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# **BMJ Open**

### An Economic Analysis of Oral Dexamethasone for Symptom Relief of Sore Throat: The UK TOAST Study

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4	2	Sore Throat: The UK TOAST Study
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	1 2	Abstract
	3	Objectives: To undertake an economic analysis assessing the cost-effectiveness of a
	4	single dose of oral dexamethasone compared to placebo for the relief of sore throat.
	5	Design: A UK-based, multicentre, two arm, individually randomised, double blind trial
	6	Setting and Population: Adults (≥18 years) with acute sore throat and painful
	7	swallowing judged to be infective in origin, recruited and randomised in primary care.
	8	Intervention: A single dose of 10mg oral dexamethasone compared to placebo given
	9	at primary care visit.
1	.0	Main Outcome: Incremental cost-effectiveness ratios (ICERs), cost per quality-
1	.1	adjusted symptom resolution using the EQ-5D-5L instrument, were estimated as part
1	2	of a cost-utility analysis performed on an intention-to-treat cohort adopting a health
1	.3	payers perspective.
1	.4	Results: Differences in health-related quality of life (HRQoL) over 7 days from
1	.5	baseline and at 24 hours in the dexamethasone compared with the placebo group
1	.6	(2.9% and 2.5% higher, respectively) were observed. After controlling for the
1	.7	baseline HRQoL imbalances, the impact of the intervention was negative but not
1	.8	statistically significant: the QALY difference was -0.00005 (95% CI: -0.0002;
1	.9	0.00011) equivalent to a loss in HRQoL of a half hour in the dexamethasone group.
2	20	The average cost per patient associated in the dexamethasone and placebo groups
2	21	in the basecase analysis was $\pounds73$ and $\pounds69$ , respectively. In the basecase
2	22	probabilistic analysis, the mean ICER was -£6,440 (95% CI: -£132,151; £126,335)
2	23	and the median ICER was -£304 (IQR:-£5,816; £3,877); suggesting considerable
2	24	uncertainty.

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2 3	1	Conclusions and relevance: The economic burden associated with sore throat is		
4 5	2	substantial and was estimated at $\pounds2.35$ bn to the healthcare services payer based on		
6 7 8	3	reported resource use and 2015 UK unit costs. There is considerable uncertainty		
9 10	4	regarding the cost-effectiveness of a single dose of oral dexamethasone as a		
11 12	5	treatment strategy and therefore insufficient evidence to support its use in clinical		
13 14	6	practice.		
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17 18	7	Trial Registration: ISRCTN17435450 http://www.isrctn.com/ISRCTN17435450		
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21 22	9	Key words: cost-utility analysis, primary care interventions, sore throat		
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3	1	Strengths and limitations of this study
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7	3	<ol> <li>The analysis undertaken provides the first detailed account of the cost of sore</li> </ol>
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9	4	throat in the UK.
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11 12	5	2. The study collected a wide range of demographic, clinical, quality of life and
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13	6	resource use data using a trial-specific daily patient diary which permitted an
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16	7	extensive exploration of uncertainty in scenario and sub-group analyses.
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18	8	3. Both health services payer and societal perspectives were assessed in the
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20	9	economic evaluation.
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22	10	4. In contrast to previous research highlighting no clinical differences across
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24	11	delayed prescription and no treatment strategies, this analysis suggests that
25	11	delayed prescription and no treatment strategies, this analysis suggests that
26	12	clinical and non-clinical benefits of the delayed prescription in addition to the
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28 29	13	dexamethasone need to be explored further.
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31	14	5. Reported resource use for HSP analysis was cross-checked with a follow-up
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33	15	patient survey and medical record review and as such where no resource use
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35	16	was identified for each patient across the data sources, the assumption of
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37	17	zero resource use for that category is justifiable but potentially leading to
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### 1 Introduction

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An estimated £400 million annually is spent on consultations and lost productivity associated with sore throat alone in the UK.<sup>1,2</sup> Almost one in ten registered UK patients will see their general practitioner (GP) every year with sore throat.<sup>3</sup> 91% of those diagnosed with tonsillitis will receive antibiotics, as will half of those recorded as 'sore throat' or 'pharyngitis'.<sup>4</sup> NICE and International guidance recognises the limited evidence for benefit of antibiotics in its advice to avoid prescriptions in the majority of patients<sup>5-6</sup>; however, prescribing rates remain disproportionately high even though patients attend mainly due to anxiety over symptoms.<sup>7</sup> A key driver for patients to attend with a sore throat is the severity of their symptoms, so affective symptomatic treatment may help reduce patient reliance on antibiotic. Furthermore where antibiotics are used for streptococcal infections more rapid clinical improvement is also plausible with steroids<sup>8</sup> which could facilitate shorter courses of antibiotics, which would improve both prescribing and the overall economic burden of sore throat. Further, negative externalities associated with over-prescribing antibiotics, predominantly the increasing issue of antimicrobial resistance<sup>9</sup>, could also be moderated. The Treatment Options without Antibiotics for Sore Throat (TOAST) trial<sup>10</sup> addressed whether or not oral corticosteroids provide clinical and cost-effective benefits through symptom relief of sore throat. The cost-effectiveness analysis alongside the TOAST trial assessed the costs and benefits of a single dose of 10mg oral dexamethasone compared to placebo for the symptom relief of sore throat.

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### 1 Methods

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 3 Intervention

TOAST was a multicentre, two arm, individually randomised, double blind trial comparing a single dose of 10mg oral dexamethasone with identical placebo in adults aged between 18 and 70 years<sup>1</sup> inclusive, presenting to primary care with acute sore throat. Recruitment took place in 42 primary care clinics in England from April 2013 to February 2015. The intervention period assessed was 7 days post-presentation and participants were followed up for 28 days to assess resource use and adverse events. A sub-group of patients in each trial arm received a delayed prescription for antibiotics at the discretion of the GP and randomisation was stratified by this decision. Further details on trial design, inclusion/ exclusion criteria and trial ethical approval are published elsewhere.<sup>6</sup> 

### 15 Outcome Measure

16 The cost-effectiveness analysis assessed quality-adjusted symptom resolution over

- the 7 day trial duration and estimated median time to complete resolution of
- symptoms and the corresponding utility gains measured by the EuroQol EQ-5D 5
- 19 level (EQ-5D-5L) index. These outcomes informed the construction of a quality-
- 20 adjusted life year (QALY) used in the cost-utility analysis. The EuroQol instrument
- has five domains (mobility, self-care, activities, pain/discomfort, and
- anxiety/depression) and five response levels ranging from no problems to severe

<sup>&</sup>lt;sup>1</sup> The trial initially recruited patients with no upper age limit and this was amended to age 70 after a suspected adverse reaction. Patients over the age of 70 recruited previous to the protocol amendment were included in the ITT analysis.

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1	problem. <sup>11</sup> This health-related quality of life (HRQoL) instrument was administered to
2	all participants at baseline and completed on each day of the seven day patient
3	diary. Each of the five dimensions in the EQ-5D-5Lversion is scored from 1 (no
4	problem) to 5 (extreme problems), generating a profile (e.g. 11245) that can be used
5	to calculate a single index score (range $-0.281 - 1.000$ ). <sup>12</sup> The differences in EQ-5D-
6	5L from baseline (day 0) at each day i.e. days 1 to 7, were estimated and results
7	from the complete case analysis (CCA) (n=337) and the intention-to-treat analysis
8	(ITT) (n=565) are presented in the <i>Online Appendix</i> (Tables A4-A5). The EQ-5D
9	instrument also generates a self-rating of HRQoL scored from 0 to 100 employing a
10	visual analogue scale (VAS); this was used in scenario analyses. Quality adjusted
11	symptom resolution at 24 and 48 hours were also reported.

### 13 Resource Use

Primary care resource utilisation was recorded in a trial patient diary for the first 7 days of the trial and was complemented by a follow-up survey sent to those with incomplete patient diaries. A primary care patient medical record review for the period from day 1 to day 28 (trial follow-up period) was also undertaken which recorded primary and secondary care contacts related to sore throat including serious adverse events (SAEs) related to the condition. Resource use included the following: visits and telephone calls to the GP; visits and telephone calls to nurses; out-of-hours calls and visits; pharmacy visits; calls to helpline '111'; A&E visits; hospitalisations; and various types of reported medication including prescribed antimicrobials and over-the-counter (OTC) medications. 

# 1 Unit Costs

Total and average costs were estimated for the intervention, antibiotic usage (up to and including day 7), OTC medication usage (for days 0-7), health resource use/medication across the trial period (for days 1-28), SAEs, and patient productivity losses associated with sick days reported (for work and education) and inability to carry out usual activities. Unit costs, presented in the **Online Appendix** (Table A1), were obtained from a number of sources including, PSSRU<sup>13</sup>, British National Formulary<sup>14</sup>, Boots Chemist<sup>15</sup>, and the NHS Electronic Tariff Database<sup>16</sup> and are reported in UK currency. Productivity losses were costed using average wage rates for those employed and minimum wage rates for students.<sup>17</sup> All cost estimates were reported in 2015 GBP using appropriate adjustments for prices retrieved where necessary.<sup>18</sup> Disaggregated average cost estimates reported were based on the full cohort in the ITT analysis assuming non-responders had zero costs. 

### 15 Analysis

Patient characteristics and reported resource use were summarised by trial arm. The primary economic analysis was conducted on an ITT basis and adopted the healthcare services payer perspective (HSP) which included the cost burden to the HSP only. Given the short-term duration of the trial, neither costs nor benefits were discounted. For the HSP the prescription administrative charge, normally applied to employed, working-age adults only in the UK<sup>19</sup>, associated with the antimicrobial was not incorporated into the cost analysis as this was considered an out-of-pocket (OOP) expense borne by the patient; this was not considered as a contribution to the HSP either i.e. reducing the net cost of care per person to the HSP, as the

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1	prescription administrative charge is not applied to everyone and the full amount may
2	not be recouped by the HSP. <sup>20</sup> In the scenario analyses, a societal costing
3	perspective (SCP) was also adopted reflecting the overall economic burden of the
4	dexamethasone relative to the placebo. This included productivity losses due to sick
5	days i.e. reported time off due to missed work or education and reported inability to
6	carry out usual activities, and OOP expenses. Further scenarios assessed sub-
7	groups based on patient characteristics. The sub-group who highlighted they were
8	current smokers at the time of the trial were assessed in a scenario analysis due to
9	the extra healthcare burden smokers have relative to non-smokers. <sup>21</sup> Descriptions of
10	all 20 analyses are presented in the <b>Online Appendix</b> (Table A2).
11	Each element of costs and outcomes were reported separately, consistent with a
12	cost-consequence analysis; the resource use reported was for the full ITT cohort (i.e.
13	no missing resource use data) and the HRQoL data reported in the disaggregated
14	format was for complete cases i.e. n=337; 60% of the full cohort. Missing HRQoL
15	data was assessed and classified as missing at random (MAR) (see <b>Online</b>
16	Appendix- Figure A1). <sup>16</sup> Multiple imputation analysis was performed for missing
17	outcome data (40%) in the ITT cohort using a number of imputations (n=60) greater
18	than the proportion of missing data. <sup>22</sup> The range of covariates included in the
19	multiple imputation analysis along with a more comprehensive presentation of
20	methods is presented (see Online Appendix- Table A3). The trial and follow-up
21	duration was 28 days in total and for consistency it was assumed that HRQoL was
22	unchanged from day 7 to day 28 using the last value brought forward technique. <sup>23</sup>
23	The average utility from baseline reported across the 28 days, calculated using area
24	under the curve (AUC) was considered 1/13th of a quality adjusted life year (QALY).
25	Baseline variation in outcomes was adjusted for incorporating multiple regression

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1	and seemingly unrelated regression techniques which estimated the baseline
2	imbalance taking into account costs and effects. <sup>16, 24</sup> QALYs exhibited a non-normal
3	distribution (see Online Appendix- Figure A2) and bootstrapping techniques using
4	1,000 iterations were applied in Microsoft Excel. <sup>25</sup> Cost-utility analysis was
5	undertaken and incremental cost-effectiveness ratios (ICERs) were estimated and
6	reported for the basecase analysis and all scenario analyses. ICERs were
7	probabilistic for the basecase analysis and deterministic for the series of scenarios
8	estimated. The analysis was undertaken in Stata version 14.1. <sup>26</sup> A cost-effectiveness
9	plane and cost-effectiveness acceptability curve (CEAC) were constructed based on
10	the bootstrapped sample means and net monetary benefit (NMB) was also assessed
11	against a range of willingness to pay thresholds up to £100,000. <sup>27</sup> The NICE
12	willingness to pay threshold of $\pounds20,000$ was adopted as a decision rule to assess
13	cost-effectiveness. <sup>27</sup>
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15	Results
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The ITT cohort (n=565) with 288 in the dexamethasone group and 277 in the 17 placebo group; descriptive statistics are presented in *Table 1*. The mean age of 18 participants was 37 years and 75% were women. There was no significant clinical 19 difference in median time to complete symptom resolution across trial arms with both 20 21 displaying complete symptom resolution by day 4; however, there was a significant difference in symptom resolution at 48 hours.<sup>28</sup> The changes in HRQoL over the 7 22 days highlight larger differences at baseline and at 24 hours with the dexamethasone 23 group reporting 2.9% and 2.5% higher utility scores, respectively (see Online 24

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1	<b>Appendix</b> - Figure A3). Differences start to diminish (<1.5%) from day 2 onwards.
2	Table 2 highlights the differences in estimated QALYs for the imputed ITT cohort.
3	After controlling for the baseline imbalances in HRQoL, the impact of the intervention
4	was negative but not statistically significant: the QALY gain was -0.00005 (95% CI: -
5	0.0002; 0.00011) equivalent to a loss in HRQoL of a half hour for the
6	dexamethasone relative to the placebo group.
7	For the sub-group who received the delayed prescription based on clinical need, a
8	statistically significant benefit was evidenced after baseline imbalances were
9	adjusted for resulting in an approximate HRQoL gain of 13.6 hours relative to the
10	control group. For the sub-group who did not receive the prescription, the
11	dexamethasone group indicated a significant QALY loss of approximately 13 hours
12	relative to the placebo group. For the patient group who reported that they were
13	current smokers a significant QALY gain from the dexamethasone of 0.0029,
14	equivalent to 1 day was evidenced. At 48 hours where a significant difference in the
15	risk ratio of symptom resolution at 48 hours in favour of the dexamethasone [RR:
16	1.31 (95% CI, 1.02 to 1.68; $P = .03$ )] was observed, the significant QALY gain
17	approximated to 3.7 hours for the current smokers sub-group.
18	The average cost per patient associated with the dexamethasone and placebo
19	groups in the basecase analysis adopting a HSP was $\pounds73$ and $\pounds69$ , respectively.
20	Table 3 highlights total costs for the categories included in the economic evaluation.
21	Average costs were higher across both trial arms for the sub-group who did not
22	receive the delayed prescription relative to the sub-group who did ( $\pounds 24$ and $\pounds 18$
23	higher in the placebo and dexamethasone groups respectively) driven by higher
24	health service utilisation; however no statistically significant impact on costs across
25	these sub-groups for the HSP was found. For the SCP, including the cost associated

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1	with inability to carry out usual activities (Scenario I), the average cost per patient
2	was £126 and £134 for the dexamethasone and placebo groups, respectively. This
3	suggests a cost-saving of $\pounds7$ per patient to society. For the sub-group who received
4	the delayed prescription there was a negligible SCP reduction in the dexamethasone
5	group of - $\pounds$ 0.18; however, for those who did not receive the delayed prescription the
6	SCP reduction for the substantial at - $\pounds$ 12 signalling strong evidence of cost-savings
7	from the use of oral dexamethasone compared to placebo.
8	In the deterministic basecase analysis (Table 4), the ICER was negative at -£81,400
9	due to the size and sign of the incremental effectiveness. In the basecase
10	probabilistic analysis, the mean ICER was -£6,440 (95% CI: -£132,151; £126,335)
11	and the median ICER was - $\pounds$ 304 (IQR:- $\pounds$ 5,816; £3,877); suggesting there is
12	considerable uncertainty around this estimate. Several societal scenarios highlighted
13	the potential for cost-savings; however, due to outcome variability, there is
14	insufficient evidence to suggest the dexamethasone is cost-effective. The cost-
15	effectiveness plane (Figure 1) presents a visual representation of the spread of the
16	variation in cost and effect pairs for the basecase probabilistic analysis emphasizing
17	the wide variation in effectiveness. Due to this uncertainty, the cost-effectiveness
18	acceptability curve (see Online Appendix- Figure A5), suggests the probability of
19	cost-effectiveness is 47.9% at a $\pounds$ 20,000 willingness to pay threshold. The mean
20	NMB was £1.80 (SD: £351) at a £20,000 willingness to pay threshold with a 43.5%
21	probability of the dexamethasone yielding a net benefit.

