

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35

This supplement contains the following items:

1. Original protocol, summary of changes.
2. Original statistical analysis plan

36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

INITIAL TRIAL PROTOCOL

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

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

Internal Reference No: CH-GH/TOAST/0006

Ethics Ref: 12/SC/0684

NRES Committee South Central - Oxford B

EudraCT Number: 2012-004330-41

Date and Version No: 1.0 01-NOV-2012

Chief Investigators:

Dr Carl Heneghan
Department of Primary Care Health Sciences
New Radcliffe House
(Off Walton Street)
Postal Address:
Department of Primary Care Health Sciences
Radcliffe Observatory Quarter
Woodstock Road
Oxford
OX2 6GG

Investigators:

Dr Gail Hayward
Dr Matthew Thomson
Dr Alastair Hay
Dr Michael Moore
Professor Paul Little
Dr Kim Harman
Dr Jane Wolstenholme
Dr Rafael Perera

Sponsor:

University of Oxford

Funder:

NSPCR

Signatures:

51 **Investigator Agreement**

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
56
57
58

Principal Investigator (Print Name)	Investigator Signature	Date
--	------------------------	------

59

Co-Investigator (Print Name)	Investigator Signature	Date
------------------------------	------------------------	------

60

61

Co-Investigator (Print Name)	Investigator Signature	Date
------------------------------	------------------------	------

62

63

64

Co-Investigator (Print Name)	Investigator Signature	Date
------------------------------	------------------------	------

65

66

Co-Investigator (Print Name)	Investigator Signature	Date
------------------------------	------------------------	------

67

68

69

Co-Investigator (Print Name)	Investigator Signature	Date
------------------------------	------------------------	------

70

71

Co-Investigator (Print Name)	Investigator Signature	Date
------------------------------	------------------------	------

72

73

74

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

80	TABLE OF CONTENTS	
81	1 SYNOPSIS	7
82	2 ABBREVIATIONS.....	9
83	3 BACKGROUND AND RATIONALE	11
84	4 OBJECTIVES	13
85	4.1 Primary Objective	13
86	4.2 Secondary Objectives.....	13
87	5 TRIAL DESIGN.....	14
88	5.1 Summary of Trial Design	14
89	5.2 Primary and Secondary Endpoints/Outcome Measures.....	14
90	5.3 Trial Participants.....	15
91	5.3.1 Overall Description of Trial Participants	15
92	5.3.2 Inclusion Criteria.....	15
93	5.3.3 Exclusion Criteria	15
94	5.4 Expenses and Benefits	16
95	5.5 Study Procedures	16
96	5.5.1 Informed Consent.....	16
97	5.5.2 Screening and Eligibility Assessment.....	17
98	5.5.3 Baseline Assessments	17
99	5.5.4 Randomisation and Codebreaking	19
100	5.5.5 Subsequent assessments	21
101	5.6 Definition of End of Trial	21
102	5.7 Discontinuation/ Withdrawal of Participants from Study Treatment.....	21
103	6 Source Data.....	22
104	7 TREATMENT OF TRIAL PARTICIPANTS	22
105	7.1 Description of Study Treatment	22
106	7.2 Storage of Study Treatment	23
107	7.3 Compliance with Study Treatment.....	23
108	7.4 Accountability of the Study Treatment.....	23
109	7.5 Concomitant Medication	24
110	7.6 Post Trial Treatment	24
111	8 SAFETY REPORTING	24
112	8.1 Definitions.....	24
113	8.2 Adverse Event (AE).....	24
114	8.3 Adverse Reaction (AR).....	25
115	8.4 Serious Adverse Event (SAE)	25
116	8.5 Serious Adverse Reaction (SAR).....	26

TOAST Statistical Analysis Plan

117	8.6	Suspected Unexpected Serious Adverse Reaction (SUSAR)	26
118	8.7	Causality	26
119	8.8	Procedures for Recording Adverse Events	26
120	8.9	Reporting Procedures for Serious Adverse Events	26
121	8.10	Data Monitoring Committee	27
122	8.11	SUSAR Reporting	27
123	8.12	Development Safety Update Reports (DSUR)	27
124	9	STATISTICS	28
125	9.1	Description of Statistical Methods	28
126		Health Economics Analysis	29
127	9.2	The Number of Participants	30
128	9.3	The Level of Statistical Significance	31
129	9.4	Criteria for the Termination of the Trial	31
130	9.5	Procedure for Accounting for Missing, Unused, and Spurious Data	31
131	9.6	Procedures for Reporting any Deviation(s) from the Original Statistical Plan	32
132	9.7	Inclusion in Analysis	32
133	10	DIRECT ACCESS TO SOURCE DATA/DOCUMENTS	32
134	11	QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES	32
135	12	Serious Breaches	33
136	13	ETHICS	34
137	13.1	Declaration of Helsinki	34
138	13.2	ICH Guidelines for Good Clinical Practice	34
139	13.3	Approvals	34
140	13.4	Participant Confidentiality	34
141	14	DATA HANDLING AND RECORD KEEPING	35
142	15	FINANCE AND INSURANCE	36
143	15.1	Compensation for harm	36
144	16	PUBLICATION POLICY	36
145	17	REFERENCES	37
146	18	APPENDIX A: STUDY FLOW CHART	39
147	19	APPENDIX B: SCHEDULE OF PROCEDURES	40
148			
149			
150			
151			
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> <ul style="list-style-type: none"> 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 <p>4) To assess predictors of response to corticosteroids including FeverPAIN score, Centor score, baseline factors and positive bacterial throat swab</p>
<p>Primary Endpoint</p>	<p>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</p>
<p>Secondary Endpoints</p>	<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

157 **2 ABBREVIATIONS**

158

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

TOAST Statistical Analysis Plan

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

159

160 3 BACKGROUND AND RATIONALE

161

162 **Epidemiology, costs and current management of sore throat**

163

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

172

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

178

179 The lost productivity associated with tonsillitis has been estimated at £190 pounds per
180 episode [7]. The weekly UK incidence of patients presenting to their GP with sore throat
181 averages at 60 per 100000 population. Extrapolating from this, we might expect a cost
182 of almost £6 per person per year in lost productivity alone (equating to £370 million at
183 2010 population figures), in addition to an estimated £60 million cost in GP consultations
184 [8].

185

186 **Rationale for testing the effectiveness of corticosteroids in sore throat**

187

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

194

195 We recently performed a systematic review and meta-analysis of randomised controlled
196 trials assessing the benefit of oral corticosteroids in sore throat, which was published in
197 the BMJ and Cochrane Library [15,16]. In our analysis of 8 eligible trials, we found that a
198 single dose of oral or intramuscular dexamethasone increased the likelihood of
199 complete resolution of pain at 24 hours by more than 3 times (relative risk 3.2, (95% CI
200 2.0 to 5.1; $p < 0.001$), absolute risk reduction 27% (95% CI 17 to 36%), number needed
201 to treat 3.7 (95%CI 2.8 to 5.9)). The mean time to onset of pain relief was reduced by
202 more than 6 hours (95% CI 3.4 to 9.3; $p < 0.001$). However, all of the included trials
203 compared steroids to placebo *in addition* to oral antibiotics. Furthermore no trials were
204 in the UK population and only one of the trials (in Israel) recruited patients presenting to
205 primary care. We have searched the International Controlled Trials Register (see
206 <http://www.controlled-trials.com/isrctn/>) to confirm there are no similar trials currently
207 conducted or registered.

