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This supplement contains the following items:
1. Original protocol, summary of changes.
2. Original statistical analysis plan

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INITIAL TRIAL PROTOCOL

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Study Title: Do oral corticosteroids provide clinical and cost-effective symptom relief for sore throat? A multi-centre, double blind, randomized, placebo-controlled trial.

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Project short name: Treatment Options without Antibiotics for Sore Throat (TOAST)

44

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Internal Reference No: CH-GH/TOAST/0006

46

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NRES Committee South Central - Oxford B

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Investigator Agreement

Version 1.0

21/04/2015

Page 2

TOAST Statistical Analysis Plan

52 "I have read this protocol and agree to abide by all provisions set forth therein.
53 I agree to comply with the International Conference on Harmonisation Tripartite Guideline on
54 Good Clinical Practice."

55

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57

58

Principal Investigator
(Print Name)

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Date

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Co-Investigator (Print Name)

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Co-Investigator (Print Name)

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Co-Investigator (Print Name)

Investigator Signature

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75 **Confidentiality Statement**

TOAST Statistical Analysis Plan

76 This document contains confidential information that must not be disclosed to anyone other
77 than the Sponsor, the Investigator Team, host NHS Trust(s), regulatory authorities, and
78 members of the Research Ethics Committee.
79

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152		AMENDMENT HISTORY	

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

153 Protocol amendments should be submitted to CTRG as sponsor before submission to the
 154 ethics committee or MHRA.

155

156 1 SYNOPSIS

Study Title	Do oral corticosteroids provide clinical and cost-effective symptom relief for sore throat? A multicentre, double blind randomized placebo-controlled trial. Project short name: Treatment Options without Antibiotics for Sore Throat (TOAST)
Internal ref. no.	CH-GH/TOAST/0006
Trial Design	Double-blind randomised placebo-controlled trial
Trial Participants	Adults aged 18 or over presenting to general practice with acute sore throat
Planned Sample Size	510
Follow-up duration	1 month
Planned Trial Period	30 months
Primary Objective	1) To investigate in adults ≥ 18 years presenting to primary care with acute sore throat if the use of a single dose of oral dexamethasone, compared with no steroid treatment leads to increased resolution or improvement in symptoms
Secondary Objectives	1) To investigate whether dexamethasone compared with placebo leads to increased resolution or improvement in symptoms in those patients who have not been prescribed antibiotics 2) To investigate whether dexamethasone compared to placebo will, in those patients offered a delayed antibiotic prescription, reduce the number of patients taking antibiotics for their sore throat within 7 days 3) To investigate whether a single dose of oral dexamethasone

	<p>compared to placebo will:</p> <p>a) reduce time away from work or education within 7 days</p> <p>b) not increase the incidence of hospital admission with complications related to sore throat, e.g. peritonsillar abscess within 28 days</p> <p>c) not increase repeat attendance at the GP within 28 days with symptoms or complications of sore throat</p> <p>d) be cost-effective</p> <p>4) To assess predictors of response to corticosteroids including FeverPAIN score, Centor score, baseline factors and positive bacterial throat swab</p>
Primary Endpoint	1) Direct report by the patient of presence or absence of complete resolution of sore throat at 24 hours by either text message or telephone
Secondary Endpoints	<p>Direct report by those patients who have not been prescribed antibiotics of presence or absence of complete resolution of sore throat at 24 hours by either text message or telephone</p> <p>Report of complete resolution of pain at 48 hours</p> <p>Report of time to onset of pain relief in hours within 7 days</p> <p>Report of time to complete symptom resolution in hours within 7 days</p> <p>Duration of moderately bad symptoms recorded by validated symptom diary over the 7 days from treatment onset.</p> <p>Severity of symptoms in the 2-4 days after seeing the doctor based on the symptom diary</p> <p>Change in ratings of sore throat pain and pain on swallowing by visual analogue scale</p> <p>Uptake of delayed antibiotic prescription within 7 days</p> <p>Time missed from work or education over subsequent 7 days</p> <p>Attendance at GP practice, A and E or Out of hours (OOH) centres within 28 days with symptoms or complications associated with sore throat e.g. peritonsillar abscess</p>

	<p>Hospital admission with related complications of sore throat within 28 days</p> <p>Use of over-the counter medications and prescription medications (including whether, if they started the delayed antibiotics, they completed the course, and whether any other antibiotics were taken) in the first 7 days</p> <p>Cost effectiveness measures: Euroqol 5D score change in 7 days and impact on usual activities over 7 days</p>
Investigational Medicinal Products	A single dose of 10 milligrams of oral dexamethasone or matched placebo
Form	Tablets, over-encapsulated into a single capsule to ensure matched placebo and active drug
Dose	10mg
Route	Oral

2 ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials & Research Governance, University of Oxford
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation

IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Oxford Radcliffe Hospitals Trust / University of Oxford Trial Management Group
TSC	Trial Steering Committee

3 BACKGROUND AND RATIONALE

Epidemiology, costs and current management of sore throat

Sore throat represents both a significant burden on the UK general practitioner and an important source of unnecessary antibiotic prescriptions. In 2006, nine patients consulted their GP with sore throat for every 100 patients registered [1]. Tonsillitis was diagnosed in 3 out of 100 patients registered, and of these, 91% received antibiotics. Half of the remaining cases, coded as sore throat or pharyngitis, also received antibiotics. Prescribing rates for sore throat are clearly disproportionately high, especially since treatment of sore throat with antibiotics provides only modest symptomatic benefit [2],[3].

Antibiotic resistance in general is still increasing across Europe and represents a growing threat to the effectiveness of antibiotics [4,5,6]. Although prescribing rates have reduced in patients presenting with the common cold, a similar decrease has not been noted for sore throat [1]. Part of the reason may be the absence of alternative symptomatic treatments, resulting in a prescribing 'vacuum'.

The lost productivity associated with tonsillitis has been estimated at £190 pounds per episode [7]. The weekly UK incidence of patients presenting to their GP with sore throat averages at 60 per 100000 population. Extrapolating from this, we might expect a cost of almost £6 per person per year in lost productivity alone (equating to £370 million at 2010 population figures), in addition to an estimated £60 million cost in GP consultations [8].

Rationale for testing the effectiveness of corticosteroids in sore throat

Corticosteroids may offer an alternative symptomatic treatment for sore throat. They are known to inhibit transcription of pro-inflammatory mediators in human airway endothelial cells which cause pharyngeal inflammation and ultimately symptoms of pain.[9] Steroids are beneficial in other upper respiratory tract infections such as acute sinusitis, croup, and infectious mononucleosis [10-13]. Short courses of high dose oral steroids are considered to be safe, in the absence of any specific contraindications [14].

We recently performed a systematic review and meta-analysis of randomised controlled trials assessing the benefit of oral corticosteroids in sore throat, which was published in the BMJ and Cochrane Library [15,16]. In our analysis of 8 eligible trials, we found that a single dose of oral or intramuscular dexamethasone increased the likelihood of complete resolution of pain at 24 hours by more than 3 times (relative risk 3.2, (95% CI 2.0 to 5.1; $p < 0.001$), absolute risk reduction 27% (95% CI 17 to 36%), number needed to treat 3.7 (95%CI 2.8 to 5.9)). The mean time to onset of pain relief was reduced by more than 6 hours (95% CI 3.4 to 9.3; $p < 0.001$). However, all of the included trials compared steroids to placebo *in addition* to oral antibiotics. Furthermore no trials were in the UK population and only one of the trials (in Israel) recruited patients presenting to primary care. We have searched the International Controlled Trials Register (see <http://www.controlled-trials.com/isrctn/>) to confirm there are no similar trials currently conducted or registered.

Justification for dose and route and known and potential risks to human participants

The dose of oral corticosteroid used in the majority of previous trials in adults was a single dose of 10mg of dexamethasone or the equivalent dose of prednisolone, either orally, or intramuscularly, or both. Those trials including children up to the age of 18 used 10mg of dexamethasone as the maximum dose. Our systematic review found no difference in the effect of oral compared to intramuscular administration of corticosteroid. Therefore this trial will use a single dose of 10mg of oral dexamethasone as the dose most commonly found to be effective and the route causing least discomfort.

Long term steroid use is known to be associated with an array of unwanted systemic side effects.[17] However, in the absence of specific contraindications,[17,18] a short (up to 1 week) course of high dose steroids is considered to be safe and associated with few side effects.[19] Our systematic review found no serious adverse events reported by any included trial and no differences in all adverse events, relapse or recurrence rates between participants receiving corticosteroids and those receiving placebo.[15]

The prospect of achieving rapid symptomatic relief with a single dose of oral steroids has exciting implications; for the possibility of improving patient treatment options, reducing unnecessary antibiotic prescriptions and reducing the economic burden of sore throat. However, evidence is required for the clinical and cost-effectiveness of oral

steroids in sore throat in the absence of antibiotics and in a UK primary care population.
We propose a randomised double blind trial comparing a single dose of oral dexamethasone to placebo in adults aged 18 or over presenting to UK primary care.

4 OBJECTIVES

4.1 Primary Objective

- 1) To investigate in adults ≥ 18 years presenting to primary care with acute sore throat if the use of a single dose of oral dexamethasone, compared with no steroid treatment leads to increased resolution or improvement in symptoms

4.2 Secondary Objectives

- 1) To investigate whether dexamethasone compared with placebo leads to increased resolution or improvement in symptoms in those patients who have not been prescribed antibiotics
- 2) To investigate whether dexamethasone compared to placebo will, in those patients offered a delayed antibiotic prescription, reduce the number of patients taking antibiotics for their sore throat within 7 days
- 3) To investigate whether a single dose of oral dexamethasone compared to placebo will:
 - a) reduce time away from work or education within 7 days
 - b) not increase the incidence of hospital admission with complications related to sore throat (e.g. peritonsillar abscess) within 28 days
 - c) not increase repeat attendance at the GP within 28 days with symptoms or complications of sore throat
 - d) be cost-effective
- 4) To assess predictors of response to corticosteroids including FeverPAIN score, Centor score, baseline factors and positive bacterial throat swab

5 TRIAL DESIGN

5.1 Summary of Trial Design

The trial will be a two arm, individually randomised; double blind trial comparing a single dose of 10mg oral dexamethasone with placebo in adults aged 18 or over presenting to primary care with sore throat. The trial will require a single visit to the GP from each participant and a one week period of participant involvement from the point of randomisation and treatment. See flow chart (Appendix A). The trial will be a multicentre trial based at Oxford, Bristol and Southampton.

5.2 Primary and Secondary Endpoints/Outcome Measures

Primary outcome:

- 1) Direct report by the patient of presence or absence of complete resolution of sore throat at 24 hours by either text message or telephone.

Secondary outcomes:

Direct report by those patients who have not been prescribed antibiotics of presence or absence of complete resolution of sore throat at 24 hours by either text message or telephone

Report of presence or absence of complete resolution of sore throat at 48 hours by either text message or telephone contact

Report of time to onset of pain relief (in hours) within 7 days

Report of time to complete symptom resolution (in hours) within 7 days

Duration of moderately bad symptoms recorded by validated symptom diary over the 7 days from treatment onset.

