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

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

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Abstract

Objectives: To undertake an economic analysis assessing the cost-effectiveness of a single dose of oral dexamethasone compared to placebo for the relief of sore throat.

Design: A UK-based, multicentre, two arm, individually randomised, double blind trial

Setting and Population: Adults (≥18 years) with acute sore throat and painful swallowing judged to be infective in origin, recruited and randomised in primary care.

Intervention: A single dose of 10mg oral dexamethasone compared to placebo given at primary care visit.

Main Outcome: Incremental cost-effectiveness ratios (ICERs), cost per quality-adjusted symptom resolution using the EQ-5D-5L instrument, were estimated as part of a cost-utility analysis performed on an intention-to-treat cohort adopting a health payers perspective.

Results: Differences in health-related quality of life (HRQoL) over 7 days from baseline and at 24 hours in the dexamethasone compared with the placebo group (2.9% and 2.5% higher, respectively) were observed. After controlling for the baseline HRQoL imbalances, the impact of the intervention was negative but not 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) and the median ICER was -£304 (IQR:-£5,816; £3,877); suggesting considerable uncertainty.

Conclusions and relevance: The economic burden associated with sore throat is substantial and was estimated at £2.35bn to the healthcare services payer based on reported resource use and 2015 UK unit costs. There is considerable uncertainty regarding the cost-effectiveness of a single dose of oral dexamethasone as a treatment strategy and therefore insufficient evidence to support its use in clinical practice.

Trial Registration: ISRCTN17435450 http://www.isrctn.com/ISRCTN17435450

Key words: cost-utility analysis, primary care interventions, sore throat

Strengths and limitations of this study

1. The analysis undertaken provides the first detailed account of the cost of sore throat in the UK.
2. 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.
3. Both health services payer and societal perspectives were assessed in the economic evaluation.
4. 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.

Introduction

An estimated £400 million annually is spent on consultations and lost productivity associated with sore throat alone in the UK.[1,2] Almost one in ten registered UK patients will see their general practitioner (GP) every year with sore throat.[3] 91% of those diagnosed with tonsillitis will receive antibiotics, as will half of those recorded as 'sore throat' or 'pharyngitis'.[4] NICE and International guidance recognises the limited evidence for benefit of antibiotics in its advice to avoid prescriptions in the majority of patients[5-6]; however, prescribing rates remain disproportionately high even though patients attend mainly due to anxiety over symptoms.[7] 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[8] 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[9], could also be moderated. The Treatment Options without Antibiotics for Sore Throat (TOAST) trial[10] 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.

Methods

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[1] 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.[6]

Outcome Measure

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 level (EQ-5D-5L) index. These outcomes informed the construction of a quality-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

[1] 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.

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

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.

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[13], British National Formulary[14], Boots Chemist[15], and the NHS Electronic Tariff Database[16] and are reported in UK currency. Productivity losses were costed using average wage rates for those employed and minimum wage rates for students.[17] All cost estimates were reported in 2015 GBP using appropriate adjustments for prices retrieved where necessary.[18] Disaggregated average cost estimates reported were based on the full cohort in the ITT analysis assuming non-responders had zero costs.

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[19], 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

prescription administrative charge is not applied to everyone and the full amount may not be recouped by the HSP.[20] In the scenario analyses, a societal costing perspective (SCP) was also adopted reflecting the overall economic burden of the dexamethasone relative to the placebo. This included productivity losses due to sick days i.e. reported time off due to missed work or education and reported inability to carry out usual activities, and OOP expenses. Further scenarios assessed sub-groups based on patient characteristics. The sub-group who highlighted they were current smokers at the time of the trial were assessed in a scenario analysis due to the extra healthcare burden smokers have relative to non-smokers.[21] Descriptions of all 20 analyses are presented in the ***Online Appendix*** (Table A2).

Each element of costs and outcomes were reported separately, consistent with a cost-consequence analysis; the resource use reported was for the full ITT cohort (i.e. no missing resource use data) and the HRQoL data reported in the disaggregated format was for complete cases i.e. n=337; 60% of the full cohort. Missing HRQoL data was assessed and classified as missing at random (MAR) (see ***Online Appendix***- Figure A1).[16] Multiple imputation analysis was performed for missing outcome data (40%) in the ITT cohort using a number of imputations (n=60) greater than the proportion of missing data.[22] The range of covariates included in the multiple imputation analysis along with a more comprehensive presentation of methods is presented (see ***Online Appendix***- Table A3***)***. The trial and follow-up duration was 28 days in total and for consistency it was assumed that HRQoL was unchanged from day 7 to day 28 using the last value brought forward technique.[23] The average utility from baseline reported across the 28 days, calculated using area under the curve (AUC) was considered 1/13th of a quality adjusted life year (QALY). Baseline variation in outcomes was adjusted for incorporating multiple regression

and seemingly unrelated regression techniques which estimated the baseline imbalance taking into account costs and effects. [16, 24] QALYs exhibited a non-normal distribution (see ***Online Appendix***- Figure A2***)*** and bootstrapping techniques using 1,000 iterations were applied in Microsoft Excel.[25] Cost-utility analysis was undertaken and incremental cost-effectiveness ratios (ICERs) were estimated and reported for the basecase analysis and all scenario analyses. ICERs were probabilistic for the basecase analysis and deterministic for the series of scenarios estimated. The analysis was undertaken in Stata version 14.1.[26] A cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) were constructed based on the bootstrapped sample means and net monetary benefit (NMB) was also assessed against a range of willingness to pay thresholds up to £100,000.[27] The NICE willingness to pay threshold of £20,000 was adopted as a decision rule to assess cost-effectiveness.[27]

Results

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 participants was 37 years and 75% were women. There was no significant clinical difference in median time to complete symptom resolution across trial arms with both displaying complete symptom resolution by day 4; however, there was a significant difference in symptom resolution at 48 hours.[28] The changes in HRQoL over the 7 days highlight larger differences at baseline and at 24 hours with the dexamethasone group reporting 2.9% and 2.5% higher utility scores, respectively (see ***Online***

Appendix- Figure A3). Differences start to diminish (<1.5%) from day 2 onwards. ***Table 2*** highlights the differences in estimated QALYs for the imputed ITT cohort. After controlling for the baseline imbalances in HRQoL, the impact of the intervention was negative but not statistically significant: the QALY gain was -0.00005 (95% CI: -0.0002; 0.00011) equivalent to a loss in HRQoL of a half hour for the dexamethasone relative to the placebo group.

For the sub-group who received the delayed prescription based on clinical need, a statistically significant benefit was evidenced after baseline imbalances were adjusted for resulting in an approximate HRQoL gain of 13.6 hours relative to the control group. For the sub-group who did not receive the prescription, the dexamethasone group indicated a significant QALY loss of approximately 13 hours relative to the placebo group. For the patient group who reported that they were current smokers a significant QALY gain from the dexamethasone of 0.0029, equivalent to 1 day was evidenced. At 48 hours where a significant difference in the risk ratio of symptom resolution at 48 hours in favour of the dexamethasone [RR: 1.31 (95% CI, 1.02 to 1.68; P = .03)] was observed, the significant QALY gain approximated to 3.7 hours for the current smokers sub-group.

The average cost per patient associated with the dexamethasone and placebo groups in the basecase analysis adopting a HSP was £73 and £69, respectively. ***Table 3*** highlights total costs for the categories included in the economic evaluation. Average costs were higher across both trial arms for the sub-group who did not receive the delayed prescription relative to the sub-group who did (£24 and £18 higher in the placebo and dexamethasone groups respectively) driven by higher health service utilisation; however no statistically significant impact on costs across these sub-groups for the HSP was found. For the SCP, including the cost associated

with inability to carry out usual activities (Scenario I), the average cost per patient was £126 and £134 for the dexamethasone and placebo groups, respectively. This suggests a cost-saving of £7 per patient to society. For the sub-group who received the delayed prescription there was a negligible SCP reduction in the dexamethasone group of -£0.18; however, for those who did not receive the delayed prescription the SCP reduction for the substantial at -£12 signalling strong evidence of cost-savings from the use of oral dexamethasone compared to placebo.

In the deterministic basecase analysis (***Table 4***), the ICER was negative at -£81,400 due to the size and sign of the incremental effectiveness. In the basecase probabilistic analysis, the mean ICER was -£6,440 (95% CI: -£132,151; £126,335) and the median ICER was -£304 (IQR:-£5,816; £3,877); suggesting there is considerable uncertainty around this estimate. Several societal scenarios highlighted the potential for cost-savings; however, due to outcome variability, there is insufficient evidence to suggest the dexamethasone is cost-effective. The cost-effectiveness plane (***Figure 1***) presents a visual representation of the spread of the variation in cost and effect pairs for the basecase probabilistic analysis emphasizing the wide variation in effectiveness. Due to this uncertainty, the cost-effectiveness 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

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[29] and one in ten due to sore throat[4], 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 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

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

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 data collection was a patient completed diary at each day of the trial follow-up: HRQoL over the 7 days was 60% complete and the resource use reported in diaries was 62% complete. 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. However, EQ-5D-5L data was collected from the patient survey only and missing data was considerable at 40%. Although robust multiple imputation techniques were applied to impute values, it is recognised that the range of covariates used to impute missing data may not reflect the degree of heterogeneity across the patient cohort. If the imputation model was mis-specified the imputation estimates could have some degree of bias.[31] Due to the high uncertainty around observed HRQoL estimates across both arms however, the limitations associated with multiple imputation are not cause for concern. In the analyses adopting a SCP, self-reported data on time unable to engage in usual activities and OTC medications purchased were not imputed for those with missing 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 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

appropriately powered trials. However, the sub-group analyses give greater understanding of the wide variation in outcomes observed.

Conclusions and policy implications

In conclusion, sore throat has a substantial economic burden on health care delivery systems with this study estimating the economic burden from a HCP in the UK at £2.35bn annually. More effective strategies for assessing and providing rapid 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 and therefore insufficient evidence to suggest cost-effectiveness or its adoption as a viable treatment strategy. However, there was evidence suggestive of potential benefits in several sub-groups which could be investigated further in follow-up trials.

