
Article:
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RESEARCH ARTICLE

REVISED Cost-effectiveness of oral versus intravenous antibiotics (OVIVA) in patients with bone and joint infection: evidence from a non-inferiority trial [version 4; peer review: 2 approved]

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Abstract

Background: Bone and joint infections are becoming increasingly common and are usually treated with surgery and a course of intravenous antibiotics. However, there is no evidence to support the superiority of intravenous therapy and there is a growing body of literature showing that oral therapy is effective in treating these infections. Given this lack of evidence the clinical trial 'Oral Versus Intravenous Antibiotics' (OVIVA) was designed to assess the clinical and cost-effectiveness of intravenous versus oral antibiotics for the treatment of bone and joint infections, using a non-inferiority design. Clinical results from the trial indicate that oral antibiotics are non-inferior to intravenous antibiotics. The aim of this paper is to evaluate the cost-effectiveness of intravenous compared to oral antibiotics for treating bone and joint infections, using data from OVIVA.
Methods: A cost-utility analysis was carried out, the main economic outcome measure was the quality adjusted life-year, measured using the EQ-5D-3L questionnaire, combined with costs to estimate cost-effectiveness over 12-months follow-up.
Results: Results show that costs were significantly lower in the oral arm compared to the intravenous arm, a difference of £2,740 (95% confidence interval £1,488 to £3,992). Results of four sensitivity analyses were consistent with the base-case results. QALYs were marginally higher in the oral arm, however this difference was not statistically significant; -0.007

Open Peer Review

Reviewer Status ✓ ✓

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(95% confidence interval -0.045 to 0.031).
Conclusions: Treating patients with bone and joint infections for the first six weeks of therapy with oral antibiotics is both less costly and does not result in detectable differences in quality of life compared to treatment with intravenous antibiotics. Adopting a practice of treating bone and joint infections with oral antibiotics early in the course of therapy could potentially save the UK National Health Service over £17 million annually.

Keywords
antibiotics, oral, intravenous, cost-effectiveness, non-inferiority, economic evaluation

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 3**

We would like to take this opportunity to thank both reviewers for taking the time to read and comment on our manuscript. We have updated this version of the manuscript to include a threshold line in Figure 2 and amended the text regarding Figure 2 to account for including an ellipse rather than confidence intervals.

Any further responses from the reviewers can be found at the end of the article

Introduction

Bone and joint infections are becoming increasingly common. In the UK, the National Health Service (NHS) conducts around 190,000 hip and knee replacement surgeries annually; of these, approximately 1% will result in post-operative infections[1,2]. In addition, there are around 70,000 neck of femur fractures, surgery for which is associated with post-operative infection in up to 2.5% of cases, and 20,000 metalware or fracture-fixations with around a 15% infection rate (Personal communication, Dr M. Scarborough, opinion). There are also approximately 5,000 diabetic foot infections and a smaller number of infections of the axial skeleton annually. Treatment for these infections is estimated to cost around £20,000 to £40,000 per patient[3–5].

These infections are usually treated with surgery and an initial course of intravenous antibiotics for 4–6 weeks. However, there is no evidence to support the superiority of intravenous therapy and, in recent years, there has been a growing body of literature showing that oral therapy is effective in treating these infections. A Cochrane review in 2013[6] found there was no benefit of intravenous compared to oral antibiotics in treating bone and joint infection. The authors judged the trials to be of moderate to high risk of bias and there was no statistically significant difference in the pooled results. Furthermore, most of the trials were conducted over 20 years ago, when there was a lower prevalence of bone and joint infections. The authors concluded that there was insufficient evidence from this review to inform a change in practice and there was a need for a randomised controlled trial to investigate this further.

Intravenous treatment requires an access device to administer the antibiotic which carries risk of infection and thromboembolic disease. Oral antibiotics do not carry these risks, are less costly and more convenient. However, oral antibiotics have a higher risk of non-adherence and gastro-intestinal intolerance[7]. Intravenous antibiotics are usually administered in a hospital setting but can be safely given in a clinic or at home, when administered outside the hospital this is called Outpatient Parenteral Antibiotic Therapy (OPAT). The OPAT team will visit the patient to administer the antibiotic, or the patient can choose to do this themselves. The OPAT team will oversee the patient's care until the course of antibiotics is completed.