208

209 **Justification for dose and route and known and potential risks to human** 210 **participants**

211

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

220

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

227

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

232 steroids in sore throat in the absence of antibiotics and in a UK primary care population.
233 We propose a randomised double blind trial comparing a single dose of oral
234 dexamethasone to placebo in adults aged 18 or over presenting to UK primary care.
235

236 **4 OBJECTIVES**

237 **4.1 Primary Objective**

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

241 **4.2 Secondary Objectives**

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

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

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

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

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

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

254 d) be cost-effective

255 4) To assess predictors of response to corticosteroids including FeverPAIN score, Centor
256 score, baseline factors and positive bacterial throat swab
257
258
259
260

261 **5 TRIAL DESIGN**

262 **5.1 Summary of Trial Design**

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

269 **5.2 Primary and Secondary Endpoints/Outcome Measures**

270 Primary outcome:

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

273

274 Secondary outcomes:

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

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

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

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

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

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

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

287 Uptake of delayed antibiotic prescription within 7 days

288 Time missed from work or education over subsequent 7 days

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

291 Hospital admission with related complications of sore throat within 28 days

292 Use of over-the counter medications and prescription medications (including whether,
293 if delayed antibiotics are taken, the course is completed, and whether any other
294 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

- 328 • Known dexamethasone allergy
- 329 • Any other significant disease or disorder which, in the opinion of the Investigator, may
- 330 either put the participants at risk because of participation in the study, or may influence
- 331 the result of the study, or the participant's ability to participate in the study
- 332 • Involvement in another clinical trial of an investigational medicinal product in the last
- 333 90 days or any other research within the last 30 days
- 334 • Recruiting primary care site is not the patients usual practice if the patient is not
- 335 expecting to still be with the primary care site in one month (i.e. temporary residents)
- 336 • Previous TOAST participation
- 337 • Patients unable to be randomised by the end of the (working) day of presentation
- 338 • Requirement for live vaccine in next 7 days

339 **5.4 Expenses and Benefits**

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

342 **5.5 Study Procedures**

343 **5.5.1 Informed Consent**

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

346

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

353

354 The participant will receive the Participant Information Sheet at their initial consultation
355 with their GP, and if eligible and interested will then be referred on to a Baseline Trial
356 Assessment with a recruiting clinician for full consent procedures and trial procedures
357 (see section 5.5.1 for full details). This will give the participants the opportunity to
358 consider the information, and the opportunity to question the recruiting clinician, their
359 GP or other independent parties to decide whether they will participate in the study.

360 Written Informed Consent will then be obtained by means of participant dated
361 signature and dated signature of the person who presented and obtained the informed

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

366 **5.5.2 Screening and Eligibility Assessment**

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

376
377 The Responsible Clinician completes their routine management, and at the clinician’s
378 discretion offers a delayed antibiotic prescription, to be collected by the patient either
379 from the recruiting clinician at their subsequent Baseline Trial Assessment, or from the
380 reception of the GP surgery according to the normal practice of the surgery. The
381 delayed antibiotic prescription will be accompanied by the following:

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

391 **5.5.3 Baseline Assessments**

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

396

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

403

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

411

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

418

419 Baseline CRF data items to be collected will include:

420 Socio-demographic factors to include:

- 421 • Age
- 422 • Gender
- 423 • Smoking history

424

425 Medications to include:

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

437

438 Symptoms will include:
439

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

442
443 Clinical examination findings will include:
444

- 445 • Presence of pharyngeal inflammation
- 446 • Presence of tonsils
- 447 • Presence of inflamed tonsils
- 448 • Presence of purulent tonsils
- 449 • Presence of cervical lymphadenopathy
- 450 • Presence of tender cervical lymphadenopathy
- 451 • Temperature and type of thermometer used for measuring

452
453 Patient completed items will include:

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

458 **5.5.4 Randomisation and Codebreaking**

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

467
468 Each site will initially be allocated to hold 2 sets of 2-3 packs of pre-randomised
469 medication, one set for those who are given an antibiotic prescription and one set for
470 those who are not. They will liaise with their local centre (the centre responsible for
471 setting up the site) when they have allocated their existing packs to trial participants
472 and reallocation of medication, if deemed necessary, will only occur within the same
473 centre and same subgroup of participants, having delayed antibiotic prescription or not
474 (see section 6.3 for details of drug distribution). They will also receive an equal number
475 of participant folders containing unique participant trial IDs. The process of recruitment
476 is as detailed in sections 5.5.1 and 5.5.2.

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

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

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

495
496 A standardised procedure for emergency unblinding will be available. The codes will
497 only be broken in case of a major adverse event (e.g. anaphylaxis; admission to
498 hospital with life threatening illness (e.g. septicaemia; meningitis; severe pneumonia
499 requiring ITU admission; death)). The randomisation code will be stored electronically
500 on a secure drive, password protected, and access will be restricted to the
501 independent statistician. If unblinding is deemed necessary the CI or designated
502 representative will inform the independent statistician to notify the relevant responsible
503 clinician of the treatment allocation for the relevant participant. The trial investigators
504 will not be informed which arm of the trial this participant was allocated to. If
505 randomisation of a participant is unblinded during the study then data for that
506 participant if available will be included in the intention to treat analysis.

507
508 The procedures for code break at the end of the trial will be as follows: once all the
509 data queries resolved, a blind data review meeting will be initiated involving the trial
510 statistician, the data manager, the trial manager and the CI. All protocol violations will
511 be reviewed and a list of study populations for analysis will be generated and signed
512 off by the CI and the statistician. At this point, the database will be locked and de-
513 coding of the allocation will be allowed.

514 **5.5.5 Subsequent assessments**

515 Participants will complete a symptom diary as well as reporting upon resolution of
516 symptoms, time to onset of pain relief and rating their pain on a visual analogue scale
517 every day for 7 days, on-line or on paper. As well as recording the severity and
518 duration of their symptoms, this will also include providing information about NHS
519 resource use, out-of-pocket expenditure, use of over-the-counter and prescription
520 medications and time off work / education or foregone leisure time. Within the
521 symptom diary we will also ask participants to complete the EuroQol EQ-5D measure
522 [20] daily for 7 days following study entry.

523

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

536

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

543 **5.6 Definition of End of Trial**

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

547

548 **5.7 Discontinuation/ Withdrawal of Participants from Study Treatment**

549 Each participant has the right to withdraw from the study at any time. In addition, the
550 investigator may discontinue a participant from the study at any time if the investigator
551 considers it would be harmful to keep a participant in the study. The reason for
552 withdrawal will be recorded in the CRF.

553

554 If the participant is withdrawn due to an adverse event, the investigator will arrange for
555 follow-up visits or telephone calls until the adverse event has resolved or stabilised or
556 until the end of the study, when participant care will return solely to the GP.
557 Participants will be retained in the trial for the purpose of intention to treat analysis
558 except when they specifically withdraw consent to this.