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2) Department of Medicine, University of Southampton

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We have read and understood BMJ Open policy on declaration of interests and declare that we have no competing interests

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

Contribution Statement:

All authors contributed to: the conception and design of the TOAST trial analysis including guidance on the health economic evaluation; the drafting and revising of this manuscript; approval of the final version of the manuscript and are accountable for all aspects of the work presented.

Each author has particular areas of expertise as follows: applied economic evaluation leads – RB & JW (joint first authors), statistical analysis SJ, NW & RP, project management, project conception, design and clinical lead- GH, clinical leadership and guidance, interpretation and policy interpretation- AH, MT, CH, PL, MM.

This research presents an honest, accurate, and transparent account of the economic evaluation of the TOAST UK study; no relevant aspects of the study have been omitted and the wide range of scenario analyses addresses both the clinical heterogeneity and variability in structural assumptions.

FIGURES AND TABLES

Figure 1: Cost-effectiveness plane

Table1: TOAST trial patient characteristics

	Placebo Group	Dexamethasone Group
All Eligible Participants (ITT)	**277 (49%)**	**288 (51%)**
Male	73 (13%)	67 (12%)
Female	204 (36%)	221 (39%)
Mean Age[a]	37.3 (SD: 14.30)	37.2 (SD: 14.36)
Current Smoker	51 (9%)	52 (9%)
ANTIBIOTIC DETAILS[b]		
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[c]	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[d] (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.

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)

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	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

	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	-£12.93
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

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

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.

Table 4: Cost-utility analysis (deterministic models)

	Control	*Intervention*	Δ in Cost	Δ in Effect[a]	ICER	Interpretation[b]
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[c]	£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[c]	£133.85	£126.42	-£7.43	-0.0038	£1,955	*Not cost-effective*

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 may 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.

REFERENCES

[1] Roos K, Claesson R, Persson U, Odegaard K. The economic cost of a streptococcal tonsillitis episode Scandinavian Journal of Primary Healthcare 1995 13: 257-260

[2] HMSO Morbidity Statistics in General practice : Fourth national Study HMSO 1994

[3] Gulliford M, Latinovic R, Charlton J, Little P, van Staa T, Ashworth M. Selective decrease in consultations and antibiotics prescribing for acute respiratory tract infection sin UK primary care up to 2006. Journal of Public Health 2009; 31(4), 512-520

[4] Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. Cochrane Database Systematic Reviews 2006; (4):CD000023.

[5] NICE guideline. Respiratory Tract Infections - antibiotic prescribing. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. 2008. National Institute for Clinical Excellence. Ref Type: Report.

[6] Centers for Disease Control and Prevention. Get Smart: Know When Antiobiotics Work in Doctor's Offices: Adult Treatment Recommendations. https://www.cdc.gov/getsmart/community/for-hcp/outpatient-hcp/adult-treatment-rec.html last updated: March 2016. Accessed June 19, 2017

[7] Guilliford MC, Dregan A, Moore M et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. BMJ Open 2014; 4(10)

[8] Hayward G, Thompson M, Heneghan C, Perera R, Del Mar C, Glasziou P. Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. BMJ 2009; 339:b2976

[9] Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ.* 2010;340(May18_2):c2096

[10] Cook J, Hayward G, Thompson M, et al. Oral corticosteroid use for clinical and cost-effective symptom relief of sore throat: study protocol for a randomized controlled trial. Trials 2014; 15, 365
DOI: 10.1186/1745-6215-15-365

[11] Devlin N, Krabbe P. "The development of new research methods for the valuation of EQ-5D-5L." European Journal of Health Economics 2013; 14(1): S1-S3

[12] Devlin N, et al 2016 Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. Office of Health Economics research paper 16/01

[13] PSSRU "Unit Costs of Health and Social Care 2015" http://www.pssru.ac.uk/project-pages/unit-costs/2015/

[14] British National Formulary (2015) https://www.medicinescomplete.com/mc/bnf/current/

[15] Boots Online Pharmacy (2015) www.boots.com

[16] Department of Health Reference Cost 2014/2015; London 2015

[17] Office of National Statistics. Annual Survey of Hours and Earnings, 2014. www.ons.gov.uk Accessed June 6, 2017

[18] Office of National Statistics. Consumer Price Inflation Index. www.ons.gov.uk Accessed June 6, 2017

[19] Pharmaceutical Services Negotiating Committee. Exemptions from the prescription charge. http://psnc.org.uk/dispensing-supply/receiving-a-prescription/patient-charges/exemptions/ Accessed June 9, 2017

[20] NHS Choices. NHS in England- help with health costs. http://www.nhs.uk/NHSEngland/Healthcosts/Pages/Prescriptioncosts.aspx Accessed June 6, 2017

[21] Wacker M, Holle R, Heinrich J, et al. The association of smoking status with healthcare utilisation, productivity loss and resulting costs: results from the population-based KORA F4 study. BMC Health Services Research 2013; 13:278

[22] Faria R, Gomes M, Epstein D, et al. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. Pharmacoeconomics 2014; 32(12):1157-70.

[23] Hunter R, Baio G, Butt T, Morris S, Round J, Freemantle N. An Educational Review of the Statistical Issues in Analysing Utility Data for Cost-Utility Analysis. Pharmacoeconomics 2015; 33(4): 355-366

[24] Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Economics 2005; 14(5):487-96.

[25] Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. Handbooks in Health Economics, Volume 2. Oxford: Oxford University Press, 2015

[26] StataCorp. Stata Statistical Software: Release 14. 14.1 ed. College Station, TX: StataCorp LP. ; 2015.

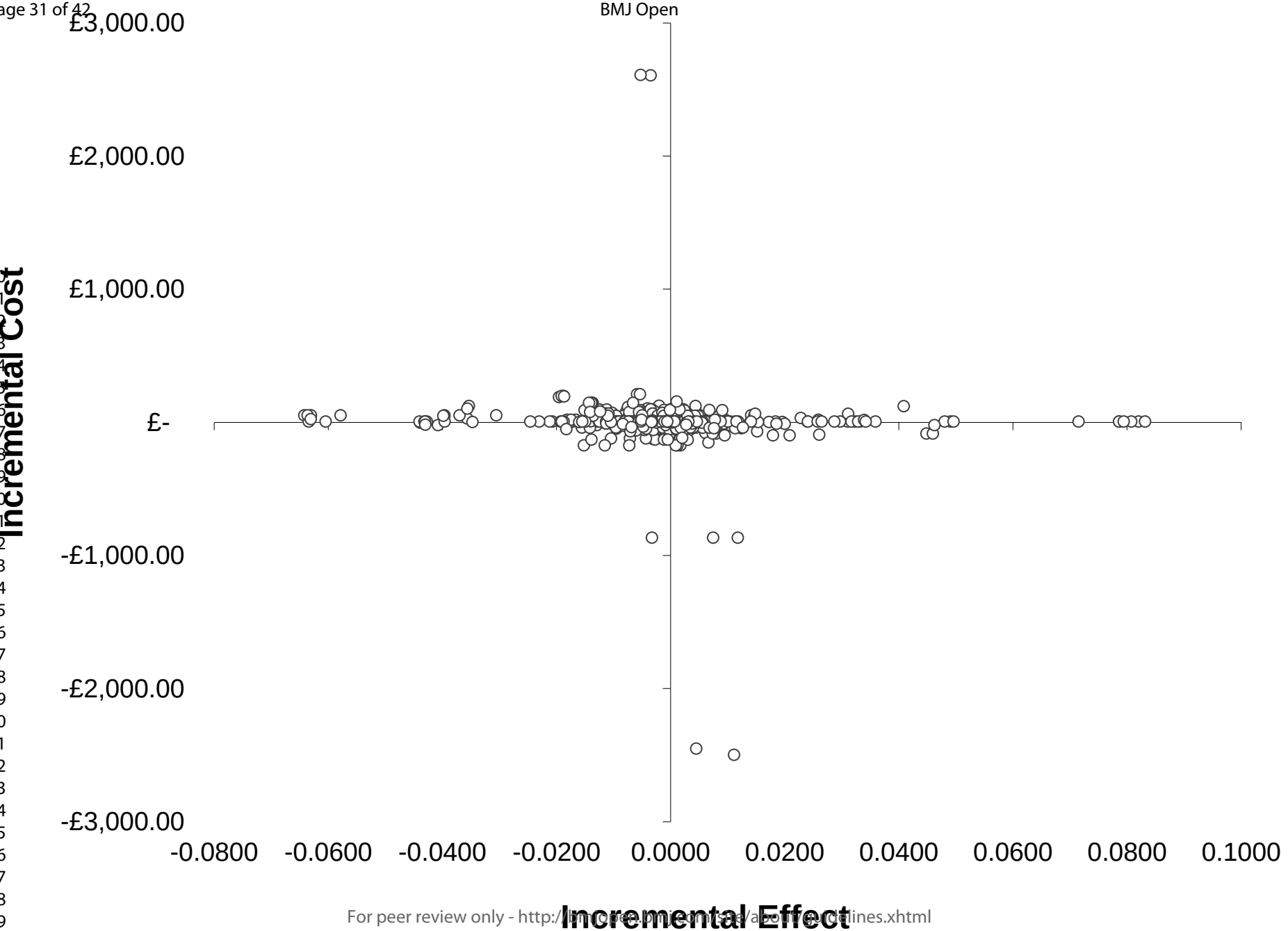
[27] NICE. Guide to methods of technology appraisal. Manchester, 2013

[28] Hayward G, Hay A, Moore M. et al. Effect of Oral Dexamethasone Without Immediate Antibiotics vs Placebo on Acute Sore Throat in Adults A Randomized Clinical Trial. JAMA 2017; 317(15):1535-1543. doi:10.1001/jama.2017.3417

[29] British Medical Association (BMA). General Practice in the UK – background briefing. April 2017 https://www.bma.org.uk/-/media/files/pdfs/.../general-practice.pdf?la=en Accessed June 19, 2017

[30] Little P, Moore M, Leydon G, Mullee M and Stuart B. Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. BMJ 2014; 348:g1606

[31] Horton NJ and Kleinman KP. Much ado about nothing: A comparison of missing data methods and software to fit incomplete data regression models. Am Stat 2017; 61(1): 79-90