Given the lack of evidence on the superiority of intravenous compared to oral antibiotics, the clinical trial "OVIVA" was designed to assess the treatment failure rate and cost-effectiveness of intravenous versus oral antibiotics for the first six weeks treatment of bone and joint infections. The study directly tested the different antibiotic administration routes via a non-inferiority design set with a margin of 7.5 percentage points above the upper 90% confidence interval around the risk difference. Clinical results from the trial indicate that oral antibiotics are non-inferior to intravenous antibiotics. The primary clinical outcome of treatment failure (infection present) occurred in 74 of 506 participants (14.6%) in the intravenous arm and in 67 of 509 participants (13.2%) in the oral arm[8].

This paper reports on the within-trial cost-effectiveness of OVIVA, estimating cost and quality-adjusted life year (QALY) differentials comparing intravenous antibiotics to oral antibiotics for the first six weeks of treatment of bone and joint infections.

Methods

Overview of analysis

OVIVA was a UK based multi-centre, open-label, randomised, controlled non-inferiority trial with 12 months follow-up. Participants were adults (18+ years) who, in the attending clinician's opinion, would normally be treated with a 6 weeks course of intravenous antibiotics for bone or joint infection. Participants started their randomised treatment within 7 days of surgery, or if no surgery for treatment of bone and joint infection, within 7 days of starting antibiotics. Participants were randomised to either intravenous or oral antibiotics for the first 6 weeks of therapy. In the intravenous arm, where it was common practice for adjunctive oral agents to be used alongside intravenous agents this was allowed. In the oral arm, if intravenous antibiotic treatment was needed for an unrelated illness, this was allowed for up to five days. Follow-on antibiotic treatment using either route of administration was allowed in both arms. Participants were recruited between June 2010 and October 2015. The primary endpoint was definite failure of infection treatment (infection present) within 12 months of randomisation. Treatment failure was identified locally by the treating clinician and categorised by a blinded end-point committee as: definite, probable and possible. The non-inferiority margin was set at 7.5%, and non-inferiority was met if the upper limit of the 90% CI around the absolute risk difference between the arms fell below this margin. Mortality was not necessarily considered a treatment failure in the absence of meeting criteria for a primary endpoint and was included in the secondary endpoint of 'serious adverse events'. Full methodological details of the trial are available in the published protocol[7].

Individual patient data from the OVIVA trial were used to perform the cost-effectiveness analysis. Outcomes were measured in terms of QALYs. The analysis had a time horizon of 12 months and an NHS and personal social services perspective, reported in GBP sterling (2015 GBP). No discounting was needed due to the short time horizon. Best practice guidance was

followed for conducting and reporting the analysis[9,10]. Cost-effectiveness was judged using incremental costs per health outcome measured against the current NICE threshold of £20,000 to £30,000. Missing resource and quality of life data were imputed using multiple imputation by chained equation[11] for the base case analysis and sensitivity analyses included a complete case analysis to explore the effect of excluding participants with missing data on the final results. Analysis was carried out in Stata 14.0 (StataCorp, College Station, TX, USA).

Resource use

Resource use data were collected using self-reported questionnaires completed at 42, 120- and 365-days post randomisation. Resource use groups comprised: antibiotic medication, intravenous administration and inpatient stays. Antibiotic resource use included all antibiotics prescribed to each participant in the 12-month follow-up period. Inpatient stays were measured in bed days and intravenous administration included the cost of intravenous line insertion and removal for each intravenous episode per participant, cost of line complications where a new line is needed, and the cost of the Outpatient Parenteral Antimicrobial Therapy (OPAT) team if applicable.

Unit costs for antibiotic medication were obtained from the British National Formulary[12]. Inpatient stays were valued using NHS reference costs[13] and intravenous administration resources and costs were taken from the literature[14] and expert opinion (Personal communication, Dr M. Scarborough). Costs were adjusted for inflation using the Hospital and Community Health Index[15]. Unit costs and their sources are presented in Table 1.