Severity of symptoms in the 2-4 days after seeing the doctor based on the symptom diary

Change in ratings of sore throat pain and pain on swallowing by visual analogue scale

Uptake of delayed antibiotic prescription within 7 days

Time missed from work or education over subsequent 7 days

Attendance at GP practice, A and E or Out of hours (OOH) centres within 28 days with symptoms or complications associated with sore throat e.g. peritonsillar abscess

Hospital admission with related complications of sore throat within 28 days

Use of over-the counter medications and prescription medications (including whether, if delayed antibiotics are taken, the course is completed, and whether any other antibiotics were taken) in the first 7 days

295 Cost effectiveness measures: Euroqol 5D score change in 7 days and impact on usual
296 activities over 7 days

297 **5.3 Trial Participants**

298 **5.3.1 Overall Description of Trial Participants**

299 Participants aged 18 years or over presenting to primary care with acute sore throat

300 **5.3.2 Inclusion Criteria**

- 301 • Aged 18 years or above
- 302 • Presenting to a primary care appointment with acute sore throat and odynophagia
303 (pain on swallowing) which is judged by the clinician to be infective in origin
- 304 • Onset of symptoms within the last 7 days
- 305 • Patient has capacity and willingness, in the view of the recruiting clinician, to give
306 consent and complete the trial paperwork, including the symptom diary

307 **5.3.3 Exclusion Criteria**

308 The participant may not enter the study if ANY of the following apply:

- 309 • Female participant who is pregnant, lactating or planning pregnancy during the course
310 of the study
- 311 • Recent (<1 month) use of inhaled or oral corticosteroids.
- 312 • Recent (<1 month) Adenotonsillectomy
- 313 • Currently or recently (<14 days) taking antibiotics
- 314 • Clear alternative diagnosis e.g. pneumonia
- 315 • Known immune-deficiency (e.g. HIV, active chemotherapy or advanced cancer)
- 316 • Scheduled elective surgery or other procedures requiring general anaesthesia during
317 next 7 days
- 318 • Participant who is terminally ill
- 319 • Symptoms or signs suggesting that hospital admission is required (e.g. completely
320 unable to swallow, very systemically unwell, peritonsillar abscess)
- 321 • Participant judged by the GP to require immediate antibiotics
- 322 • History of severe affective disorders including steroid-induced psychiatric illness
- 323 • British National Formulary (BNF) listed contra-indications to oral steroids
- 324 • Existing symptoms that are also side effects of, oral steroids
- 325 • Patients taking other interacting medication (e.g. phenytoin and anti-coagulants).
326 Clinicians will be asked to use the BNF and their clinical prescribing systems to check
327 for interactions for all patients

- Known dexamethasone allergy
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study
- Involvement in another clinical trial of an investigational medicinal product in the last 90 days or any other research within the last 30 days
- Recruiting primary care site is not the patients usual practice if the patient is not expecting to still be with the primary care site in one month (i.e. temporary residents)
- Previous TOAST participation
- Patients unable to be randomised by the end of the (working) day of presentation
- Requirement for live vaccine in next 7 days

5.4 Expenses and Benefits

We do not anticipate any visits in addition to normal care and do not intend to offer any other payment for involvement in the study.

5.5 Study Procedures

5.5.1 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information Sheet and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will receive the Participant Information Sheet at their initial consultation with their GP, and if eligible and interested will then be referred on to a Baseline Trial Assessment with a recruiting clinician for full consent procedures and trial procedures (see section 5.5.1 for full details). This will give the participants the opportunity to consider the information, and the opportunity to question the recruiting clinician, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed

consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

5.5.2 Screening and Eligibility Assessment

The primary care site will give adults presenting with sore throat a Participant Information Sheet (PIS) which details what is involved in trial participation. During the initial consultation the primary care clinician (referred to from now onwards as the "Responsible Clinician") will discuss trial participation and screen the inclusion/exclusion criteria. The Responsible Clinician may be a triage nurse if the GP judges that he/she is competent to perform the baseline assessment and eligibility screening. Any patient who is not eligible to participate or declines to participate will be recorded on the screening log with reasons for ineligibility or declining (if known) and have no further involvement in the trial.

The Responsible Clinician completes their routine management, and at the clinician's discretion offers a delayed antibiotic prescription, to be collected by the patient either from the recruiting clinician at their subsequent Baseline Trial Assessment, or from the reception of the GP surgery according to the normal practice of the surgery. The delayed antibiotic prescription will be accompanied by the following:

- Reassurance that antibiotics are often not needed immediately and information about the disadvantages of antibiotics
- Information about the natural history of sore throat and advice to use regular pain relief
- Instructions for the antibiotics to be collected / used after 3-5 days if the patient feels their symptoms not starting to settle or sooner if their symptoms are getting significantly worse.
- A brief information leaflet containing instructions and explanation regarding a delayed prescription to reinforce these points.

5.5.3 Baseline Assessments

By the end of the day of the initial consultation, no longer than 6 hours later, potentially eligible patients proceed to a 'Baseline Trial Assessment' with a primary care clinician allocated by the practice to recruit patients or a member of the research team (from here on known as the "Recruiting Clinician").

At this meeting a full trial explanation is given and time is allowed for the participant to ask any questions they may have, and then written consent will be obtained. The Recruiting Clinician will use the secure, web-based data collection platform (hosted by the University of Oxford) to enter the participant's baseline data and confirm eligibility using a standard computer within the GP practice. Once the online database confirms eligibility, randomisation will proceed as detailed in section 5.5.3.

The Recruiting Clinician will give the participant standardised instructions regarding how to complete the symptom diary and other response forms and will observe the participant taking the trial medication, oral corticosteroid or placebo. The Recruiting Clinician will record the participant's contact details for the 24 and 48 hour data collection contacts. Those participants for whom the GP has deemed a delayed antibiotic prescription appropriate will be provided with the prescription if this is the normal practice of the surgery.

The Recruiting Clinician will take a bacterial throat swab. These will be analysed for streptococcus A, C and G. The participant's date of birth, sex and the participant trial ID number will be used as identifiers for these swabs. The participant's practice will not be informed of the results of these swabs, except in the rare event that an unusual and potentially dangerous pathogen is detected by bacterial throat swab and the medically qualified principle investigators feel it is appropriate to inform the practice.

Baseline CRF data items to be collected will include:

Socio-demographic factors to include:

- Age
- Gender
- Smoking history

Medications to include:

- Decision whether or not to offer delayed antibiotic script and if offered, type dose, dosing regimen and duration of antibiotics prescribed as well as whether the practice left the script for collection at reception or gave it to the patient at the baseline recruitment meeting
- Any other advised treatment, including
 - Analgesia – paracetamol aspirin ibuprofen
 - Gargle
 - Difflam
 - Zinc
 - Steam
 - Other

Symptoms will include:

- Duration of sore throat and odynophagia
- Presence or absence of cough, hoarse voice, coryza, fever in last 24 hours

Clinical examination findings will include:

- Presence of pharyngeal inflammation
- Presence of tonsils
- Presence of inflamed tonsils
- Presence of purulent tonsils
- Presence of cervical lymphadenopathy
- Presence of tender cervical lymphadenopathy
- Temperature and type of thermometer used for measuring

Patient completed items will include:

- Ratings of throat soreness, pain on swallowing and difficulty swallowing using visual analogue scales
- Baseline severity ratings using symptom diary
- EuroQol EQ5D score [20]

5.5.4 Randomisation and Codebreaking

Randomisation will be performed by the Oxford Primary Care Clinical Trials Unit and will be stratified by centre (Oxford, Bristol and Southampton) and by receipt or not of delayed antibiotic prescription using a block randomisation with variable block size. An independent statistician based in the Department of Primary Care Sciences at the University of Oxford will generate the randomisation schedule. They will produce a list of 560 4-digit unique medication IDs, these will be printed on the medication labels, in variable block sizes stratified as above. This statistician will not be involved in any other aspect of the trial.

Each site will initially be allocated to hold 2 sets of 2-3 packs of pre-randomised medication, one set for those who are given an antibiotic prescription and one set for those who are not. They will liaise with their local centre (the centre responsible for setting up the site) when they have allocated their existing packs to trial participants and reallocation of medication, if deemed necessary, will only occur within the same centre and same subgroup of participants, having delayed antibiotic prescription or not (see section 6.3 for details of drug distribution). They will also receive an equal number of participant folders containing unique participant trial IDs. The process of recruitment is as detailed in sections 5.5.1 and 5.5.2.

The Recruiting Clinician will allocate the patient one pack of medication from the appropriate set of pre-randomised medications and they will record the unique

medication ID on the baseline CRF. The Recruiting Clinician will inform their local study centre (Oxford, Bristol or Southampton) which medication has been allocated to which participant trial ID and the local study centre will keep a log of all allocated medication and participant trial IDs. The Recruiting Clinician will also enter the participant trial ID on the drug allocation log at site against the allocated medication ID.

The trial investigators have reviewed the clinical safety of the study and do not feel that a 24-hour un-blinding service is required; the only major adverse event where clinical management might be affected by this knowledge is anaphylaxis, and, as the medication will be taken by the participant under observation in the general practice during working hours, this will be managed in hours if required. Participant s will remain in the practice for 10 minutes after the medication has been taken to ensure that any immediate reaction can be treated. In the very rare event that analysis of the bacterial throat swab reveals an unusual and potentially dangerous pathogen; the Chief Investigators will be contacted to assess the need for emergency unblinding and informing the participant's practice. This information will only be received, and the practice contactable, in office hours.

A standardised procedure for emergency unblinding will be available. The codes will only be broken in case of a major adverse event (e.g. anaphylaxis; admission to hospital with life threatening illness (e.g. septicaemia; meningitis; severe pneumonia requiring ITU admission; death)). The randomisation code will be stored electronically on a secure drive, password protected, and access will be restricted to the independent statistician. If unblinding is deemed necessary the CI or designated representative will inform the independent statistician to notify the relevant responsible clinician of the treatment allocation for the relevant participant. The trial investigators will not be informed which arm of the trial this participant was allocated to. If randomisation of a participant is unblinded during the study then data for that participant if available will be included in the intention to treat analysis.

The procedures for code break at the end of the trial will be as follows: once all the data queries resolved, a blind data review meeting will be initiated involving the trial statistician, the data manager, the trial manager and the CI. All protocol violations will be reviewed and a list of study populations for analysis will be generated and signed off by the CI and the statistician. At this point, the database will be locked and de-coding of the allocation will be allowed.

5.5.5 Subsequent assessments

Participants will complete a symptom diary as well as reporting upon resolution of symptoms, time to onset of pain relief and rating their pain on a visual analogue scale every day for 7 days, on-line or on paper. As well as recording the severity and duration of their symptoms, this will also include providing information about NHS resource use, out-of-pocket expenditure, use of over-the-counter and prescription medications and time off work / education or foregone leisure time. Within the symptom diary we will also ask participants to complete the EuroQol EQ-5D measure [20] daily for 7 days following study entry.