TOAST ONLINE APPENDIX

Table A1- Trial Resource Use Costs

TOAST TRIAL UNIT COSTS (2015 £)				
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	Ibuprofen (NSAIDS)	£ 0.60	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc3	Anaesthetic spray	£ 1.25	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc4	Anaesthetic lozenges	£ 1.40	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc5	Decongestant	£ 1.00	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc6	Lozenges (non-analgesic)	£ 0.66	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc7	Other analgesia (cocodamol/ cough medicine, etc.)	£ 1.05	per recommended daily dose	Boots Pharmacy Generic Brand, 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, University 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).
B	HSP	Basecase was adjusted to remove those over age 70 (seven in each arm removed) (n=551).
C	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.
H	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.
K	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.
M	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).
O	SCP	Option I was restricted to those who did not receive a delayed prescription (n=342).
P	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

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 • Symptom resolution at 24 hours and 48 hours • A treatment arm identifier • A dichotomous variable to highlight patient experienced an SAE • A dichotomous variable for delayed antibiotic prescription given • Costs: intervention, antibiotics, OTC medication, resource use day 1-7, resource use day 8-28, missed work/ education, missed usual activities • Patient characteristics: gender, age, employment status, location of care, current smoker, a 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 multiply imputed generating 60 datasets using predictive mean matching and separately by treatment allocation 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 following is the STATA code used: "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 VAS_day7 sae outlier resol48 cost_reportedantibiouse totalcost_OTC resourceusediary_cost resourceuseFU_cost missed_days_costday1tounk cost_usualact1tounk trt delayed_script Male worker age current_smoker location age71andover, saving(MI_aggregated, replace) m(60) match genmiss(indmiss) by(trt) seed(10)"

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

	Control	Intervention	Diff (I-C)	% Δ (I-C)
EQ-5D-5L Imputed Full ITT				
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[1]	6.289	6.354	0.0652	1.04%
EQ-5D VAS Imputed Full 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[2]	70.44	70.27	-0.162	-0.23%
Delayed Prescription- Imputed ITT Cohort				
	Control	Intervention	Diff (I-C)	% Δ (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[1]	6.2569	6.3943	0.1374	2.20%
No Delayed Prescription- Imputed 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[1]	6.3099	6.3281	0.0182	0.29%

1. *Quality-adjusted week estimated using area under the curve estimation.*
2. *Average VAS score estimated average across baseline to day 7.*

Table A5: Quality of Life Analysis for Complete Cases (unadjusted)

EQ-5D-5L Analysis				
	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 Δ (%) from Baseline at 24 hrs	0.087 (11.8)	0.087 (11.5)	0	ns
Average Δ (%) 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 Δ (%) from Baseline at 24 hrs	8 (16)	9 (17)	1	ns
Average Δ (%) from Baseline at 48 hrs	15 (31)	13 (25)	-2	ns
EQ-5D-5L Sub-group Analysis				
	Delayed Script	No Delayed Script	Difference (Delayed-No Script)	P value
	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 Δ (%) from Baseline	0.195 (27.5)	0.143 (18.7)	0.052	0.001
Average Δ (%) from Baseline at 24 hrs	0.119 (20.7)	0.092 (14.1)	0.027	ns
Average Δ (%) from Baseline at 48 hrs	0.180 (31.3)	0.151 (23.3)	0.029	ns