Total costs per participant were calculated by assigning unit costs to within trial resource use for each participant.

Health outcomes

The economic outcome was the QALY, a measure combining both quality and length of life. Quality of life data were collected using the EQ-5D-3L questionnaire[16], administered at baseline, 14 days, 42 days, 120 days, 365 days. EQ-5D-3L responses were valued using a UK tariff[17]. Standard area-under-the-curve methods were used to calculate QALYs[18], which were adjusted for baseline utility by including baseline utility as an explanatory variable[19].

Missing data

Excluding participants with missing data can lead to loss of power and biased results because of a reduced sample size[20]. Because of this, the missing data was analysed for type of missingness[9,11,21]. Base-case data had missing resource and quality of life data; these missing data were imputed using multiple imputation by chained equation (MICE), which assumes data are missing at random[11]. The effect of missing data was explored using both mean and multiple imputation. Missing cost values were imputed at the aggregate total cost level and missing quality of life data were replaced at utility score level at each EQ-5D-3L follow-up point using multiple imputation.

The regression analyses used to impute missing data included the same explanatory variables used in the missing data imputation in the clinical analysis[8].

Assumptions

The following additional assumptions were made:

- As intervention resource use was not separately identified we have treated all resource use in the first 6-week period after randomisation as intervention resource use.

- The cost of a line insertion and removal was applied to the initial 6-week period of the intervention. In addition, it was assumed that an intravenous episode with a gap of two days or less between intravenous drugs did not require a new line to be inserted and a cost was not applied for insertion/removal. If the gap between episodes was greater than two days, it was

Table 1. Unit costs and sources.

Resource	Unit cost	Source
Antibiotic	Various	British National Formulary[12]
Inpatient stay	£296/overnight stay	NHS reference costs[13]
Intravenous administration		
Insertion: PICC[1]	£190	Expert opinion
Removal	£34	Expert opinion
OPAT type		
District nurse	£58 per hour	NHS reference costs[13]
Inpatient (Hospital infusion centre)	£109 per hour	NHS reference costs[13]

[1]Only 6 patients were reported to have a Hickman line inserted and the majority of patients had a PICC line. To be consistent within the IV arm, we assumed a constant cost for a PICC line for all patients. A Hickman line is likely to increase costs only marginally in the IV arm as these lines involve a surgeon's time to be inserted. OPAT, outpatient parenteral antimicrobial therapy. Insertion is based on nursing time (Band 7/8a) and equipment used. Removal is based on 15 minutes nurse time plus equipment.

assumed that a new line had to be inserted and the old line was removed, and a cost was assigned accordingly.

- The OPAT type recorded at the 42-day follow-up visit was used for each participant for all intravenous episodes in the 12-month follow-up period.
- Durations of antibiotics, intravenous episodes and inpatient stays per participant were truncated at 365 days.
- OPAT costs were applied at one hour per day when applicable.
- Where participants had an OPAT type of 'inpatient' and their intravenous episode extended beyond the inpatient stay, a weighted average cost of 2/5 Self-Administrating and 3/5 District Nurse was applied to the length of intravenous episode following discharge from hospital, this was the proportion of District Nurse to self-administering OPAT witnessed in the trial. The same weighted average was applied to participants with missing OPAT type.

Data analysis

The base-case analysis used an intention to treat approach conducted on the multiple imputed dataset. Total mean costs, QALYs and associated standard errors were presented as well as the difference in total mean costs and QALYs between arms and a 95% confidence interval. Cost and QALY differences were estimated using a multivariate Generalised Linear Model with an identify link and Gauss distribution for QALY estimates and a Gamma distribution for cost estimation. In addition, covariates adjusted for in the QALY estimation were baseline utilities and age. An incremental cost-effectiveness ratio (ICER) is also presented; representing the difference in costs divided by the difference in QALYs. Participants with censored data (not due to death during the follow-up period) had costs and QALYs extrapolated using multiple imputation.

