of presentation" as reasons for same day recruitment are detailed on p23;

Amendment No.	Protocol Version No.	Date issued	Author(s) of change	Details of changes made
				c) deletion of "Patient is immunocompetent" – this is covered in exclusion criteria; d) insertion of "themselves" to clarify Patients' capacity and willingness to give informed consent and complete trial paperwork without support from anyone else. 16) Updated exclusion criteria (Section 10.2, p19) to reflect changes and clarifications to eligibility criteria on Case Report Form following recommendations from the Trial Steering Committee and feedback from pre-piloting GP practices to make the exclusion criteria clearer and easier to complete. 17) Change from 5 years to 2 years for GCP-training timeframe (p21) as contradicted wording in Section 10.6, p22. 18) Clarification of process for completion of participant registration details by Recruiting Clinician using paper copy of CRF only, with paper and data entry management process explanation (p25 and then throughout). 19) Addition of a third £5 voucher to be given to the participants after completion of the second week's symptom diary questions (including the weekly telephone call questions), as an extra incentive to encourage follow-up rates (p25). 20) Insertion of sub-heading "11.3.1 Withdrawal from the trial" (p26), on advice from Trial Steering Committee for purposes of clarity. 21) Amended wording "required number of" symptom diaries…"are received, thereby replacing any participants who have withdrawn before symptom diary outcomes are collected" to compensate withdrawals (p27) 22) Deletion of "full and summary PIS" from trial paperwork in Patient Packs as they are now not included in the Packs (p27). 23) Amended medicine storage and temperature monitoring at GP sites to reflect changes in storage requirements by the German manufacturer (Galen) as notified to the MHRA (application approved 24/10/2012), (p27/28). 24) Section 14.2.1, (p32) Change to period of interest for notification of SAEs from 3 months to 28 days from trial entry as an SAE occurring beyond 28 days is unlikely to be due to the trial IMP with provision for Responsible Clinicians to be able to report a related SAE beyond 28 days. 25) Spelling correction "treatment" (p34) 26) Spelling correction "breastfeeding" (p34). 27) Insertion of additional wording to clarify the trial paperwork handling process, Section 18, p39.
2	**1.3**	**19/04/2013**	**Harriet Downing**	**CHANGES TO THE TEXT** 1) Further refinement of the definition of source data for CRFs, patient symptom diaries and the primary care notes review (p13)

Amendment No.	Protocol Version No.	Date issued	Author(s) of change	Details of changes made
				2) Clarification that patients who complete the online symptom diary and who therefore do not return an empty paper copy will still receive a £5 voucher (section 11.2, p25) 3) Section 12.2, p27: the wording has been amended to specify that the secure environment in which the trial IMP is stored must be a locked cabinet or room. **OTHER CHANGES** 4) Update trial Gantt chart (section 4.1, p10) 5) Updating of Appendix 3 to include the new, current version of UH Bristol Research Safety Standard Operating Procedure v4.0 (February 2012)
3	**1.4**	**05/09/2013**	**SDH, HD**	**CHANGES TO THE TEXT** 1) Insertion of additional Exclusion Criteria, point 15, relating to the winter influenza vaccination programme 2013/2014 only: "**(For winter 2013/2014 only)** patient is aged **70 or 79** and due to receive the shingles vaccine in conjuction with the influenza vaccine" – the shingles vaccine is a live vaccine but will be given with the inactive influenza vaccine (section 10.2, p20). 2) Change of wording in Exclusion Criteria, point 16 **"Current OR previous history of:"** relating to live vaccine (L) to accurately reflect time periods as stated in the Summary of Product Characteristics GALEN prednisolone 20mg; change from "in the next **3 months**" to "in the next **8 weeks**" and addition of "**or has received a live vaccine in the previous 2 weeks**" (section 10.2, p20). 3) Clarification in Exclusion Criteria, point 16 "**Current history only**:" any exclusion of patients with uncontrolled hypertension (N) or any other contra-indication/caution for steroids (P) is as per the routine clinical judgement of the Responsible Clinician (section 10.2, p20). 4) Clarification that, for eligible patients requiring a delayed antibiotic prescription, the Responsible Clinician should provide one that is post-dated by at least one working day after the recruitment interview (section 9.6, p18; section 10.2, p19; section 11.1, p22-23; section 12.6, p28). 5) Additional wording included re: patients' availability to be contacted by the trial team following recruitment: • Section 6, p14: the wording has been amended to specify that patients must be available to receive the weekly telephone calls from the trial team. • Clarification in Inclusion Criteria, point 7 as well as being able and willing, patients must be available to receive the weekly follow-up telephone calls (section 10.1, p19). 6) Clarification that although same day recruitment is preferred, patients can be recruited on the next working day following their routine consultation, as long as any delayed prescription that the