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

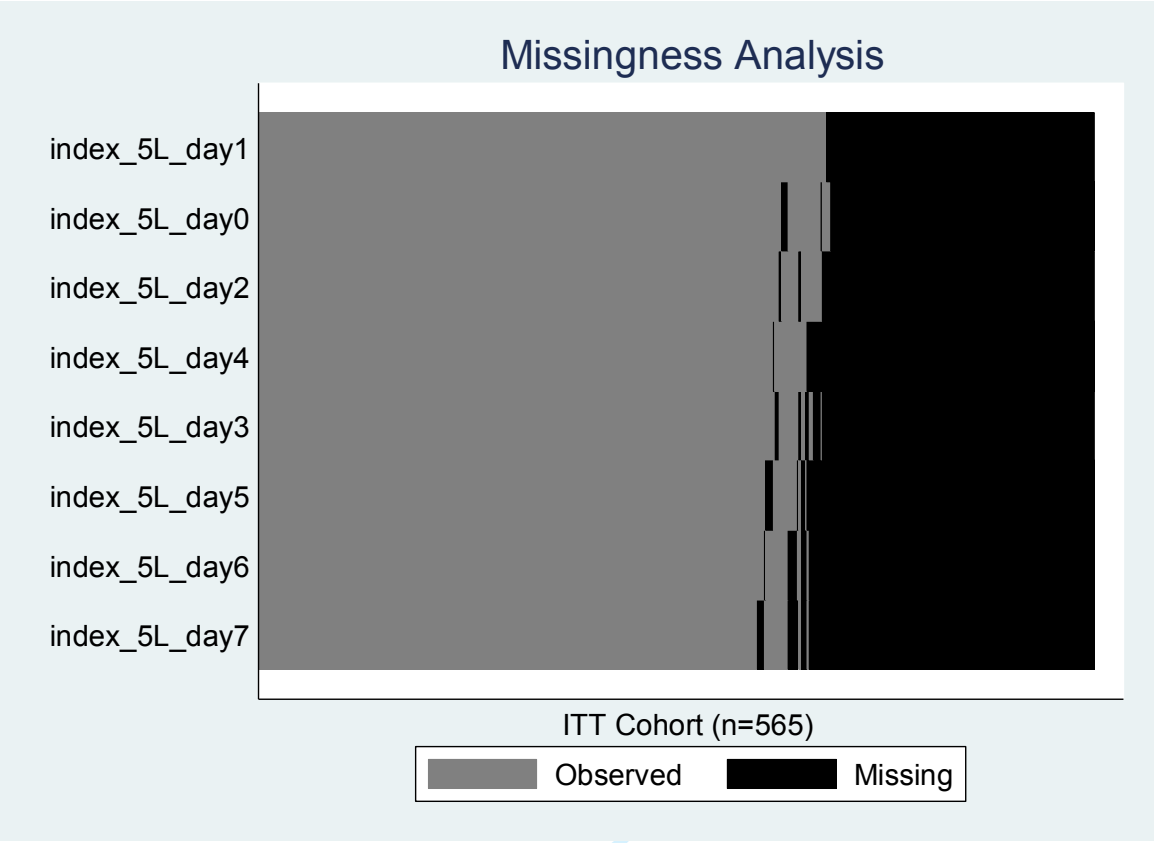


Figure A2: QALY distribution by treatment arm

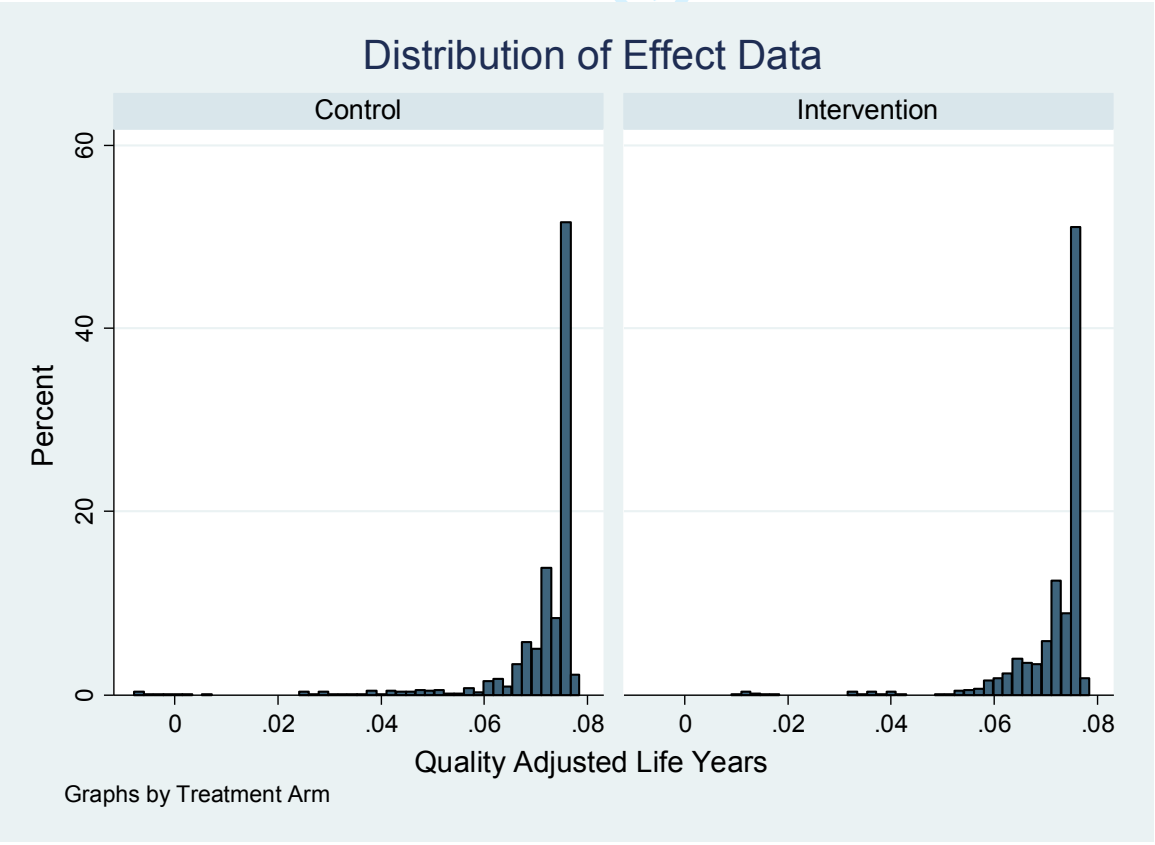


Figure A3: EQ-5D-5L Imputed Scores for ITT Cohort

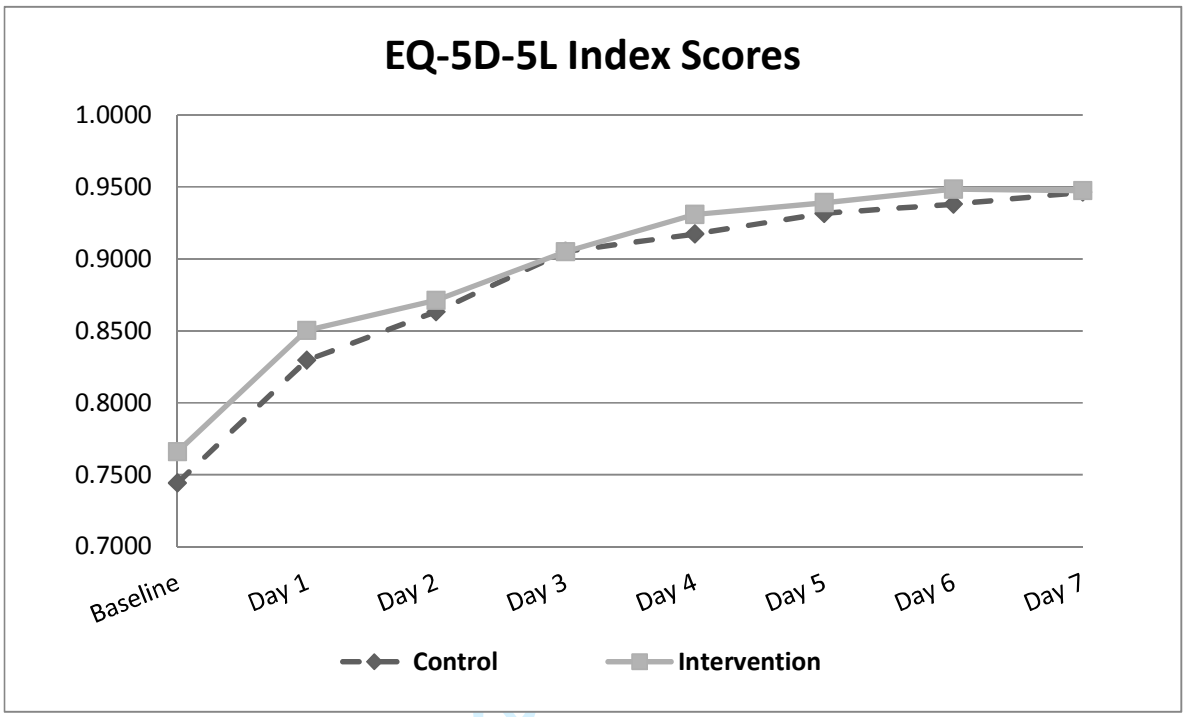


Figure A4: EQ-5D Visual Analogue Scale Imputed Scores for ITT Cohort

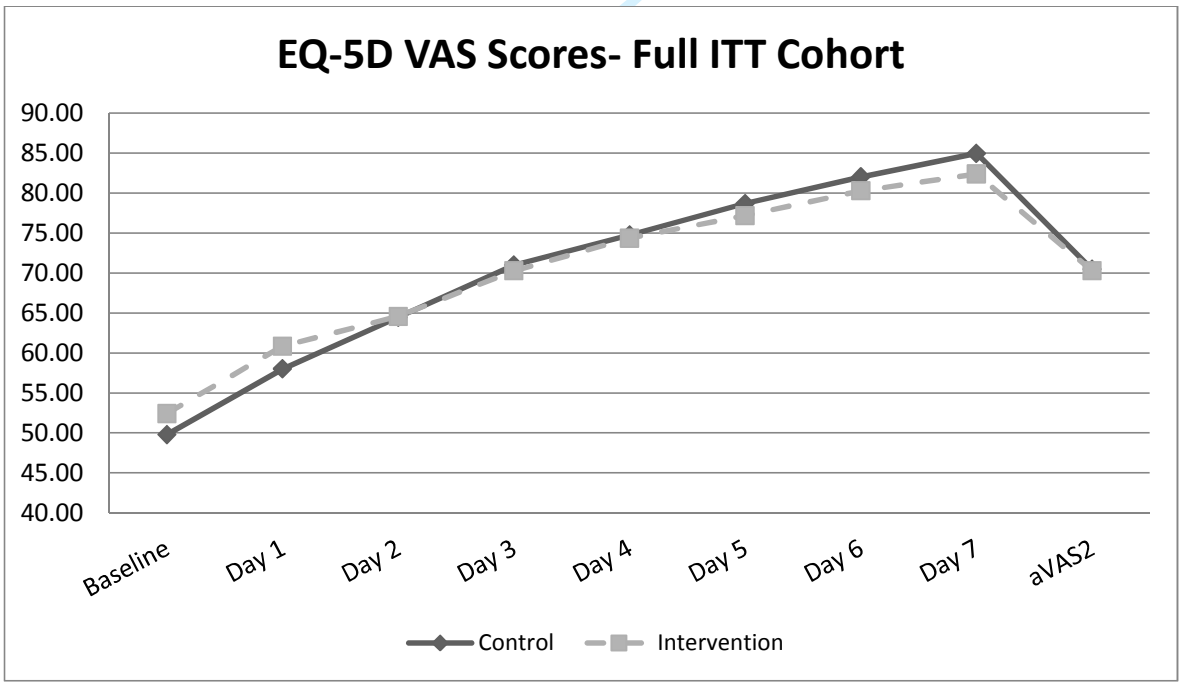
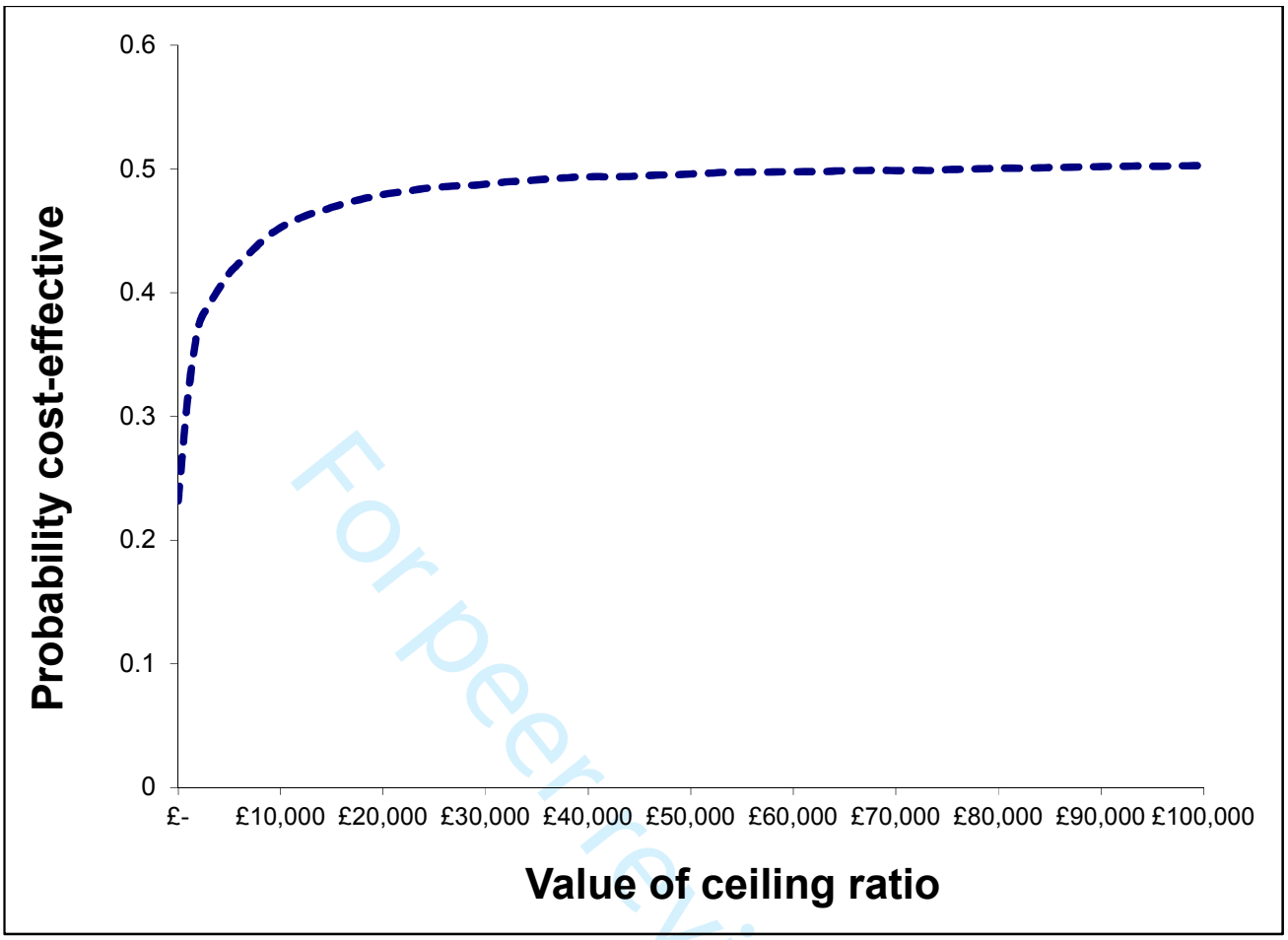


Figure A5: Cost-effectiveness Acceptability Curve



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

The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been endorsed and co-published by the following journals:

BJOG: An International Journal of Obstetrics and Gynaecology
BMC Medicine 2013; 11:80
BMJ 2013;346:f1049
Clinical Therapeutics 27 March 2013 (Article in Press DOI: 10.1016/j.clinthera.2013.03.003)
Cost Effectiveness and Resource Allocation 2013 11:6.
The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print]
International Journal of Technology Assessment in Health Care
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			
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	n/a

		outcomes and say why appropriate.	6
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	6&7
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	7&8
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	n/a
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	n/a
Estimating resources and costs	13a	*Single study-based economic evaluation:* 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	*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 cost. Describe any adjustments made to approximate to opportunity costs.	7
Currency, price date, and conversion	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 model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	8&9&10
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	8&9&10
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.	8&9&10
Results			
Study parameters	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 & Online appendix

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	*Single 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).	11-12 25
	20b	*Model-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.	11-12 25
Characterising heterogeneity	21	If 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.	11-12 25
Discussion			
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 International Committee of Medical Journal Editors recommendations.	16-17

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

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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.