To explore the uncertainty around the cost and QALY differences and the resulting ICER, a non-parametric bootstrapping technique was employed with 1,000 iterations based on the unadjusted, non-imputed data. Results are presented using a cost-effectiveness plane, showing all 1,000 cost-effectiveness pairs.

The analysis was conducted using Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.)

Sensitivity analysis

Four sensitivity analyses were conducted: complete case analysis, mean imputation and two different assumptions for OPAT costs. Instead of using the above weighted average for participants with missing OPAT type, two scenarios were explored by varying the OPAT cost: applying solely the cost of a District Nurse, and applying solely the cost of Self-Administration. The sensitivity analyses results were analysed using the 2 sample t-test.

Ethical approval

Research Ethics Committee Ref: 13/SC/0016 South Central Oxford REC B. Written informed consent was obtained from each participant by good clinical practice-trained research staff after assessing their understanding of the patient information sheet.

Results

Baseline characteristics are presented in Table 2. The participants were well matched with no significant differences.

A total of 1,054 participants were recruited between June 2010 and October 2015; 527 in each arm, with 39 having no end-point data. In total, 23 participants died during the trial. Clinical results from the trial indicate that oral antibiotics are non-inferior to intravenous antibiotics with regards to definitive treatment failure. Treatment failure occurred in 74 of 506 participants (14.6%) in the intravenous arm and in 67 of 509 participants (13.2%) in the oral arm. The difference in risk, oral (PO) compared to intravenous (IV), of definitive failure in the intention-to-treat analysis was -1.4 percentage points (95% confidence interval, -5.6 to 2.9). These results were mirrored in the complete case intention-to-treat population, the per-protocol analysis (at least 4 weeks of randomised treatment received) and worst-case scenario analysis. These results are presented in more detail in the clinical trial paper[8].

Resource use

Only 26 participants (2.5%) had missing resource use data; 12 in the intravenous arm and 14 in the oral arm. The results for complete case resource use are presented in Table 3, split between resources used in the initial 42-day intervention period and the remaining post-intervention period.

From the results in Table 3, it can be seen that for intervention resource use there was a statistically significant difference between arms in mean antibiotic and intravenous therapy duration. There were no statistically significant differences between arms in mean number of antibiotic prescriptions, number of inpatient admissions or inpatient duration. For resource use during the post-intervention period there was only a statistically significant difference between arms for intravenous therapy duration. This is mirrored at a total level where the only statistically significant difference between arms was for intravenous therapy; the mean total number of days for which intravenous therapy was received was 34.62 days longer in the intravenous arm. Table 4 presents the mean costs in both arms for unadjusted complete cases.

The difference between arms in mean antibiotic and intravenous costs was statistically significant for intervention, post-intervention and total costs. However, there was only a statistically significant difference in mean total intervention costs, not for total post-intervention costs, £2,215 (95% CI £1,462 to £2,969) and £511 (95% CI -£343 to £1,366), respectively. This smaller and non-significant difference in total post-intervention costs is mainly due to lower intravenous costs after the initial 6-week intervention period.

Table 2. Baseline characteristics of participants.

Characteristic	Intravenous (n=527)	Oral (n=527)	Total (n=1054)
Age, years			
Median (interquartile range)	61 (49–70)	60 (49–70)	60 (49–70)
Range	18–92	18–91	18–92
Sex			
Male, number (%)	320 (60.7)	358 (67.9)	678 (64.3)
Baseline surgical procedure, number (%)			
No implant or device present; debridement of chronic osteomyelitis performed	153 (29.0)	169 (32.1)	322 (30.6)
No implant or device present; debridement of chronic osteomyelitis not performed	25 (4.7)	29 (5.5)	54 (5.1)
Debridement and implant retention	124 (23.5)	123 (23.3)	247 (23.4)
Removal of orthopaedic device for infection	89 (16.9)	78 (14.8)	167 (15.8)
Prosthetic joint implant removed	68 (12.9)	67 (12.7)	135 (12.8)
Prosthetic joint implant, one-stage revision	47 (8.9)	43 (8.2)	90 (8.5)
Surgery for discitis, spinal osteomyelitis, or epidural abscess; debridement performed	8 (1.5)	5 (0.9)	13 (1.2)
Surgery for discitis, spinal osteomyelitis, or epidural abscess; debridement not performed	13 (2.5)	13 (2.5)	26 (2.5)

The total mean cost combining intervention and non-intervention costs was £13,275 in the intravenous arm compared to £10,549 in the oral arm, a difference of £2,727, a statistically significant result.