559

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

563 **6 SOURCE DATA**

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

568

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

573

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

577

578 **7 TREATMENT OF TRIAL PARTICIPANTS**

579 **7.1 Description of Study Treatment**

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

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

585

586 The labelling of medication packs will conform to Annexe 13 (GMP) and Article 13.3 of
587 Directive 2001/20/EC. A template label will be approved by the clinical trial team and
588 provided to the manufacturer by the Chief Investigator. Each medication pack label will
589 be printed with a unique medication ID number to ensure Dexamethasone and placebo
590 medicine packs are indistinguishable and thus maintain allocation concealment (see
591 5.5.3 for randomisation process). This randomised medication ID shall form the
592 identifier on the open code break document sent with each delivery of medication
593 packs to the clinical trials unit. The medicines will be received from the manufacturer
594 and stored securely by the clinical trials unit.

595

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

604

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

607 **7.2 Storage of Study Treatment**

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

610 **7.3 Compliance with Study Treatment**

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

613 **7.4 Accountability of the Study Treatment**

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

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

621
622 In the event that medication needs to be redistributed a drug redistribution log must be
623 completed to document the unique medication ID and must include a minimum of one
624 release signature (origin site staff), one transporter signature (PC-CTU staff) and one
625 receiving signature (new site staff).

626
627 Site-specific procedures will be followed in relation to disposing of and arranging for
628 destruction of expired trial medication. Standard GP site procedures should be
629 followed and the drug destruction log should be completed with the following details:
630 Date, unique medication ID, expiry date, quantity to be destroyed (number of tablets),
631 staff initials to confirm destruction.

632 **7.5 Concomitant Medication**

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

639 **7.6 Post Trial Treatment**

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

642 **8 SAFETY REPORTING**

643 **8.1 Definitions**

644 **8.2 Adverse Event (AE)**

645 An AE or adverse experience is:

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

649

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

653 **8.3 Adverse Reaction (AR)**

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

658

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

662 **8.4 Serious Adverse Event (SAE)**

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

- 664 • Results in death,
- 665 • Is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers
666 to an event in which the participant was at risk of death at the time of the event; it does
667 not refer to an event which hypothetically might have caused death if it were more
668 severe.
- 669 • Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- 670 • Results in persistent or significant disability/incapacity, or
- 671 • Is a congenital anomaly/birth defect.
- 672 • Other important medical events. NOTE: Other events that may not result in death, are
673 not life threatening, or do not require hospitalisation, may be considered a serious
674 adverse event when, based upon appropriate medical judgement, the event may
675 jeopardise the patient and may require medical or surgical intervention to prevent one
676 of the outcomes listed above.

677

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

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

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

688 **8.5 Serious Adverse Reaction (SAR)**

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

692 **8.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)**

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

696 **8.7 Causality**

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

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

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

703 **8.8 Procedures for Recording Adverse Events**

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

710
711 A participant may voluntarily withdraw from the trial due to what he or she perceives as
712 an intolerable AE. AEs that result in a participant's withdrawal from the study will be
713 recorded on the withdrawal form. The relationship of AEs to the study medication will
714 be assessed by a medically qualified investigator. The severity of events will be
715 assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

716

717 **8.9 Reporting Procedures for Serious Adverse Events**

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

725 **8.10 Data Monitoring Committee**

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

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

740 The Data Management Group will also, as required:

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

743 **8.11 SUSAR Reporting**

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

751 **8.12 Development Safety Update Reports (DSUR)**

752 In addition to the expedited reporting above, the CI shall submit once a year
753 throughout the clinical trial on the anniversary of the CTA or on request a Development
754 Update Safety Report (DSUR) to the Competent Authority (MHRA in the UK), Ethics
755 Committee, Host NHS Trust and sponsor. The report will be in line with PC-CTU SOP
756 TM19 "Pharmacovigilance".
757

758 **9 STATISTICS**

759 **9.1 Description of Statistical Methods**

760

761 **Statistical analysis for effectiveness and safety**

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

769

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

780

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

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

790

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

793

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

796 **Health Economics Analysis**

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

805

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

816

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

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

830

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

835

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

841

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

847

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

858 **9.2 The Number of Participants**

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

864

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

870 **9.3 The Level of Statistical Significance**

871 5% significance level is used to calculate number of participants required for the trial.

872 **9.4 Criteria for the Termination of the Trial.**

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

881 **9.5 Procedure for Accounting for Missing, Unused, and Spurious Data.**

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

889

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

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

896 **9.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan**

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

901 **9.7 Inclusion in Analysis**

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

904

905 **10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

906

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

911

912 **11 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES**

913

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

919

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

925

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

929 • DMC- to review and monitor the accruing data to ensure the rights, safety and
930 wellbeing of the trial participants. They will provide an interim analysis if requested by
931 the TSC. They will make recommendations to the TSC about how the study is
932 operating, any ethical or safety issues and any data being produced from other
933 relevant studies that might impact the trial.

934 • TMG- is responsible for the day to day running of the trial, including monitoring all
935 aspects of the trial and ensuring that the protocol is being adhered to.

936 • TSC- to provide overall supervision of the trial on behalf of the Sponsor and the
937 Funder to ensure that it is being conducted in accordance with ICH-GCP. The TSC
938 will review the trial regularly, agree any amendments and provide advice on all
939 aspects of the trial.

940

941 **12 SERIOUS BREACHES**

942

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

947 (a) the safety or physical or mental integrity of the subjects of the trial; or

948 (b) the scientific value of the trial".

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

952 • Possible serious breach is identified by a member of the study team; either through
953 site monitoring or audit visits, or through a whistle blower or a complaint from within or
954 outside the University.

955 • A written record of the incident will be made and once all necessary information is
956 gathered the information is reviewed by the relevant staff e.g. the QA manager, if
957 appropriate, and recorded on the Serious Breaches Assessment Form, TM25_B

958 • If considered to be a serious breach the CI will be asked to confirm this decision and
959 to contact the CTRG.

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

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

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

967

968 **13 ETHICS**

969 **13.1 Declaration of Helsinki**

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

972 **13.2 ICH Guidelines for Good Clinical Practice**

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

976 **13.3 Approvals**

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

981

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

984 **13.4 Participant Confidentiality**

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

990

991

992 **14 DATA HANDLING AND RECORD KEEPING**

993

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

999

1000 All patients will be consented using pre-printed paper consent forms including the
1001 unique patient ID. Pre-paid envelopes will be provided to return consent forms (and
1002 Clinical Record Forms if applicable) to the trial centres, where the data will be entered
1003 by centre trial administrators.

1004

1005 Data collection and management will be conducted using a secure, web-based, system
1006 developed in conjunction with the clinical trials unit. The system will incorporate data
1007 entry and validation rules to reduce data entry errors, and management functions to
1008 facilitate auditing and data quality assurance. Parallel paper-based data capture forms
1009 will be available to those patients and clinicians who prefer this option. Data Protection
1010 requirements will be embedded into the design of the web-based system and enforced
1011 by best practice trial management procedures. The Clinical Data Manager will oversee
1012 the process of electronic data validation and manual listings, sending out Data
1013 Clarification Forms (DCFs) when required and following these up until the queries are
1014 resolved.

1015

1016 Once the last patient is enrolled, prior to database lock a dataset review will be
1017 undertaken by the Information System Manager and Trial Statistician. All critical data
1018 items are 100% checked against original Source Data Documents to ensure accuracy,
1019 an error rate is established across all fields to ensure a consistently accurate dataset.