Participants will be e-mailed, telephoned or texted at 24 and 48 hours to support collection of the primary outcome and secondary outcomes and additionally telephoned in the first 96 hours if required to support and encourage completion of the symptom diary. Follow-up will be undertaken by research assistant's at all three centres. Follow-up will continue for 7 days from the initial day of recruitment. Participants will be asked to report in the diary any use of medications, including whether they obtained and completed the delayed antibiotic prescription. If participants do not complete the symptom diary over the 7 days we will send them a short questionnaire after this in order to collect information for key secondary outcomes, if needed they will be phoned in order to help them complete the questionnaire. All paper diaries and questionnaires will be sent back to the PC-CTU in pre-paid envelopes.

A review of the primary care notes will be undertaken by the recruiting primary care site one month post-randomisation, to record repeat presentation to the GP, Accident and Emergency department or Out-of-Hours primary care centres with symptoms or complications of sore throat, hospital admissions and use of prescription medications. Baseline information about past medical history and acute and repeat medication usage will also be collected.

5.6 Definition of End of Trial

The end of trial will be once the primary outcome data has been collected for 408 patients and the one month follow-up notes review of the four hundred and eighth participant has been performed.

5.7 Discontinuation/ Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it would be harmful to keep a participant in the study. The reason for withdrawal will be recorded 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 or until the end of the study, when participant care will return solely to the GP. Participants will be retained in the trial for the purpose of intention to treat analysis except when they specifically withdraw consent to this.

If a participant is found to be ineligible after they have been randomised then they will be removed from the trial. Their data will also be removed from the intention to treat analysis.

6 SOURCE DATA

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, general practice medical records (from which medical history and previous and concurrent medication may be summarised into the CRF, as well as follow-up data at one month).

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). In this study the CRF will be used as the source document for the documentation of inclusion and exclusion criteria, and baseline assessment information.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant ID, not by name.

7 TREATMENT OF TRIAL PARTICIPANTS

7.1 Description of Study Treatment

The study treatment used in this trial will be a single 10mg dose of dexamethasone taken orally. The dose will take the form of 5 x 2mg dexamethasone tablets over-encapsulated into a single capsule and an over-encapsulated placebo identical in size,

colour and taste. The drug acquisition, over-encapsulation, packaging and labelling will be performed by Nottingham University Hospitals NHS Trust.

The labelling of medication packs will conform to Annexe 13 (GMP) and Article 13.3 of Directive 2001/20/EC. A template label will be approved by the clinical trial team and provided to the manufacturer by the Chief Investigator. Each medication pack label will be printed with a unique medication ID number to ensure Dexamethasone and placebo medicine packs are indistinguishable and thus maintain allocation concealment (see 5.5.3 for randomisation process). This randomised medication ID shall form the identifier on the open code break document sent with each delivery of medication packs to the clinical trials unit. The medicines will be received from the manufacturer and stored securely by the clinical trials unit.

The trial centres will be responsible for supplying the medication packs to the GP practices in their area (see 6.4 for details on distribution), 4 – 6 packs at any one time, such that clinicians can draw from their allocation as recruitment proceeds. Trial centres will keep a log of medication packs sent to a GP practice, with all medication packs signed for on receipt at the GP practice. Sites will liaise with their local centre when more packs are required, and the local centre will then liaise with the Oxford centre to send a further block to the local centre. At all times the medicines must be stored at room temperature.

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

7.2 Storage of Study Treatment

The study drug and placebo can be stored below 25°C and out of direct sunlight and will be kept securely in the Oxford Primary Care Clinical Trials Unit.

7.3 Compliance with Study Treatment

The participant will be observed taking the single dose of study medication once they have provided full informed consent.

7.4 Accountability of the Study Treatment

The study medication will be supplied by Nottingham University Hospitals NHS Trust to the clinical trials unit. All movements of study medication between Nottingham University Hospitals NHS Trust and CTU will be documented. The CTU will send on

the allocated drugs to the local centres who will distribute this out to the sites in their area. The CTU will keep logs of all medication IDs and where each drug is sent to, local centres will keep logs of all drugs allocated to them and the GP surgeries will keep local drug accountability logs, including drug allocation logs.

In the event that medication needs to be redistributed a drug redistribution log must be completed to document the unique medication ID and must include a minimum of one release signature (origin site staff), one transporter signature (PC-CTU staff) and one receiving signature (new site staff).

Site-specific procedures will be followed in relation to disposing of and arranging for destruction of expired trial medication. Standard GP site procedures should be followed and the drug destruction log should be completed with the following details: Date, unique medication ID, expiry date, quantity to be destroyed (number of tablets), staff initials to confirm destruction.

7.5 Concomitant Medication

Throughout the study the Responsible Clinician may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in the exclusion criteria. If these are required, the participant will stay in the trial for purposes of intention to treat analysis. Any medication, other than the study medication, taken during the study will be recorded in the symptom diary or noted on notes review.

7.6 Post Trial Treatment

Following the single dose of oral dexamethasone participants will continue normal medical care by their general practitioner.

8 SAFETY REPORTING

8.1 Definitions

8.2 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment (the study medication).

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

8.3 Adverse Reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

8.4 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" 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.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events. NOTE: Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria

usually associated with events that pose a threat to a participant's life or functioning as defined in the bullet points above. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.5 Serious Adverse Reaction (SAR)

An adverse event (expected or unexpected) that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

8.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an approved product).

8.7 Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

8.8 Procedures for Recording Adverse Events

Dexamethasone is a commonly used medication in a primary care setting; it has well defined safety profiles and is being used in this trial for authorised indications. As a result of this no non-serious adverse events will be recorded in this study. All Serious Adverse Events (SAEs) occurring during the one month participants are enrolled on the trial will be recorded as detailed in Section 8.9 Reporting Procedures for Serious Adverse Events.

A participant may voluntarily withdraw from the trial due to what he or she perceives as an intolerable AE. AEs that result in a participant's withdrawal from the study will be recorded on the withdrawal form. The relationship of AEs to the study medication will be assessed by a medically qualified investigator. The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

8.9 Reporting Procedures for Serious Adverse Events

All SAEs must be reported to the PC-CTU within one working day of discovery or notification of the event. PC-CTU will perform an initial check of the report, request any additional information and ensure it is reviewed by the CI on a weekly basis. The PC-CTU will also ensure that it is reviewed at the next Data Monitoring Committee meeting. All SAE information must be recorded on an SAE forms and faxed to PC-CTU. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form and faxed to PC-CTU.

8.10 Data Monitoring Committee

The appointed and independent Data Monitoring Committee (DMC) will conduct a review of all SAEs for the study reported during the quarter and cumulatively. They will report their findings to the Trial Steering Committee who will in turn report to the Trial Management Group. The main aims of this review are as follows:

- To ensure the safety and rights of each patient in the trial
- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To monitor the trial data and review and analyse as outlined in the Statistical Analysis Plan, systematically or as requested by the TSC
- To seek additional advice or information from investigators where required
- To evaluate the risk, in terms of safety and ethics, of the trial continuing and take appropriate action where necessary
- To act or advise, through the Chairman or other consultant, on incidents occurring between meetings that require rapid assessment

The Data Management Group will also, as required:

- Request provision of training specific groups within the Trust or University
- Request internal audits either in the Trust or University, where necessary

8.11 SUSAR Reporting

In collaboration with CTRG and DMC Medical Monitor, the CI will report all SUSARs to the Competent Authorities (MHRA in the UK), the Research Ethics Committee concerned and Host NHS Trusts. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. Any additional relevant information should be reported within 8 days of the initial report. The CI will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

8.12 Development Safety Update Reports (DSUR)

In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical trial on the anniversary of the CTA or on request a Development Update Safety Report (DSUR) to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and sponsor. The report will be in line with PC-CTU SOP TM19 "Pharmacovigilance".

9 STATISTICS

9.1 Description of Statistical Methods

Statistical analysis for effectiveness and safety

The primary analysis will be intention to treat assuming no resolution for missing data. The proportion of complete resolution at 24 hours reported by participants will be compared between two treatment arms using logistic regression model adjusting for whether participants are prescribed antibiotics or not. The proportion of complete resolution at 24 hours in those participants who have not been prescribed antibiotics on which this trial is powered will be compared using logistic regression model. Odds ratio and their 95% confidence interval (CI) will be reported.

Logistic regression adjusting for whether participants are prescribed antibiotics or not will be also performed to estimate the differences in the proportions of binary secondary outcomes including reported complete resolution at 48 hours, hospital admission within 28 days, attendance at GP practice, A and E or out of hours centres within 28 days with symptoms or complications associated with sore throat and uptake of delayed antibiotic prescription within 7 days. Odds ratio and 95% CI will be reported. Whether positive bacterial throat swab, FeverPAIN score, Centor score and other baseline factors could predict the response to corticosteroid will be explored. Use of over-the-counter and prescribed medicine other than antibiotics will be summarised and compared using a chi-square test.

Mean and SDs for reported time to onset of pain relief, time to complete resolution of pain, duration of moderately bad symptoms recorded by validated symptom diary, and time missed from work or education over the 7 days from treatment onset will be calculated and compared between two treatment arms using a linear regression adjusting for antibiotics prescription. We will use data from participants' diary on sore throat pain, pain on swallowing and difficulty in swallowing by visual analogue scale

within 7 days post randomisation to calculate areas under the curves as proxies for a summary measurement and tested for a difference between two arms using a linear regression adjusted for antibiotics prescription.

Symptoms of interest will be summarised in the proportions and difference between two treatment arms and 95% CI will be calculated.

Full description of the methods to be used will be stated in a trial statistical analysis plan.

Health Economics Analysis

The objective of the economic evaluation is to establish the difference in costs associated with administering oral corticosteroids versus placebo for sore throat, and relate this cost differential to any difference in health benefits found. The economic evaluation will be undertaken alongside the trial using widely accepted methods and will take an NHS perspective. An evaluation from a wider societal perspective will also be undertaken (as a component of the cost-consequences analysis) as productivity losses and absenteeism is likely to be associated with sore throat. The costing exercise will identify the NHS services used.

The economic evaluation has been designed as a cost-utility analysis, using the participant's EQ-5D-5L scores (using a published UK population valuation set and EuroQOL crosswalk algorithm[21]) as the main economic outcome measure. However, the performance and sensitivity of the EQ-5D in this participant group and over such a short follow-up period is uncertain, so its appropriateness will be investigated by assessing its construct validity and sensitivity to change within the trial. Due to the likely limitations in using EQ-5D as the outcome measure, the cost-utility analysis will be supplemented by a cost-consequences analysis using a number of outcome measures (e.g. symptomatic days avoided, EQ-5D disaggregated by domain, days off work/education) as the measure of health benefit.

Individual-level resource use data will be collected using resource-use questionnaires/diary and GP records. The resource use data will cover general practice, medications and hospital services. It will also include a question relating to time-off work and usual activities due to experiencing a sore throat. These resource items will be documented by the participants over the one-month follow-up period and will be collected using a resource-use questionnaire/diary. In the questionnaire,

participants will log NHS services use: the number and type of GP or practice nurse visits (e.g. own home, clinic, practice, out of ours, phone), prescription use, over the counter medication use, and hospital A & E, outpatient or inpatient stays that are directly related to their sore throat. This health service resource utilisation will be valued using appropriate unit costs obtained from widely used sources, such as the most recent version of Unit Costs of Health and Social Care [22] and NHS reference costs.

EQ-5D-5L data will be collected using the standard questionnaire format developed by the EuroQol group. The symptom and resource-use diary will collect participant specific self-reported time away from work/education. Both will be completed at baseline and over the 7 day follow up period.