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

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

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Abstract

Objectives: To undertake an economic analysis assessing the cost-effectiveness of a single dose of oral dexamethasone compared to placebo for the relief of sore throat.

Design: A UK-based, multicentre, two arm, individually randomised, double blind trial

Setting and Population: Adults (≥18 years) with acute sore throat and painful swallowing judged to be infective in origin, recruited and randomised in primary care.

Intervention: A single dose of 10mg oral dexamethasone compared to placebo given at primary care visit.

Main Outcome: Incremental cost-effectiveness ratios (ICERs), cost per quality-adjusted symptom resolution using the EQ-5D-5L instrument, were estimated as part of a cost-utility analysis performed on an intention-to-treat cohort adopting a health payers perspective.

Results: Differences in health-related quality of life (HRQoL) over 7 days from baseline and at 24 hours in the dexamethasone compared with the placebo group (2.9% and 2.5% higher, respectively) were observed. After controlling for the baseline HRQoL imbalances, the economic impact of the intervention was not 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) and the median ICER was -£304 (IQR:-£5,816; £3,877); suggesting considerable uncertainty.

Conclusions and relevance: The economic burden associated with sore throat is substantial and was estimated at £2.35bn to the healthcare services payer based on reported resource use and 2015 UK unit costs. There is considerable uncertainty regarding the cost-effectiveness of a single dose of oral dexamethasone as a treatment strategy and therefore insufficient evidence to support its use in clinical practice.

Trial Registration: ISRCTN17435450 http://www.isrctn.com/ISRCTN17435450

Key words: cost-utility analysis, primary care interventions, sore throat

Strengths and limitations of this study

1. The analysis undertaken provides the first detailed account of the cost of sore throat in the UK.
2. 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.
3. Both health services payer and societal perspectives were assessed in the economic evaluation.
4. 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.

Introduction

An estimated £400 million annually is spent on consultations and lost productivity associated with sore throat alone in the UK.[1,2] Almost one in ten registered UK patients will see their general practitioner (GP) every year with sore throat.[3] 91% of those diagnosed with tonsillitis will receive antibiotics, as will half of those recorded as 'sore throat' or 'pharyngitis'.[4] NICE and International guidance recognises the limited evidence for benefit of antibiotics in its advice to avoid prescriptions in the majority of patients[5-6]; however, prescribing rates remain disproportionately high even though patients attend mainly due to anxiety over symptoms.[7] 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[8] 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[9], could also be moderated. The Treatment Options without Antibiotics for Sore Throat (TOAST) trial[10] 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.[11] 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

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[1] 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.[6] The research protocol was approved by the National Research Ethics Committee South Central (12/SC/0684).

Outcome Measure

The cost-effectiveness analysis assessed quality-adjusted symptom resolution over the 7 day trial duration and estimated median time to complete resolution of

[1] 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.

symptoms and the corresponding utility gains measured by the EuroQol EQ-5D 5 level (EQ-5D-5L) index. These outcomes informed the construction of a quality-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 problem.[12] This health-related quality of life (HRQoL) instrument was administered to all participants at baseline and completed on each day of the seven day patient diary. Each of the five dimensions in the EQ-5D-5Lversion is scored from 1 (no problem) to 5 (extreme problems), generating a profile (e.g. 11245) that can be used to calculate a single index score (range -0.281 – 1.000).[13] The EQ-5D instrument also generates a self-rating of HRQoL scored from 0 to 100 employing a visual analogue scale (VAS); this was used in scenario analyses. Quality adjusted symptom resolution at 24 and 48 hours were also reported.

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. SAEs included in the analysis were those classified as such by the trial protocol; and detailed in the main trial paper.[11] 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.

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[14], British National Formulary[15], Boots Chemist[16], and the NHS Electronic Tariff Database[17] and are reported in UK currency. Productivity losses were costed using average wage rates for those employed and minimum wage rates for students.[18] All cost estimates were reported in 2015 GBP using appropriate adjustments for prices retrieved where necessary.[19] Disaggregated average cost estimates reported were based on the full cohort in the ITT analysis assuming non-responders had zero costs.

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[20], 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 prescription administrative charge is not applied to everyone and the full amount may not be recouped by the HSP.[21] In the scenario analyses, a societal costing perspective (SCP) was also adopted reflecting the overall economic burden of the dexamethasone relative to the placebo. This included productivity losses due to sick days i.e. reported time off due to missed work or education and reported inability to carry out usual activities, and OOP expenses. Further scenarios assessed sub-groups based on patient characteristics. The sub-group who highlighted they were current smokers at the time of the trial were assessed in a scenario analysis due to the extra healthcare burden smokers have relative to non-smokers.[22] Descriptions of all 20 analyses are presented in the ***Online Appendix*** (Table A2).

Each element of costs and outcomes were reported separately, consistent with a cost-consequence analysis; the resource use reported was for the full ITT cohort (i.e. no missing resource use data) and the HRQoL data reported in the disaggregated format was for complete cases i.e. n=337; 60% of the full cohort. Missing HRQoL data was assessed and classified as missing at random (MAR) (see ***Online Appendix***- Figure A1).[16] Multiple imputation analysis was performed for missing outcome data (40%) in the ITT cohort using a number of imputations (n=60) greater than the proportion of missing data.[23] The range of covariates included in the multiple imputation analysis along with a more comprehensive presentation of methods is presented (see ***Online Appendix***- Table A3***)***. The trial and follow-up

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

Results

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

participants was 37 years and 75% were women. There was no significant clinical difference in median time to complete symptom resolution across trial arms with both displaying complete symptom resolution by day 4; however, there was a significant difference in symptom resolution at 48 hours.[11] The changes in HRQoL over the 7 days highlight larger differences at baseline and at 24 hours with the dexamethasone group reporting 2.9% and 2.5% higher utility scores, respectively (see ***Online Appendix***- Figures A3-4). Differences start to diminish (<1.5%) from day 2 onwards. ***Table 2*** highlights the differences in estimated QALYs for the imputed ITT cohort. After controlling for the baseline imbalances in HRQoL, the impact of the intervention was negative but not statistically significant: the QALY gain was -0.00005 (95% CI: -0.0002; 0.00011) equivalent to a loss in HRQoL of a half hour for the dexamethasone relative to the placebo group. Unadjusted differences in HRQoL for the ITT and complete case cohorts are presented in the ***Online Appendix*** (see-Figures A4-5).

For the sub-group who received the delayed prescription based on clinical need, a statistically significant benefit was evidenced after baseline imbalances were adjusted for resulting in an approximate HRQoL gain of 13.6 hours relative to the control group. For the sub-group who did not receive the prescription, the dexamethasone group indicated a significant QALY loss of approximately 13 hours relative to the placebo group. For the patient group who reported that they were current smokers a significant QALY gain from the dexamethasone of 0.0029, equivalent to 1 day was evidenced. At 48 hours where a significant difference in the risk ratio of symptom resolution at 48 hours in favour of the dexamethasone [RR: 1.31 (95% CI, 1.02 to 1.68; P = .03)] was observed, the significant QALY gain approximated to 3.7 hours for the current smokers sub-group.

The average cost per patient associated with the dexamethasone and placebo groups in the basecase analysis adopting a HSP was £73 and £69, respectively. ***Table 3*** highlights total costs for the categories included in the economic evaluation. Average costs were higher across both trial arms for the sub-group who did not receive the delayed prescription relative to the sub-group who did (£24 and £18 higher in the placebo and dexamethasone groups respectively) driven by higher health service utilisation; however no statistically significant impact on costs across these sub-groups for the HSP was found. For the SCP, including the cost associated with inability to carry out usual activities (Scenario I), the average cost per patient was £126 and £134 for the dexamethasone and placebo groups, respectively. This suggests a cost-saving of £7 per patient to society. For the sub-group who received the delayed prescription there was a negligible SCP reduction in the dexamethasone group of -£0.18; however, for those who did not receive the delayed prescription the SCP reduction for the substantial at -£12 signalling strong evidence of cost-savings from the use of oral dexamethasone compared to placebo.

In the deterministic basecase analysis (***Table 4***), the ICER was negative at -£81,400 due to the size and sign of the incremental effectiveness. In the basecase probabilistic analysis, the mean ICER was -£6,440 (95% CI: -£132,151; £126,335) and the median ICER was -£304 (IQR:-£5,816; £3,877); suggesting there is considerable uncertainty around this estimate. Several societal scenarios highlighted the potential for cost-savings; however, due to outcome variability, there is insufficient evidence to suggest the dexamethasone is cost-effective. The cost-effectiveness plane (***Figure 1***) presents a visual representation of the spread of the variation in cost and effect pairs for the basecase probabilistic analysis emphasizing the wide variation in effectiveness. Due to this uncertainty, the cost-effectiveness

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

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[29] and one in ten due to sore throat[4], 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 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. GPs selected patients who were perceived to be in greater clinical need for the delayed prescription sub-arm of the trial; as this sub-group may have had increased severity of symptoms relative to their counterparts, they had more scope to improve from a clinical and HRQoL perspective which in part may explain the variation in HRQoL for the sub-groups. Additionally the average costs of those in the 'no delayed prescription' sub-group who received intervention or placebo were 30% and 45% times higher, respectively, than those in the comparative sub-group who received the delayed prescription. Cost differences observed across sub-groups were primarily driven by higher reported health service use contacts across the trial and follow-up periods: 210% increase in the 'no delayed prescription' sub-groups overall and 157% and 286% higher for the intervention and placebo arms, respectively. Caution is needed in interpreting this variation as the trial was not powered for sub-group analysis of resource use and response rates were low. Previous research did not find any clinical differences across delayed prescription and no treatment strategies[30]; however our findings suggest that the clinical and non-clinical benefits of the delayed prescription in addition to the dexamethasone need to be explored further.

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

sub-group, we feel the range of budgetary, clinical and environmental benefits of reducing antibiotic usage need to be explored further given the evidence highlighted in this study.