1020

1021 Patient contact information will be collected at baseline in paper form and faxed to the
1022 relevant study centre. A copy of the patients contact details consent form will be sent to
1023 the PC-CTU. This information will be used to contact the patient to collect details for the
1024 primary outcome at 24, 48 and once more up to 96 hours after the patient has joined the
1025 trial, and for further follow that might be required. The follow up contact will be co-
1026 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.

1058

1059

1060

1061 **17 REFERENCES**

- 1062 1) Gulliford M, Latinovic R, Charlton J, Little P, van Staa T, Ashworth M. Selective
 1063 decrease in consultations and antibiotics prescribing for acute respiratory tract
 1064 infection in UK primary care up to 2006 *Journal of Public Health* 2009; 31(4), 512-
 1065 520.
- 1066 2) Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database*
 1067 *Syst Rev* 2006;(4):CD000023.
- 1068 3) NICE guideline. Respiratory Tract Infections - antibiotic prescribing. Prescribing of
 1069 antibiotics for self limiting respiratory tract infections in adults and children in primary
 1070 care. 2008. National Institute for Clinical Excellence. Ref Type: Report.
- 1071 4) European Centre for Disease Prevention and Control. Antimicrobial resistance
 1072 surveillance in Europe 2010. Annual Report of the European Antimicrobial Resistance
 1073 Surveillance Network (EARS-Net). Stockholm: ECDC; 2011
- 1074 5) Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in
 1075 primary care on antimicrobial resistance in individual patients: systematic review and
 1076 meta-analysis. *BMJ* 2010; 340(may18_2):c209
- 1077 6) Standing Medical Advisory Committee S-GoAR. The path of least resistance. London:
 1078 Department of Health, 1998. Ref Type: Generic.
- 1079 7) Roos K, Claesson R, Persson U, Odegaard K. The economic cost of a streptococcal
 1080 tonsillitis episode *Scandinavian Journal of Primary Healthcare* 1995 13: 257-260
- 1081 8) Little P and Williamson I. Sore throat management in family practice *Family Practice*
 1082 1996 13: 317 - 321
- 1083 9) Mygind N, Nielsen LP, Hoffmann HJ, Shukla A, Blumberg G, Dahl R, et al. Mode of
 1084 action of intranasal corticosteroids. *Journal of Allergy and Clinical Immunology*
 1085 2001;108(1 Suppl):S16-25.
- 1086 10) Zalmanovici A, Yaphe J. Steroids for acute sinusitis. *Cochrane Database Syst Rev*
 1087 2007;(2):CD005149.
- 1088 11) Russell K, Wiebe N, Saenz A, Ausejo SM, Johnson D, Hartling L et al. Glucocorticoids
 1089 for croup. *Cochrane Database Syst Rev* 2004;(1):CD001955.
- 1090 12) Candy B, Hotopf M. Steroids for symptom control in infectious mononucleosis.
 1091 *Cochrane Database Syst Rev* 2006;3:CD004402.
- 1092 13) Venekamp RP, Thompson MJ, Hayward G, Heneghan CJ, Del Mar CB, Perera R,
 1093 Glasziou PP, Rovers MM. Systemic corticosteroids for acute sinusitis. *Cochrane*
 1094 *Database Syst Rev* 2011, Issue 12. Art. No.: CD008115. DOI:
 1095 10.1002/14651858.CD008115.pub2.
- 1096 14) Weinberger F. Safety of Oral Corticosteroids. *European Journal of Respiratory*
 1097 *Diseases*. Supplement. 122: 243-251
- 1098 15) Hayward G, Thompson M, Heneghan C, Perera R, Del Mar C, Glasziou P.
 1099 [Corticosteroids for pain relief in sore throat: systematic review and meta-analysis.](#)
 1100 *BMJ*. 2009 Aug 6;339
- 1101 16) Thompson MJ, Hayward G, Heneghan CJ, Perera R, Glasziou PP, Del Mar CB.
 1102 Corticosteroids for sore throat (Protocol). *Cochrane Database of Systematic Reviews*
 1103 2010, Issue 1.
- 1104 17) Weinberger M. Safety of oral corticosteroids. *Eur J Respir Dis Suppl* 1982; 122:243-
 1105 251.
- 1106 18) Goodman-Goodman, Gilman. The Pharmacological Basis of Therapeutics. 10 ed.
 1107 New York: McGraw-Hill; 2001.
- 1108 19) Sullivan FM, Swan IRC, Donnan PT, Morrison JM, Smith BH, McKinstry B et al. Early
 1109 Treatment with Prednisolone or Acyclovir in Bell's Palsy. *N Engl J Med* 2007;
 1110 357(16):1598-1607
- 1111 20) Williams A. The Role of the EuroQol instrument in QALY calculations. Centre for
 1112 Health Economics: University of York, 1995).

TOAST Statistical Analysis Plan

- 1113 21) Dolan P, Gudex C, Kind P, Williams A. A social tariff for EuroQol: Results from a UK
1114 general population survey. Centre for Health Economics: University of York, 1995.
- 1115 22) Curtis L. Unit Costs of Health and Social Care 2009 PSSRU, University of Kent at
1116 Canterbury; 2010
- 1117 23) Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for
1118 analysing healthcare resources and costs. *Health Economics*. 2011;20:897-916
- 1119 24) Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al.
1120 Probabilistic sensitivity analysis for NICE technology assessment: not an optional
1121 extra. *Health Economics* 2005;14:339-47
1122
1123
- 1124