Individual costs will be estimated by combining the resource use and unit cost data. We will estimate and report mean total costs by trial arm [23] and disaggregate these according to their burden on primary care and other care sectors. We will extrapolate our analysis of health service resource use and costs to explore the potential cost impact of prescribing oral corticosteroids on a national scale.

To aid decision-makers and to provide a transparency to our cost-effectiveness analysis we will analyse and report our costs and outcomes by trial allocation in a disaggregated format. Resource-use and costs will be reported by NHS sector. Outcomes will be reported in terms of symptom/pain-free days, EQ-5D (overall scores and by domain), days off work/education.

Mean costs and outcomes will be compared between the trial arms, using appropriate methods. The primary cost analysis will compare costs at one-month post-randomisation. In the event of one treatment not dominating another, an incremental cost-per-quality adjusted days (QAD) will be estimated using the EQ-5D. Uncertainty in the confidence to be placed on the economic analysis results will be explored through deterministic and probabilistic sensitivity analysis and presented by estimating cost-effectiveness acceptability curves [24]. The sensitivity analyses will explore uncertainties in the trial data and analysis methods, including the possibility that consultation/re-consultation rates for those in the placebo arm may differ from current standard care.

9.2 The Number of Participants

Based on the results of our systematic review of 8 studies, the average absolute increase in participants reporting complete resolution of pain at 24 hours with corticosteroids in addition to antibiotics and analgesia was 27% [15]. The minimum absolute increase from individual trials was 18% (11% vs 29%). To achieve this effect size with 90% power, our conservative estimate of sample size is 204 patients.

In the UK antibiotics are prescribed to approximately 50% of participants presenting with sore throat [1]. Given that our first secondary objective is to detect a clinically significant difference in proportions of participants not having been prescribed antibiotics, we will require an initial sample of 408 patients. A sample size of 510 allows for loss to follow-up of 20%.

9.3 The Level of Statistical Significance

5% significance level is used to calculate number of participants required for the trial.

9.4 Criteria for the Termination of the Trial.

No formal interim analysis is planned to stop the trial early. Dexamethasone is already licenced and used at this dosage in a wide variety of disorders as well as in the control of cerebral oedema. In our systematic review we found no serious adverse events reported by any included trial. No differences were found in all adverse events, relapse or recurrence rates between participants receiving corticosteroids and those receiving placebo, hence we anticipate that the likelihood of serious adverse events (SAEs) associated with a single dose of dexamethasone 10mg taken orally will be extremely low. We have therefore not defined any criteria for termination for safety.

9.5 Procedure for Accounting for Missing, Unused, and Spurious Data.

The percentage of missing outcome data will be compared between two arms and a logistic model will be used to assess whether covariates significantly predict dropout. If little is known about the missing mechanism or there is any concern about validity of the expected missingness due to treatment failure (i.e. assuming no complete resolution), sensitivity analysis will be performed with plausible non-ignorable missing scenarios and complete cases. These will be detailed in the separate statistical analysis plan.

During statistical data review and analysis, any anomalies in the data will be investigated and discussed with the trial management team. The data investigation will be broad and flexible and focus on variability of the data, consistency, dispersion,

outliers, inliers, relationships between variables and relationships over time. The statistical data review will be fully documented with all the output dated. If fraud is proved, fraudulent data will be removed from the analysis.

9.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

We do not anticipate any deviation from the statistical plan outlined above. However, provision for alternative methods and changes to analyses will be included in the statistical analysis plan as specified in the PC-CTU's SOP ST01.01 "Statistical Analysis Plan".

9.7 Inclusion in Analysis

We will be analysing our data using ITT. All randomised participants will be included in the analysis, assuming no complete resolution for missing data.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. Individual GP practices will be required to give access to the bodies described above and this will outlined in the Site Agreement.

11 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and PC-CTU Standard Operating Procedures. The monitoring will be performed by the PC-CTU Quality Assurance Manager or equivalent. All investigators and trial related site staff will receive training in trial procedures and ICH GCP.

Regular monitoring will be performed by the PC-CTU according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written Standard Operating Procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and the applicable regulatory requirements.

An independent Data Monitoring Committee (DMC), Trial Management Group (TMG) and Trial Steering Committee (TSC) will be appointed in line with standard CTU procedures. The responsibilities of each group are as follows:

- DMC- to review and monitor the accruing data to ensure the rights, safety and wellbeing of the trial participants. They will provide an interim analysis if requested by the TSC. They will make recommendations to the TSC about how the study is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial.
- TMG- is responsible for the day to day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to.
- TSC- to provide overall supervision of the trial on behalf of the Sponsor and the Funder to ensure that it is being conducted in accordance with ICH-GCP. The TSC will review the trial regularly, agree any amendments and provide advice on all aspects of the trial.

12 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the sponsor becoming aware of the breach. A serious breach is defined as "A breach of GCP or the trial protocol which is likely to effect to a significant degree –

- (a) the safety or physical or mental integrity of the subjects of the trial; or
- (b) the scientific value of the trial".

In the event that a serious breach is suspected CTRG should be contacted within one working day of knowledge. In line with PC-CTU SOP TM25 "Related Deviations and Serious Breaches" the process for reporting is as follows:

- Possible serious breach is identified by a member of the study team; either through site monitoring or audit visits, or through a whistle blower or a complaint from within or outside the University.
- A written record of the incident will be made and once all necessary information is gathered the information is reviewed by the relevant staff e.g. the QA manager, if appropriate, and recorded on the Serious Breaches Assessment Form, TM25_B
- If considered to be a serious breach the CI will be asked to confirm this decision and to contact the CTRG.

• If the event is a serious breach the CTRG will inform the MHRA within 7 days. Day 1 is considered as the day the incident is confirmed as serious by both the team and the CTRG.

• The incident will be followed up by the CTRG in conjunction with the trials team.

• The PC-CTU will review all documentation to see what might have led to the breach and put in place A Corrective Action Preventative Action Plan in collaboration with the CTRG.

13 ETHICS

13.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996, including training in GCP for clinicians as required.

13.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

14 DATA HANDLING AND RECORD KEEPING

Data Management will be performed in accordance with PC-CTU SOP DM1 “Data Management”. Study specific procedures will be outlined in a Data Management Plan (DMP) to ensure that high quality data are produced for statistical analysis. The DMP is reviewed and signed by all applicable parties including the Trial Manager and the Trial Statistician prior to the first patient being enrolled.

All patients will be consented using pre-printed paper consent forms including the unique patient ID. Pre-paid envelopes will be provided to return consent forms (and Clinical Record Forms if applicable) to the trial centres, where the data will be entered by centre trial administrators.

Data collection and management will be conducted using a secure, web-based, system developed in conjunction with the clinical trials unit. The system will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance. Parallel paper-based data capture forms will be available to those patients and clinicians who prefer this option. Data Protection requirements will be embedded into the design of the web-based system and enforced by best practice trial management procedures. The Clinical Data Manager will oversee the process of electronic data validation and manual listings, sending out Data Clarification Forms (DCFs) when required and following these up until the queries are resolved.

Once the last patient is enrolled, prior to database lock a dataset review will be undertaken by the Information System Manager and Trial Statistician. All critical data items are 100% checked against original Source Data Documents to ensure accuracy, an error rate is established across all fields to ensure a consistently accurate dataset.

Patient contact information will be collected at baseline in paper form and faxed to the relevant study centre. A copy of the patients contact details consent form will be sent to the PC-CTU. This information will be used to contact the patient to collect details for the primary outcome at 24, 48 and once more up to 96 hours after the patient has joined the trial, and for further follow that might be required. The follow up contact will be co-ordinated by a researcher at the relevant study centre. The contact details will be stored

1027 at the centre separately from all other trial data and will be anonymised as soon as the
1028 required contact has been completed.

1029

1030 At the conclusion of the trial and after the database has been locked, all essential
1031 documents will be archived for at least 5 years in accordance with the PC-CTU's SOP
1032 TM24 "Archiving". The Chief Investigator is responsible for authorising retrieval and
1033 disposal of archived material.

1034

1035 **15 FINANCE AND INSURANCE**

1036

1037 The trial will be funded by the National Institute for Health Research School of Primary
1038 Care Research

1039 **15.1 Compensation for harm**

1040 Negligent Harm: Indemnity and/or compensation for negligent harm arising specifically
1041 from an accidental injury for which the University is legally liable as the Research
1042 Sponsor will be covered by the University of Oxford. The NHS will owe a duty of care
1043 to those undergoing clinical treatment, with Trust Indemnity available through the NHS
1044 Litigation Authority Scheme.

1045

1046 Non-Negligent Harm: Indemnity and/or compensation for harm arising specifically from
1047 an accidental injury, and occurring as a consequence of the Research Subjects'
1048 participation in the trial for which the University is the Research Sponsor will be
1049 covered by the University of Oxford.

1050

1051 **16 PUBLICATION POLICY**

1052

1053 The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press
1054 releases and any other publications arising from the study. Authors will acknowledge
1055 that the study was funded by the NIHR School of Primary Care Research. Authorship
1056 will be determined in accordance with the ICMJE guidelines and other contributors will
1057 be acknowledged.

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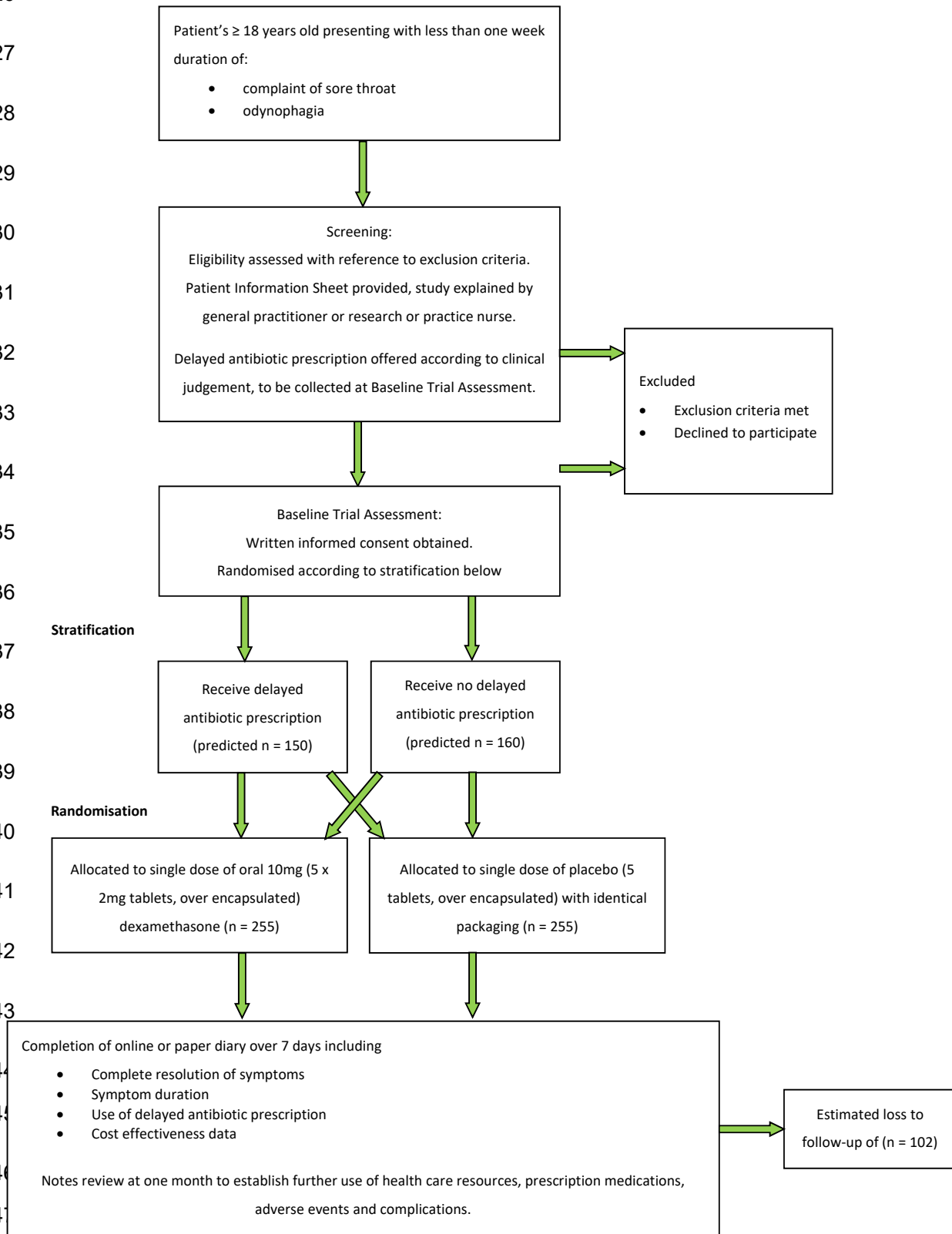
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18 APPENDIX A: STUDY FLOW CHART