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#### Discussion

The analysis undertaken provides the first detailed account of the cost of sore throat in the UK estimating that on average, costs of treating sore throat to the healthcare services payer are approximately £69 per patient and to society £134. With approximately 340 million consultations annually in the UK<sup>29</sup> and one in ten due to sore throat<sup>4</sup>, the economic burden is estimated at £2.35bn (or £4.56bn to society) based on UK unit costs. The average cost difference was £4.07 (higher in the dexamethasone group): the dexamethasone group cost differential was £5.04 i.e. the cost to the HSP of the single dose of oral dexamethasone. Therefore from the HSP, there is insufficient evidence to suggest the intervention is cost-effective and there is some evidence to suggest the intervention may be producing a negative impact on el.eu HRQoL across the whole cohort. 

### Strengths and limitations of the study

The study collected a wide range of demographic, clinical, quality of life and resource use data using a trial-specific daily patient diary which permitted an extensive exploration of uncertainty in scenario and sub-group analyses. Sub-group analysis indicated that for those who received the delayed antibiotic prescription and the dexamethasone versus those who received the delayed prescription and the placebo, the effect on HRQoL was positive and significant and therefore the resulting ICERs were cost-effective at £4,950 per QALY gain. In contrast the placebo sub-group not given the delayed prescription had a significantly negative effect. GP's selected patients who were perceived to be in greater clinical need for the delayed

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1	prescription sub-arm of the trial; as this sub-group may have had increased severity
2	of symptoms relative to their counterparts, they had more scope to improve from a
3	clinical and HRQoL perspective which in part may explain the variation in HRQoL for
4	the sub-groups. Additionally the average costs of those in the 'no delayed
5	prescription' sub-group who received intervention or placebo were 30% and 45%
6	times higher, respectively, than those in the sub-group who received the delayed
7	prescription. Cost differences observed across sub-groups were primarily driven by
8	higher reported health service use contacts across the trial and follow-up periods:
9	210% increase in the 'no delayed prescription' sub-groups overall and 157% and
10	286% higher for the intervention and placebo arms, respectively. Previous research
11	did not find any clinical differences across delayed prescription and no treatment
12	strategies <sup>30</sup> ; however our findings suggest that the clinical and non-clinical benefits
13	of the delayed prescription in addition to the dexamethasone need to be explored
14	further.

When assessing the impact of the dexamethasone on those who reported being current smokers (n=103, equally distributed between trial arms), there was a significant increase in HRQoL from baseline suggestive of cost-effectiveness for smokers: ICER £6,533. Due to higher risk of prolonged symptoms compared to previous smokers or non-smokers, this intervention may provide an interactive antiinflammatory perhaps akin to effects in patients with exacerbations of chronic obstructive pulmonary disease, primarily caused by smoking.

Adoption of a SCP highlighted cost-savings for the intervention relative to the control group. The main driver of difference in the range of scenarios adopting a SCP was the cost associated with missing work or education due to sickness. However, there Page 15 of 42

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were also differences in reported OTC medication usage across trial arms and sub groups that may influence recovery.

The study is not without its limitations. Missing data was an issue as the main tool for 3 data collection was a patient completed diary at each day of the trial follow-up: 4 5 HRQoL over the 7 days was 60% complete and the resource use reported in diaries 6 was 62% complete. Reported resource use for HSP analysis was cross-checked 7 with a follow-up patient survey and medical record review and as such where no 8 resource use was identified for each patient across the data sources, the assumption 9 of zero resource use for that category is justifiable but potentially leading to some bias in cost estimates. However, EQ-5D-5L data was collected from the patient 10 11 survey only and missing data was considerable at 40%. Although robust multiple 12 imputation techniques were applied to impute values, it is recognised that the range 13 of covariates used to impute missing data may not reflect the degree of 14 heterogeneity across the patient cohort. If the imputation model was mis-specified the imputation estimates could have some degree of bias.<sup>31</sup> Due to the high 15 uncertainty around observed HRQoL estimates across both arms however, the 16 limitations associated with multiple imputation are not cause for concern. In the 17 18 analyses adopting a SCP, self-reported data on time unable to engage in usual 19 activities and OTC medications purchased were not imputed for those with missing 20 data and assumed zero for non-responders. The total cost burden to society is more than likely underestimated as a result and the SCP cost difference across both arms 21 22 may not be as representative as the HCP cost difference.

Further limitations include the interpretation of the sub-group analyses given the
small sample sizes and limitations of the data outlined. The findings based on the
sub-group analyses should be interpreted with caution and need to be assessed with

1	appropriately powered trials. However, the sub-group analyses give greater
2	understanding of the wide variation in outcomes observed.
3	
4	Conclusions and policy implications
5	In conclusion, sore throat has a substantial economic burden on health care delivery
6	systems with this study estimating the economic burden from a HCP in the UK at
7	£2.35bn annually. More effective strategies for assessing and providing rapid
8	symptom relief could reduce the cost burden as well as improve clinical and HRQoL
9	outcomes. The findings of this study suggest there is considerable uncertainty in
10	relation to the effectiveness and HRQoL benefit of dexamethasone for sore throat
11	and therefore insufficient evidence to suggest cost-effectiveness or its adoption as a
12	viable treatment strategy. However, there was evidence suggestive of potential
13	benefits in several sub-groups which could be investigated further in follow-up trials.
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3	
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5	All authors contributed to: the conception and design of the TOAST trial analysis
6	including guidance on the health economic evaluation; the drafting and revising of
7	this manuscript; approval of the final version of the manuscript and are accountable
8	for all aspects of the work presented.
9	Each author has particular areas of expertise as follows: applied economic
10	evaluation leads – RB & JW (joint first authors), statistical analysis SJ, NW & RP,
11	project management, project conception, design and clinical lead- GH, clinical
12	leadership and guidance, interpretation and policy interpretation- AH, MT, CH, PL,
13	MM.
14	
15	
16	This research presents an honest, accurate, and transparent account of the
17	economic evaluation of the TOAST UK study; no relevant aspects of the study have
18	been omitted and the wide range of scenario analyses addresses both the clinical
19	heterogeneity and variability in structural assumptions.
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3 FIGURE	S AND TABLES
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# Table1: TOAST trial patient characteristics

	Placebo Group	Dexamethason Group
All Eligible Participants (ITT)	277 (49%)	288 (51%)
Male	73 (13%)	67 (12%)
Female	204 (36%)	221 (39%)
Mean Age <sup>a</sup>	37.3 (SD: 14.30)	37.2 (SD: 14.36)
Current Smoker	51 (9%)	52 (9%)
ANTIBIOTIC DETAILS <sup>b</sup>		
Given Delayed Prescription	108 (19%)	115 (20%)
Reported taking antibiotics	42 (7%)	34 (6%)
Not Given Delayed Prescription	169 (30%)	173 (31%)
Reported taking antibiotics	16 (3%)	16 (3%)
Total reported antibiotics usage	58 (10%)	50 (9%)
RESOURCE USE		
Reported using OTC Meds (days 1-7)	178 (32%)	173 (31%)
Reported Resource Use (days 1-7)	69 (12%)	67 (12%)
Reported Resource Use in Follow-Up (days 8- 28)	20 (4%)	30 (5%)
SAE <sup>c</sup>	1 (<1%)	1 (<1%)
Other AE	1 (<1%)	0 (0%)
EMPLOYMENT STATUS/ SICK DAYS		
Reported Working Full-Time (22 years and over)	149 (26%)	145 (26%)
Reported Working Part-Time (22 years and over)	40 (7%)	39 (7%)
Assumed in FT/ PT Education <sup>d</sup> (18-22 years)	28 (5%)	33 (6%)
Unemployed	60 (11%)	71 (13%)
Sick Days- Proportion Reporting >1 hr Missing (days 0-7)	104 (18%)	89 (16%)
Sick Days- Proportion Reporting >1 hr Missing (days 1-7)	72 (13%)	60 (11%)
Usual Activities- Proportion Reporting >1 hr Missing (days 0-7)	137 (24%)	127 (22%)
Usual Activities- Proportion Reporting >1 hr Missing (days 1-7)	98 (17%)	104 (18%)

### NOTES:

a. Mean age was estimated using the ITT population previous to the amendment to inclusion criteria constricting the upper age limit to 70 years. 14 patients were over 70 years evenly distributed across both arms.

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b. Antibiotics reported for 'sore throat' are included if prescribed within the 7 day trial period and were administered outside a secondary care setting. This deviates slightly from the clinical paper analysis classification of overall antibiotic use which included antibiotics administered in secondary care for one patient in the control group.

c. SAE's included were categorised as 'Suspected Serious Adverse Reaction' in the clinical paper. Although 3 such events were reported, one was linked to a further SAE ultimately resulting in death and so was excluded from the economic analysis.

*d.* Those aged 18-21 years reporting 'yes' to FT/ PT work/education question in the baseline survey were all categorised into education for purposes of costing productivity losses in a scenario. (See Online Appendix)

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# Table 2: Quality-adjusted life year (QALY) analysis

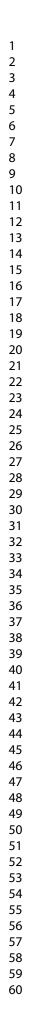
	Placebo (n=277*) Mean (SE)	Dexamethasone (n=288*) Mean (SE)	Difference (Dexamethasone - Placebo)	P Value
Imputed unadjusted QALYS	0.07165 (0.0006)	0.07199 (0.0005)	0.00034 (0.0009)	P < 0.000
Imputed QALYs, adjusted for baseline differences	0.07672 (0.0004)	0.07677 (0.0005)	-0.00005 (0.00008)	P = 0.522
Imputed QALYs for those given delayed prescription (adjusted)	0.0743 (0.0005)	0.0759 (0.0006)	0.00155 (0.0001)	P < 0.000
Imputed QALYs for those not given a delayed prescription (adjusted)	0.0785 (0.0005)	0.0770 (0.0007)	-0.00149 (0.0001)	P < 0.000
Imputed QALYs with patients removed who experienced SAE or AE (adjusted) (n=562)	0.0768 (0.0004)	0.0767 (0.0005)	-0.00006 (0.00008)	P = 0.473
Imputed QALYs with patients removed who were over 70 years (adjusted) (n=551)	0.0766 (0.0004)	0.0765 (0.0005)	-0.000123 (0.00008)	P = 0.128
Imputed QALYs with patients who were current smokers only (adjusted) (n=103)	0.0738 (0.0008)	0.0768 (0.0010)	0.00294 (0.00018)	P < 0.000
Imputed QALYs at 24 hours, adjusted for baseline differences	0.00270 (0.000008)	0.00271 (0.000010)	0.00001 (0.000002)	P < 0.000
Imputed QALYs at 48 hours, adjusted for baseline differences in HRQoL	0.00535 (0.000025)	0.00538 (0.000031)	0.00003 (0.000005)	P < 0.000
Imputed QALYs at 48 hours, adjusted for baseline differences in HRQoL and RR of symptom resolution	0.00492 (0.000024)	0.00534 (0.000029)	0.000422 (0.000005)	P < 0.000

\*This sample size is based on 60 imputed data sets. SE: standard error.

## Table 3: Cost analysis

Cost Bundle Category	Description	Total Cost 2015 USD			Average Cost 2015 USD		
		Placebo	Dexa- methasone	(Dex- Placebo)	Placebo	Dexa- methasone	(Dex- Placebo)
Intervention Cost associated with the intervention.		£12,188	£14,124	£1,936	£44	£49.04	£5.04
Antibiotics- Cohort A	Cost associated with antibiotics reported in patient survey, follow-up survey and medical records	£164	£138	-£26	£1	£0.48	-£0.11
Antibiotics- Cohort B	Cost associated with antibiotics reported in patient survey and medical records only.	£154	£128	-£26	£1	£0.44	-£0.11
Antibiotics- Societal	Cost associated with antibiotics inclusive of the patient co- payment for prescriptions.	£689	£581	-£108	£2	£2.02	-£0.47
Antibiotics B- Societal			£538	-£108	£2	£1.87	-£0.46
Antibiotics- Societal for Workers	Cost associated with antibiotics inclusive of the patient co- payment for prescriptions for workers only.	£623	£474	-£149	£2	£1.65	-£0.60
Antibiotics B- Societal for Workers	ntibiotics B- coietal for Cost associated with antibiotics inclusive		£431	-£116	£2	£1.50	-£0.48
Over-the-counter (OTC)			£648	-£20	£2	£2.25	-£0.16
Resource Use- Patient Diary	Cost associated with resource use reported in the patient diary.	£2,639	£2,732	£93	£10	£9.49	-£0.04
Resource Use- Follow-up Survey	Cost associated with resource use reported in the follow-up survey.	£4,082	£4,008	-£74	£15	£13.92	-£0.82
Productivity Losses- Day 0-7 and Follow-up	Cost of missed days due to illness reported in the	£22,668	£19,469	-£3,199	£82	£67.60	-£14.23

Productivity	patient diary and follow-up survey. Cost of missed days						
Losses (B)- Day 0- 7 and Follow-up	due to illness assuming all 18-21 year olds were in education.	£21,505	£18,634	-£2,871	£78	£64.70	-£12.93
Productivity Losses- Day 1-7 and Follow-up	Cost of missed days due to illness reported in the patient diary from day 1 and follow-up survey.	£14,846	£12,699	-£2,147	£54	£44.09	-£9.50
Productivity Losses (B)- Day 1- 7 and Follow-up	Cost of missed days due to illness (from day 1) assuming all 18-21 year olds were in education.	£14,176	£12,140	-£2,036	£51	£42.15	-£9.02
Usual Activities- Day 0-7 and Follow-up	Cost associated with missing time due to illness for usual activities reported in the patient dairy and follow-up survey.	£4,904	£5,052	£148	£18	£17.54	-£0.16
Usual Activities- Day 1-7 and Follow-up	Cost associated with missing time due to illness (from day 1) for usual activities reported in the patient dairy and follow-up survey.	£3,444	£3,672	£228	£12	£12.75	£0.32
Total HSP Costs- Primary Analysis		£19,073	£21,002	£1,929	£68.86	£72.92	£4.07
Total HSP Costs- without SAE's/ AEs (n=562) Option (A)		£15,610	£18,349	£2,739	£56.76	£63.93	£7.17
Total HSP Costs- Delayed Prescription		£5,830	£7,119.00	£1,289	£53.99	£61.90	£7.91
Total HSP Costs- No Delayed Prescription		£13,243	£13,883	£640	£78.36	£80.25	£1.89
Total HSP Costs- Smokers Only (n=103)		£6,059	£2,787	-£3,272	£118.81	£53.60	-£65.21
Total SCP Option (I)		£37,076	£36,409	-£667	£133.85	£126.42	-£7.43
Total SCP without SAE's/ AEs (n=562)		£33,012	£33,726	-£667	£120.04	£117.51	-£2.53



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Total SCP-	£12,995	£13,816	£821	£120.32	£120.14	-£0.18
Delayed						
Prescription						
Total SCP-	£24,081	£22,593	-£1,488	£142.49	£130.59	-£11.90
No Delayed		·				
Prescription						
Total SCP-	£8,739	£3,259	-£5,480	£171.35	£62.68	-£108.67
Smokers Only						
(n=103)						

NOTE: Cohort A has an additional 8 patients included who reported antibiotic use in follow-up surveys only.