1125 **18 APPENDIX A: STUDY FLOW CHART**

1126

1127

1128

1129

1130

1131

1132

1133

1134

1135

1136

1137

1138

1139

1140

1141

1142

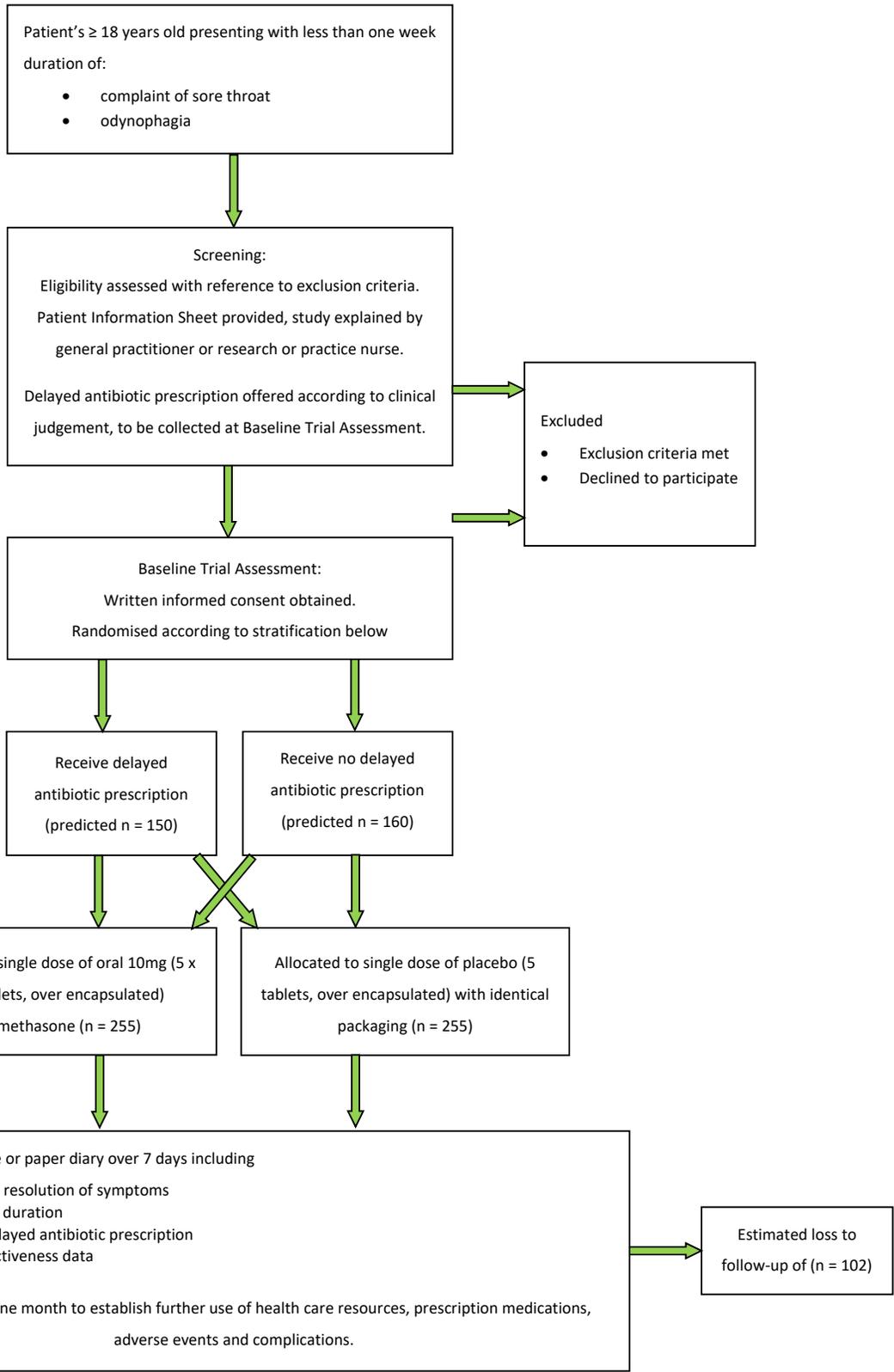
1143

1144

1145

1146

1147



1148

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 Clinician

² Performed by GP

³ Performed by local centre

⁴ Performed by Patient

⁵ If Needed

⁶ Either/ Or

1150

Version 1.0

21/04/2015

Page 40

1151

1152

1153

1154 **Amendments**

1155 There have been 7 amendments to the protocol.

1156 **Amendment 1**, 10-APR-2013, was to clarify some data points, ensuring that the CRFs and
1157 protocol were reflective of each other.

1158 **Amendment 2**, 08-JUL-2013, amended the sample size and added to the follow up process
1159 the addition of a £10 thank you for those who return their completed Symptom Diary to the
1160 PC-CTU and also added in additional reminder text messages to remind participants to
1161 complete and return the Symptom Diary.

1162 **Amendment 3**, 02-SEP-2013, added Johanna Maughan and Julie Allen as investigators on
1163 the trial.

1164 **Amendment 4**, 14-FEB-2014, added an upper age limit of 70 years to the
1165 inclusion/exclusion criteria.

1166 **Amendment 5**, 02-JUN-2014, listed additional research sites.

1167 **Amendment 6**, 23-JUL-2014 increased the value of the gift card sent to participants to £20
1168 and clarified the wording of SAE reporting within the protocol.

1169 **Amendment 7**, 16-FEB-2015, listed an additional research site.

1170

1171

1172

1173

1174

1175

1176

1177

1178

1179

1180

1181

1182

1183

1184

1185

1186
1187
1188
1189
1190
1191

INITIAL AND FINAL SAP

1192
1193
1194

STATISTICAL ANALYSIS PLAN

Version 1.0

21 April 2015

1195 **Do oral corticosteroids provide clinical and cost-effective**
1196 **symptom relief for sore throat? A multi-centre, double**
1197 **blind, randomised, placebo controlled trial.**

1198 Project short name: Treatment Options without Antibiotics for
1199 Sore Throat (TOAST)

1200 Ethics reference: 12/SC/0684

1201 EudraCT Number: 2012-004330-41

1202

	NAME	TITLE	SIGNATURE	DATE
Written by:	Dr Jill Mollison	Senior Medical Statistician		
Reviewed by:	Nicola Williams	Senior Medical Statistician		
Approved by:	Professor Carl Henegan	Chief Investigator		

1203

1204 Version History

Version:	Version Date:	Changes:
1.0	21 April 2015	

1205
1206

1207	TABLE OF CONTENTS	
1208	Table of Contents.....	43
1209	1 Introduction.....	45
1210	1.1 Preface	45
1211	1.2 Purpose and scope of the plan.....	45
1212	1.3 Trial overview	45
1213	1.4 Objectives.....	46
1214	1.5 Trial design	47
1215	1.6 Outcomes measures	47
1216	1.6.1 Primary outcome.....	47
1217	1.6.2 Secondary outcomes	47
1218	1.7 Target population.....	52
1219	1.8 Sample size	53
1220	1.9 Randomisation and blinding in the analysis stage.....	53
1221	2 Analysis – General considerations	54
1222	2.1 Descriptive statistics	54
1223	2.2 Characteristics of participants	54
1224	2.3 Definition of population for analysis.....	55
1225	2.4 Pooling of investigational sites	55
1226	2.5 Data Monitoring Committee And Interim Analyses.....	55
1227	3 PRIMARY ANALYSIS.....	56
1228	3.1 Primary outcome	56
1229	3.2 Handling missing data	56
1230	3.3 Handling outliers.....	56
1231	3.4 Handling multi-centre/clustered data	56
1232	3.5 Multiple comparisons and multiplicity	57
1233	3.6 Model assumptions.....	57
1234	4 SECONDARY OBJECTIVES	57
1235	4.1 Primary outcome	57
1236	4.2 Secondary outcomes.....	57
1237	4.3 Tertiary/Other outcomes.....	59
1238	5 SENSITIVITY ANALYSIS.....	59
1239	6 SUBGROUP ANALYSES.....	59
1240	7 ADDITIONAL EXPLORATORY ANALYSIS	60
1241	8 SAFETY ANALYSIS.....	60
1242	9 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP.....	60

TOAST Statistical Analysis Plan

1243	10	References	62
1244	11	Appendices	63
1245			
1246			

1247 **1 INTRODUCTION**

1248

1249 **1.1 Preface**

1250 This document details the statistical analysis that will be adopted for the TOAST trial.

1251 This analysis plan supports version 6.0 (14/07/2014) of the TOAST protocol.

1252 The trial statistician, chief investigator and trial managers are:

1253 Chief investigator: Professor Carl Heneghan

1254 Trial Manager: Julie Allan

1255 Trial Statistician: Merryn Voysey

1256

1257 **1.2 Purpose and scope of the plan**

1258 This document details the proposed presentation and analysis for the main paper(s)
1259 reporting results of the TOAST trial. The results reported in these papers should follow the
1260 strategy set out here. Subsequent analyses of a more exploratory nature will not be bound
1261 by this strategy, though they are expected to follow the broad principles laid down here. The
1262 principles are not intended to curtail exploratory analyses (for e.g. to decide cutpoints for
1263 categorisation of continuous variables), nor to prohibit accepted practices (e.g. data
1264 transformation prior to analysis), but they are intended to establish the rules that will be
1265 followed, as closely as possible, when analysing and reporting the trial.