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1149 **19 APPENDIX B: SCHEDULE OF PROCEDURES**

Actions	Screening	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14	30 Day follow up
Informed consent ¹	✓ ⁶	✓ ⁶									
Demographics ¹		✓									
Medical history ¹		✓									✓
Concomitant medications ¹		✓									✓
Physical examination ¹		✓									
Throat Swab ¹		✓									
Eligibility assessment ¹	✓										
Randomisation ¹		✓									
Dispensing of study drugs ¹		✓									
Compliance ¹		✓									
Writing of Prescription ²	✓										
Giving of Prescription ¹		✓									
Adverse event assessments ²											✓
Follow-up Contact ³			✓	✓		✓ ⁵					
Symptom Diary ⁴		✓	✓	✓	✓	✓	✓	✓	✓		
Follow-up Questionnaire ⁴										✓ ⁵	
Review of NHS usage											✓

¹ Performed by GP Surgery staff- Responsible / Recruiting Clinician² Performed by GP³ Performed by local centre⁴ Performed by Patient⁵ If Needed⁶ Either/ Or

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Amendments

There have been 7 amendments to the protocol.

Amendment 1, 10-APR-2013, was to clarify some data points, ensuring that the CRFs and protocol were reflective of each other.

Amendment 2, 08-JUL-2013, amended the sample size and added to the follow up process the addition of a £10 thank you for those who return their completed Symptom Diary to the PC-CTU and also added in additional reminder text messages to remind participants to complete and return the Symptom Diary.

Amendment 3, 02-SEP-2013, added Johanna Maughan and Julie Allen as investigators on the trial.

Amendment 4, 14-FEB-2014, added an upper age limit of 70 years to the inclusion/exclusion criteria.

Amendment 5, 02-JUN-2014, listed additional research sites.

Amendment 6, 23-JUL-2014 increased the value of the gift card sent to participants to £20 and clarified the wording of SAE reporting within the protocol.

Amendment 7, 16-FEB-2015, listed an additional research site.

INITIAL AND FINAL SAP**STATISTICAL ANALYSIS PLAN**

Version 1.0

21 April 2015

Do oral corticosteroids provide clinical and cost-effective symptom relief for sore throat? A multi-centre, double blind, randomised, placebo controlled trial.

Project short name: Treatment Options without Antibiotics for Sore Throat (TOAST)

Ethics reference: 12/SC/0684

EudraCT Number: 2012-004330-41

	NAME	TITLE	SIGNATURE	DATE
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Approved by:	Professor Carl Henegan	Chief Investigator		

Version History

Version:	Version Date:	Changes:
1.0	21 April 2015	

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1 INTRODUCTION

1.1 Preface

This document details the statistical analysis that will be adopted for the TOAST trial.

This analysis plan supports version 6.0 (14/07/2014) of the TOAST protocol.

The trial statistician, chief investigator and trial managers are:

Chief investigator: Professor Carl Heneghan

Trial Manager: Julie Allan

Trial Statistician: Merryn Voysey

1.2 Purpose and scope of the plan

This document details the proposed presentation and analysis for the main paper(s) reporting results of the TOAST trial. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analyses (for e.g. to decide cutpoints for categorisation of continuous variables), nor to prohibit accepted practices (e.g. data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

The analysis of the cost-effectiveness data is not covered within this analysis plan.

1.3 Trial overview

Sore throat represents both a significant burden on the UK general practitioner and an important source of unnecessary antibiotic prescriptions. Corticosteroids may offer an alternative symptomatic treatment for sore throat.

1281

1282 **1.4 Objectives**

1283 Primary objective: To investigate in adults ≥ 18 years and ≤ 70 years¹ presenting to primary
1284 care with acute sore throat if the use of a single dose of oral dexamethasone, compared with
1285 no steroid treatment leads to increased resolution or improvement in symptoms

1286 ¹ Participants over 70 years are included up until Protocol amendment

1287 Secondary objectives

1288 1) To investigate whether dexamethasone compared with placebo leads to increased
1289 resolution or improvement in symptoms in those patients who have not been prescribed
1290 antibiotics

1291 2) To investigate whether dexamethasone compared to placebo will, in those patients
1292 offered a delayed antibiotic prescription, reduce the number of patients taking antibiotics for
1293 their sore throat within 7 days

1294 3) To investigate whether a single dose of oral dexamethasone compared to placebo will:

1295 a) reduce time away from work or education within 7 days

1296 b) not increase the incidence of hospital admission with complications related to sore throat
1297 (e.g. peritonsillar abscess) within 28 days

1298 c) not increase repeat attendance at the GP within 28 days with symptoms or complications
1299 of sore throat

1300 d) be cost-effective

1301 4) To assess predictors of response to corticosteroids including FeverPAIN score, Centor
1302 score, baseline factors and positive bacterial throat swab.

1.5 Trial design

TOAST is a two arm, individually randomised, double blind trial comparing a single dose of 10mg oral dexamethasone with placebo in adults aged between 18 and 70 years inclusive presenting to primary care with sore throat. The trial will require a single visit to the GP from each participant and a one week period of participant involvement from the point of randomisation and treatment. The trial will be a multicentre trial based at Oxford, Bristol and Southampton.

TOAST aims to recruit 566 patients.

The schedule of procedures is detailed in Appendix 1.

1.6 Outcomes measures

Participants were telephoned or texted at 24 and 48 hours following randomisation for collection of the primary and secondary outcomes. Participants completed a symptom diary reporting on resolution of symptoms, time to onset of pain relief, and rating their pain on a visual analogue scale every day for 7 days. In addition participants provide information about NHS resource use, out-of-pocket expenditure, use of over-the-counter and prescription medications and time off work/education and foregone leisure time. Participants who failed to return a symptom diary at the end of the study were sent a brief FU questionnaire. Case notes were reviewed after one month following randomisation to collect information on use of NHS resources in the 28 days following the initial trial appointment.

The outcomes assessment schedule is contained in Appendix 2.

1.6.1 Primary outcome

- 1) Direct report by the patient of presence or absence of complete resolution of sore throat at 24 hours by either text message or telephone.

Where no response to text/telephone at 24 hours exists, the participant's diary response to Q1 on day1 will be used and where no diary has been returned, or response is missing, the short FU questionnaire (Question 1) will be used. Discrepancies in reporting may exist, thus the first reported outcome (text/telephone) will be taken as the valid response since it is most timely to the outcome. If no text/telephone response is available the source of data for the primary outcome will be considered in the order detailed above (i.e. text/telephone, diary, FU). For each participant the source of data will be recorded. Any participants who have no information after looking at each of the data sources will be included in the analysis assuming 'no resolution'.

1.6.2 Secondary outcomes

- 1) Direct report by those patients who have not been prescribed antibiotics of presence or absence of complete resolution of sore throat at 24 hours by either text message or telephone

Only patients who were not prescribed a delayed antibiotic prescription will be included in the analysis (baseline assessment Q7 *delpres*=0 (no)).

Where no response to text/telephone at 24 hours exists, the participant's diary response to Q1 on day1 (*d1res/24*) will be used and where no diary has been returned or response is missing the short FU questionnaire Question 1 (*reso/24*) will be used. Discrepancies in reporting may exist, thus the first reported outcome (text/telephone) will be taken as the valid response since it is most timely to the outcome. If no text/telephone response is available the source of data for the primary outcome will be considered in the order detailed above (i.e. text/telephone, diary, FU). For each participant the source of data will be recorded. Any participants who have no information after looking at each of the data sources will be included in the analysis assuming 'no resolution'. This analysis will include those patients who subsequently started antibiotics despite not being given a delayed prescription at the index consultation

This analysis will also be repeated for the group of patients who received a delayed antibiotic prescription (baseline assessment Q7 *delpres* = 1, 2).

Secondary outcomes 2-6 and 8-11 will be analysed for all trial participants and in addition the analyses will be repeated separately for the two groups of participants defined by whether or not they were given a delayed antibiotic prescription.

- 2) Report of presence or absence of complete resolution of sore throat at 48 hours by either text message or telephone contact

This analysis includes all participants randomised. Where no response to text/telephone at 48 hours exists, the participant's diary response to Q1 on day2 (*d2res/24*) will be used and where no diary has been returned or response is missing the short FU questionnaire Question 2 (*reso/48*) will be used. Discrepancies in reporting may exist, thus the first reported outcome (text/telephone) will be taken as the valid response since it is most timely to the outcome. If no text/telephone response is available the source of data for the primary outcome will be considered in the order detailed above (i.e. text/telephone, diary, FU). For each participant the source of data will be recorded. Any participants who have no information after looking at each of the data sources will be included in the analysis assuming 'no resolution'.

- 3) Report of time to onset of pain relief (in hours) within 7 days

For each participant, the following items of information will be required; whether their sore throat became less painful during the 7 days (section1: Q2 Diary), the day and time their sore throat became less painful. The time reported for onset of pain relief will be converted to 24 hour clock. In cases where the minutes are missing, but hour has been reported the minutes will be assumed to be 0 and the participant will be included in the analysis. If a participant does not record am/pm and the time is ambiguous, the time of onset of pain relief will be recorded as missing.

Time to onset (in hours) will be computed as the difference between the time on Day 0 that medication was taken (Baseline *medtime*) to the day and time (24 hour clock) the participant's sore throat became less painful (Section 1 Question 2a of symptom). Only participants who returned a symptom diary will be included in the analysis. Participants who stop completing symptom diaries will be censored at the last recorded time their status was known.