Multiple imputation results reflect the complete case results presented above (a difference of £2,727), with intravenous mean costs £2,740 (£1,488 to £3,992) higher than in the oral arm, statistically significant.

Health outcomes: QALYs

The utility values and missing data proportions for each follow-up point for the EQ-5D-3L questionnaire are presented in Table 5, along with complete case QALYs. For EQ-5D-5L results the proportion of missing data is similar in both arms. Participants in the oral antibiotic arm started from a slightly higher utility at baseline; 0.330 (SD 0.379) compared to 0.298 (SD 0.363). At the 14-day follow-up the mean utility was higher in the intravenous arm compared to the oral antibiotics arm; 0.437 (SD 0.304) compared to 0.421 (SD 0.338). The mean utilities for the remainder of the follow-up points revert to being higher in the oral arm. There were no statistically significant differences in mean utilities at any follow-up point. The utilities in both arms improved at each follow-up point compared to the previous one.

The mean EQ-5D-3L utilities, along with 95% confidence intervals are presented in Figure 1.

Complete case QALYs results mirror those of the utilities with no statistically significant differences between arms at any follow-up point; intravenous 0.558 (SD 0.265) compared to oral 0.535 (SD 0.300). Results consider a zero-utility score for participants who died during the trial.

Multiple imputation results are provided in Table 6. These reflect the complete case results; there is no statistically significant difference in QALYs; however, the results now favour the oral arm.

Cost-effectiveness analysis

In the incremental analysis (Table 7) base-case mean costs were observed to be lower in the oral arm and mean QALYs were higher in the oral arm, suggesting that the strategy of treating bone and joint infections with oral antibiotics is a dominant strategy (cheaper and with higher QALYs). The results of the sensitivity analyses indicate that the base-case conclusions were robust. Results for complete case, using mean imputation and altering the costs of OPAT were all consistent with the results from the base-case analysis; the total mean cost difference for all scenarios were within the range of £2,617 to £2,887. All of these results showed a statistically significant difference between arms. The results of multiple imputation and complete case QALYs show no statistically significant differences between arms. Uncertainty surrounding this result is explored further in the next section.

Uncertainty

The main uncertainty in the results relates to QALYs; the difference in QALYs between arms is not statistically significant.

The cost-effectiveness plane presented in Figure 2, shows 1,000 bootstrap samples of the ICER, along with a point estimate illustrating the mean differences in costs and QALYs between treatment arms. The graph also includes a 95%

Table 3. Mean resource use per participant (complete case).

Resource type	Intravenous N=515 (97.7%)	Oral N=513 (97.3%)		
	Mean (SD)	Mean (SD)	Difference‡	95% confidence interval
Intervention period (Day 1 – 42)				
Number of antibiotic prescriptions	3.53 (2.15)	3.53 (2.31)	0.002	-0.271 to 0.275
Antibiotic duration (days)*†	38.18 (32.64)	30.47 (29.12)	7.71	3.92 to 11.49
Number of inpatient admissions	1 (0)	1 (0)	0	N/A
Inpatient duration (days)	17.71 (14.83)	17.22 (18.62)	0.492	-1.57 to 2.55
Total number of days IV therapy was received*†	40.08 (30.52)	11.86 (27.45)	28.22	24.66 to 31.77
Post-intervention period (Day 43 – 365)				
Number of antibiotic prescriptions	3.17 (3.08)	2.90 (3.00)	0.274	-0.098 to 0.647
Antibiotic duration (days)	151.6 (181.6)	155.1 (161.2)	-3.53	-24.54 to 17.48
Number of inpatient admissions	0.829 (1.15)	0.821 (1.11)	0.008	-0.130 to 0.147
Inpatient duration (days)	8.51 (16.78)	9.13 (18.11)	-0.618	-2.76 to 1.52
Total number of days IV therapy was received	12.50 (34.83)	6.10 (18.49)	6.40	2.99 to 9.81
Total				
Number of antibiotic prescriptions	6.70 (3.74)	6.43 (3.93)	0.276	-0.194 to 0.746
Antibiotic duration (days)	189.8 (177.5)	185.6 (156.3)	4.18	-16.29 to 24.65
Number of inpatient admissions	1.83 (1.15)	1.82 (1.11)	0.01	-0.129 to 0.147
Inpatient duration (days)	26.22 (24.28)	26.35 (28.47)	-0.125	-3.36 to 3.11
Total number of days IV therapy was received	52.58 (40.37)	17.96 (33.52)	34.62	30.08 to 39.16