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 anti-inflammatory 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 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 data collection was a patient completed diary at each day of the trial follow-up: HRQoL over the 7 days was 60% complete and the resource use reported in diaries was 62% complete. The initial response rate was much lower and a protocol amendment which allowed the use of incentives for patients who returned diaries was introduced. 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. However, EQ-5D-5L data was collected from the patient survey only and missing data was considerable at 40%. Although robust multiple imputation techniques were applied to impute values, it is recognised that the range of covariates used to impute missing data may not reflect the degree of heterogeneity across the patient cohort and therefore some bias may remain in terms of the resource use and outcomes reported versus those that were not. If the imputation model was mis-specified the imputation estimates could have some degree of bias.[31] Due to the high uncertainty around observed HRQoL estimates across both arms however, the limitations associated with multiple imputation are not cause for concern. In the analyses adopting a SCP, self-reported data on time unable to engage in usual activities and OTC medications purchased were not imputed for those with missing 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 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 appropriately powered trials. However, the sub-group analyses give greater understanding of the wide variation in outcomes observed.

Conclusions and policy implications

In conclusion, sore throat has a substantial economic burden on health care delivery systems with this study estimating the economic burden from a HCP in the UK at £2.35bn annually. More effective strategies for assessing and providing rapid

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 and therefore insufficient evidence to suggest cost-effectiveness or its adoption as a viable treatment strategy. However, there was evidence suggestive of potential benefits in several sub-groups which could be investigated further in follow-up trials.

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2) Department of Medicine, University of Southampton

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We have read and understood BMJ Open policy on declaration of interests and declare that we have no competing interests

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

Contribution Statement:

All authors contributed to: the conception and design of the TOAST trial analysis including guidance on the health economic evaluation; the drafting and revising of this manuscript; approval of the final version of the manuscript and are accountable for all aspects of the work presented.

Each author has particular areas of expertise as follows: applied economic evaluation leads – RB & JW (joint first authors), statistical analysis SJ, NW & RP, project management, project conception, design and clinical lead- GH, clinical leadership and guidance, interpretation and policy interpretation- AH, MT, CH, PL, MM.

This research presents an honest, accurate, and transparent account of the economic evaluation of the TOAST UK study; no relevant aspects of the study have been omitted and the wide range of scenario analyses addresses both the clinical heterogeneity and variability in structural assumptions.

FIGURES AND TABLES

Figure 1: Cost-effectiveness plane

Table1: TOAST trial patient characteristics

	Placebo Group	Dexamethasone Group
All Eligible Participants (ITT)	**277 (49%)**	**288 (51%)**
Male	73 (13%)	67 (12%)
Female	204 (36%)	221 (39%)
Mean Age[a]	37.3 (SD: 14.30)	37.2 (SD: 14.36)
Current Smoker	51 (9%)	52 (9%)
ANTIBIOTIC DETAILS[b]		
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[c]	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[d] (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)

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	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

	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	-£12.93
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

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

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.

Table 4: Cost-utility analysis (deterministic models)

Scenarios[a]	*Control*	*Intervention*	Δ in Cost	Δ in Effect[b]	ICER	Interpretation[c]
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[d]	£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 [d]	£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 may 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.

REFERENCES

[1] Roos K, Claesson R, Persson U, Odegaard K. The economic cost of a streptococcal tonsillitis episode Scandinavian Journal of Primary Healthcare 1995 13: 257-260

[2] HMSO Morbidity Statistics in General practice : Fourth national Study HMSO 1994

[3] Gulliford M, Latinovic R, Charlton J, Little P, van Staa T, Ashworth M. Selective decrease in consultations and antibiotics prescribing for acute respiratory tract infection sin UK primary care up to 2006. Journal of Public Health 2009; 31(4), 512-520

[4] Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. Cochrane Database Systematic Reviews 2006; (4):CD000023.

[5] NICE guideline. Respiratory Tract Infections - antibiotic prescribing. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. 2008. National Institute for Clinical Excellence. Ref Type: Report.

[6] Centers for Disease Control and Prevention. Get Smart: Know When Antiobiotics Work in Doctor's Offices: Adult Treatment Recommendations. https://www.cdc.gov/getsmart/community/for-hcp/outpatient-hcp/adult-treatment-rec.html last updated: March 2016. Accessed June 19, 2017

[7] Guilliford MC, Dregan A, Moore M et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. BMJ Open 2014; 4(10)

[8] Hayward G, Thompson M, Heneghan C, Perera R, Del Mar C, Glasziou P. Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. BMJ 2009; 339:b2976

[9] Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ.* 2010;340(May18_2):c2096

[10] Cook J, Hayward G, Thompson M, et al. Oral corticosteroid use for clinical and cost-effective symptom relief of sore throat: study protocol for a randomized controlled trial. Trials 2014; 15, 365

DOI: 10.1186/1745-6215-15-365

11 Hayward G, Hay A, Moore M. et al. Effect of Oral Dexamethasone Without Immediate Antibiotics vs Placebo on Acute Sore Throat in Adults A Randomized Clinical Trial. JAMA 2017; 317(15):1535-1543. doi:10.1001/jama.2017.3417

12 Devlin N, Krabbe P. "The development of new research methods for the valuation of EQ-5D-5L." European Journal of Health Economics 2013; 14(1): S1-S3

13 Devlin N, et al 2016 Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England. Office of Health Economics research paper 16/01

14 PSSRU "Unit Costs of Health and Social Care 2015" http://www.pssru.ac.uk/project-pages/unit-costs/2015/

15 British National Formulary (2015) https://www.medicinescomplete.com/mc/bnf/current/

16 Boots Online Pharmacy (2015) www.boots.com

17 Department of Health Reference Cost 2014/2015; London 2015

18 Office of National Statistics. Annual Survey of Hours and Earnings, 2014. www.ons.gov.uk Accessed June 6, 2017

19 Office of National Statistics. Consumer Price Inflation Index. www.ons.gov.uk Accessed June 6, 2017

20 Pharmaceutical Services Negotiating Committee. Exemptions from the prescription charge. http://psnc.org.uk/dispensing-supply/receiving-a-prescription/patient-charges/exemptions/ Accessed June 9, 2017

21 NHS Choices. NHS in England- help with health costs. http://www.nhs.uk/NHSEngland/Healthcosts/Pages/Prescriptioncosts.aspx Accessed June 6, 2017

22 Wacker M, Holle R, Heinrich J, et al. The association of smoking status with healthcare utilisation, productivity loss and resulting costs: results from the population-based KORA F4 study. BMC Health Services Research 2013; 13:278

23 Faria R, Gomes M, Epstein D, et al. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. Pharmacoeconomics 2014; 32(12):1157-70.

24 Hunter R, Baio G, Butt T, Morris S, Round J, Freemantle N. An Educational Review of the Statistical Issues in Analysing Utility Data for Cost-Utility Analysis. Pharmacoeconomics 2015; 33(4): 355-366

[25] Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Economics 2005; 14(5):487-96.

[26] Glick HA, Doshi JA, Sonnad SS, Polsky D. Economic Evaluation in Clinical Trials. Handbooks in Health Economics, Volume 2. Oxford: Oxford University Press, 2015

[27] StataCorp. Stata Statistical Software: Release 14. 14.1 ed. College Station, TX: StataCorp LP. ; 2015.

[28] NICE. Guide to methods of technology appraisal. Manchester, 2013

[29] British Medical Association (BMA). General Practice in the UK – background briefing. April 2017 https://www.bma.org.uk/-/media/files/pdfs/.../general-practice.pdf?la=en Accessed June 19, 2017

[30] Little P, Moore M, Leydon G, Mullee M and Stuart B. Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. BMJ 2014; 348:g1606

[31] Horton NJ and Kleinman KP. Much ado about nothing: A comparison of missing data methods and software to fit incomplete data regression models. Am Stat 2017; 61(1): 79-90

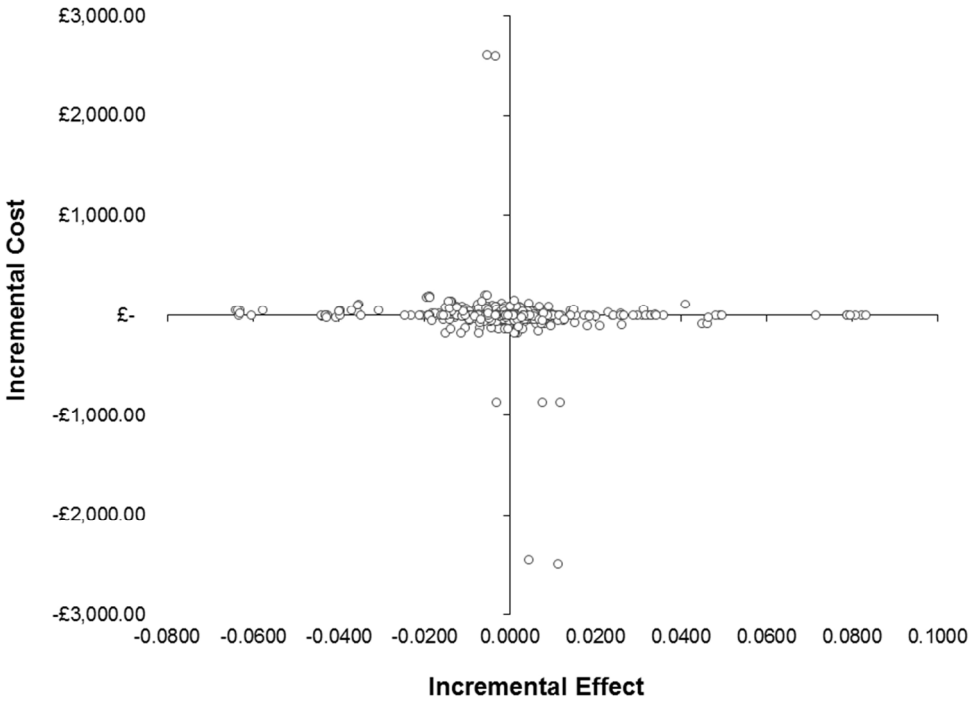


Figure 1: Cost-effectiveness plane

TOAST ONLINE APPENDIX

Table A1- Trial Resource Use Costs

TOAST TRIAL UNIT COSTS (2015 £)				
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	Ibuprofen (NSAIDS)	£ 0.60	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc3	Anaesthetic spray	£ 1.25	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc4	Anaesthetic lozenges	£ 1.40	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc5	Decongestant	£ 1.00	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc6	Lozenges (non-analgesic)	£ 0.66	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc7	Other analgesia (cocodamol/ cough medicine, etc.)	£ 1.05	per recommended daily dose	Boots Pharmacy Generic Brand, 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, University 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).
B	HSP	Basecase was adjusted to remove those over age 70 (seven in each arm removed) (n=551).
C	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.
H	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.
K	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.
M	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).
O	SCP	Option I was restricted to those who did not receive a delayed prescription (n=342).
P	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