Cohort B does not include these patients in keeping with the statistical analysis plan outlined for the clinical analysis.

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	Control	Intervention	∆ in Cost	∆ in Effect <sup>ª</sup>	ICER	Interpretation <sup>b</sup>			
	Healthcare Services Payer Perspective								
Basecase	£68.86	£72.92	£4.07	-0.00005	-£81,400	Not cost-effective			
Scenario A	£56.76	£63.93	£7.17	-0.00010	-£71,700	Not cost-effective			
Scenario B	£69.22	£73.37	£4.15	-0.00012	-£33,850	Not cost-effective			
Scenario C	£53.99	£61.90	£7.92	0.00160	£4,950	Cost-effective			
Scenario D	£78.36	£80.25	£1.89	-0.0015	-£1,260	Not cost-effective			
Scenario E	£57.58	£77.18	£19.60	0.0030	£6,533	Cost-effective			
Scenario F	£68.86	£72.92	£4.07	0.00001	£407,000	Not cost-effective			
Scenario G	£68.86	£72.92	£4.07	0.00042	£9,690	Cost-effective			
Scenario H <sup>c</sup>	£68.86	£72.92	£4.07	-0.0038	-£1,071	Not cost-effective			
		Soc	cietal Cost Persp	ective					
Scenario I	£133.85	£126.42	-£7.43	-0.00005	£148,600	Not cost-effective			
Scenario J	£167.36	154.72	-£12.64	-0.00005	£252,800	Not cost-effective			
Scenario K	£120.04	£117.51	-£2.53	-0.00010	£25,300	Not cost-effective			
Scenario L	£135.51	£127.59	-£7.92	-0.00005	£158,400	Not cost-effective			
Scenario M	£135.23	£127.44	-£7.79	-0.00005	£155,800	Not cost-effective			
Scenario N	£120.32	£120.14	-£0.18	0.00160	-£112	Cost-effective & Cost-saving			
Scenario O	£142.49	£130.59	-£11.90	-0.00150	£7,933	Not cost-effective			
Scenario P	£171.35	£62.68	-£108.67	0.0030	-£36,223	Cost-effective & Cost-saving			
Scenario Q	£133.85	£126.42	-£7.43	0.00001	-£743,000	Cost-effective & Cost-saving			
Scenario R	£133.85	£126.42	-£7.43	0.00042	-£17,690	Cost-effective & Cost-saving			
Scenario S <sup>c</sup>	£133.85	£126.42	-£7.43	-0.0038	£1,955	Not cost-effective			

# Table 4: Cost-utility analysis (deterministic models)

NOTES:

a. Changes in effect have been adjusted for baseline differences for each model and are representative of an annual timeframe (see Table 2 for more details).

b. Not cost-effective is suggested if the effect is negative and therefore the ICER is negative; not cost-effective <u>may</u> also be suggested when the ICER is positive due to both a negative cost and effect i.e. positioned in the South-West quadrant of the cost-effectiveness plane, depending on the WTP threshold. As the stated WTP threshold is £20,000 per QALY gain, all positive ICERs due to positive costs and effects that are over £20,000 are also deemed not cost-effective. Also note that confidence intervals were not reported as the analysis are deterministic and non-linear; therefore confidence intervals could not be meaningfully interpreted. c. Average unadjusted EQ-VAS scores across baseline to day 7 are presented in the online appendix. After adjustments for imbalance at baseline, the incremental effect was negative at -0.174 at day 7. The change in effect presented in the table above has been adjusted to represent an annual timeframe consistent with cost per QALY interpretation.

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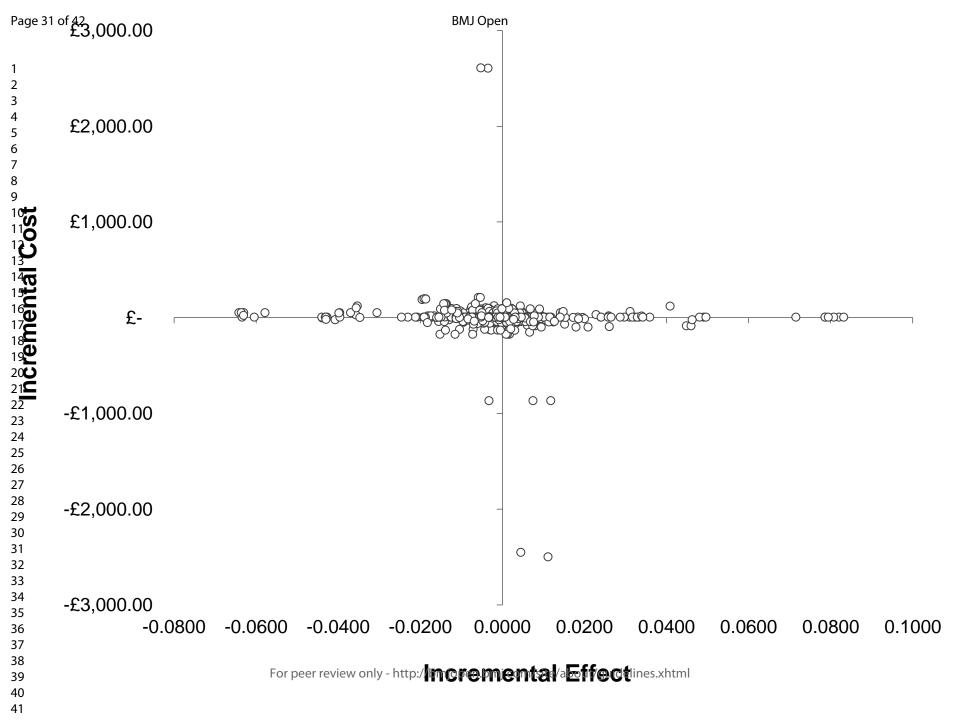
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# **TOAST ONLINE APPENDIX**

### Table A1- Trial Resource Use Costs

Cost ID	Cost Description	2015 (£)	Measure	Details
Int1	Oral Steroid	£ 5.04	1 dose	single 10mg dose of oral dexamethasone, BNF 2015
Int2	GP Visit	£ 44.00	11.7 minute consult	PSSRU 2015
Int3	Pharmacist	£6.00	5 minute consult	British National Formulary (BNF) 2015
Anti1	Penicillin	£ 0.04	per 250mg tab	BNF 2015
Anti2	Erythromycin	£ 0.04	per 250mg tab	BNF 2015
Anti3	Clarithromycin	£ 0.21	per 500mg tab	BNF 2015
Anti4	Amoxicillin	£ 0.08	per 500mg tab	BNF 2015
Anti5	Coamoxiclav	£ 0.20	per 500mg tab	BNF 2015
Anti6	Doxycycline	£ 0.14	per 500mg tab	BNF 2015
Otc1	Paracetamol	£0.24	per recommended daily dose	Boots Pharmacy Generic Brand 2015
Otc2	lbuprofen (NSAIDS)	£0.60	per recommended daily dose	Boots Pharmacy Generic Brand 2015
Otc3	Anaesthetic spray	£ 1.25	per recommended daily dose	Boots Pharmacy Generic Bran 2015
Otc4	Anaesthetic lozenges	£ 1.40	per recommended daily dose	Boots Pharmacy Generic Bran 2015
Otc5	Decongestant	£ 1.00	per recommended daily dose	Boots Pharmacy Generic Bran 2015
Otc6	Lozenges (non-analgesic)	£ 0.66	per recommended daily dose	Boots Pharmacy Generic Bran 2015
Otc7	Other analgesia (cocodamol/ cough medicine, etc.)	£ 1.05	per recommended daily dose	Boots Pharmacy Generic Bran 2015
Wage1	Cost of an adult working day	£ 119.37	median gross annual earnings	Office of National Statistics (UK)
Wage2	Minimum wage day rate	£ 53.60	October 2015 value	Office of National Statistics (UK)
Admin1	NHS prescription charge	£ 8.20		National Health Service (UK)- (NHS)
Res1	GP Nurse	£ 14.47	15.5 minute consult	PSSRU 2015
Res2	GP Telephone Call	£ 27.00	7.1 minute call	PSSRU 2015
Res3	Out-of-Hours GP Clinic	£ 69.53		NAO.org
Res4	111 Telephone Advice	£8.14		Micro-costing study, Universit of Sheffield
Res5	A&E	£ 140.59	Average weighted cost	NHS Ref Costs 2015
Res6	Hospital Bed Day - average	£ 613.63	Average weighted cost	NHS Ref Costs 2015
Pres1	Codeine (co-codamol 30/500)	£ 0.06	per tablet	BNF 2015
Pres2	Codeine Linctus	£ 0.16	15mg/ 5 ml	BNF 2015
Pres3	Benzydamine (Difflam Oromucosal Spray)	£ 1.41	0.15% Spray/ 1 ml	BNF 2015
Pres4	Benzyl Penicillin & Metronidazole IV	£ 12.24	Daily dose (TBC)	BNF 2015

Table A2- Summary of Economic Analysis Scenarios

Options	Perspective	Details
Basecase	HSP	The basecase scenario included the net cost of the intervention i.e. the cost of the once-off medication, the cost of antibiotics used and the cost of resource use reported including serious adverse events. The adjusted QALY estimate was adopted as the outcome measure.
A	HSP	Basecase was adjusted to remove effects and costs of serious adverse events (one in each arm) and adverse events (one in the control group) (n=562).
В	HSP	Basecase was adjusted to remove those over age 70 (seven in each arm removed) (n=551).
С	HSP	Basecase was restricted to only those who received a delayed prescription (n=223).
D	HSP	Basecase was restricted to those who did not receive a delayed prescription (n=342).
E	HSP	Basecase was restricted to only those reporting current smoker status (n=103).
F	HSP	Basecase was adjusted and the imputed EQ-5D-5L differences from baseline at 24 hours were used as the outcome measure.
G	HSP	Basecase was adjusted and the imputed EQ-5D-5L differences from baseline at 48 hours were used as the outcome measure.
Н	HSP	Basecase was adjusted and the imputed EQ-VAS averages from baseline to Day 7 were used as the outcome measure.
I	SCP	Basecase was combined with costs associated with over-the-counter medications used , productivity losses due to missed days at work/ school for days 1 to 7 of the trial follow-up and costs associated with inability to carry out usual activities for days 1 to 7.
J	SCP	Basecase was combined with costs associated with over-the-counter medications used , productivity losses due to missed days at work/ school for days 0 to 7 of the trial follow-up and costs associated with inability to carry out usual activities for days 0 to 7.
К	SCP	Option I was adjusted to remove costs of serious adverse events (one in each arm) and adverse events (one in the control group) (n=562).
L	SCP	Option I was combined with antibiotic prescription charges that would be paid by workers/ students.
м	SCP	Option I was combined with antibiotic prescription charges that would be paid by workers only.
N	SCP	Option I was restricted to only those who received a delayed prescription (n=223).
0	SCP	Option I was restricted to those who did not receive a delayed prescription (n=342).
Ρ	SCP	Option I was restricted to only those reporting current smoker status (n=103).
Q	SCP	Option I adopted the outcome measured at 24 hours
R	SCP	Option I adopted the outcome measured at 48 hours
S	SCP	Option I was adjusted and the imputed EQ-VAS averages from baseline to Day 7 were used as the outcome measure.

The follo	The following variables were used in the multiple imputation dataset:						
	• EQ-5D-5L index values for day 0-7						
	EQ-VAS scores for day 0-7						
	<ul> <li>Symptom resolution at 24 hours and 48 hours</li> </ul>						
	A treatment arm identifier						
	A dichotomous variable to highlight patient experienced an SAE						
	A dichotomous variable for delayed antibiotic prescription given						
	<ul> <li>Costs: intervention, antibiotics, OTC medication, resource use day 1-7, resource use day 8- 28, missed work/ education, missed usual activities</li> </ul>						
	<ul> <li>Patient characteristics: gender, age, employment status, location of care, current smoker, a</li> </ul>						
	dichotomous variable for those aged 71 and over.						
The 'ICE'	command in STATA was used for multiple imputation using chained equations was used. The data						
was muli	iply imputed generating 60 datasets using predictive mean matching and separately by treatment						
allocatio	n based on the variation present in the complete data above. The 'seed' add-on sets a random						
number	seed (this was set at 10), which is useful to improve consistency across imputations.						
The follo	wing is the STATA code used:						
index_5L VAS_day resource	x_5L_day0 index_5L_day1 index_5L_day2 index_5L_day3 index_5L_day4 index_5L_day5 _day6 index_5L_day7 VAS_day0 VAS_day1 VAS_day2 VAS_day3 VAS_day4 VAS_day5 VAS_day6 7 sae outlier resol48 cost_reportedantibiouse totalcost_OTC resourceusediary_cost useFU_cost missed_days_costday1tounk cost_usualact1tounk trt delayed_script Male worker age smoker location age71andover, saving(MI_aggregated, replace) m(60) match genmiss(indmiss) ed(10)"						