*The antibiotic duration sums the duration of all antibiotic use, including simultaneous use. For example, if a patient was on two different antibiotics for a period of five days, this would add to a duration of ten days. Intravenous duration includes the length of intravenous episodes where an intravenous line was needed to administer intravenous antibiotics (including more than one intravenous antibiotic taken at the same time as another).

†Antibiotic and IV therapy in the intervention period was not readily available from the data, the duration of these therapies were calculated by including all therapies finishing on or within 42 days of the start of first therapy treatment. SD, standard deviation; IV, intravenous

‡Difference between arms was calculated using t-tests

confidence ellipse from the bootstrap samples, and a line illustrating the £30,000 threshold currently used by NICE to assess cost-effectiveness[9]. All bootstrap samples had a lower cost in the oral arm compared to the intravenous arm, and the majority of cost-effectiveness pairs fall into the south-east quadrant, where higher QALYs and lower costs can be observed for the oral arm as compared with the intravenous arm, making an oral intervention dominant for these samples.

Discussion

Statement of principal findings

The difference in costs between arms was £2,740 in the base case results; the use of oral antibiotics in the early treatment of bone or joint infection is significantly cheaper compared to the use of intravenous antibiotics. The results of the EQ-5D-3L questionnaires reflected the trial primary outcome of definitive failures; there was no statistically significant difference in QALYs between arms. This is reinforced by a post-hoc regression of QALYs on 'definite failure', which confirmed that the EQ-5D-3L measure is sensitive to the endpoint, but the endpoint did not differ between arms. With oral antibiotics being clinically non-inferior to intravenous, no statistically significant difference in QALYs plus the costs in the oral arm being significantly less than in the intravenous arm during the trial, the results of the trial suggest that treating patients with bone and joint infections with oral antibiotics is a dominant strategy.

Table 4. Unadjusted costs (complete case).

Cost category	Intravenous N=515 (97.7%)	Oral N=513 (97.3%)		
	Mean (SD)	Mean (SD)	Difference‡	95% confidence interval
Intervention period (Day 1 – 42)				
Antibiotics	£786 (£915)	£435 (£569)	£351	£257 to £443
Inpatient stays	£5,239 (£4,388)	£5,093 (£5,508)	£146	-£464 to £755
Intravenous costs	£2,950 (£2,555)	£1,231 (£1,304	£1,719	£1,471 to £1,968
Total intervention costs	**£8,974 (£6,114)**	**£6,759 (£6,196)**	**£2,215**	**£1,462 to £2,969**
Post-intervention period (Day 43 – 365)				
Antibiotics	£1,206 (£2,497)	£772 (£1,865)	£434	£164 to £704
Inpatient stays	£2,517 (£4,963)	£2,700 (£5,358)	-£183	-£815 to £449
Intravenous costs	£577 (£1,566)	£318 (£801)	£259	£107 to £412
Total non-intervention	**£4,301 (£7,060)**	**£3,790 (£6,899)**	**£511**	**-£343 to £1,366**
Total				
Antibiotics	£1,992 (£2,545)	£1,207 (£2,043)	£785	£502 to £1,067
Inpatient stays	£7,756 (£7,183)	£7,793 (£8,420)	-£37	-£995 to £920
Intravenous costs	£3,527 (£2,920)	£1,548 (£1,618)	£1,979	£1,690 to £2,268
Total costs	**£13,275 (£10,113)**	**£10,549 (10,371)**	**£2,727**	**£1,473 to £3,980**

SD, standard deviation.