4) Report of time to complete symptom resolution (in hours) within 7 days

The time reported for complete symptom resolution will be converted to 24 hour clock. In cases where the minutes are missing but hour has been recorded the minutes will be assumed to be 0 and the participant will be included in the analysis. In cases where am/pm is missing and the time is ambiguous, time of complete resolution will be recorded as missing.

The number of hours from time medication taken (Baseline *medtime*) on day 0 to the day and time their sore throat was completely resolved (Section 1, Question 1a of symptom diary) will be computed for each participant. Only participants who returned a symptom diary with a valid time for complete resolution will be included in the analysis. Participants who stop completing symptom diaries will be censored at the last recorded time their status was known.

5) Duration of moderately bad symptoms recorded by validated symptom diary over the 7 days from treatment onset.

Question 5 records how bad the following symptoms (sore throat, pain on swallowing, difficulty swallowing, feeling unwell, cough, fever, sleep disturbance, tender glands in neck, change in mood, vomiting) have been in the last 24 hours, for each of the 7 days from treatment onset. Only participants who returned a symptom diary will be included in the analysis. The number of days that the participant reported moderately bad symptoms over the 7 days following randomisation will be used in the analysis to compare the clinical burden

1415 between the randomised groups. The days with moderately bad or worse symptoms do not
1416 need to be continuous.

1417 For each day the number of participants recording their symptoms will be reported by
1418 randomised group.

1419

1420

1421

1422 6) Change in ratings of sore throat pain, difficulty swallowing and pain on swallowing by
1423 visual analogue scale

1424

1425 For days 1 to 7, the change in rating from day 0 (d0sore, d0pain, d0diff) will be computed.
1426 Change in rating = Day 0 rating – day 1 rating, day 0 rating – day 2 rating etc. A positive
1427 change indicates reduction in pain/difficulty. Only patients with valid responses to section 3
1428 in the symptom diary will be included.

1429

1430 For each of the three symptoms, two analyses will be undertaken:

1431

- 1432 (i) To compare the overall burden of sore throat over the 7 days from
1433 randomisation, AUC summary statistics will be estimated and compared
1434 between the randomised groups [Bell et al, 2014]. .
- 1435 (ii) To evaluate whether the intervention has an immediate effect, a comparison
1436 of the mean change from baseline to day 1 and mean change from baseline
1437 to day 2 between the randomised groups will be carried out. This is where the
1438 greatest difference is likely to be seen and is clinically relevant.

1439

1440

1441 7) Uptake of delayed antibiotic prescription within 7 days

1442 Only participants who were given a delayed antibiotic prescription (baseline Q7 *delpres*=1,2
1443 (given to participant or left at reception)) will be included in this analysis.

1444 The symptom diary asks about antibiotic use daily (Q6). Each of the 7 days of the symptom
1445 diary will be examined. The FU questionnaire asks about antibiotic use (Q7 *antibio*). If the
1446 participant responds yes to Q7, the day they started taking antibiotics (*antibiody*) will be
1447 checked to ensure it is ≤ 7 days. The information from the symptom diary will be considered
1448 first. If this symptom diary has not been returned the FU questionnaire will be considered.
1449 Participants who complete only part of the symptom diary will be included in the analysis.

1450 Numerator = number of participants who report taking antibiotics during 7 days

1451 Denominator = Number of randomised patients given delayed prescription and returned
1452 symptom diary or FU questionnaire

1453 The number (%) of participants who were given a delayed prescription but who did not return
 1454 a symptom diary or a FU questionnaire will be reported per randomised group.

1455

1456 8) Time missed from work or education over subsequent 7 days

1457 Question 8 section 2 in the symptom diary records participants missed time from
 1458 work/education over 7 days. The diary categorises time missed from work in categories (1-
 1459 2hrs, 3-4 hrs, 5-6hrs, 7-8 hrs and >8hrs.) In order to allow the computation of total number
 1460 of hours work/education missed over the subsequent 7 days, each category will take the
 1461 middle value (i.e. 1.5, 3.5, 5.5, 7.5 and 8.5). The FU questionnaire (Q5 muchwork) requests
 1462 free text to indicate how much time they took off work. This will be converted to hours (with
 1463 an assumption that 1 day = 8 hours) with a maximum of 7 days. The total number of hours
 1464 missed over the 7 days will be summed for each participant who is in paid work or education
 1465 (Q4 baseline *workedu*).

1466 Two derived variables

1467 (i) Whether a participant reported missing any work/school over the 7 days.
 1468 Randomisation should ensure that similar proportion of participants in each
 1469 randomised group is in work/education. For each randomised group the
 1470 proportion missing work/education will be computed using the total number of
 1471 patients who completed a symptom diary or follow up questionnaire

1472 (ii) The total number of hours of work/education missed for each participant who
 1473 completed symptom diary or FU questionnaire.

1474

1475 9) Attendance at GP practice, A and E or Out of hours (OOH) centres within 28 days
 1476 with symptoms or complications associated with sore throat e.g. peritonsillar abscess

1477 These data are collected within the one month notes review. The one month notes review
 1478 will be performed and coded for all participants before unblinding. The reason for
 1479 attendance will be coded as related to or not related to sore throat separately by 2 clinically
 1480 qualified investigators prior to unblinding.

1481 Telephone contact with GP, practice nurse, 111 or OOH service will be included in addition
 1482 to attendance.

1483 A new binary variable will be derived for each participant for attendance (including telephone
 1484 contact) within 28 days **AND** with symptoms or complications associated with sore throat.
 1485 [*nhsevent1/7* = 0 to 10 will be coded as attendance/contact AND symptoms/complications to
 1486 be coded by clinician as associated with sore throat – derived variable from *nhsrson1/7* and
 1487 *nhsoutc1/7*].

1488 Participants may contact NHS facilities more than once in the 28 days following their initial
 1489 trial appointment. A second variable will be generated as the number of

1490 attendances/contacts with symptoms or complications associated with sore throat for each
1491 participant.

1492 10) Hospital admission with related complications of sore throat within 28 days

1493 Information regarding hospital admission is contained in one month notes review. If
1494 *nhsevt1/7* = 13 and the reason (*nhsrson1/7*) or outcome (*nhsoutc1/7*) was a complication
1495 associated with sore throat (coded by clinician), a new variable will be generated indicating
1496 hospital admission with related complications of sore throat (1=yes, 0=No).

1497 Hospital admission = 1, if *nhsevt1/7* = 13 AND complication of sore throat.

1498

1499 11) Use of over-the counter medications and prescription medications in the first 7 days

1500 Did the participant use any over the counter medications or prescription medications for
1501 sore throat symptom relief , including (i) analgesia (oral analgesia as listed in the BNF
1502 section 4.7 and topical local anaesthetics and anti-inflammatories in spray, linctus and
1503 lozenge formulations) , (ii) antibiotics for sore throat and (iii) antibiotics for any other
1504 indication and if so, for how many days?

1505 A new variable will be derived using Q7 (days1-7) symptom diary and Q8 FU
1506 questionnaire and one month notes review to indicate whether the participant used any
1507 other treatments since taking the trial medication. The number of days using additional
1508 medications can be computed for participants who returned the symptom diary and notes
1509 review but not for those who returned the FU questionnaire. The number of participants
1510 contributing to the analysis of number of days, will be reported. Medications issued in
1511 the first seven days will be coded by 2 clinicians independently into subgroups described
1512 above.

1513 Medication use will be reported in the following subgroups; (i) oral or topical analgesia
1514 including, lozenges linctus and sprays where they contain a local anaesthetic or anti-
1515 inflammatory, (ii) antibiotics for sore throat and (iii) antibiotics for other indication sin
1516 addition to overall OTC or prescription medication use.

1517

1518

1519 1.7 Target population

1520 Participants aged between 18 and 70 years inclusive, presenting to primary care with acute
1521 sore throat.

1522 Inclusion Criteria

- 1523 • Aged between 18 and 70 years, inclusive (We will include patients aged over 70 who
1524 were recruited before the protocol was amended)
- 1525 • Presenting to a primary care appointment with acute sore throat and odynophagia
1526 (pain on swallowing) which is judged by the clinician to be infective in origin

- 1527 • Onset of symptoms within the last 7 days
- 1528 • Patient has capacity and willingness, in the view of the recruiting clinician, to give
- 1529 consent and complete the trial paperwork, including the symptom diary

1530 Exclusion Criteria

1531 The participant may not enter the study if ANY of the following apply:

- 1532 • Female participant who is pregnant, lactating or planning pregnancy during the
- 1533 course of the study
- 1534 • Recent (<1 month) use of inhaled or oral corticosteroids.
- 1535 • Recent (<1 month) Adenotonsillectomy
- 1536 • Currently or recently (<14 days) taking antibiotics
- 1537 • Clear alternative diagnosis e.g. pneumonia
- 1538 • Known immune-deficiency (e.g. HIV, active chemotherapy or advanced cancer)
- 1539 • Scheduled elective surgery or other procedures requiring general anaesthesia during
- 1540 next 7 days
- 1541 • Participant who is terminally ill
- 1542 • Symptoms or signs suggesting that hospital admission is required (e.g. completely
- 1543 unable to swallow, very systemically unwell, peritonsillar abscess)
- 1544 • Participant judged by the GP to require immediate antibiotics
- 1545 • History of severe affective disorders including steroid-induced psychiatric illness
- 1546 • British National Formulary (BNF) listed contra-indications to oral steroids
- 1547

1548 1.8 Sample size

1549 Based on the results of our systematic review of 8 studies, the average absolute increase in
 1550 participants reporting complete resolution of pain at 24 hours with corticosteroids in addition
 1551 to antibiotics and analgesia was 27% [Hayward BMJ 2009]. The minimum absolute increase
 1552 from individual trials was 18% (11% vs 29%). To achieve this effect size with 90% power, our
 1553 conservative estimate of sample size is 226 patients.

1554 In the UK antibiotics are prescribed to approximately 50% of participants presenting with
 1555 sore throat [Gulliford 2009]. Given that our first secondary objective is to detect a clinically
 1556 significant difference in proportions of participants reporting complete resolution of pain at 24
 1557 hours, in participants not having been prescribed antibiotics, we will require an initial sample
 1558 of 452 patients. A sample size of 566 allows for loss to follow-up of 20% (or 532 for 15% lost
 1559 to follow-up).

1560

1561 1.9 Randomisation and blinding in the analysis stage

1562 Randomisation was performed by the Oxford Primary Care Clinical Trials Unit and was
 1563 stratified by centre (Oxford, Bristol and Southampton) and receipt or not of delayed antibiotic
 1564 prescription using block randomisation with variable block size. An independent statistician
 1565 not involved in any other aspect of the trial generated the randomisation schedule.

Once all the data queries have been resolved, a blind data review meeting will be initiated involving the trial statistician, the data manager, the trial manager and the CI. All protocol violations will be reviewed and a list of study populations for analysis will be generated and signed off by the CI and the statistician. At this point, the database will be locked and decoding of the allocation will be allowed.

Participants found to be ineligible after they have been randomised will be removed from the trial. Their data will be removed and they will not be included in the analysis.