Amendment No.	Protocol Version No.	Date issued	Author(s) of change	Details of changes made
				Responsible Clinician intends to provide is post-dated by at least one working day after the recruitment interview, and that the delayed prescription is kept at the practice and given to the patient at their recruitment interview (section 11.1, p23). 7) To include the option of conducting the Recruitment Interview at the participant's home in line with the GP practice's normal home visiting procedures, if this is more convenient for the patient or for the GP practice and the use of calibrated weighing scales (section 11.1, p25). 8) We will ask verbal consent from each patient at the final 28 day telephone call to allow their GP practice to be informed which trial medication (prednisolone or placebo) the patient had been allocated, once data analysis has been completed (section 17, p36) .
Minor amendment 3	**1.5**	**22/01/2014**	**HD**	**CHANGES TO THE TEXT** 1) Clarification of exclusion criterion 10.2.4 (same day antibiotic requirement to treat another infection unrelated to their acute cough) that the use of topical antibiotics does not preclude OSAC trial participation (page 19) 2) Correct the GCP training timeframe from 2 years to 5 years in Section 10.6 (page 21) due to typographical error.
Minor amendment 6	**1.6**	**15/10/2014**	**HD**	**CHANGES TO THE TEXT** 1) Amendment of the Exclusion Criteria, point 15, relating to the winter influenza vaccination programme, in order to keep the trial in line with a change in NHS guidance between the 2013/14 and 2014/15 winter influenza vaccination programme, which targets those aged 70, 78 or 79 (rather than aged 70 or 79 as in 2013/14) as from 01 September 2014. Therefore the above exclusion criteria needs to be amended from ""(For winter 2013/2014 only) patient is aged 70 or 79 and due to receive the shingles vaccine in conjunction with the influenza vaccine" to read: "(For winter 2014/2015 only) patient is aged 70, 78 or 79 and due to receive the shingles vaccine in conjunction with the influenza vaccine" (section 10.2.15, page 20). 2) Update to the description of the duration of the trial to reflect the recruitment end date which has been amended from 30 April 2014 to 27 October 2014. The 27 October is the last day on which any patient may be recruited to the trial (section 8.8, page 18).

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29. Appendices

29.1 Appendix 1 - Trial Steering Committee terms of reference

As agreed at the inaugural meeting of the TSC and DMC, 5 July 2012:

1. To monitor and supervise the progress of the Oral Steroids for Acute Cough trial towards its interim and overall objectives, adherence to the protocol, adherence to the requirements of the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice, and to the principle that the rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society;

2. To review at regular intervals new information of relevance to the research question (e.g. other related trials);

3. To consider the recommendations of the Data Monitoring Committee;

4. To provide a quality assurance function regarding trial process issues (e.g. protocol adherence);

5. To agree proposals for substantial protocol amendments (process to be developed by trial manager) and provide advice to the sponsor and funder regarding approvals of such amendments;

6. In the light of 1, 2 and 3, to advise the Chief Investigator, Trial Sponsor, Trial Funder, Host Institution and other relevant parties on all appropriate aspects of the trial;

7. In the light of 1, 2 and 3, to inform the NIHR School for Primary Care Research and relevant Research Boards on the progress of the trial;

8. In the light of 1, 2 and 3 to provide advice to the investigators on all aspects of the trial;

9. To advise the TMG and the Funder (the NIHR School for Primary Care Research) on publicity and the presentation of all aspects of the trial.