‡Difference between arms was calculated using t-tests

There was no statistically significant difference in antibiotic duration in the post-intervention period suggesting that participants in the oral arm were not prescribed more antibiotics once finished on the intervention antibiotic. This is reflected by the difference between arms in the number of antibiotic prescriptions during the post intervention period not being statistically significant. As expected, the mean number of days that intravenous therapy was received during the intervention period was significantly higher in the intravenous arm; 28.22 days (95% confidence interval 24.66 to 31.77). Interestingly there was a significant difference in the post-intervention period also; 6.40 days (95% confidence interval 2.99 to 9.81). We found no significant difference in mean inpatient stay duration; however, there was a significant difference for median inpatient stay duration; 14 days (interquartile range 11 to 21) in the intravenous arm and 11 days (interquartile range 8 to 20) in the oral arm ($p<0.001$)[8].

Exploring uncertainty in the results using non-parametric bootstrapping, and for the bootstrap sample taken, there is a 100% probability that the oral strategy is cost saving. There is a 67% probability that the oral strategy results in higher QALY values than the intravenous strategy. This confirms prior evidence of clinical non-inferiority. Results from sensitivity analyses were consistent with the base case results.

A post-hoc analysis estimating mean costs for intravenous and oral antibiotics for a 42-day course out with the intention to treat population was conducted. The mean cost of a 6-week course of antibiotics (drug only) was £997 (SD £873) for intra- venous antibiotics and £188 (SD £648) for oral antibiotics, highlighting the higher costs for intravenous drugs.

Strengths and limitations of the research

This is the first economic evaluation of oral versus intravenous antibiotics for treating bone and joint infections. The trial was a large inclusive, pragmatic trial with most participants following their allocated treatment and retention was high[8].

Table 5. EQ-5D-3L and quality adjusted life-years; complete cases.

Timepoint	EQ-5D-5L complete cases						Quality adjusted life-years complete cases					
	Intravenous		Oral				Intravenous		Oral			
	Mean (SD)	N (%)	Mean (SD)	N (%)	Difference (SE) ‡	95% confidence interval	Mean (SD)	N (%)	Mean (SD)	N (%)	Difference (SE) ‡	95% confidence interval
Baseline	0.298 (0.363)	386 (73.2%)	0.330 (0.379)	388 (73.6%)	-0.032 (0.027)	-0.085 to 0.020						
14 days	0.437 (0.304)	308 (58.4%)	0.421 (0.338)	309 (58.6%)	0.016 (0.026)	-0.035 to 0.067	0.014 (0.011)	297 (56.3%)	0.014 (0.012)	300 (56.9%)	-0.0001 (0.0009)	-0.0020 to 0.0017)
42 days	0.513 (0.316)	366 (69.4%)	0.531 (0.330)	374 (71.0%)	-0.018 (0.024)	-0.064 to 0.029	0.037 (0.022)	265 (50.3%)	0.037 (0.023)	274 (52.0%)	-0.0002 (0.0019)	-0.0039 to 0.0036
120 days	0.534 (0.337)	312 (59.2%)	0.544 (0.354)	306 (58.1%)	-0.011 (0.028)	-0.065 to 0.044	0.111 (0.063)	280 (53.1%)	0.116 (0.064)	279 (52.9%)	-0.0045 (0.0054)	-0.0150 to 0.0060
365 days	0.564 (0.339)	301 (57.1%)	0.576 (0.346)	286 (54.3%)	-0.016 (0.028)	-0.067 to 0.044	0.365 (0.200)	224 (46.3%)	0.365 (0.213)	228 (43.3%)	-0.0003 (0.0191)	-0.0378 to 0.0372
Total year							0.558 (0.265)	179 (34.0%)	0.535 (0.300)	182 (31.8%)	0.023 (0.030)	-0.036 to 0.081

SD, standard deviation; N, number; SE, standard error.