2 ANALYSIS – GENERAL CONSIDERATIONS

2.1 Descriptive statistics

Data are collected via text, telephone, symptom diary, FU questionnaire and case note review. The number of participants who submitted texts at 24 hours and 48 hours, returned symptom diaries and FU questionnaires and had case note review completed will be reported by randomised group stratified by centre and whether the participant was given a delayed antibiotic prescription.

2.2 Characteristics of participants

Descriptive statistics within each randomised group will be presented for baseline characteristics (i.e. duration of sore throat and pain on swallowing at study entry), demographic characteristics (age, gender, smoking status and whether the patient is in paid work or education), baseline symptoms (e.g. sore throat, runny nose, cough, hoarse voice, fever, headache, muscle ache, abdominal pain, disturbed sleep), baseline physical examination findings (including FeverPAIN score, Centor score) and whether the patient was given a delayed antibiotic prescription. Frequencies and percentages will be reported for categorical variables and for continuous variables, the mean and standard deviation will be reported for normally distributed continuous variables and median and interquartile range for skewed continuous data. No formal statistical testing will be applied to test for any difference between randomised groups with respect to baseline characteristics. In addition, patient characteristics will be presented by randomised group separately for the two groups of participants defined by whether they received a delayed prescription or not.

Description and derivation of FeverPAIN and CENTOR score.

The FeverPAIN score ranges from 0 to 5 with 1 point for each of 5 items: fever in past 24 hours, purulence, rapid (within 3 days attendance), very inflamed tonsils and no cough or cold symptoms. In the model, FeverPAIN will be classified as 3 categories [ref PRISM} low scores (0,1) [antibiotics would not be offered], intermediate scores (2,3) [delayed antibiotics] and high scores (4,5) [immediate antibiotics].

Derivation of FeverPAIN score

Data from baseline assessment form will be used to compute the score for each participant.

Q3k Fever in last 24 hours *sympk* (slight, moderate or severe = 1)

Q4 purulence *pexpur* (yes=1)

Dayssore (≤ 3 days=1)

Q4 very inflamed tonsils *pexinfl* (yes and severe= 1)

Q3e no cough during illness *sympe* (none = 1)

The Centor score was first derived in 1981 and includes four variables with equal weighting. The score ranges from 0 to 4 (original score) with a higher score more predictive of a positive culture. NICE guidance CG69 suggests a clinician should consider immediate antibiotic prescribing for a score of ≥ 3 .

Derivation of Centor score

Centor score is computed using data from the baseline assessment form.

History of fever (*sympf*) (slight, moderate or severe =1)

Tonsillar exudates *pexphar* (yes=1)

Tender anterior cervical adenopathy *pextend* (yes=1)

Absence of cough *sympe* (none =1)

2.3 Definition of population for analysis

Ineligible participants (i.e. not in the target population) who were randomised in error will be detailed in the CONSORT flow chart and will be excluded from all analyses.

The primary analysis will be by intention to treat (ITT). All eligible randomised patients will be included in the analysis of the primary outcome, assuming no complete resolution for any missing data.

2.4 Pooling of investigational sites

Randomisation was stratified by centre (Oxford, Bristol and Southampton). Centre will be adjusted for in the analysis by including a centre variable which will be fitted as a fixed effect in the statistical models.

2.5 Data Monitoring Committee And Interim Analyses

The analysis plan for interim analysis requested by the DMEC is contained in a separate analysis plan.

1639

1640 **3 PRIMARY ANALYSIS**1641 **3.1 Primary outcome**

1642 The primary outcome is the proportion of patients with complete resolution of sore throat at
1643 24 hours. There may be multiple sources for the primary outcome. These data are primarily
1644 collected by text. The order in which data sources will be used is detailed in section 1.6.1.

1645 After examination of all sources of data, any participant with missing information with respect
1646 to the primary outcome will be analysed as 'not resolved'. The proportion of participants
1647 with missing information with respect to the primary outcome will be documented by
1648 randomised group and by centre.

1649 A log-binomial regression model will be applied to the data. Treatment effect will be reported
1650 as a relative risk and 95% confidence interval and will be adjusted for centre and whether the
1651 patient was prescribed antibiotics or not. In addition, the Absolute Risk Reduction (ARR) and
1652 Number Needed to Treat (NNT) with corresponding 95% confidence intervals will be
1653 computed and reported. A cross-tabulation of primary outcome by data source (i.e.
1654 text/telephone, symptom diary, FU questionnaire) will identify discrepancies between the
1655 sources for each participant.

1656

1657 **3.2 Handling missing data**

1658 The protocol states that if there is any missing information with respect to the primary
1659 outcome, it should be analysed as 'not resolved'. Therefore, the primary analysis makes the
1660 assumption that all participants who failed to respond at 24hours had no complete resolution
1661 of their symptoms i.e the missing data mechanism that is assumed in the primary analysis is
1662 MNAR. Sensitivity analyses will explore missing data assumptions.

1663 To explore the pattern of missing outcomes with respect to primary outcome, the percentage
1664 of missing data will be compared between the two randomised arms. In addition a logistic
1665 regression model will be fitted to assess whether baseline covariates (i.e. centre, age,
1666 gender, smoking status, paid work/education, Centor and feverPain score, randomised
1667 group) significantly predict non-response of the primary outcome.

1668

1669 **3.3 Handling outliers**

1670 Outliers should not be an issue, since the outcomes are typically categorical with specified
1671 lower and upper limits.

1672 **3.4 Handling multi-centre/clustered data**

There is potential for clustering of outcomes within centres (Oxford, Bristol and Southampton) with particular respect to missing data. This will be explored descriptively. In addition, centre will be fitted as a covariate in the statistical models.

3.5 Multiple comparisons and multiplicity

A single primary outcome has been specified, in a two randomised group trial, hence there are no issues of multiplicity.

3.6 Model assumptions

The log binomial model to be fitted to these data includes only categorical covariates, therefore there should not be any problem with convergence. However, if the model fails to converge, a Poisson regression with robust standard errors will be applied to the data.

4 SECONDARY OBJECTIVES

4.1 Primary outcome

In patients who were not given a delayed prescription for antibiotics, complete resolution of sore throat at 24 hours. Analysis will follow that outlined above for the analysis of the primary outcome.

A log-binomial regression model will be applied to the data. Treatment effect will be reported as a relative risk and 95% confidence interval. In addition, the Absolute Risk Reduction (ARR) and Number Needed to Treat (NNT) with corresponding 95% confidence intervals will be computed and reported. The model will include randomised group and the stratification variable, centre.

The above analysis will be repeated for the participants who were given a delayed prescription.

4.2 Secondary outcomes

Secondary outcomes have been grouped by variable type. Analysis will be conducted on all patients randomised. In addition, the analysis will be repeated for the two subgroups of patients defined by whether they received a delayed prescription or not. These two groups of patients will be considered separately.

Binary secondary outcomes (i.e. complete resolution of sore throat at 48 hours, attendance at GP practice/out-of-hours/A&E within 28 days with symptoms or complications associated with sore throat, hospital admission with related complications of sore throat within 28 days, uptake of delayed antibiotic prescription, use of OTC medications,) will be analysed using the

same principles as the primary analysis of the primary outcome. The frequency (percentage) within each randomised group will be presented. A log binomial model will be fitted to the data with randomised group, centre and, if applicable, whether the patient was prescribed delayed antibiotics or not included as covariates. Relative risks with 95% confidence intervals will be presented.

Pseudo continuous (time missed from work or education). The mean (SD) will be reported for each group and the difference and 95% CI will be computed using linear regression with adjustment for centre and if applicable, delayed antibiotic prescription. Assumptions of linear regression will be assessed and if violated a Mann-Whitney test will be adopted and the median (IQR) will be used to summarise the data and difference in medians (95%CI) will be reported.

Time to event (time to onset of pain relief, time to complete resolution,)

Kaplan Meier curves will be presented. A Cox regression model will be used to test whether time to event differs between the randomised groups. The median (interquartile range) for each randomised group will be presented. The model will include randomised group and if applicable, whether they received a delayed antibiotic prescription. A hazard ratio and 95% confidence interval will be reported to present the difference in time to event between the randomised groups.

Count (duration of moderately bad symptoms)

The analysis will be repeated for each symptom.

The event rate will be computed for each randomised group. To compare the randomised groups, a random effects negative binomial model will be fitted to the data. The dependent variable is the number of days with symptom. The explanatory variables will include number of days diary completed for that symptom (as an offset), randomised group, centre, and if applicable, whether the patient was given a delayed antibiotic prescription. The incidence rate ratio and 95% confidence interval will be reported for randomised group.

Change in ratings of sore throat pain, difficulty swallowing and pain on swallowing

This analysis will be repeated for each symptom.

The mean change from baseline to each day (1-7) will be plotted graphically by randomised group. Two analyses will be conducted.

- (i) AUC will be used as summary statistic. For each symptom, AUC summary statistics will be computed for each group [Bell et al, 2014]. A mixed model including a random intercept, randomised group, day of assessment, interaction term of group by day, severity of symptom at day 0, centre and if applicable, whether patient received a delayed prescription will be fitted to the data for each symptom. The AUC for each group is estimated using a linear combination of the parameter estimates after a model has been fit. The difference in AUC between the groups will be estimated using a contrast for the AUC summary statistics. The difference in summary AUC and 95% confidence interval will be reported.

1748 (ii) The mean change from baseline to day 1 and mean change from baseline to day
1749 2 will be compared between the two groups using linear regression models. The
1750 linear regression model will include severity on day 0, centre and if applicable,
1751 whether the patient received a delayed antibiotic prescription. The adjusted
1752 difference in mean change and 95% confidence interval will be reported. The
1753 number of participants contributing data will be reported by randomised group.

1754

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1756 **4.3 Tertiary/Other outcomes**

1757 None

1758 **5 SENSITIVITY ANALYSIS**

1759 Sensitivity analysis will be conducted on the primary outcome and secondary outcomes 1
1760 and 2 only. The primary analysis assumed that missing responses had the worst outcome.
1761 The following sensitivity analyses are planned to explore the impact of this assumption.

1762 (i) An ITT analyses will be conducted where missing responses will be assumed
1763 to be 'completely resolved'.

1764 (ii) An ITT analyses will be conducted and multiple imputation will be used to
1765 replace the missing data with plausible values. The Multiple Imputation (MI)
1766 model will include any variables that have been identified as predictive of non-
1767 response and any variables that are to be included in the analysis model.

1768 (iii) A complete case analysis will be conducted using only those patients with a
1769 valid response.

1770

1771 **6 SUBGROUP ANALYSES**

1772 No subgroup analyses were pre specified in the protocol. Two subgroups were identified
1773 during preparation of the SAP and prior to data lock.

1774 **1. Patient Severity**

1775 The outcome is complete resolution at 24 hours (primary outcome). It is hypothesised that
1776 patients with a more severe sore throat may have more beneficial effect from the steroids.

1777 Patient severity is defined using Centor score with a cut off of <3 and ≥3.

1778 Analysis will follow the strategy outlined in section 3.1. To test for a differential effect of the
1779 intervention in more severe patients, an interaction term shall be fitted to the model.

1780

1781 **2. Participant took rescue medication on day 1 or 2 post randomisation.**

1782 The outcome is complete resolution at 48 hours (secondary outcome). It is hypothesised
 1783 that the effect of the intervention may be masked in patients who take medication (e.g.
 1784 analgesics) in the first couple of days.