	E	Q-5D-5L Imputed Full	ITT	
	Control	Intervention	Diff (I-C)	% ∆ (I-0
Baseline	0.746	0.766	0.0196	2.62%
Day 1	0.829	0.848	0.0189	2.28%
Day 2	0.861	0.871	0.0092	1.07%
Day 3	0.904	0.907	0.0023	0.25%
Day 4	0.918	0.931	0.0132	1.43%
Day 5	0.932	0.940	0.0074	0.79%
Day 6	0.939	0.950	0.0112	1.19%
Day 7	0.947	0.949	0.0028	0.30%
QAW <sup>1</sup>	6.289	6.354	0.0652	1.04%
		EQ-5D VAS Imputed Fu		
	Control	Intervention	Diff (I-C)	% ∆ (I-0
Baseline	49.78	52.41	2.631	5.29%
Day 1	57.99	60.83	2.840	4.90%
Day 2	64.44	64.57	0.126	0.19%
Day 3	70.98	70.27	-0.714	-1.01%
Day 4	74.74	74.35	-0.389	-0.52%
Day 5	78.66	77.16	-1.497	-1.90%
Day 6	81.99	80.25	-1.733	-2.11%
Day 7	84.94	82.37	-2.571	-3.03%
aVAS <sup>2</sup>	70.44	70.27	-0.162	-0.23%
	Delaye	d Prescription- Impute	d ITT Cohort	
	Control	Intervention	Diff (I-C)	% ∆ (I-0
Baseline	0.7431	0.7303	-0.0128	-1.72%
Day 1	0.8158	0.8404	0.0246	3.01%
Day 2	0.8384	0.8576	0.0193	2.30%
Day 3	0.9061	0.9180	0.0119	1.31%
Day 4	0.9180	0.9441	0.0261	2.85%
Day 5	0.9276	0.9579	0.0303	3.27%
Day 6	0.9390	0.9649	0.0259	2.76%
Day 7	0.9480	0.9663	0.0183	1.93%
<b>QAW</b> <sup>1</sup>	6.2569	6.3943	0.1374	2.20%
		ed Prescription- Imput		
	Control	Intervention	Diff (I-C)	% Δ (I-C
Baseline	0.7480	0.7892	0.0411	5.50%
basenne	0.8381	0.8535	0.0154	1.84%
Day 1	0.0001		0.0004	0.35%
	0.8762	0.8793	0.0031	0.5570
Day 1		0.8793 0.8993	-0.0031	
Day 1 Day 2	0.8762			-0.46%
Day 1 Day 2 Day 3	0.8762 0.9035	0.8993	-0.0041	-0.46% 0.50%
Day 1 Day 2 Day 3 Day 4	0.8762 0.9035 0.9179	0.8993 0.9225	-0.0041 0.0046	-0.46% 0.50% -0.83%
Day 1 Day 2 Day 3 Day 4 Day 5	0.8762 0.9035 0.9179 0.9351	0.8993 0.9225 0.9273	-0.0041 0.0046 -0.0078	-0.46% -0.50% -0.83% 0.14% -0.79%

Table A4: Quality of Life Analysis for ITT Impute Cohort (unadjusted)

2. Average VAS score estimated average across baseline to day 7.

Table A5: Quality of Life Analysis for Complete Cases (unadjusted)
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	EQ-5D-5L Analys	is		
	Control	Intervention	Difference (I-C)	P value
	n=172	n=165		
Baseline	0.735	0.755	0.021	ns
Day 1	0.821	0.843	0.021	ns
Day 2	0.862	0.871	0.01	ns
Day 3	0.899	0.903	0.004	ns
Day 4	0.916	0.926	0.01	ns
Day 5	0.929	0.933	0.003	ns
Day 6	0.939	0.947	0.007	ns
Day 7	0.947	0.951	0.004	ns
Average (Day 1-7)	0.902	0.91	0.008	ns
Average Δ (%) from Baseline	0.167 (22.7)	0.155 (20.5)	-0.012	ns
Average $\Delta$ (%) from Baseline at 24 hrs	0.087 (11.8)	0.087 (11.5)	0	ns
Average $\Delta$ (%) from Baseline at 48 hrs	0.107 (14.6)	0.101 (13.4)	-0.005	ns
	EQ-VAS Analysis			
	Control	Intervention	Difference (I-C)	P value
	n=166	n=161		
Baseline	49	52	3	ns
Day 1	57	61	4	ns
Day 2	64	65	1	ns
Day 3	70	70	0	ns
Day 4	75	74	-1	ns
Day 5	79	77	-2	ns
Day 6	82	80	-2	ns
Day 7	86	83	-3	ns
Average (Day 1-7)	73	73	0	ns
Average Δ (%) from Baseline	24 (49)	21 (40)	-3	ns
Average $\Delta$ (%) from Baseline at 24 hrs	8 (16)	9 (17)	1	ns
Average $\Delta$ (%) from Baseline at 48 hrs	15 (31)	13 (25)	-2	ns
	EQ-5D-5L Sub-gro	oup Analysis		
	Delayed Script	No Delayed	Difference	P value
	.,	Script	(Delayed-No Script)	
	n=121	n=216		
Baseline	0.709	0.765	-0.055	0.005
Day 1	0.813	0.842	-0.029	0.059
Day 2	0.878	0.846	-0.032	0.041
Day 3	0.903	0.9	0.003	ns
Day 4	0.925	0.919	0.006	ns
Day 5	0.935	0.929	0.006	ns
Day 6	0.948	0.94	0.008	ns
Day 7	0.959	0.943	0.016	ns
Average (Day 1-7)	0.904	0.907	-0.003	
Average $\Delta$ (%) from Baseline	0.195 (27.5)	0.143 (18.7)	0.052	0.001
Average $\Delta$ (%) from Baseline at 24 hrs	0.119 (20.7)	0.092 (14.1)	0.027	ns
Average $\Delta$ (%) from Baseline at 48 hrs	0.180 (31.3)	0.151 (23.3)	0.029	ns

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#### Figure A1: Missingness assessment in EQ-5D-5L

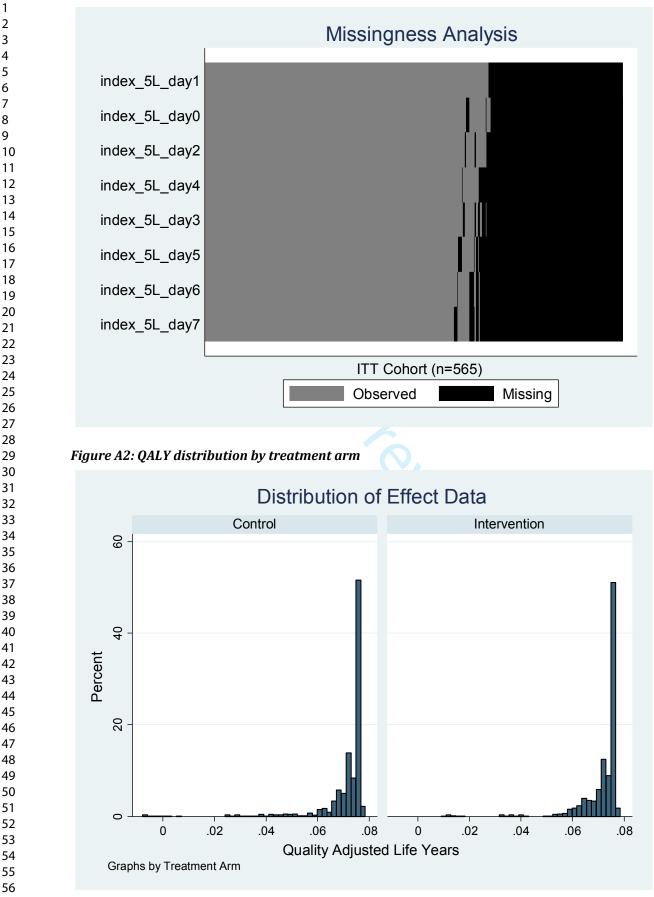


Figure A3: EQ-5D-5L Imputed Scores for ITT Cohort

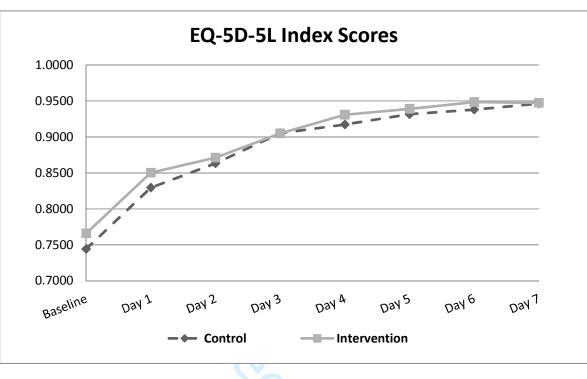
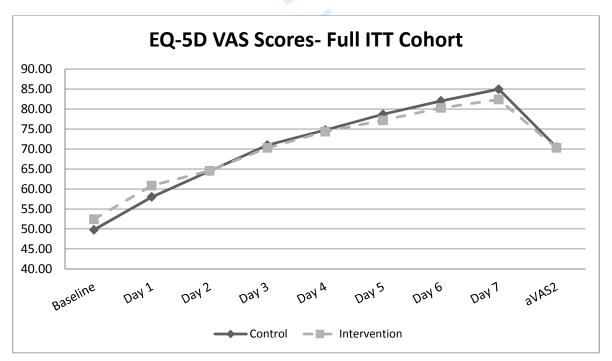
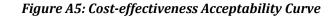
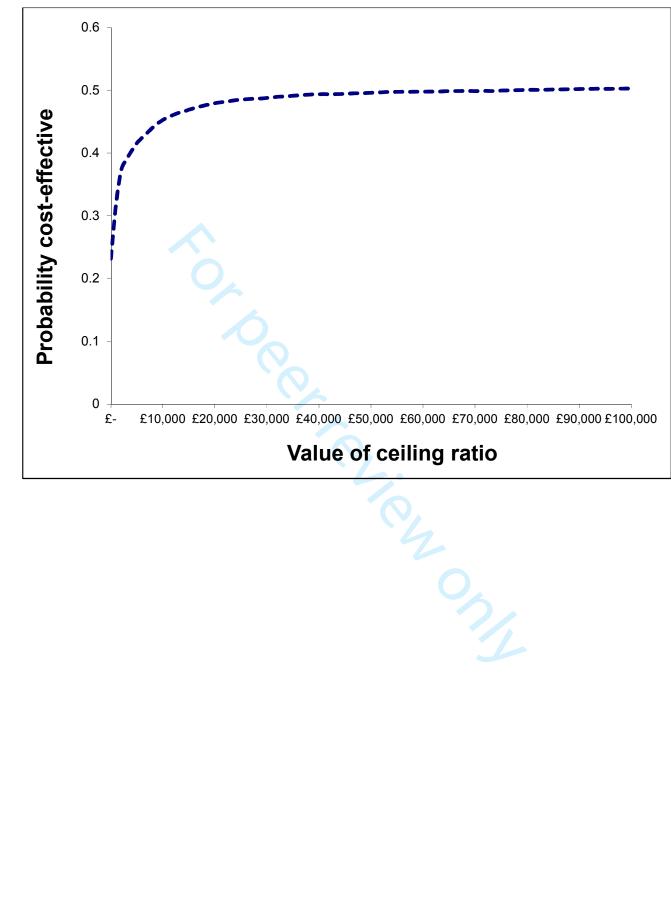


Figure A4: EQ-5D Visual Analogue Scale Imputed Scores for ITT Cohort







	Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 1
1 2 <b>*</b>	"An ELONOMIC Analysis of ORAL Dexa methasone for Symptom Rehel of sore THROAT: The UK TOUST STUDY " The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been
3	The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been
4	endorsed and co-published by the following journals:
5	
6	BJOG: An International Journal of Obstetrics and Gynaecology
7 8	BMC Medicine 2013; 11:80
9	<u>BMJ 2013;346:f1049</u>
10	<u>Clinical Therapeutics 27 March 2013 (Article in Press DOI: 10.1016/j.clinthera.2013.03.003)</u>
11	Cost Effectiveness and Resource Allocation 2013 11:6.
12	The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print]
13 14	International Journal of Technology Assessment in Health Care
14	Journal of Medical Economics 2013 Mar 25. [Epub ahead of print]

Pharmacoeconomics 2013 Mar 26. [Epub ahead of print]

Value in Health 2013 March - April;16(2):e1-e5

## **CHEERS** Checklist

# Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1   1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	3\$4
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	
		Present the study question and its relevance for health policy or practice decisions.	5
Methods		7	
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	6
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	9	Report the choice of discount rate(s) used for costs and	nja



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			outcomes and say why appropriate.	6
Choice of h outcomes	nealth	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of	6a7
Measureme effectivene		11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	728
		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	nla
Measuremo valuation o based outco	f preference	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	nla
Estimating and costs		13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	7
		13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	7
Currency, j and conver		14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	8
Choice of r	nodel	15	Describe and give reasons for the specific type of decision- analytical model used. Providing a figure to show model structure is strongly recommended.	809010
Assumptio	ns	16	Describe all structural or other assumptions underpinning the decision-analytical model.	829410
Analytical	methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	NUME AND ADDRESS OF ADDRESS OF ADDRESS OF
Results				
Study para	meters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	10-12 Continé appendi

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Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 3

Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well	10-12
		as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	\$ 21-2
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	11-12
		of methodological assumptions (such as discount rate, study perspective).	25
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	11-12 25
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between	11-12
		subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	25
<b>Discussion</b> Study findings, limitations,	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the	13 -
generalisability, and current knowledge		generalisability of the findings and how the findings fit with current knowledge.	1-2
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	16
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence	,
		of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	(6-

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The CHEERS Statement may be accessed by the publication links above.

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <u>http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp</u>

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.



# **BMJ Open**

# An Economic Analysis of Oral Dexamethasone for Symptom Relief of Sore Throat: The UK TOAST Study

Journal:	BMJ Open
Journal.	
Manuscript ID	bmjopen-2017-019184.R1
Article Type:	Research
Date Submitted by the Author:	07-Feb-2018
Complete List of Authors:	Burns, Richeal; University of Oxford, Nuffield Department of Population Health Wolstenholme, Jane; University of Oxford, Nuffield Department of Population Health Jawad, Sena; Neonatal Data Analysis Unit, Deapratment of Medicine, Imperial College London Williams, Nicola; Nuffield Department of Primary Care Health Sciences, University of Oxford Thompson, Matthew; University of Washington, Department of Family Medicine Perera, Rafael; University of Oxford, Primary Health Care Hay, Alastair; University of Bristol, School of Social and Community Medicine Heneghan, Carl; Oxford University, Primary Health Care Little, Paul; University of Southampton, Medical School, Moore, Michael; Three Swans Surgery Hayward, Gail; Oxford University, Department of Primary Care Health Sciences
<b>Primary Subject Heading</b> :	Health economics
Secondary Subject Heading:	Medical management, Health policy, Ear, nose and throat/otolaryngology
Keywords:	cost-utility analysis, PRIMARY CARE, sore throat

SCHOLARONE<sup>™</sup> Manuscripts

BMJ Open

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3	1	Title: An Economic Analysis of Oral Dexamethasone for Symptom Relief of
4	2	Sore Throat: The UK TOAST Study
5 6	-	
7	3	Authors: Richéal M Burns* PhD, Jane Wolstenholme* PhD, Sena Jawad MSc, Nicola
8	4	Williams MSc, Matthew Thompson PhD, Rafael Perera D.Phil, Alastair D Hay
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12	6	Hayward D.Phil, on behalf of the TOAST Trial Investigators
13		
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# 1 Abstract