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 • Symptom resolution at 24 hours and 48 hours • A treatment arm identifier • A dichotomous variable to highlight patient experienced an SAE • A dichotomous variable for delayed antibiotic prescription given • Costs: intervention, antibiotics, OTC medication, resource use day 1-7, resource use day 8-28, missed work/ education, missed usual activities • Patient characteristics: gender, age, employment status, location of care, current smoker, a 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 multiply imputed generating 60 datasets using predictive mean matching and separately by treatment allocation 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 following is the STATA code used: "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 VAS_day7 sae outlier resol48 cost_reportedantibiouse totalcost_OTC resourceusediary_cost resourceuseFU_cost missed_days_costday1tounk cost_usualact1tounk trt delayed_script Male worker age current_smoker location age71andover, saving(MI_aggregated, replace) m(60) match genmiss(indmiss) by(trt) seed(10)"

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

EQ-5D-5L Imputed Full ITT				
	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[1]	6.289	6.354	0.0652	1.04%
EQ-5D VAS Imputed Full 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[2]	70.44	70.27	-0.162	-0.23%
Delayed Prescription- Imputed ITT Cohort				
	Control	Intervention	Diff (I-C)	% Δ (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[1]	6.2569	6.3943	0.1374	2.20%
No Delayed Prescription- Imputed 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[1]	6.3099	6.3281	0.0182	0.29%

1. *Quality-adjusted week estimated using area under the curve estimation.*
2. *Average VAS score estimated average across baseline to day 7.*

Table A5: Quality of Life Analysis for Complete Cases (unadjusted)

EQ-5D-5L Analysis				
	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 Δ (%) from Baseline at 24 hrs	0.087 (11.8)	0.087 (11.5)	0	ns
Average Δ (%) 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 Δ (%) from Baseline at 24 hrs	8 (16)	9 (17)	1	ns
Average Δ (%) from Baseline at 48 hrs	15 (31)	13 (25)	-2	ns
EQ-5D-5L Sub-group Analysis				
	Delayed Script	No Delayed Script	Difference (Delayed-No Script)	P value
	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 Δ (%) from Baseline	0.195 (27.5)	0.143 (18.7)	0.052	0.001
Average Δ (%) from Baseline at 24 hrs	0.119 (20.7)	0.092 (14.1)	0.027	ns
Average Δ (%) from Baseline at 48 hrs	0.180 (31.3)	0.151 (23.3)	0.029	ns