1266 The analysis strategy will be available on request when the principal papers are submitted
1267 for publication in a journal. Suggestions for subsequent analyses by journal editors or
1268 referees, will be considered carefully, and carried out as far as possible in line with the
1269 principles of this analysis strategy; if reported, the source of the suggestion will be
1270 acknowledged.

1271 Any deviations from the statistical analysis plan will be described and justified in the final
1272 report of the trial. The analysis should be carried out by an identified, appropriately qualified
1273 and experienced statistician, who should ensure the integrity of the data during their
1274 processing. Examples of such procedures include quality control and evaluation procedures.

1275 The analysis of the cost-effectiveness data is not covered within this analysis plan.

1276

1277 **1.3 Trial overview**

1278 Sore throat represents both a significant burden on the UK general practitioner and an
1279 important source of unnecessary antibiotic prescriptions. Corticosteroids may offer an
1280 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.

1303 **1.5 Trial design**

1304 TOAST is a two arm, individually randomised, double blind trial comparing a single dose of
1305 10mg oral dexamethasone with placebo in adults aged between 18 and 70 years inclusive
1306 presenting to primary care with sore throat. The trial will require a single visit to the GP from
1307 each participant and a one week period of participant involvement from the point of
1308 randomisation and treatment. The trial will be a multicentre trial based at Oxford, Bristol and
1309 Southampton.

1310 TOAST aims to recruit 566 patients.

1311 The schedule of procedures is detailed in Appendix 1.

1312 **1.6 Outcomes measures**

1313 Participants were telephoned or texted at 24 and 48 hours following randomisation for
1314 collection of the primary and secondary outcomes. Participants completed a symptom diary
1315 reporting on resolution of symptoms, time to onset of pain relief, and rating their pain on a
1316 visual analogue scale every day for 7 days. In addition participants provide information
1317 about NHS resource use, out-of-pocket expenditure, use of over-the-counter and prescription
1318 medications and time off work/education and foregone leisure time. Participants who failed
1319 to return a symptom diary at the end of the study were sent a brief FU questionnaire. Case
1320 notes were reviewed after one month following randomisation to collect information on use of
1321 NHS resources in the 28 days following the initial trial appointment.

1322 The outcomes assessment schedule is contained in Appendix 2.

1323 **1.6.1 Primary outcome**

1324

1325 1) Direct report by the patient of presence or absence of complete resolution of sore
1326 throat at 24 hours by either text message or telephone.

1327 Where no response to text/telephone at 24 hours exists, the participant's diary response to
1328 Q1 on day1 will be used and where no diary has been returned, or response is missing, the
1329 short FU questionnaire (Question 1) will be used. Discrepancies in reporting may exist, thus
1330 the first reported outcome (text/telephone) will be taken as the valid response since it is most
1331 timely to the outcome. If no text/telephone response is available the source of data for the
1332 primary outcome will be considered in the order detailed above (i.e. text/telephone, diary,
1333 FU). For each participant the source of data will be recorded. Any participants who have no
1334 information after looking at each of the data sources will be included in the analysis
1335 assuming 'no resolution'.

1336

1337

1338 **1.6.2 Secondary outcomes**

1339

1340 1) Direct report by those patients who have not been prescribed antibiotics of presence
1341 or absence of complete resolution of sore throat at 24 hours by either text message
1342 or telephone

1343 Only patients who were not prescribed a delayed antibiotic prescription will be included in
1344 the analysis (baseline assessment Q7 *delpres*=0 (no)).

1345 Where no response to text/telephone at 24 hours exists, the participant's diary response
1346 to Q1 on day1 (*d1res/24*) will be used and where no diary has been returned or response
1347 is missing the short FU questionnaire Question 1 (*reso/24*) will be used. Discrepancies in
1348 reporting may exist, thus the first reported outcome (text/telephone) will be taken as the
1349 valid response since it is most timely to the outcome. If no text/telephone response is
1350 available the source of data for the primary outcome will be considered in the order
1351 detailed above (i.e. text/telephone, diary, FU). For each participant the source of data will
1352 be recorded. Any participants who have no information after looking at each of the data
1353 sources will be included in the analysis assuming 'no resolution'. This analysis will
1354 include those patients who subsequently started antibiotics despite not being given a
1355 delayed prescription at the index consultation

1356

1357 This analysis will also be repeated for the group of patients who received a delayed antibiotic
1358 prescription (baseline assessment Q7 *delpres* = 1, 2).

1359

1360

1361 **Secondary outcomes 2-6 and 8-11 will be analysed for all trial participants and in**
1362 **addition the analyses will be repeated separately for the two groups of participants**
1363 **defined by whether or not they were given a delayed antibiotic prescription.**

1364 2) Report of presence or absence of complete resolution of sore throat at 48 hours by
1365 either text message or telephone contact

1366 This analysis includes all participants randomised. Where no response to text/telephone at
1367 48 hours exists, the participant's diary response to Q1 on day2 (*d2res/24*) will be used and
1368 where no diary has been returned or response is missing the short FU questionnaire
1369 Question 2 (*reso/48*) will be used. Discrepancies in reporting may exist, thus the first
1370 reported outcome (text/telephone) will be taken as the valid response since it is most timely
1371 to the outcome. If no text/telephone response is available the source of data for the primary
1372 outcome will be considered in the order detailed above (i.e. text/telephone, diary, FU). For
1373 each participant the source of data will be recorded. Any participants who have no
1374 information after looking at each of the data sources will be included in the analysis
1375 assuming 'no resolution'.

1376

1377 3) Report of time to onset of pain relief (in hours) within 7 days

1378 For each participant, the following items of information will be required; whether their sore
1379 throat became less painful during the 7 days (section1: Q2 Diary), the day and time their
1380 sore throat became less painful. The time reported for onset of pain relief will be converted
1381 to 24 hour clock. In cases where the minutes are missing, but hour has been reported the
1382 minutes will be assumed to be 0 and the participant will be included in the analysis. If a
1383 participant does not record am/pm and the time is ambiguous, the time of onset of pain relief
1384 will be recorded as missing.

1385 Time to onset (in hours) will be computed as the difference between the time on Day 0 that
1386 medication was taken (Baseline *medtime*) to the day and time (24 hour clock) the
1387 participant's sore throat became less painful (Section 1 Question 2a of symptom). Only
1388 participants who returned a symptom diary will be included in the analysis. Participants who
1389 stop completing symptom diaries will be censored at the last recorded time their status was
1390 known.

1391

1392 4) Report of time to complete symptom resolution (in hours) within 7 days

1393 The time reported for complete symptom resolution will be converted to 24 hour clock. In
1394 cases where the minutes are missing but hour has been recorded the minutes will be
1395 assumed to be 0 and the participant will be included in the analysis. In cases where am/pm
1396 is missing and the time is ambiguous, time of complete resolution will be recorded as
1397 missing.

1398

1399 The number of hours from time medication taken (Baseline *medtime*) on day 0 to the day
1400 and time their sore throat was completely resolved (Section 1, Question 1a of symptom
1401 diary) will be computed for each participant. Only participants who returned a symptom diary
1402 with a valid time for complete resolution will be included in the analysis. Participants who
1403 stop completing symptom diaries will be censored at the last recorded time their status was
1404 known.