2

3	Objectives: To undertake an economic analysis assessing the cost-effectiveness of a
4	single dose of oral dexamethasone compared to placebo for the relief of sore throat.
5	Design: A UK-based, multicentre, two arm, individually randomised, double blind trial
6	Setting and Population: Adults (≥18 years) with acute sore throat and painful
7	swallowing judged to be infective in origin, recruited and randomised in primary care.
8	Intervention: A single dose of 10mg oral dexamethasone compared to placebo given
9	at primary care visit.
10	Main Outcome: Incremental cost-effectiveness ratios (ICERs), cost per quality-
11	adjusted symptom resolution using the EQ-5D-5L instrument, were estimated as part
12	of a cost-utility analysis performed on an intention-to-treat cohort adopting a health
13	payers perspective.
14	Results: Differences in health-related quality of life (HRQoL) over 7 days from
15	baseline and at 24 hours in the dexamethasone compared with the placebo group
16	(2.9% and 2.5% higher, respectively) were observed. After controlling for the
17	baseline HRQoL imbalances, the economic impact of the intervention was not
18	statistically significant: the QALY difference was -0.00005 (95% CI: -0.0002;
18 19	
	statistically significant: the QALY difference was -0.00005 (95% CI: -0.0002;
19	statistically significant: the QALY difference was -0.00005 (95% CI: -0.0002; 0.00011) equivalent to a loss in HRQoL of a half hour in the dexamethasone group.
19 20	statistically significant: the QALY difference was -0.00005 (95% CI: -0.0002; 0.00011) equivalent to a loss in HRQoL of a half hour in the dexamethasone group. The average cost per patient associated in the dexamethasone and placebo groups
19 20 21	statistically significant: the QALY difference was -0.00005 (95% CI: -0.0002; 0.00011) equivalent to a loss in HRQoL of a half hour in the dexamethasone group. The average cost per patient associated in the dexamethasone and placebo groups in the basecase analysis was £73 and £69, respectively. In the basecase
19 20 21 22	statistically significant: the QALY difference was -0.00005 (95% CI: -0.0002; 0.00011) equivalent to a loss in HRQoL of a half hour in the dexamethasone group. The average cost per patient associated in the dexamethasone and placebo groups in the basecase analysis was £73 and £69, respectively. In the basecase probabilistic analysis, the mean ICER was -£6,440 (95% CI: -£132,151; £126,335)

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2 3	1	Conclusions and relevance: The economic burden associated with sore throat is
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5 6	2	substantial and was estimated at £2.35bn to the healthcare services payer based on
7	3	reported resource use and 2015 UK unit costs. There is considerable uncertainty
8 9	4	regarding the cost-effectiveness of a single dose of oral dexamethasone as a
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12 13	5	treatment strategy and therefore insufficient evidence to support its use in clinical
14	6	practice.
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17 18	7	Trial Registration: ISRCTN17435450 http://www.isrctn.com/ISRCTN17435450
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# Strengths and limitations of this study

- The analysis undertaken provides the first detailed account of the cost of sore throat in the UK.
- 5 2. The study collected a wide range of demographic, clinical, quality of life and
   6 resource use data using a trial-specific daily patient diary which permitted an
   7 extensive exploration of uncertainty in scenario and sub-group analyses.
  - Both health services payer and societal perspectives were assessed in the
     economic evaluation.
- In contrast to previous research highlighting no clinical differences across
   delayed prescription and no treatment strategies, this analysis suggests that
   clinical and non-clinical benefits of the delayed prescription in addition to the
   dexamethasone need to be explored further.
- 5. Reported resource use for HSP analysis was cross-checked with a follow-up patient survey and medical record review and as such where no resource use was identified for each patient across the data sources, the assumption of zero resource use for that category is justifiable but potentially leading to some bias in cost estimates.

#### 1 Introduction

An estimated £400 million annually is spent on consultations and lost productivity associated with sore throat alone in the UK.<sup>1,2</sup> Almost one in ten registered UK patients will see their general practitioner (GP) every year with sore throat.<sup>3</sup> 91% of those diagnosed with tonsillitis will receive antibiotics, as will half of those recorded as 'sore throat' or 'pharyngitis'.<sup>4</sup> NICE and International guidance recognises the limited evidence for benefit of antibiotics in its advice to avoid prescriptions in the majority of patients<sup>5-6</sup>; however, prescribing rates remain disproportionately high even though patients attend mainly due to anxiety over symptoms.<sup>7</sup> A key driver for patients to attend with a sore throat is the severity of their symptoms, so affective symptomatic treatment may help reduce patient reliance on antibiotic. Furthermore where antibiotics are used for streptococcal infections more rapid clinical improvement is also plausible with steroids<sup>8</sup> which could facilitate shorter courses of antibiotics, which would improve both prescribing and the overall economic burden of sore throat. Further, negative externalities associated with over-prescribing antibiotics, predominantly the increasing issue of antimicrobial resistance<sup>9</sup>, could also be moderated. The Treatment Options without Antibiotics for Sore Throat (TOAST) trial<sup>10</sup> addressed whether or not oral corticosteroids provide clinical and cost-effective benefits through symptom relief of sore throat. The findings of the trial highlighted no clinical impact of a single dose of oral dexamethasone compared with placebo for resolution of symptoms at 24 hours; however, at 48 hours there was a significant improvement for patients receiving the intervention.<sup>11</sup> The cost-effectiveness analysis alongside the TOAST trial assessed the costs and benefits of 

a single dose of 10mg oral dexamethasone compared to placebo for the symptom
relief of sore throat.

#### Methods

#### 6 Intervention

TOAST was a multicentre, two arm, individually randomised, double blind trial comparing a single dose of 10mg oral dexamethasone with identical placebo in adults aged between 18 and 70 years<sup>1</sup> inclusive, presenting to primary care with acute sore throat. Recruitment took place in 42 primary care clinics in England from April 2013 to February 2015. The intervention period assessed was 7 days post-presentation and participants were followed up for 28 days to assess resource use and adverse events. A sub-group of patients in each trial arm received a delayed prescription for antibiotics at the discretion of the GP and randomisation was stratified by this decision. Further details on trial design, are published elsewhere.<sup>6</sup> The research protocol was approved by the National Research Ethics Committee South Central (12/SC/0684). 

### 19 Outcome Measure

20 The cost-effectiveness analysis assessed quality-adjusted symptom resolution over

the 7 day trial duration and estimated median time to complete resolution of

<sup>&</sup>lt;sup>1</sup> The trial initially recruited patients with no upper age limit and this was amended to age 70 after a serious adverse reaction (hospitalisation for pneumonia and subsequent death, in a patient receiving placebo). Patients over the age of 70 recruited previous to the protocol amendment were included in the ITT analysis.

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1	symptoms and the corresponding utility gains measured by the EuroQol EQ-5D 5
2	level (EQ-5D-5L) index. These outcomes informed the construction of a quality-
3	adjusted life year (QALY) used in the cost-utility analysis. The EuroQol instrument
4	has five domains (mobility, self-care, activities, pain/discomfort, and
5	anxiety/depression) and five response levels ranging from no problems to severe
6	problem. <sup>12</sup> This health-related quality of life (HRQoL) instrument was administered to
7	all participants at baseline and completed on each day of the seven day patient
8	diary. Each of the five dimensions in the EQ-5D-5Lversion is scored from 1 (no
9	problem) to 5 (extreme problems), generating a profile (e.g. 11245) that can be used
10	to calculate a single index score (range -0.281 – 1.000). <sup>13</sup> The EQ-5D instrument
11	also generates a self-rating of HRQoL scored from 0 to 100 employing a visual
12	analogue scale (VAS); this was used in scenario analyses. Quality adjusted
13	symptom resolution at 24 and 48 hours were also reported.
14	
15	Resource Use

#### Resource Use 15

16 Primary care resource utilisation was recorded in a trial patient diary for the first 7 17 days of the trial and was complemented by a follow-up survey sent to those with 18 incomplete patient diaries. A primary care patient medical record review for the period from day 1 to day 28 (trial follow-up period) was also undertaken which 19 20 recorded primary and secondary care contacts related to sore throat including serious adverse events (SAEs) related to the condition. SAEs included in the 21 analysis were those classified as such by the trial protocol; and detailed in the main 22 trial paper.<sup>11</sup> Resource use included the following: visits and telephone calls to the 23 GP; visits and telephone calls to nurses; out-of-hours calls and visits; pharmacy 24

visits; calls to helpline '111'; A&E visits; hospitalisations; and various types of
reported medication including prescribed antimicrobials and over-the-counter (OTC)
medications.

5 Unit Costs

Total and average costs were estimated for the intervention, antibiotic usage (up to and including day 7), OTC medication usage (for days 0-7), health resource use/medication across the trial period (for days 1-28), SAEs, and patient productivity losses associated with sick days reported (for work and education) and inability to carry out usual activities. Unit costs, presented in the **Online Appendix** (Table A1), were obtained from a number of sources including, PSSRU<sup>14</sup>, British National Formulary<sup>15</sup>, Boots Chemist<sup>16</sup>, and the NHS Electronic Tariff Database<sup>17</sup> and are reported in UK currency. Productivity losses were costed using average wage rates for those employed and minimum wage rates for students.<sup>18</sup> All cost estimates were reported in 2015 GBP using appropriate adjustments for prices retrieved where necessary.<sup>19</sup> Disaggregated average cost estimates reported were based on the full cohort in the ITT analysis assuming non-responders had zero costs. 

19 Analysis

Patient characteristics and reported resource use were summarised by trial arm. The
primary economic analysis was conducted on an ITT basis and adopted the
healthcare services payer perspective (HSP) which included the cost burden to the
HSP only. Given the short-term duration of the trial, neither costs nor benefits were

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1	discounted. For the HSP the prescription administrative charge, normally applied to
2	employed, working-age adults only in the UK <sup>20</sup> , associated with the antimicrobial was
3	not incorporated into the cost analysis as this was considered an out-of-pocket
4	(OOP) expense borne by the patient; this was not considered as a contribution to the
5	HSP either i.e. reducing the net cost of care per person to the HSP, as the
6	prescription administrative charge is not applied to everyone and the full amount may
7	not be recouped by the HSP. <sup>21</sup> In the scenario analyses, a societal costing
8	perspective (SCP) was also adopted reflecting the overall economic burden of the
9	dexamethasone relative to the placebo. This included productivity losses due to sick
10	days i.e. reported time off due to missed work or education and reported inability to
11	carry out usual activities, and OOP expenses. Further scenarios assessed sub-
12	groups based on patient characteristics. The sub-group who highlighted they were
13	current smokers at the time of the trial were assessed in a scenario analysis due to
14	the extra healthcare burden smokers have relative to non-smokers. <sup>22</sup> Descriptions of
15	all 20 analyses are presented in the <b>Online Appendix</b> (Table A2).
16	Each element of costs and outcomes were reported separately, consistent with a
17	cost-consequence analysis; the resource use reported was for the full ITT cohort (i.e.
18	no missing resource use data) and the HRQoL data reported in the disaggregated
19	format was for complete cases i.e. n=337; 60% of the full cohort. Missing HRQoL
20	data was assessed and classified as missing at random (MAR) (see Online
21	Appendix- Figure A1). <sup>16</sup> Multiple imputation analysis was performed for missing
22	outcome data (40%) in the ITT cohort using a number of imputations (n=60) greater
23	than the proportion of missing data. <sup>23</sup> The range of covariates included in the
24	multiple imputation analysis along with a more comprehensive presentation of
25	methods is presented (see Online Appendix- Table A3). The trial and follow-up

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1	duration was 28 days in total and for consistency it was assumed that HRQoL was
2	unchanged from day 7 to day 28 using the last value brought forward technique. <sup>24</sup>
3	The average utility from baseline reported across the 28 days, calculated using area
4	under the curve (AUC) was considered 1/13th of a quality adjusted life year (QALY).
5	Baseline variation in outcomes was adjusted for incorporating multiple regression
6	and seemingly unrelated regression techniques which estimated the baseline
7	imbalance taking into account costs and effects. <sup>16, 25</sup> QALYs exhibited a non-normal
8	distribution (see Online Appendix- Figure A2) and bootstrapping techniques using
9	1,000 iterations were applied in Microsoft Excel. <sup>26</sup> The differences in EQ-5D-5L from
10	baseline (day 0) at each day i.e. days 1 to 7, were estimated and results from the
11	complete case analysis (CCA) (n=337) and the intention-to-treat analysis (ITT)
12	(n=565) are presented in the <b>Online Appendix</b> (Tables A4-A5). Cost-utility analysis
13	was undertaken and incremental cost-effectiveness ratios (ICERs) were estimated
14	and reported for the basecase analysis and all scenario analyses. ICERs were
15	probabilistic for the basecase analysis and deterministic for the series of scenarios
16	estimated. The analysis was undertaken in Stata version 14.1. <sup>27</sup> A cost-effectiveness
17	plane and cost-effectiveness acceptability curve (CEAC) were constructed based on
18	the bootstrapped sample means and net monetary benefit (NMB) was also assessed
19	against a range of willingness to pay thresholds up to £100,000. <sup>28</sup> The NICE
20	willingness to pay threshold of $\pounds20,000$ was adopted as a decision rule to assess
21	cost-effectiveness. <sup>27</sup>
22	Results
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- The ITT cohort (n=565) with 288 in the dexamethasone group and 277 in the
- placebo group; descriptive statistics are presented in *Table 1*. The mean age of

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2 3	1	participants was 37 years and 75% were women. There was no significant clinical
4 5	2	difference in median time to complete symptom resolution across trial arms with both
6 7 8	3	displaying complete symptom resolution by day 4; however, there was a significant
9 10	4	difference in symptom resolution at 48 hours. <sup>11</sup> The changes in HRQoL over the 7
10 11 12	5	days highlight larger differences at baseline and at 24 hours with the dexamethasone
13 14	6	group reporting 2.9% and 2.5% higher utility scores, respectively (see Online
15 16	7	Appendix- Figures A3-4). Differences start to diminish (<1.5%) from day 2 onwards.
17 18	8	Table 2 highlights the differences in estimated QALYs for the imputed ITT cohort.
19 20	9	After controlling for the baseline imbalances in HRQoL, the impact of the intervention
21 22	10	was negative but not statistically significant: the QALY gain was -0.00005 (95% CI: -
23 24 25	11	0.0002; 0.00011) equivalent to a loss in HRQoL of a half hour for the
25 26 27	12	dexamethasone relative to the placebo group. Unadjusted differences in HRQoL for
28 29	13	the ITT and complete case cohorts are presented in the <b>Online Appendix</b> (see-
30 31	14	Figures A4-5).
32 33		
34 35	15	For the sub-group who received the delayed prescription based on clinical need, a
36 37	16	statistically significant benefit was evidenced after baseline imbalances were
38 39	17	adjusted for resulting in an approximate HRQoL gain of 13.6 hours relative to the
40 41	18	control group. For the sub-group who did not receive the prescription, the
42 43	19	dexamethasone group indicated a significant QALY loss of approximately 13 hours
44 45	20	relative to the placebo group. For the patient group who reported that they were
46 47	21	current smokers a significant QALY gain from the dexamethasone of 0.0029,
48 49	22	equivalent to 1 day was evidenced. At 48 hours where a significant difference in the
50 51	23	risk ratio of symptom resolution at 48 hours in favour of the dexamethasone [RR:
52 53	24	1.31 (95% CI, 1.02 to 1.68; P = .03)] was observed, the significant QALY gain
54 55 56	25	approximated to 3.7 hours for the current smokers sub-group.
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1	The average cost per patient associated with the dexamethasone and placebo
2	groups in the basecase analysis adopting a HSP was £73 and £69, respectively.
3	Table 3 highlights total costs for the categories included in the economic evaluation.
4	Average costs were higher across both trial arms for the sub-group who did not
5	receive the delayed prescription relative to the sub-group who did (£24 and £18
6	higher in the placebo and dexamethasone groups respectively) driven by higher
7	health service utilisation; however no statistically significant impact on costs across
8	these sub-groups for the HSP was found. For the SCP, including the cost associated
9	with inability to carry out usual activities (Scenario I), the average cost per patient
10	was £126 and £134 for the dexamethasone and placebo groups, respectively. This
11	suggests a cost-saving of £7 per patient to society. For the sub-group who received
12	the delayed prescription there was a negligible SCP reduction in the dexamethasone
13	group of - $\pounds$ 0.18; however, for those who did not receive the delayed prescription the
14	SCP reduction for the substantial at -£12 signalling strong evidence of cost-savings
15	from the use of oral dexamethasone compared to placebo.
16	In the deterministic basecase analysis ( <i>Table 4</i> ), the ICER was negative at -£81,400
17	due to the size and sign of the incremental effectiveness. In the basecase
18	probabilistic analysis, the mean ICER was -£6,440 (95% CI: -£132,151; £126,335)
19	and the median ICER was -£304 (IQR:-£5,816; £3,877); suggesting there is
20	considerable uncertainty around this estimate. Several societal scenarios highlighted
21	the potential for cost-savings; however, due to outcome variability, there is
22	insufficient evidence to suggest the dexamethasone is cost-effective. The cost-
23	effectiveness plane ( <i>Figure 1</i> ) presents a visual representation of the spread of the
24	variation in cost and effect pairs for the basecase probabilistic analysis emphasizing
25	the wide variation in effectiveness. Due to this uncertainty, the cost-effectiveness

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acceptability curve (see *Online Appendix*- Figure A5), suggests the probability of
cost-effectiveness is 47.9% at a £20,000 willingness to pay threshold. The mean
NMB was £1.80 (SD: £351) at a £20,000 willingness to pay threshold with a 43.5%
probability of the dexamethasone yielding a net benefit.