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

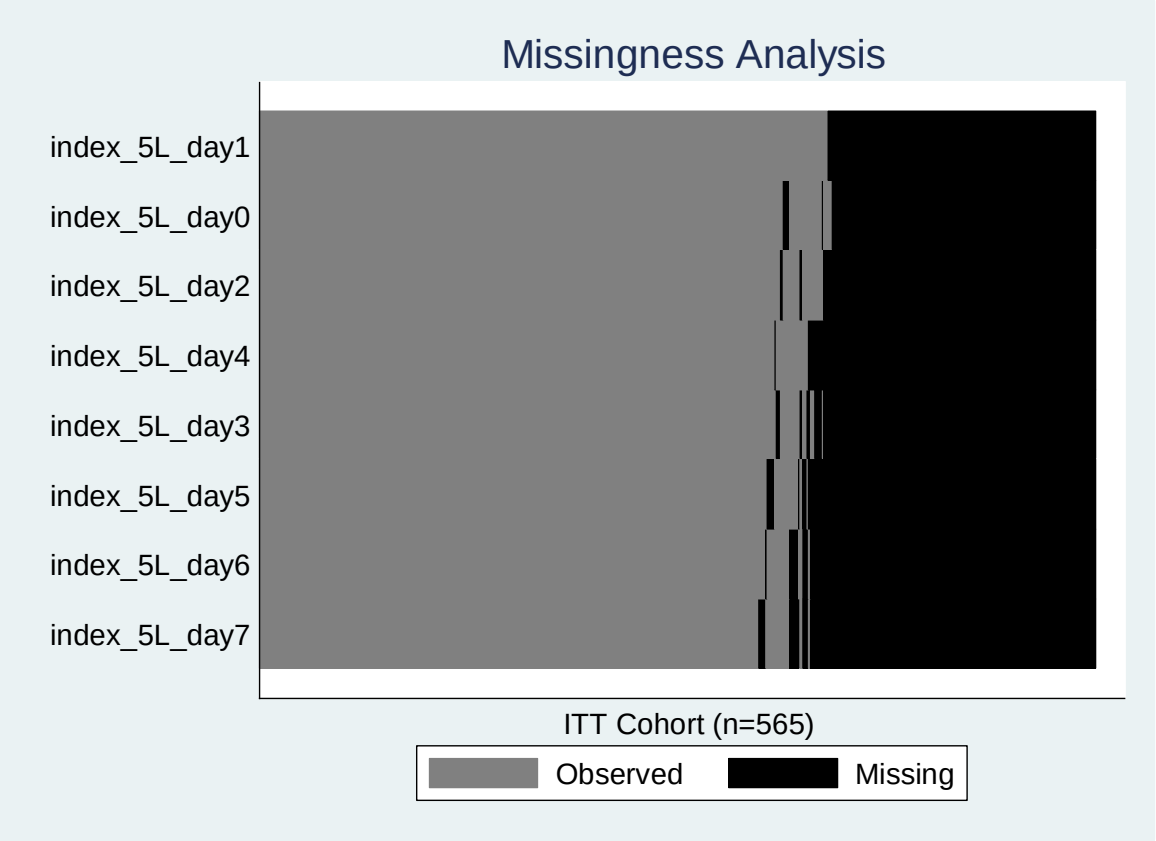


Figure A2: QALY distribution by treatment arm

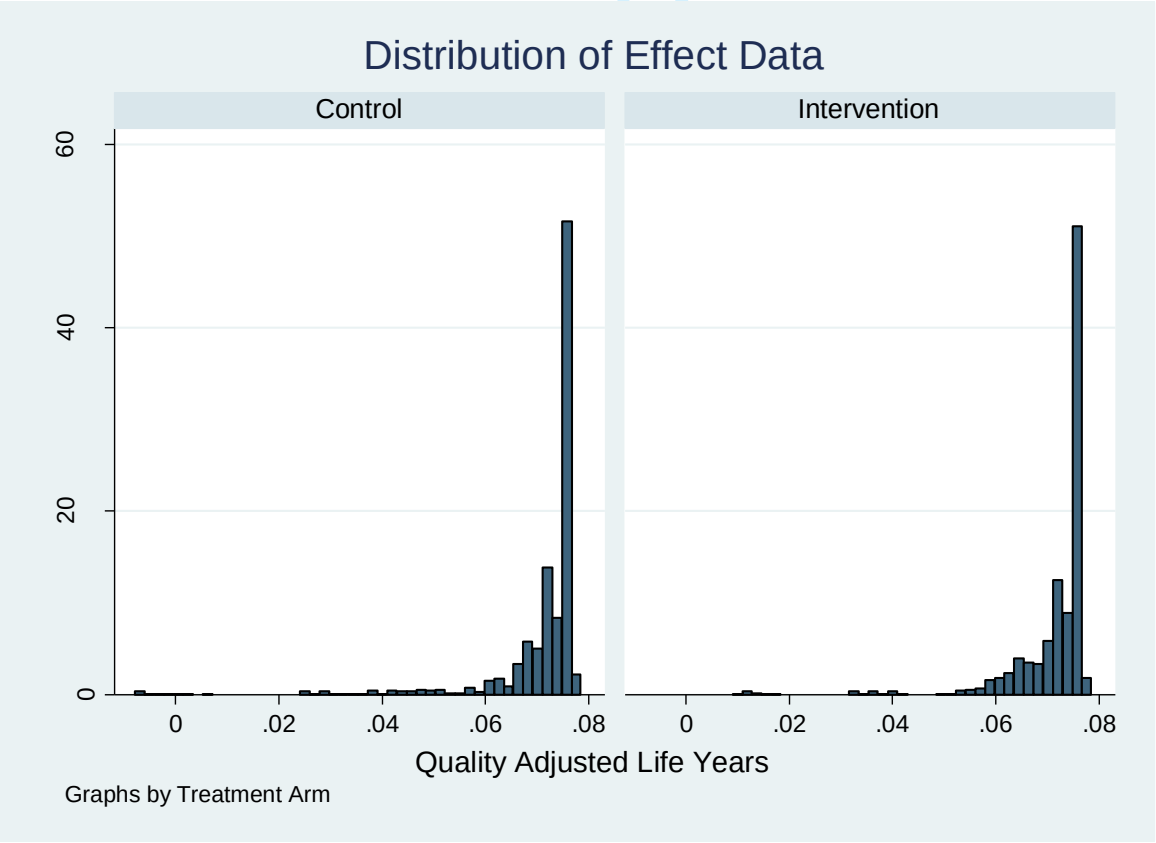


Figure A3: EQ-5D-5L Imputed Scores for ITT Cohort

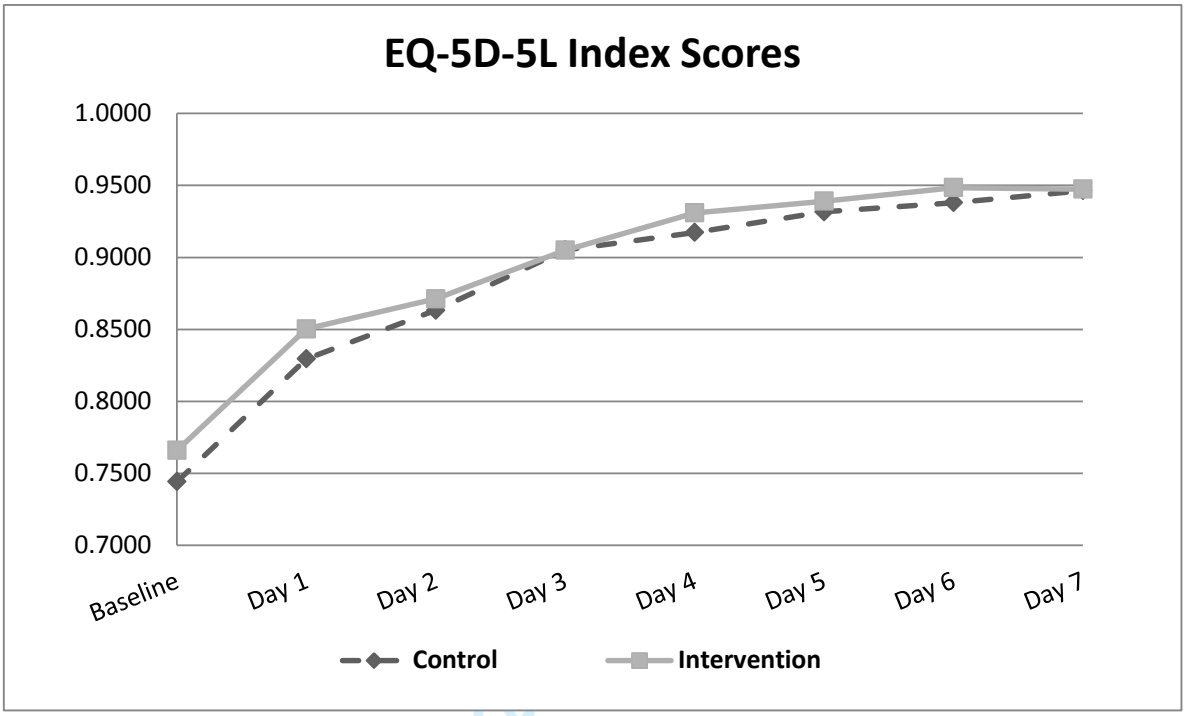


Figure A4: EQ-5D Visual Analogue Scale Imputed Scores for ITT Cohort

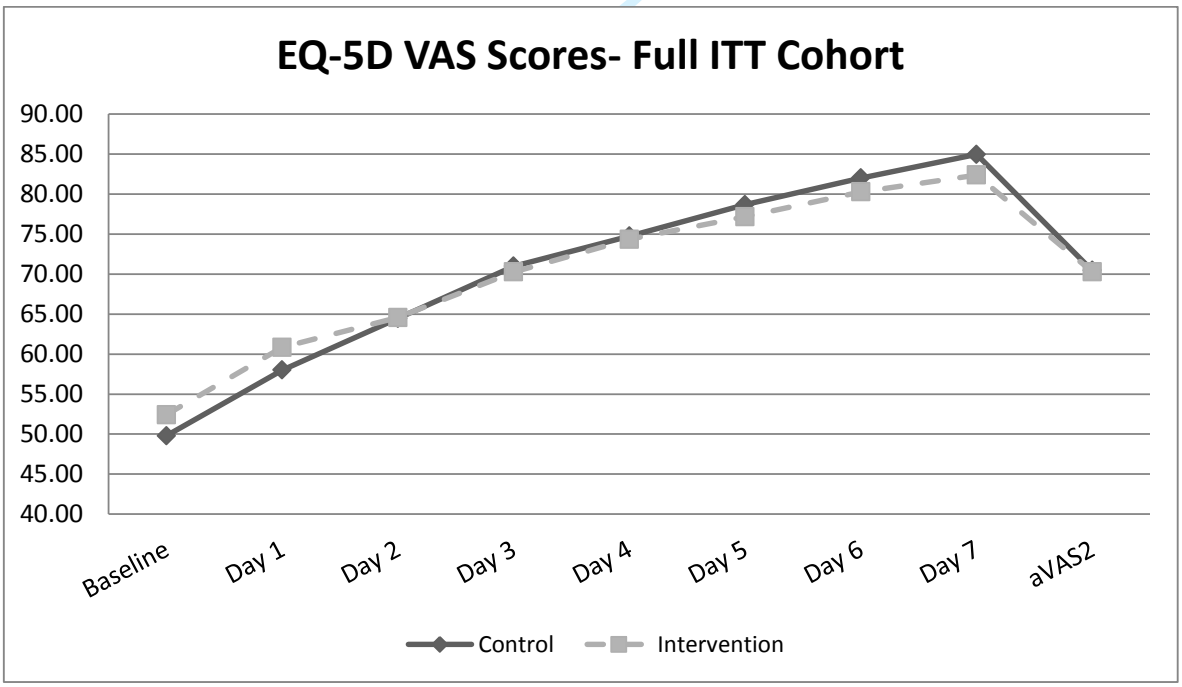
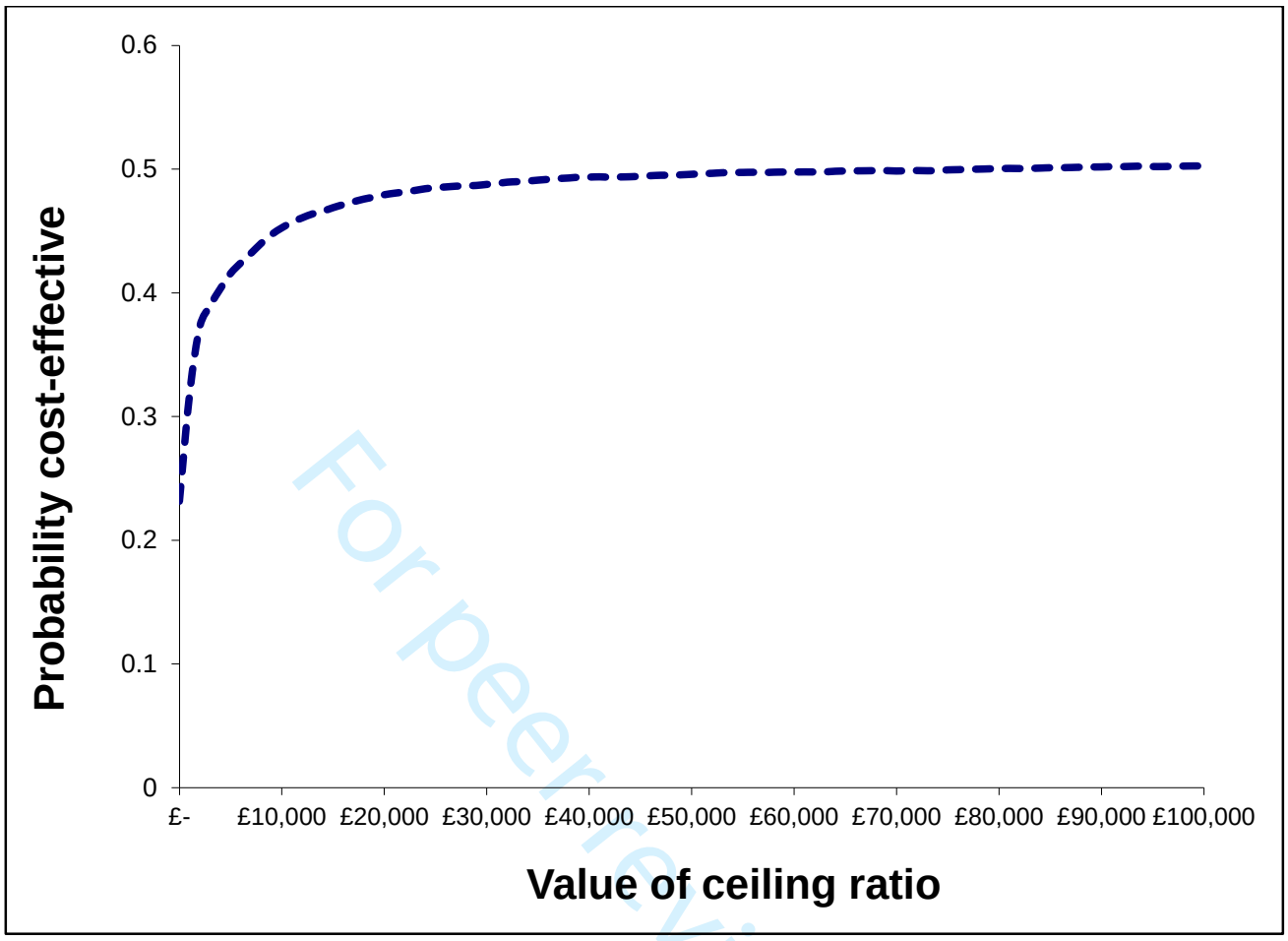


Figure A5: Cost-effectiveness Acceptability Curve



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

The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been endorsed and co-published by the following journals:

BJOG: An International Journal of Obstetrics and Gynaecology
BMC Medicine 2013; 11:80
BMJ 2013;346:f1049
Clinical Therapeutics 27 March 2013 (Article in Press DOI: 10.1016/j.clinthera.2013.03.003)
Cost Effectiveness and Resource Allocation 2013 11:6.
The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print]
International Journal of Technology Assessment in Health Care
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			
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	n/a

		outcomes and say why appropriate.	6
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	6&7
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	7&8
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	n/a
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	n/a
Estimating resources and costs	13a	*Single study-based economic evaluation:* 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	*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 cost. Describe any adjustments made to approximate to opportunity costs.	7
Currency, price date, and conversion	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 model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	8&9&10
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	8&9&10
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.	8&9&10
Results			
Study parameters	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 & Online appendix

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	*Single 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).	11-12 25
	20b	*Model-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.	11-12 25
Characterising heterogeneity	21	If 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.	11-12 25
Discussion			
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 International Committee of Medical Journal Editors recommendations.	16-17

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.