1405

1406

1407 5) Duration of moderately bad symptoms recorded by validated symptom diary over the
1408 7 days from treatment onset.

1409 Question 5 records how bad the following symptoms (sore throat, pain on swallowing,
1410 difficulty swallowing, feeling unwell, cough, fever, sleep disturbance, tender glands in neck,
1411 change in mood, vomiting) have been in the last 24 hours, for each of the 7 days from
1412 treatment onset. Only participants who returned a symptom diary will be included in the
1413 analysis. The number of days that the participant reported moderately bad symptoms over
1414 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 [*nhsevt1/7* = 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 *nhsevnt1/7* = 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 *nhsevnt1/7* = 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.

1566 Once all the data queries have been resolved, a blind data review meeting will be initiated
1567 involving the trial statistician, the data manager, the trial manager and the CI. All protocol
1568 violations will be reviewed and a list of study populations for analysis will be generated and
1569 signed off by the CI and the statistician. At this point, the database will be locked and de-
1570 coding of the allocation will be allowed.

1571 Participants found to be ineligible after they have been randomised will be removed from the
1572 trial. Their data will be removed and they will not be included in the analysis.

1573 **2 ANALYSIS – GENERAL CONSIDERATIONS**

1574 **2.1 Descriptive statistics**

1575 Data are collected via text, telephone, symptom diary, FU questionnaire and case note
1576 review. The number of participants who submitted texts at 24 hours and 48 hours, returned
1577 symptom diaries and FU questionnaires and had case note review completed will be
1578 reported by randomised group stratified by centre and whether the participant was given a
1579 delayed antibiotic prescription.

1580

1581 **2.2 Characteristics of participants**

1582 Descriptive statistics within each randomised group will be presented for baseline
1583 characteristics (i.e. duration of sore throat and pain on swallowing at study entry),
1584 demographic characteristics (age, gender, smoking status and whether the patient is in paid
1585 work or education), baseline symptoms (e.g. sore throat, runny nose, cough, hoarse voice,
1586 fever, headache, muscle ache, abdominal pain, disturbed sleep), baseline physical
1587 examination findings (including FeverPAIN score, Centor score) and whether the patient was
1588 given a delayed antibiotic prescription. Frequencies and percentages will be reported for
1589 categorical variables and for continuous variables, the mean and standard deviation will be
1590 reported for normally distributed continuous variables and median and interquartile range for
1591 skewed continuous data. No formal statistical testing will be applied to test for any difference
1592 between randomised groups with respect to baseline characteristics. In addition, patient
1593 characteristics will be presented by randomised group separately for the two groups of
1594 participants defined by whether they received a delayed prescription or not.

1595

1596 **Description and derivation of FeverPAIN and CENTOR score.**

1597 The FeverPAIN score ranges from 0 to 5 with 1 point for each of 5 items: fever in past 24
1598 hours, purulence, rapid (within 3 days attendance), very inflamed tonsils and no cough or
1599 cold symptoms. In the model, FeverPAIN will be classified as 3 categories [ref PRISM] low
1600 scores (0,1) [antibiotics would not be offered], intermediate scores (2,3) [delayed antibiotics]
1601 and high scores (4,5) [immediate antibiotics].

1602 **Derivation of FeverPAIN score**

1603 Data from baseline assessment form will be used to compute the score for each participant.

1604

1605 Q3k Fever in last 24 hours *sympk* (slight, moderate or severe = 1)

1606 Q4 purulence *pexpur* (yes=1)

1607 *Dayssore* (≤ 3 days=1)

1608 Q4 very inflamed tonsils *pexinfl* (yes and severe= 1)

1609 Q3e no cough during illness *sympe* (none = 1)

1610

1611 The Centor score was first derived in 1981 and includes four variables with equal weighting.

1612 The score ranges from 0 to 4 (original score) with a higher score more predictive of a positive

1613 culture. NICE guidance CG69 suggests a clinician should consider immediate antibiotic

1614 prescribing for a score of ≥ 3 .

1615

1616 **Derivation of Centor score**

1617 Centor score is computed using data from the baseline assessment form.

1618

1619 History of fever (*sympf*) (slight, moderate or severe =1)

1620 Tonsillar exudates *pexphar* (yes=1)

1621 Tender anterior cervical adenopathy *pextend* (yes=1)

1622 Absence of cough *sympe* (none =1)

1623

1624 **2.3 Definition of population for analysis**

1625 Ineligible participants (i.e. not in the target population) who were randomised in error will be
1626 detailed in the CONSORT flow chart and will be excluded from all analyses.

1627 The primary analysis will be by intention to treat (ITT). All eligible randomised patients will be
1628 included in the analysis of the primary outcome, assuming no complete resolution for any
1629 missing data.

1630

1631 **2.4 Pooling of investigational sites**

1632 Randomisation was stratified by centre (Oxford, Bristol and Southampton). Centre will be
1633 adjusted for in the analysis by including a centre variable which will be fitted as a fixed effect
1634 in the statistical models.

1635

1636 **2.5 Data Monitoring Committee And Interim Analyses**

1637 The analysis plan for interim analysis requested by the DMEC is contained in a separate
1638 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**

1673 There is potential for clustering of outcomes within centres (Oxford, Bristol and
1674 Southampton) with particular respect to missing data. This will be explored descriptively. In
1675 addition, centre will be fitted as a covariate in the statistical models.
1676

1677 **3.5 Multiple comparisons and multiplicity**

1678 A single primary outcome has been specified, in a two randomised group trial, hence there
1679 are no issues of multiplicity.

1680 **3.6 Model assumptions**

1681 The log binomial model to be fitted to these data includes only categorical covariates,
1682 therefore there should not be any problem with convergence. However, if the model fails to
1683 converge, a Poisson regression with robust standard errors will be applied to the data.
1684

1685 **4 SECONDARY OBJECTIVES**

1686 **4.1 Primary outcome**

1687 In patients who were not given a delayed prescription for antibiotics, complete resolution of
1688 sore throat at 24 hours. Analysis will follow that outlined above for the analysis of the
1689 primary outcome.

1690 A log-binomial regression model will be applied to the data. Treatment effect will be reported
1691 as a relative risk and 95% confidence interval. In addition, the Absolute Risk Reduction
1692 (ARR) and Number Needed to Treat (NNT) with corresponding 95% confidence intervals will
1693 be computed and reported. The model will include randomised group and the stratification
1694 variable, centre.

1695

1696 The above analysis will be repeated for the participants who were given a delayed
1697 prescription.

1698

1699 **4.2 Secondary outcomes**

1700 Secondary outcomes have been grouped by variable type. Analysis will be conducted on all
1701 patients randomised. In addition, the analysis will be repeated for the two subgroups of
1702 patients defined by whether they received a delayed prescription or not. These two groups
1703 of patients will be considered separately.

1704 *Binary secondary outcomes* (i.e. complete resolution of sore throat at 48 hours, attendance
1705 at GP practice/out-of-hours/A&E within 28 days with symptoms or complications associated
1706 with sore throat, hospital admission with related complications of sore throat within 28 days,
1707 uptake of delayed antibiotic prescription, use of OTC medications,) will be analysed using the

1708 same principles as the primary analysis of the primary outcome. The frequency (percentage)
1709 within each randomised group will be presented. A log binomial model will be fitted to the
1710 data with randomised group, centre and, if applicable, whether the patient was prescribed
1711 delayed antibiotics or not included as covariates. Relative risks with 95% confidence
1712 intervals will be presented.