Discussion

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The analysis undertaken provides the first detailed account of the cost of sore throat 9 10 in the UK estimating that on average, costs of treating sore throat to the healthcare 11 services payer are approximately £69 per patient and to society £134. With approximately 340 million consultations annually in the UK<sup>29</sup> and one in ten due to 12 sore throat<sup>4</sup>, the economic burden is estimated at £2.35bn (or £4.56bn to society) 13 14 based on UK unit costs. The average cost difference was £4.07 (higher in the dexamethasone group): the dexamethasone group cost differential was £5.04 i.e. the 15 cost to the HSP of the single dose of oral dexamethasone. Therefore from the HSP, 16 17 there is insufficient evidence to suggest the intervention is cost-effective and there is 18 some evidence to suggest the intervention may be producing a negative impact on HRQoL across the whole cohort. 19

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Strengths and limitations of the study

22 The study collected a wide range of demographic, clinical, quality of life and resource

use data using a trial-specific daily patient diary which permitted an extensive

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1	exploration of uncertainty in scenario and sub-group analyses. Sub-group analysis
2	indicated that for those who received the delayed antibiotic prescription and the
3	dexamethasone versus those who received the delayed prescription and the
4	placebo, the effect on HRQoL was positive and significant and therefore the resulting
5	ICERs were cost-effective at £4,950 per QALY gain. In contrast the placebo sub-
6	group not given the delayed prescription had a significantly negative effect. GPs
7	selected patients who were perceived to be in greater clinical need for the delayed
8	prescription sub-arm of the trial; as this sub-group may have had increased severity
9	of symptoms relative to their counterparts, they had more scope to improve from a
10	clinical and HRQoL perspective which in part may explain the variation in HRQoL for
11	the sub-groups. Additionally the average costs of those in the 'no delayed
12	prescription' sub-group who received intervention or placebo were 30% and 45%
13	times higher, respectively, than those in the comparative sub-group who received the
14	delayed prescription. Cost differences observed across sub-groups were primarily
15	driven by higher reported health service use contacts across the trial and follow-up
16	periods: 210% increase in the 'no delayed prescription' sub-groups overall and 157%
17	and 286% higher for the intervention and placebo arms, respectively. Caution is
18	needed in interpreting this variation as the trial was not powered for sub-group
19	analysis of resource use and response rates were low. Previous research did not
20	find any clinical differences across delayed prescription and no treatment
21	strategies <sup>30</sup> ; however our findings suggest that the clinical and non-clinical benefits
22	of the delayed prescription in addition to the dexamethasone need to be explored
23	further.
24	Although only a slight reduction in antibiotic usage was observed in the intervention

Although only a slight reduction in antibiotic usage was observed in the intervention
arm relative to the placebo i.e. 3% less reported use for the delayed prescription

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2 3	1	sub-group, we feel the range of budgetary, clinical and environmental benefits of
4 5 6	2	reducing antibiotic usage need to be explored further given the evidence highlighted
7 8 9	3	in this study.
9 10 11	4	When assessing the impact of the dexamethasone on those who reported being
12 13	5	current smokers (n=103, equally distributed between trial arms), there was a
14 15	6	significant increase in HRQoL from baseline suggestive of cost-effectiveness for
16 17	7	smokers: ICER £6,533. Due to higher risk of prolonged symptoms compared to
18 19	8	previous smokers or non-smokers, this intervention may provide an interactive anti-
20 21	9	inflammatory perhaps akin to effects in patients with exacerbations of chronic
22 23 24	10	obstructive pulmonary disease, primarily caused by smoking.
25 26 27	11	Adoption of a SCP highlighted cost-savings for the intervention relative to the control
28 29	12	group. The main driver of difference in the range of scenarios adopting a SCP was
30 31	13	the cost associated with missing work or education due to sickness. However, there
32 33	14	were also differences in reported OTC medication usage across trial arms and sub-
34 35 36	15	groups that may influence recovery.
37 38	16	The study is not without its limitations. Missing data was an issue as the main tool for
39 40	17	data collection was a patient completed diary at each day of the trial follow-up:
41 42 43	18	HRQoL over the 7 days was 60% complete and the resource use reported in diaries
43 44 45	19	was 62% complete. The initial response rate was much lower and a protocol
46 47	20	amendment which allowed the use of incentives for patients who returned diaries
48 49	21	was introduced. Reported resource use for HSP analysis was cross-checked with a
50 51	22	follow-up patient survey and medical record review and as such where no resource
52 53	23	use was identified for each patient across the data sources, the assumption of zero
54 55 56	24	resource use for that category is justifiable but potentially leading to some bias in
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1	cost estimates. However, EQ-5D-5L data was collected from the patient survey only
2	and missing data was considerable at 40%. Although robust multiple imputation
3	techniques were applied to impute values, it is recognised that the range of
4	covariates used to impute missing data may not reflect the degree of heterogeneity
5	across the patient cohort and therefore some bias may remain in terms of the
6	resource use and outcomes reported versus those that were not. If the imputation
7	model was mis-specified the imputation estimates could have some degree of bias. <sup>31</sup>
8	Due to the high uncertainty around observed HRQoL estimates across both arms
9	however, the limitations associated with multiple imputation are not cause for
10	concern. In the analyses adopting a SCP, self-reported data on time unable to
11	engage in usual activities and OTC medications purchased were not imputed for
12	those with missing data and assumed zero for non-responders. The total cost burden
13	to society is more than likely underestimated as a result and the SCP cost difference
14	across both arms may not be as representative as the HCP cost difference.
15	Further limitations include the interpretation of the sub-group analyses given the
16	small sample sizes and limitations of the data outlined. The findings based on the
17	sub-group analyses should be interpreted with caution and need to be assessed with
18	appropriately powered trials. However, the sub-group analyses give greater
19	understanding of the wide variation in outcomes observed.
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21	Conclusions and policy implications
22	In conclusion, sore throat has a substantial economic burden on health care delivery
23	systems with this study estimating the economic burden from a HCP in the UK at
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24 £2.35bn annually. More effective strategies for assessing and providing rapid

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symptom relief could reduce the cost burden as well as improve clinical and HRQoL

outcomes. The findings of this study suggest there is considerable uncertainty in

relation to the effectiveness and HRQoL benefit of dexamethasone for sore throat

viable treatment strategy. However, there was evidence suggestive of potential

and therefore insufficient evidence to suggest cost-effectiveness or its adoption as a

benefits in several sub-groups which could be investigated further in follow-up trials.

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6 Data Sharing:

7 There is no additional data available for this study.

9 Competing Interests:

10 We have read and understood BMJ Open policy on declaration of interests and

11 declare that we have no competing interests

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23 Protocol and Ethics:

24 The protocol, informed consent form, participant information sheet and any proposed

advertising material have received appropriate Research Ethics Committee (REC),

regulatory authorities (MHRA in the UK), and host institution(s) approval (REC

27 reference: 12/SC/0684 NRES Committee South Central - Oxford B).

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3	1	Contribution Statement:
4 5		
6	2	All authors contributed to: the conception and design of the TOAST trial analysis
7	3	including guidance on the health economic evaluation; the drafting and revising of
8	4	this manuscript; approval of the final version of the manuscript and are accountable
9 10		
11	5	for all aspects of the work presented.
12	6	Each author has particular areas of expertise as follows: applied economic
13		
14 15	7	evaluation leads – RB & JW (joint first authors), statistical analysis SJ, NW & RP,
16	8	project management, project conception, design and clinical lead- GH, clinical
17	9	leadership and guidance, interpretation and policy interpretation- AH, MT, CH, PL,
18 19		MM.
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26	13	This research presents an honest, accurate, and transparent account of the
27 28	14	economic evaluation of the TOAST UK study; no relevant aspects of the study have
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30	15	been omitted and the wide range of scenario analyses addresses both the clinical
31 32	16	heterogeneity and variability in structural assumptions.
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# FIGURES AND TABLES

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	Placebo Group	Dexamethasone Group
All Eligible Participants (ITT)	277 (49%)	288 (51%)
Male	73 (13%)	67 (12%)
Female	204 (36%)	221 (39%)
Mean Age <sup>a</sup>	37.3 (SD: 14.30)	37.2 (SD: 14.36)
Current Smoker	51 (9%)	52 (9%)
ANTIBIOTIC DETAILS <sup>b</sup>		
Given Delayed Prescription	108 (19%)	115 (20%)
Reported taking antibiotics	42 (7%)	34 (6%)
Not Given Delayed Prescription	169 (30%)	173 (31%)
Reported taking antibiotics	16 (3%)	16 (3%)
Total reported antibiotics usage	58 (10%)	50 (9%)
RESOURCE USE		
Reported using OTC Meds (days 1-7)	178 (32%)	173 (31%)
Reported Resource Use (days 1-7)	69 (12%)	67 (12%)
Reported Resource Use in Follow-Up (days 8- 28)	20 (4%)	30 (5%)
SAE <sup>c</sup>	1 (<1%)	1 (<1%)
Other AE	1 (<1%)	0 (0%)
EMPLOYMENT STATUS/ SICK DAYS		
Reported Working Full-Time (22 years and over)	149 (26%)	145 (26%)
Reported Working Part-Time (22 years and over)	40 (7%)	39 (7%)
Assumed in FT/ PT Education <sup>d</sup> (18-22 years)	28 (5%)	33 (6%)
Unemployed	60 (11%)	71 (13%)
Sick Days- Proportion Reporting >1 hr Missing (days 0-7)	104 (18%)	89 (16%)
Sick Days- Proportion Reporting >1 hr Missing (days 1-7)	72 (13%)	60 (11%)
Usual Activities- Proportion Reporting >1 hr Missing (days 0-7)	137 (24%)	127 (22%)
Usual Activities- Proportion Reporting >1 hr Missing (days 1-7)	98 (17%)	104 (18%)

NOTES: Percentages in brackets represent proportion of full trial cohort (n=565)

a. Mean age was estimated using the ITT population previous to the amendment to inclusion criteria constricting the upper age limit to 70 years. 14 patients were over 70 years evenly distributed across both arms.

b. Antibiotics reported for 'sore throat' are included if prescribed within the 7 day trial period and were administered outside a secondary care setting. This deviates slightly from the clinical paper analysis classification of overall antibiotic use which included antibiotics administered in secondary care for one patient in the control group.

c. SAE's included were categorised as 'Suspected Serious Adverse Reaction' in the clinical paper. Although 3 such events were reported, one was linked to a further SAE ultimately resulting in death and so was excluded from the economic analysis.

d. Those aged 18-21 years reporting 'yes' to FT/ PT work/education question in the baseline survey were all categorised into education for purposes of costing productivity losses in a scenario. (See Online Appendix)

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# Table 2: Quality-adjusted life year (QALY) analysis

	Placebo (n=277*) Mean (SE)	Dexamethasone (n=288*) Mean (SE)	Difference (Dexamethasone - Placebo)	P Value
Imputed unadjusted QALYS	0.07165 (0.0006)	0.07199 (0.0005)	0.00034 (0.0009)	P < 0.000
Imputed QALYs, adjusted for baseline differences	0.07672 (0.0004)	0.07677 (0.0005)	-0.00005 (0.00008)	P = 0.522
Imputed QALYs for those given delayed prescription (adjusted)	0.0743 (0.0005)	0.0759 (0.0006)	0.00155 (0.0001)	P < 0.000
Imputed QALYs for those not given a delayed prescription (adjusted)	0.0785 (0.0005)	0.0770 (0.0007)	-0.00149 (0.0001)	P < 0.000
Imputed QALYs with patients removed who experienced SAE or AE (adjusted) (n=562)	0.0768 (0.0004)	0.0767 (0.0005)	-0.00006 (0.00008)	P = 0.473
Imputed QALYs with patients removed who were over 70 years (adjusted) (n=551)	0.0766 (0.0004)	0.0765 (0.0005)	-0.000123 (0.00008)	P = 0.128
Imputed QALYs with patients who were current smokers only (adjusted) (n=103)	0.0738 (0.0008)	0.0768 (0.0010)	0.00294 (0.00018)	P < 0.000
Imputed QALYs at 24 hours, adjusted for baseline differences	0.00270 (0.000008)	0.00271 (0.000010)	0.00001 (0.000002)	P < 0.000
Imputed QALYs at 48 hours, adjusted for baseline differences in HRQoL	0.00535 (0.000025)	0.00538 (0.000031)	0.00003 (0.000005)	P < 0.000
Imputed QALYs at 48 hours, adjusted for baseline differences in HRQoL and RR of symptom resolution	0.00492 (0.000024)	0.00534 (0.000029)	0.000422 (0.000005)	P < 0.000

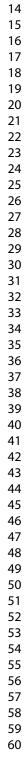
\*This sample size is based on 60 imputed data sets. SE: standard error.