1785 Rescue medication is defined as those medications listed in the British National Formulary
 1786 British National Formulary section 4.7 which are available over the counter and topical local
 1787 anaesthetic and anti-inflammatory preparations and will be adjudicated by two clinicians.

1788 Analysis will follow the strategy outlined above in Section 4.2. To test for a differential effect
 1789 of the intervention in patients who took rescue medication or not, an interaction term shall be
 1790 fitted to the model.

1791 **7 ADDITIONAL EXPLORATORY ANALYSIS**

1792 (i) In the participants who were not offered a delayed prescription, is there a
 1793 difference between the randomised groups in the proportion of participants
 1794 who subsequently start a course of antibiotics for their sore throat?

1795 Only participants with *delpres* = 'No' recorded for Q7: baseline will be included in this
 1796 analysis.

1797 Starting a course of antibiotics will be derived using Q6 in sect2 for each day of symptom
 1798 diary or Q7 (*antibio*) in FU questionnaire (ensure start date (*antibody*) ≤ 7 days).

1799 Only patients who returned a symptom diary or FU questionnaire will be included in the
 1800 analysis.

1801 Analysis will follow strategy for analysis of binary outcome variable (Section 4.2).

1802

1803 **8 SAFETY ANALYSIS**

1804 All patients randomised will be included in the safety analysis.

1805 All serious adverse events (SAE) occurring during the one month participants are enrolled in
 1806 the trial shall be detailed and reported by treatment group. The overall incidence of patients
 1807 experiencing at least one SAE will be compared between the randomised groups using a Chi
 1808 squared test and the difference in proportions with 95% confidence intervals will be
 1809 presented. Where a patient reports more than one of the same type of event, separate
 1810 tables will be presented showing a) counts of events and b) counts of participants
 1811 experiencing at least one type of this event.

1812

1813 **9 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP**

1814 In the protocol v6.0, the primary outcome is defined as "direct report by the patient of
 1815 presence or absence of complete resolution of sore throat at 24 hours by either text
 1816 message or telephone". In the analysis plan, the primary outcome will, in addition, use

1817 information obtained via the symptom diary or FU questionnaire only if the participant has not
1818 responded by text/telephone.

1819 In addition to the analysis that was detailed in the protocol v6.0, the analysis of the primary
1820 and secondary outcomes (where specified) will in addition be analysed by the two groups of
1821 patients defined by receipt of delayed prescription or not. This is not a subgroup analyses
1822 but two separate analyses of the randomised groups in patients who have received a
1823 delayed antibiotic prescription and those that did not. The Protocol v6.0 specified that the
1824 primary analysis would be repeated in the group of patients who did not receive an antibiotic
1825 prescription. This has been expanded to all outcomes and also for the group who received
1826 an antibiotic prescription. The analyses for the group receiving delayed antibiotics may not
1827 be reported in the main paper, which will probably focus on the no delayed antibiotic
1828 prescription group results.

1829 The protocol v6.0 specified the use of logistic regression for analysis of the dichotomous
1830 primary and secondary outcomes. The published protocol (Cook *et al*) specified a
1831 generalised linear model (GLM) for binary data (of which logistic regression is one example).
1832 This statistical analysis plan has specified a different GLM, the log binomial model to
1833 analyse these data. The use of the log link in the log binomial model (as opposed to the logit
1834 link in the logistic model) results in estimation of the effect size as a relative risk (rather than
1835 the odds ratio that would result from logistic regression). The log binomial model was
1836 chosen over the logistic since relative risks are considered more appropriate (as odds ratios
1837 tend to overestimate the effect of the intervention when the proportion of patients with the
1838 outcome of interest is not small (e.g. <15%)).

1839 A secondary outcome was specified as 'attendance at GP practice, A and E or out of hours
1840 within 28 days of symptoms or complications associated with sore throat'. In the analysis,
1841 telephone contact with GP practice, 111 or out of hours will also be included in this outcome.

1842 In the protocol v6.0, time to onset of pain relief and time to complete resolution of pain were
1843 to be summarised using the mean and standard deviation and analysed using linear
1844 regression. To allow for the possibility that some participants symptoms may not completely
1845 resolve during the 7 days or for participants who do not complete all 7 days of the symptom
1846 diary, the preferred method of analysis will be by Cox regression.

1847 In the protocol v6.0 duration of moderately bad systems was to be summarised using the
1848 mean and standard deviation. In preparation of the analysis plan, it was agreed that a count
1849 of the number of days the participant recorded moderately bad or worse symptoms was the
1850 most appropriate outcome. Since the number of days need not be continuous or participants
1851 may not complete all 7 days of the diary, a negative binomial model to compare the number
1852 of days between the two groups was considered more appropriate.

1853 In the protocol v6.0 areas under the curves were to be calculated as a summary
1854 measurement for each participant. In the analysis, AUC summary statistics are to be
1855 calculated for each randomised group. AUC summary measures can be problematic when
1856 some data for a participant is missing. The AUC summary statistic approach utilises a mixed
1857 model to calculate the AUC and thus can implicitly account for missing participant data.

1858

1859 **10 REFERENCES**

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1878 **11 APPENDICES**

1879 Appendix I. Schedule of procedures

1880

Procedure	Screen ing	Baseline (less than 6 hours after screenin g)	24 hours (text)	48 hours (text)	Teleph one call in first few days	Daily for 7 days (symptom diary)	After 7 days (brief FU questionn aire)	One month (Case note review)
Eligibility check	x							
Delayed antibiotic prescription offered	x							
Informed consent		X						
Demographics		X						
Past medical history, medication usage								x
Current medication (delayed antibiotic script, type and dose and duration, collection point, other advised treatment)		X						
Clinical examination, assessment of symptoms, patient reported items.		X						
Randomisation		X						
Trial medication taken		X						
Bacterial throat swab		X						
Primary outcome measurements		x	x	x	x	x	x	
Secondary outcome measurements		X	x	x	x	x	x	

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1882

Use of NHS facilities								x
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1883 Appendix II. Outcome assessment schedule

Procedure	Baseline (less than 6 hours after screening)	24 hours (text)	48 hours (text)	Teleph one call in first few days	Daily for 7 days (symptom diary)	After 7 days (brief FU questionnaire)	One month (Case note review)
Primary outcome Complete resolution of sore throat at 24 hours		X (1)		X (2)	X (3)	X (4)	
Secondary outcomes							
Complete resolution at 24 hrs in those not prescribed antibiotics		X (1)		X (2)	X (3)	X (4)	
Complete resolution at 48 hours			X (1)	X (2)	X (3)	X (4)	
Time to onset of pain relief					X (1)	X (2)	
Time to complete resolution					X (1)	X (2)	
Difficulty swallowing, pain on swallowing over 7 days					X		
Duration of moderately bad symptoms over 7 days					X		
Severity of symptoms in days 2-4					X (1)	X (2)	
Change in ratings of sore throat pain, pain on swallowing					X		

by VAS							
Uptake of delayed antibiotic prescription at 7 days					X (1)	X (2)	
Attendance at GP practice, A&E, OOH within 28 days							X
Hospital admission within 28 days					X		X
Use of over the counter medications and prescription medications in first 7 days					X (1)	X (2)	

1884

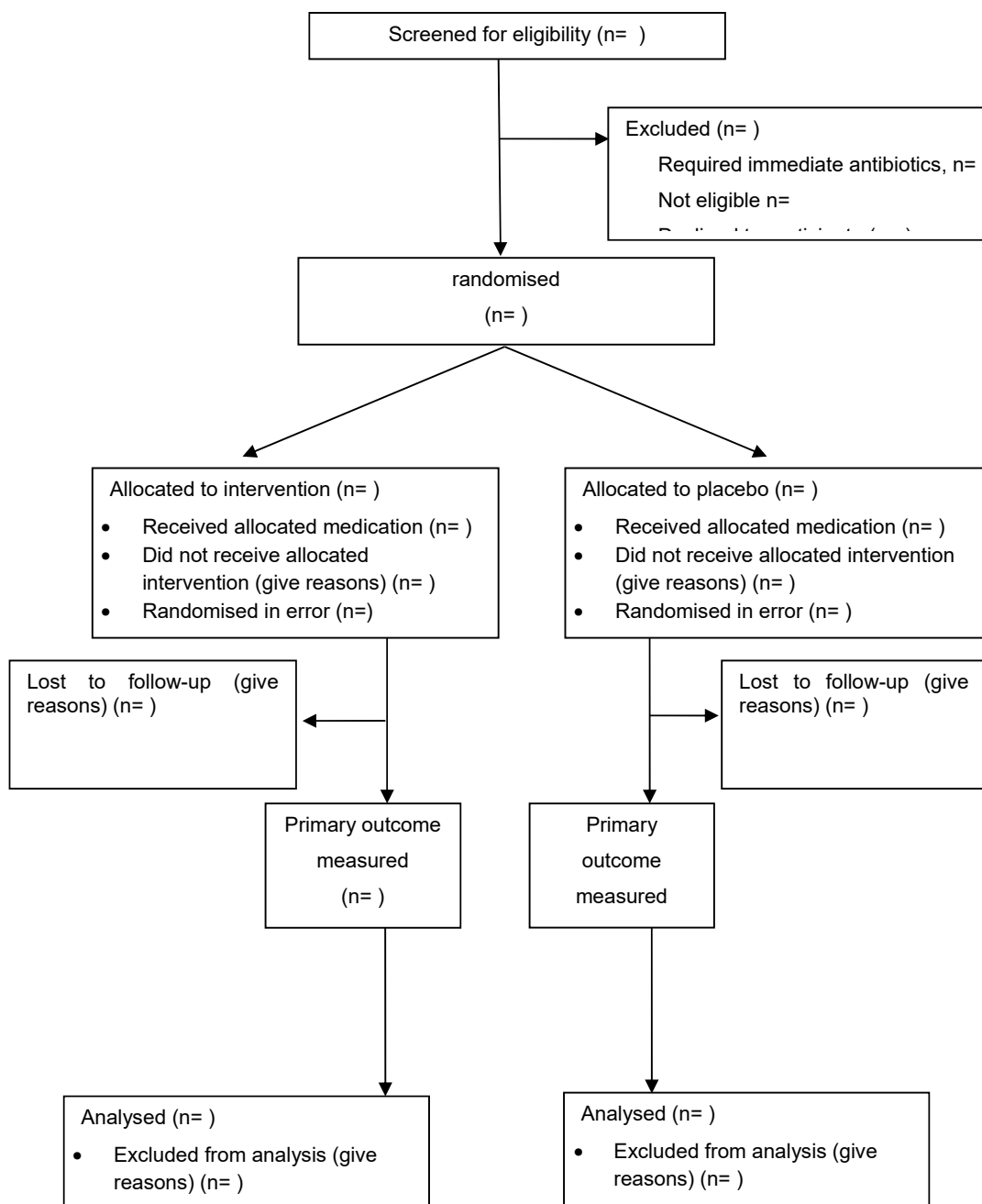
1885 *Footnote*

1886 X (1), X (2) etc denotes multiple sources of data and indicates the order in which the source
 1887 will be used to record the outcome for each participant.

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1889 Appendix III. Flow diagram of trial participants

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