1713 *Pseudo continuous* (time missed from work or education). The mean (SD) will be reported
1714 for each group and the difference and 95% CI will be computed using linear regression with
1715 adjustment for centre and if applicable, delayed antibiotic prescription. Assumptions of linear
1716 regression will be assessed and if violated a Mann-Whitney test will be adopted and the
1717 median (IQR) will be used to summarise the data and difference in medians (95%CI) will be
1718 reported.

1719 *Time to event* (time to onset of pain relief, time to complete resolution,)

1720 Kaplan Meier curves will be presented. A Cox regression model will be used to test whether
1721 time to event differs between the randomised groups. The median (interquartile range) for
1722 each randomised group will be presented. The model will include randomised group and if
1723 applicable, whether they received a delayed antibiotic prescription. A hazard ratio and 95%
1724 confidence interval will be reported to present the difference in time to event between the
1725 randomised groups.

1726 *Count (duration of moderately bad symptoms)*

1727 The analysis will be repeated for each symptom.

1728

1729 The event rate will be computed for each randomised group. To compare the randomised
1730 groups, a random effects negative binomial model will be fitted to the data. The dependent
1731 variable is the number of days with symptom. The explanatory variables will include number
1732 of days diary completed for that symptom (as an offset), randomised group, centre, and if
1733 applicable, whether the patient was given a delayed antibiotic prescription. The incidence
1734 rate ratio and 95% confidence interval will be reported for randomised group.

1735 *Change in ratings of sore throat pain, difficulty swallowing and pain on swallowing*

1736 This analysis will be repeated for each symptom.

1737 The mean change from baseline to each day (1-7) will be plotted graphically by randomised
1738 group. Two analyses will be conducted.

1739 (i) AUC will be used as summary statistic. For each symptom, AUC summary
1740 statistics will be computed for each group [Bell et al, 2014]. A mixed model
1741 including a random intercept, randomised group, day of assessment, interaction
1742 term of group by day, severity of symptom at day 0, centre and if applicable,
1743 whether patient received a delayed prescription will be fitted to the data for each
1744 symptom. The AUC for each group is estimated using a linear combination of the
1745 parameter estimates after a model has been fit. The difference in AUC between
1746 the groups will be estimated using a contrast for the AUC summary statistics.
1747 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

1755

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**

1860 Little P, Hobbs FDR, Moore M et al. Clinical score and rapid antigen detection test to guide
1861 antibiotic use for sore throats: randomised controlled trial of PRISM (primary care
1862 streptococcal management). BMJ 2013.

1863 NICE guidance CG69 www.nice.org.uk/CG069:

1864 Bell M, King M, Fairclough D. Bias in area under the curve for longitudinal clinical trials with
1865 missing patient reported outcome data: summary measures versus summary statistics.
1866 SAGE Open 2014;1-12.

1867

1868

1869

1870

1871

1872

1873

1874

1875

1876

1877

1878 **11 APPENDICES**
 1879 Appendix I. Schedule of procedures
 1880

Procedure	Screening	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)
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	

TOAST Statistical Analysis Plan

Use of NHS facilities									x
-----------------------	--	--	--	--	--	--	--	--	---

1881

1882

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

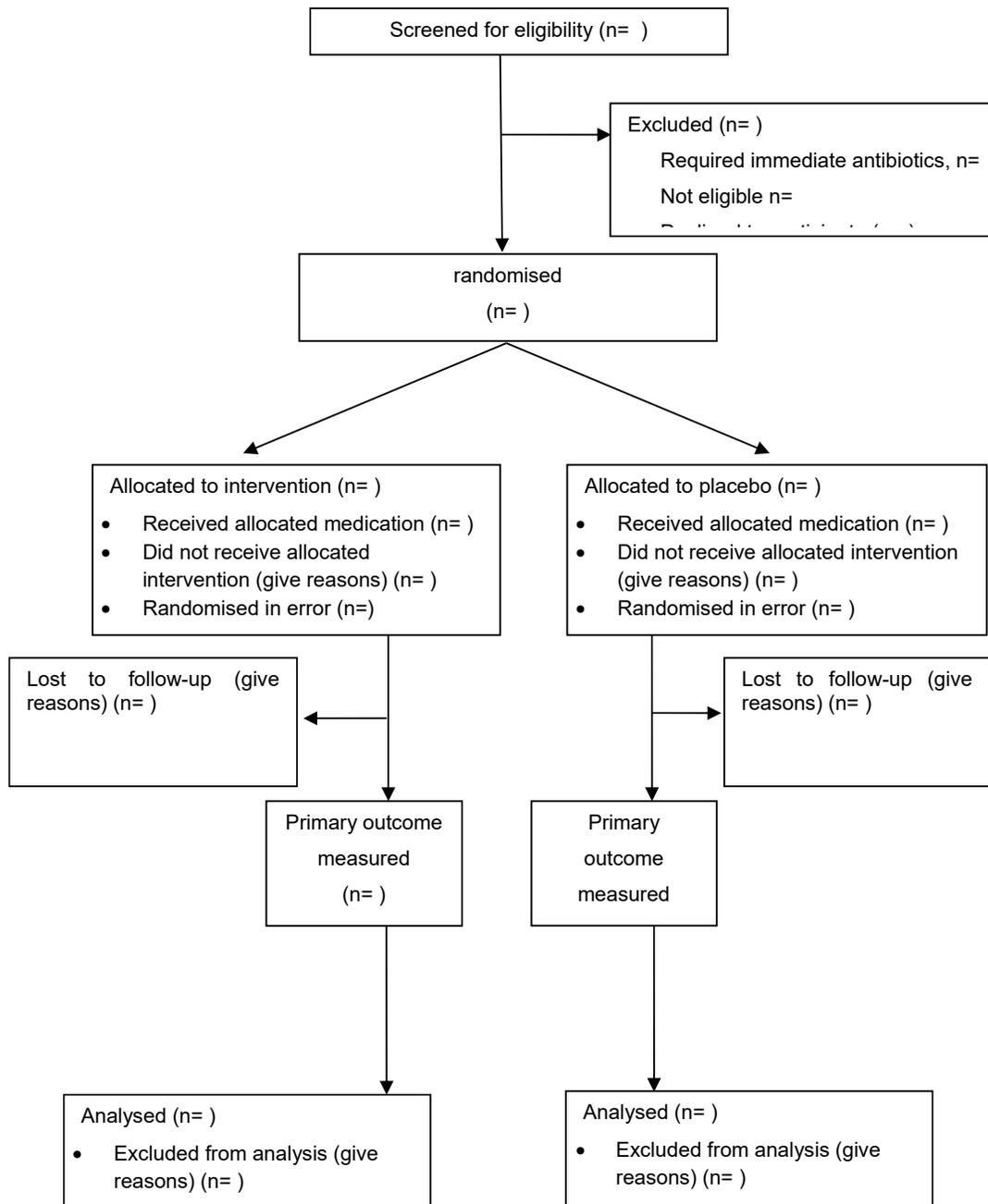
1885 *Footnote*

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.

1888

1889 Appendix III. Flow diagram of trial participants

1890



1891
1892
1893
1894
1895
1896
1897
1898