29.2 Appendix 2 - Data Monitoring Committee terms of reference

As agreed at the inaugural meeting of the TSC and DMC, 5 July 2012:

1. To monitor the data from interim analyses, unblinded if appropriate, plus any additional safety issues for the Oral Steroids for Acute Cough trial and relevant information from other sources (including data emerging from other related studies);

2. To make recommendations following each meeting to the TSC on whether (the safety, rights and well-being of the trial participants being paramount) there are, in the light of 1., any ethical or safety reasons why the trial should not continue;

3. To determine if additional interim analyses of trial data should be undertaken, to consider any requests for release of interim trial data and make recommendations to the TSC on the advisability of this;

4. To provide a quality assurance function regarding trial data;

5. In the event of further funding being required, to provide to the Chief Investigator, TSC, Trial Sponsor or Trial Funder information and advice on the data gathered to date that will not compromise the integrity of the trial;

6. The Chair of the DM(E)C is directly answerable to the trial funder and to the trial sponsor;

7. The DM(E)C will be provided with the opportunity to seek input to data monitoring issues from the Patient / Public Representatives, if needed.

29.3 Appendix 3 - Serious Adverse Event Form

See separate PDF document provided with this application.

29.4 Appendix 4 - Centre Responsibilities

29.4.1 Bristol centre (in addition to the responsibilities of all centres):

1. Responsibility for obtaining trial-wide R&D and ethics approvals, and adhering to the standards of research governance as required by the trial Sponsor;
2. Drug accountability;
3. Management of the trial Investigational Medicinal Product;
4. Maintenance of the Trial Master File;
5. Development of all trial documentation and patient packs, and distributing these to the trial centres;
6. Overseeing the development, quality assurance and distribution to centres of the trial medicines (Medicines will be distributed to centres by UH Bristol, and this distribution process will be overseen by the Bristol trial centre);
7. Development of trial-wide standard operating procedures and training protocols;
8. Working with the PCRN SW clinical lead to explore the most effective strategies for maximising recruitment to the trial;
9. Working with patient representatives to explore strategies for improving the acceptability of the trial treatment (should this prove to be a challenge to recruitment) and for minimising loss to patient follow-up in daily symptom diary completion;
10. Ensuring that all trial centres provide comprehensive training to participating clinicians through nurse-led peer support for recruiting primary care teams, scrutiny / monitoring of online data (and paperwork including consent forms), occasional site visits;
11. Facilitating the monitoring of trial centres by UH Bristol;
12. Monitoring trial progress using management information provided by the trial database (accruals, follow-up rates, data completeness etc) and in response to qualitative feedback from the trial centres obtained through regular communications and trial management group meetings;
13. Co-ordinating initial and quarterly applications for Service Support Costs for local primary care sites (initial application, and quarterly reimbursements);
14. Monitoring the research grant and ensuring the trial is conducted within the budget;
15. Co-ordinating monthly meetings of the Trial Management Group, twice-yearly meetings of the Trial Steering Committee and Data Monitoring Committee, and other meetings regarding the governance or science of the trial, as required;
16. Conducting trial data analyses and writing first drafts of papers;
17. Producing reports for the funder, ethics committee, Sponsor and other boards as required and reporting accruals to the UKCRN.

29.4.2 Oxford centre (in addition to the responsibilities of all centres):

1. Development of the web-based database and hosting infrastructure, including operationalisation (via the database) of the randomisation procedure.

29.4.3 All centres:

This list covers the main responsibilities of trial centres and is not exhaustive:

1. Working with local PCRN to identify suitable (research-experienced, high-recruiting and GCP-trained) GP practices;
2. Conducting site visits, explaining the trial to primary care clinical teams;
3. Sending sites recruitment packs that contain consent forms, symptom diaries and medications;
4. Entering data from paper collection forms onto the online database;
5. Ensuring site adherence to trial protocol through the provision of comprehensive training to participating clinicians, scrutiny / monitoring of online data (and paperwork including consent forms) and occasional site visits;
6. Facilitating the visit of monitors from UH Bristol;
7. Conducting telephone follow up calls, texts and / or emails (previous studies have shown these improve symptom diary and cost data completion rates) though patients will have the option of completing data online to reduce the burden of phone calls as much as possible;

8. Maintaining a centre site file with current versions of the protocol and trial documents, records of relevant R&D approvals and staff paperwork (GCP certificates, CVs, letters of access where appropriate), comprehensive documentation of any protocol deviations and auditing activities;
9. Administering Service Support Costs for local primary care sites in line with local CLRN schedules and procedures;
10. Reporting all AEs, SAEs and SUSARs within agreed timeframes;
11. Maintaining centre data for accruals, screening, withdrawals, SAEs and any corrections / changes to patient data.