# Table 3: Cost analysis

Cost Bundle Category	Description	Tot	al Cost 2015 U	JSD	Aver	age Cost 2015	USD
		Placebo	Dexa- methasone	(Dex- Placebo)	Placebo	Dexa- methasone	(Dex- Placebo)
Intervention	Cost associated with the intervention.	£12,188	£14,124	£1,936	£44	£49.04	£5.04
Antibiotics- Cohort A	Cost associated with antibiotics reported in patient survey, follow-up survey and medical records	£164	£138	-£26	£1	£0.48	-£0.11
Antibiotics- Cohort B	Cost associated with antibiotics reported in patient survey and medical records only.	£154	£128	-£26	£1	£0.44	-£0.11
Antibiotics- Societal	Cost associated with antibiotics inclusive of the patient co- payment for prescriptions.	£689	£581	-£108	£2	£2.02	-£0.47
Antibiotics B- Societal	Cost associated with antibiotics inclusive of the patient co- payment for prescriptions for Cohort B.	£646	£538	-£108	£2	£1.87	-£0.46
Antibiotics- Societal for Workers	Cost associated with antibiotics inclusive of the patient co- payment for prescriptions for workers only.	£623	£474	-£149	£2	£1.65	-£0.60
Antibiotics B- Societal for Workers	Cost associated with antibiotics inclusive of the patient co- payment for prescriptions for workers only in Cohort B.	£547	£431	-£116	£2	£1.50	-£0.48
Over-the-counter (OTC)	Cost associated with reported OTC in the patient diary and follow-up survey.	£668	£648	-£20	£2	£2.25	-£0.16
Resource Use- Patient Diary	Cost associated with resource use reported in the patient diary.	£2,639	£2,732	£93	£10	£9.49	-£0.04
Resource Use- Follow-up Survey	Cost associated with resource use reported in the follow-up survey.	£4,082	£4,008	-£74	£15	£13.92	-£0.82
Productivity Losses- Day 0-7 and Follow-up	Cost of missed days due to illness reported in the	£22,668	£19,469	-£3,199	£82	£67.60	-£14.23

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	patient diary and follow-up survey.						
Productivity Losses (B)- Day 0- 7 and Follow-up	Cost of missed days due to illness assuming all 18-21 year olds were in education.	£21,505	£18,634	-£2,871	£78	£64.70	-£12
Productivity Losses- Day 1-7 and Follow-up	Cost of missed days due to illness reported in the patient diary from day 1 and follow-up survey.	£14,846	£12,699	-£2,147	£54	£44.09	-£9.
Productivity Losses (B)- Day 1- 7 and Follow-up	Cost of missed days due to illness (from day 1) assuming all 18-21 year olds were in education.	£14,176	£12,140	-£2,036	£51	£42.15	-£9.
Usual Activities- Day 0-7 and Follow-up	Cost associated with missing time due to illness for usual activities reported in the patient dairy and follow-up survey.	£4,904	£5,052	£148	£18	£17.54	-£0.
Usual Activities- Day 1-7 and Follow-up	Cost associated with missing time due to illness (from day 1) for usual activities reported in the patient dairy and follow-up survey.	£3,444	£3,672	£228	£12	£12.75	£0.
Total HSP Costs- Primary Analysis		£19,073	£21,002	£1,929	£68.86	£72.92	£4.0
Total HSP Costs- without SAE's/ AEs (n=562) Option (A)		£15,610	£18,349	£2,739	£56.76	£63.93	£7.1
Total HSP Costs- Delayed Prescription		£5,830	£7,119.00	£1,289	£53.99	£61.90	£7.9
Total HSP Costs- No Delayed Prescription		£13,243	£13,883	£640	£78.36	£80.25	£1.8
Total HSP Costs- Smokers Only (n=103) Total SCP Option (I)		£6,059 £37,076	£2,787 £36,409	-£3,272 -£667	£118.81 £133.85	£53.60 £126.42	-£65. -£7.4
Total SCP without SAE's/ AEs (n=562)		£33,012	£33,726	-£667	£120.04	£117.51	-£2.5



Total SCP-	£12,995	£13,816	£821	£120.32	£120.14	-£0.18
Delayed						
Prescription						
Total SCP-	£24,081	£22,593	-£1,488	£142.49	£130.59	-£11.90
No Delayed		-				
Prescription						
Total SCP-	£8,739	£3,259	-£5,480	£171.35	£62.68	-£108.67
Smokers Only			,			
(n=103)						

NOTE: Cohort A has an additional 8 patients included who reported antibiotic use in follow-up surveys only.

Cohort B does not include these patients in keeping with the statistical analysis plan outlined for the clinical analysis. to beet terien only

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Table 4: Cost-utility analysis	(deterministic models)
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Scenarios <sup>a</sup>	Control	Intervention	∆ in Cost	∆ in Effect <sup>b</sup>	ICER	Interpretation <sup>c</sup>		
Healthcare Services Payer Perspective								
Basecase	£68.86	£72.92	£4.07	-0.00005	-£81,400	Not cost-effective		
Scenario A	£56.76	£63.93	£7.17	-0.00010	-£71,700	Not cost-effective		
Scenario B	£69.22	£73.37	£4.15	-0.00012	-£33,850	Not cost-effective		
Scenario C	£53.99	£61.90	£7.92	0.00160	£4,950	Cost-effective		
Scenario D	£78.36	£80.25	£1.89	-0.0015	-£1,260	Not cost-effective		
Scenario E	£57.58	£77.18	£19.60	0.0030	£6,533	Cost-effective		
Scenario F	£68.86	£72.92	£4.07	0.00001	£407,000	Not cost-effective		
Scenario G	£68.86	£72.92	£4.07	0.00042	£9,690	Cost-effective		
Scenario H <sup>d</sup>	£68.86	£72.92	£4.07	-0.0038	-£1,071	Not cost-effective		
Societal Cost Perspective								
Scenario I	£133.85	£126.42	-£7.43	-0.00005	£148,600	Not cost-effective		
Scenario J	£167.36	154.72	-£12.64	-0.00005	£252,800	Not cost-effective		
Scenario K	£120.04	£117.51	-£2.53	-0.00010	£25,300	Not cost-effective		
Scenario L	£135.51	£127.59	-£7.92	-0.00005	£158,400	Not cost-effective		
Scenario M	£135.23	£127.44	-£7.79	-0.00005	£155,800	Not cost-effective		
Scenario N	£120.32	£120.14	-£0.18	0.00160	-£112	Cost-effective & Cost-saving		
Scenario O	£142.49	£130.59	-£11.90	-0.00150	£7,933	Not cost-effective		
Scenario P	£171.35	£62.68	-£108.67	0.0030	-£36,223	Cost-effective & Cost-saving		
Scenario Q	£133.85	£126.42	-£7.43	0.00001	-£743,000	Cost-effective & Cost-saving		
Scenario R	£133.85	£126.42	-£7.43	0.00042	-£17,690	Cost-effective & Cost-saving		
Scenario S <sup>d</sup>	£133.85	£126.42	-£7.43	-0.0038	£1,955	Not cost-effective		

NOTES:

a. Full scenario details are presented in the supplementary file.

b. Changes in effect have been adjusted for baseline differences for each model and are representative of an annual timeframe (see Table 2 for more details).

c. Not cost-effective is suggested if the effect is negative and therefore the ICER is negative; not cost-effective <u>may</u> also be suggested when the ICER is positive due to both a negative cost and effect i.e. positioned in the South-West quadrant of the cost-effectiveness plane, depending on the WTP threshold. As the stated WTP threshold is £20,000 per QALY gain, all positive ICERs due to positive costs and effects that are over £20,000 are also deemed not cost-effective. Also note that confidence intervals were not reported as the analysis are deterministic and non-linear; therefore confidence intervals could not be meaningfully interpreted. d. Average unadjusted EQ-VAS scores across baseline to day 7 are presented in the online appendix. After adjustments for imbalance at baseline, the incremental effect was negative at -0.174 at day 7. The change in effect presented in the table above has been adjusted to represent an annual timeframe consistent with cost per QALY interpretation.

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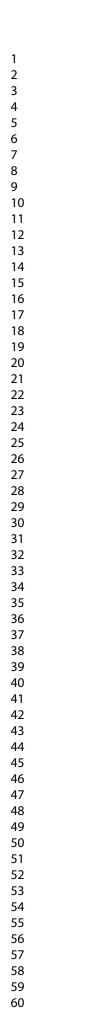
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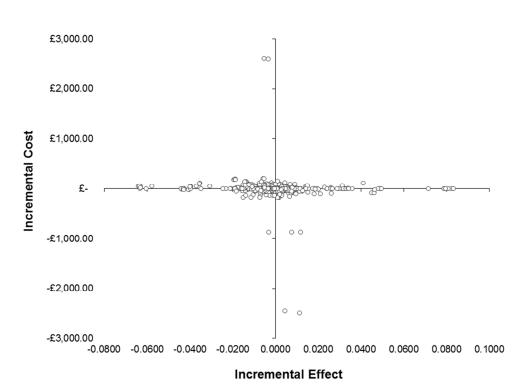
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## **TOAST ONLINE APPENDIX**

#### Table A1- Trial Resource Use Costs

Cost ID	Cost Description	2015 (£)	Measure	Details
Int1	Oral Steroid	£ 5.04	1 dose	single 10mg dose of oral dexamethasone, BNF 2015
Int2	GP Visit	£ 44.00	11.7 minute consult	PSSRU 2015
Int3	Pharmacist	£ 6.00	5 minute consult	British National Formulary (BNF) 2015
Anti1	Penicillin	£ 0.04	per 250mg tab	BNF 2015
Anti2	Erythromycin	£ 0.04	per 250mg tab	BNF 2015
Anti3	Clarithromycin	£0.21	per 500mg tab	BNF 2015
Anti4	Amoxicillin	£ 0.08	per 500mg tab	BNF 2015
Anti5	Coamoxiclav	£ 0.20	per 500mg tab	BNF 2015
Anti6	Doxycycline	£ 0.14	per 500mg tab	BNF 2015
Otc1	Paracetamol	£ 0.24	per recommended daily dose	Boots Pharmacy Generic Bran 2015
Otc2	Ibuprofen (NSAIDS)	£ 0.60	per recommended daily dose	Boots Pharmacy Generic Bran 2015
Otc3	Anaesthetic spray	£ 1.25	per recommended daily dose	Boots Pharmacy Generic Bran 2015
Otc4	Anaesthetic lozenges	£ 1.40	per recommended daily dose	Boots Pharmacy Generic Brar 2015
Otc5	Decongestant	£ 1.00	per recommended daily dose	Boots Pharmacy Generic Brar 2015
Otc6	Lozenges (non-analgesic)	£ 0.66	per recommended daily dose	Boots Pharmacy Generic Brar 2015
Otc7	Other analgesia (cocodamol/	£ 1.05	per recommended	Boots Pharmacy Generic Bran
Wage1	cough medicine, etc.) Cost of an adult working day	£ 119.37	daily dose median gross annual earnings	2015 Office of National Statistics (UK)
Wage2	Minimum wage day rate	£ 53.60	October 2015 value	Office of National Statistics (UK)
Admin1	NHS prescription charge	£ 8.20		National Health Service (UK)- (NHS)
Res1	GP Nurse	£ 14.47	15.5 minute consult	PSSRU 2015
Res2	GP Telephone Call	£ 27.00	7.1 minute call	PSSRU 2015
Res3	Out-of-Hours GP Clinic	£ 69.53		NAO.org
Res4	111 Telephone Advice	£ 8.14		Micro-costing study, Universi of Sheffield
Res5	A&E	£ 140.59	Average weighted cost	NHS Ref Costs 2015
Res6	Hospital Bed Day – average	£ 613.63	Average weighted cost	NHS Ref Costs 2015
Pres1	Codeine (co-codamol 30/500)	£ 0.06	per tablet	BNF 2015
Pres2	Codeine Linctus	£ 0.16	15mg/ 5 ml	BNF 2015
Pres3	Benzydamine (Difflam Oromucosal Spray)	£ 1.41	0.15% Spray/ 1 ml	BNF 2015
Pres4	Benzyl Penicillin & Metronidazole IV	£ 12.24	Daily dose (TBC)	BNF 2015

Table A2- Summary of Economic Analysis Scenarios

Options	Perspective	Details
Basecase	HSP	The basecase scenario included the net cost of the intervention i.e. the cost of the once-off medication, the cost of antibiotics used and the cost of resource use reported including serious adverse events. The adjusted QALY estimate was adopted as the outcome measure.
Α	HSP	Basecase was adjusted to remove effects and costs of serious adverse events (one in each arm) and adverse events (one in the control group) (n=562).
В	HSP	Basecase was adjusted to remove those over age 70 (seven in each arm removed) (n=551).
С	HSP	Basecase was restricted to only those who received a delayed prescription (n=223).
D	HSP	Basecase was restricted to those who did not receive a delayed prescription (n=342).
E	HSP	Basecase was restricted to only those reporting current smoker status (n=103).
F	HSP	Basecase was adjusted and the imputed EQ-5D-5L differences from baseline at 24 hours were used as the outcome measure.
G	HSP	Basecase was adjusted and the imputed EQ-5D-5L differences from baseline at 48 hours were used as the outcome measure.
н	HSP	Basecase was adjusted and the imputed EQ-VAS averages from baseline to Day 7 were used as the outcome measure.
I	SCP	Basecase was combined with costs associated with over-the-counter medications used , productivity losses due to missed days at work/ school for days 1 to 7 of the trial follow-up and costs associated with inability to carry out usual activities for days 1 to 7.
J	SCP	Basecase was combined with costs associated with over-the-counter medications used , productivity losses due to missed days at work/ school for days 0 to 7 of the trial follow-up and costs associated with inability to carry out usual activities for days 0 to 7.
К	SCP	Option I was adjusted to remove costs of serious adverse events (one in each arm) and adverse events (one in the control group) (n=562).
L	SCP	Option I was combined with antibiotic prescription charges that would be paid by workers/ students.
М	SCP	Option I was combined with antibiotic prescription charges that would be paid by workers only.
Ν	SCP	Option I was restricted to only those who received a delayed prescription (n=223).
0	SCP	Option I was restricted to those who did not receive a delayed prescription (n=342).
Р	SCP	Option I was restricted to only those reporting current smoker status (n=103).
Q	SCP	Option I adopted the outcome measured at 24 hours
R	SCP	Option I adopted the outcome measured at 48 hours
S	SCP	Option I was adjusted and the imputed EQ-VAS averages from baseline to Day 7 were used as the outcome measure.

# Table A3: Summary of multiple imputation analysis methods

1	
2	The following variables were used in the multiple imputation dataset:
3	
4 5	
6	• EQ-5D-5L index values for day 0-7
7	• EQ-VAS scores for day 0-7
8	Symptom resolution at 24 hours and 48 hours
9	A treatment arm identifier
10	<ul> <li>A dichotomous variable to highlight patient experienced an SAE</li> </ul>
11 12	<ul> <li>A dichotomous variable for delayed antibiotic prescription given</li> </ul>
12	• Costs: intervention, antibiotics, OTC medication, resource use day 1-7, resource use day 8-
14	28, missed work/ education, missed usual activities
15	• Patient characteristics: gender, age, employment status, location of care, current smoker, a
16	dichotomous variable for those aged 71 and over.
17	
18	
19	The 'ICE' command in STATA was used for multiple imputation using chained equations was used. The data
20	
21 22	was multiply imputed generating 60 datasets using predictive mean matching and separately by treatment
23	allocation based on the variation present in the complete data above. The 'seed' add-on sets a random
24	number seed (this was set at 10), which is useful to improve consistency across imputations.
25	
26 27	The falle in it is a state and
27 28	The following is the STATA code used:
20	"ico index EL dayO index EL day1 index EL day2 index EL day2 index EL day5
30	<pre>"ice index_5L_day0 index_5L_day1 index_5L_day2 index_5L_day3 index_5L_day4 index_5L_day5 index_5L_day6 index_5L_day7 VAS_day0 VAS_day1 VAS_day2 VAS_day3 VAS_day4 VAS_day5 VAS_day6</pre>
31	VAS_day7 sae outlier resol48 cost_reportedantibiouse totalcost_OTC resourceusediary_cost
32	resourceuseFU_cost missed_days_costday1tounk cost_usualact1tounk trt delayed_script Male worker age
33	current_smoker location age71andover, saving(MI_aggregated, replace) m(60) match genmiss(indmiss)
34 35	by(trt) seed(10)"
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8	3
59 50	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table A4: Quality of Life Analysis for ITT Impute Cohort (unadju	ısted)
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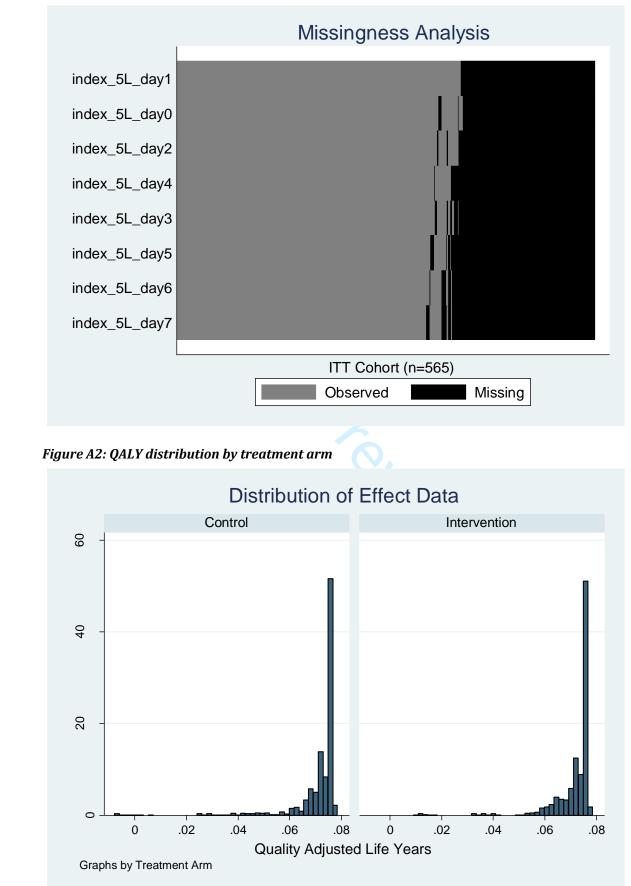
	E	Q-5D-5L Imputed Full	ІТТ	
	Control	Intervention	Diff (I-C)	% Δ (I-C)
Baseline	0.746	0.766	0.0196	2.62%
Day 1	0.829	0.848	0.0189	2.28%
Day 2	0.861	0.871	0.0092	1.07%
Day 3	0.904	0.907	0.0023	0.25%
Day 4	0.918	0.931	0.0132	1.43%
Day 5	0.932	0.940	0.0074	0.79%
Day 6	0.939	0.950	0.0112	1.19%
Day 7	0.947	0.949	0.0028	0.30%
QAW <sup>1</sup>	6.289	6.354	0.0652	1.04%
		EQ-5D VAS Imputed Fu	ull ITT	
	Control	Intervention	Diff (I-C)	% Δ (I-C)
Baseline	49.78	52.41	2.631	5.29%
Day 1	57.99	60.83	2.840	4.90%
Day 2	64.44	64.57	0.126	0.19%
Day 3	70.98	70.27	-0.714	-1.01%
Day 4	74.74	74.35	-0.389	-0.52%
Day 5	78.66	77.16	-1.497	-1.90%
Day 6	81.99	80.25	-1.733	-2.11%
Day 7	84.94	82.37	-2.571	-3.03%
aVAS <sup>2</sup>	70.44	70.27	-0.162	-0.23%
	Delaye	d Prescription- Impute	d ITT Cohort	
	Control	Intervention	Diff (I-C)	% ∆ (I-C)
Baseline	0.7431	0.7303	-0.0128	-1.72%
Day 1	0.8158	0.8404	0.0246	3.01%
Day 2	0.8384	0.8576	0.0193	2.30%
Day 3	0.9061	0.9180	0.0119	1.31%
Day 4	0.9180	0.9441	0.0261	2.85%
Day 5	0.9276	0.9579	0.0303	3.27%
Day 6	0.9390	0.9649	0.0259	2.76%
Day 7	0.9480	0.9663	0.0183	1.93%
QAW <sup>1</sup>	6.2569	6.3943	0.1374	2.20%
	No Delay	ed Prescription- Impu	ted ITT Cohort	
	Control	Intervention	Diff (I-C)	% Δ (I-C)
Baseline	0.7480	0.7892	0.0411	5.50%
Day 1	0.8381	0.8535	0.0154	1.84%
Day 2	0.8762	0.8793	0.0031	0.35%
Day 3	0.9035	0.8993	-0.0041	-0.46%
Day 4	0.9179	0.9225	0.0046	0.50%
Day 5	0.9351	0.9273	-0.0078	-0.83%
Day 6	0.9382	0.9396	0.0014	0.14%
Day 7	0.9457	0.9382	-0.0075	-0.79%
QAW <sup>1</sup>				

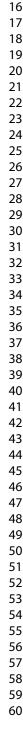
2. Average VAS score estimated average across baseline to day 7.

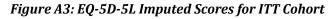
	EQ-5D-5L Analysi	s		
	Control	Intervention	Difference (I-C)	P value
	n=172	n=165		
Baseline	0.735	0.755	0.021	ns
Day 1	0.821	0.843	0.021	ns
Day 2	0.862	0.871	0.01	ns
Day 3	0.899	0.903	0.004	ns
Day 4	0.916	0.926	0.01	ns
Day 5	0.929	0.933	0.003	ns
Day 6	0.939	0.947	0.007	ns
Day 7	0.947	0.951	0.004	ns
Average (Day 1-7)	0.902	0.91	0.008	ns
Average Δ (%) from Baseline	0.167 (22.7)	0.155 (20.5)	-0.012	ns
Average $\Delta$ (%) from Baseline at 24 hrs	0.087 (11.8)	0.087 (11.5)	0	ns
Average $\Delta$ (%) from Baseline at 48 hrs	0.107 (14.6)	0.101 (13.4)	-0.005	ns
	EQ-VAS Analysis			
	Control	Intervention	Difference (I-C)	P valu
	n=166	n=161	( - )	
Baseline	49	52	3	ns
Day 1	57	61	4	ns
Day 2	64	65	1	ns
Day 3	70	70	0	ns
Day 4	75	74	-1	ns
Day 5	79	77	-2	ns
Day 6	82	80	-2	ns
Day 7	86	83	-3	ns
Average (Day 1-7)	73	73	0	ns
Average $\Delta$ (%) from Baseline	24 (49)	21 (40)	-3	ns
Average $\Delta$ (%) from Baseline at 24 hrs	8 (16)	9 (17)	1	ns
Average $\Delta$ (%) from Baseline at 48 hrs	15 (31)	13 (25)	-2	ns
				-
	EQ-5D-5L Sub-gro Delayed Script	No Delayed	Difference	P value
	Delayed Script	Script	(Delayed-No Script)	i valu
	n=121	n=216		
Baseline	0.709	0.765	-0.055	0.005
Day 1	0.813	0.842	-0.029	0.059
Day 2	0.878	0.846	-0.032	0.041
Day 3	0.903	0.9	0.003	ns
Day 4	0.925	0.919	0.006	ns
Day 5	0.935	0.929	0.006	ns
Day 6	0.948	0.94	0.008	ns
Day 7	0.959	0.943	0.016	ns
Average (Day 1-7)	0.904	0.907	-0.003	115
Average (Day 1-7) Average $\Delta$ (%) from Baseline	0.195 (27.5)	0.907	0.052	0.001
	0.119 (20.7)	0.092 (14.1)	0.027	ns
Average $\Delta$ (%) from Baseline at 24 hrs				

Table AF, Quality of Life Analysis for Complete Cases (unadjusted)

Figure A1: Missingness assessment in EQ-5D-5L







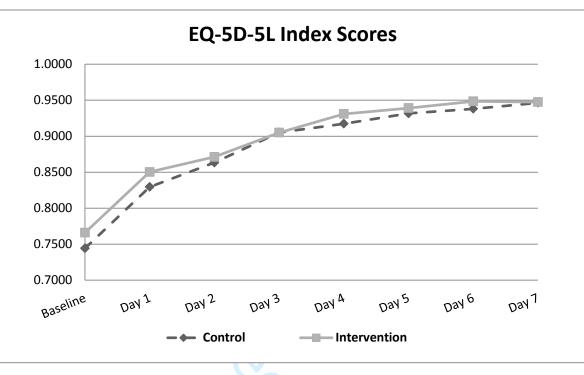
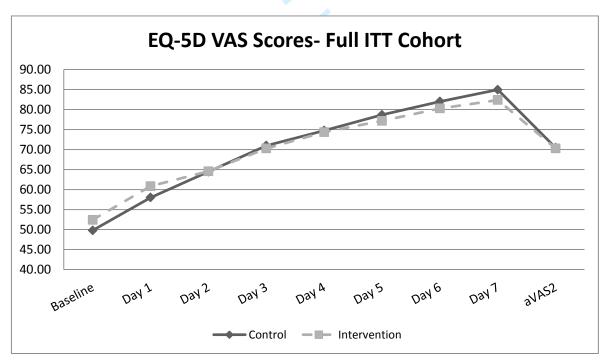
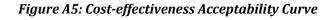
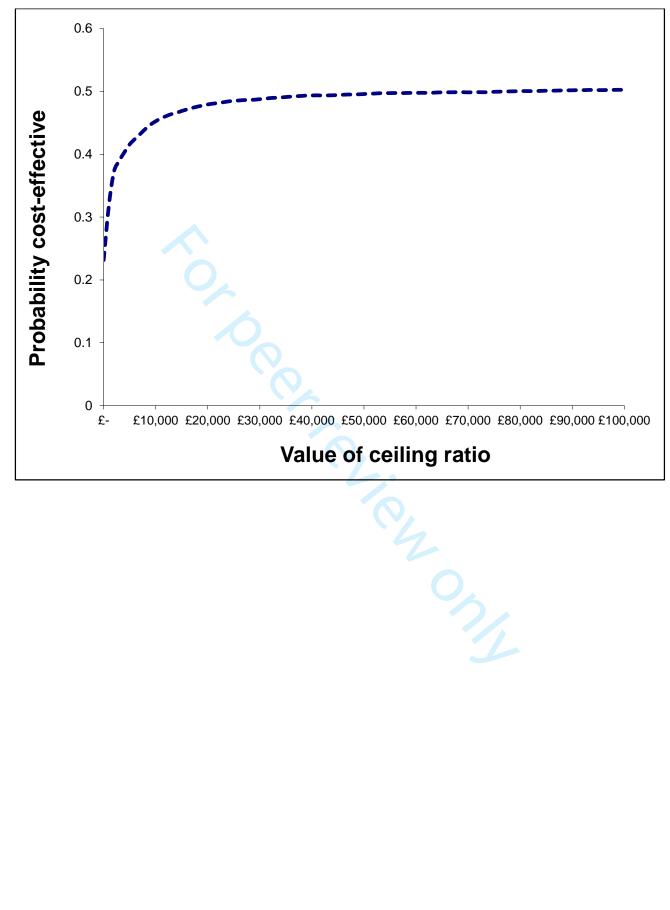


Figure A4: EQ-5D Visual Analogue Scale Imputed Scores for ITT Cohort







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Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 1

<sup>1</sup> "	"An ECONOMIC Analysis OF ORAL Dexa methasone for Symptom Rehel OF SORE THROAT: The UK TOWST STUDY " The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been
2 🔭	OF SORE THROAT THE UK TOAST STUDY !!
3	The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been
4	endorsed and co-published by the following journals:
5 6	
7	BJOG: An International Journal of Obstetrics and Gynaecology
8	BMC Medicine 2013; 11:80
9	<u>BMJ 2013;346:f1049</u>
10	<u>Clinical Therapeutics 27 March 2013 (Article in Press DOI: 10.1016/j.clinthera.2013.03.003)</u>
11	Cost Effectiveness and Resource Allocation 2013 11:6.
12	The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print]
13 14	International Journal of Technology Assessment in Health Care
14	Journal of Medical Economics 2013 Mar 25. [Epub ahead of print]
16	Pharmacoeconomics 2013 Mar 26. [Epub ahead of print]
17	Value in Health 2013 March - April;16(2):e1-e5
18	
19	CHEERS Checklist
20	Items to include when reporting economic evaluations of health interventions
21	
22	

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1   1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	3\$4
Introduction			
Background and	3	Provide an explicit statement of the broader context for the	
objectives		study.	
		Present the study question and its relevance for health policy or practice decisions.	5
Methods		,	
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	6
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	9	Report the choice of discount rate(s) used for costs and	nla



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Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 2

		outcomes and say why appropriate.	6
Choice of health	10	Describe what outcomes were used as the measure(s) of	
outcomes		benefit in the evaluation and their relevance for the type of analysis performed.	ja7
Measurement of	11a	Single study-based estimates: Describe fully the design	
effectiveness		features of the single effectiveness study and why the single	728
		study was a sufficient source of clinical effectiveness data.	440
	11b	Synthesis-based estimates: Describe fully the methods used for	
		identification of included studies and synthesis of clinical	nla
Measurement and	1 12	effectiveness data. If applicable, describe the population and methods used to	
valuation of prefe		elicit preferences for outcomes.	
based outcomes			nla
Estimating resour	rces 13a	Single study-based economic evaluation: Describe approaches	
and costs		used to estimate resource use associated with the alternative	
		interventions. Describe primary or secondary research methods	
		for valuing each resource item in terms of its unit cost.	5
		Describe any adjustments made to approximate to opportunity	+
	1.01	costs.	
	13b	Model-based economic evaluation: Describe approaches and	
		data sources used to estimate resource use associated with	
		model health states. Describe primary or secondary research	
		methods for valuing each resource item in terms of its unit	h
		cost. Describe any adjustments made to approximate to	+
Curronau prica d	ate, 14	opportunity costs. Report the dates of the estimated resource quantities and unit	
Currency, price d and conversion	ale, 14	costs. Describe methods for adjusting estimated unit costs to	
		the year of reported costs if necessary. Describe methods for	
		converting costs into a common currency base and the	1
		exchange rate.	Ъ
Choice of model	15	Describe and give reasons for the specific type of decision-	
		analytical model used. Providing a figure to show model	949410
		structure is strongly recommended.	899910
Assumptions	16	Describe all structural or other assumptions underpinning the	8 ब 9 a l
		decision-analytical model.	
Analytical metho	ds 17	Describe all analytical methods supporting the evaluation. This	
		could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling	
		data; approaches to validate or make adjustments (such as half	
		cycle corrections) to a model; and methods for handling	
	×	population heterogeneity and uncertainty.	849410
Dogulta		, , ,	
Results Study parameters	18	Report the values, ranges, references, and, if used, probability	
Study parameters	10	distributions for all parameters. Report reasons or sources for	
		distributions used to represent uncertainty where appropriate.	
		Providing a table to show the input values is strongly	12-12
		recommended.	10-1
		3	10-12 Online appendi
			and
		(SPOR	appendi

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**BMJ** Open Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 3

Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	10-12 21-25
Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	11-12 25
		of methodological assumptions (such as discount rate, study perspective).	25
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty	11-12 25
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between	11-12
		other observed variability in effects that are not reducible by more information.	25
<b>Discussion</b> Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	13 - 15
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	16
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with	(1-17
For consistency, the Cl	HEERS	International Committee of Medical Journal Editors recommendations.	
	outcomes Characterising uncertainty Characterising heterogeneity <b>Discussion</b> Study findings, limitations, generalisability, and current knowledge <b>Other</b> Source of funding Conflicts of interest	outcomesCharacterising uncertainty20a20b20bCharacterising heterogeneity21Discussion Study findings, limitations, generalisability, and current knowledge22Other Source of funding23Conflicts of interest24	outcomescategories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.Characterising uncertainty20aSingle study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).20bModel-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.Characterising heterogeneity21If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.Discussion Study findings, generalisability, and current knowledge22Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.Other Source of funding23Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.Conflicts of interest24Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The CHEERS Statement may be accessed by the publication links above.

The ISPOR CHEERS Task Force Report provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the Value in Health link or via the ISPOR Health Economic Evaluation Publication Guidelines - CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