‡Difference between arms was calculated using t-tests

Wellcome Open Research 2020, 4:108 Last updated: 08 JAN 2020

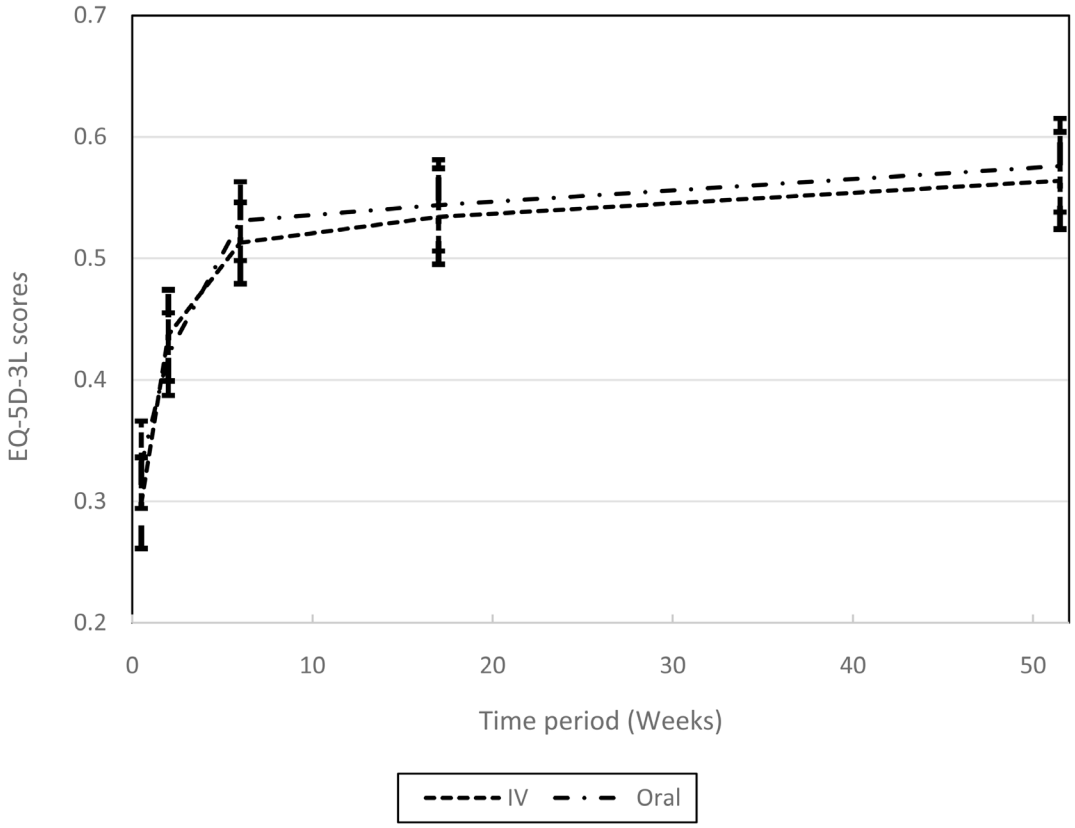

Figure 1. Complete case mean EQ-5D-3L utilities at baseline and follow-ups, with 95% confidence intervals.

Table 6. Multiple imputation results – total mean quality-adjusted life years (QALYs).

Intravenous mean QALYs (SE)	Oral mean QALYs (SE)	Difference (95% confidence interval)
0.537 (0.013)	0.545 (0.015)	-0.007 (-0.045 to 0.031)

SE, standard error

Table 7. Incremental cost-effectiveness results – base case and sensitivity analysis.

Analysis	Intravenous Mean costs (SE)	Oral Mean costs (SE)	Difference (95% confidence interval) ‡	Intravenous Mean QALYs (SE)	Oral Mean QALYs (SE)	Difference (95% confidence interval)‡	Incremental cost per QALY
Base case (Multiple imputation)	£13,274 (£446)	£10,534 (£453)	£2,740 (£1,488 to £3,992)	0.537 (0.013)	0.545 (0.015)	-0.007 (-0.045 to 0.031)	Oral antibiotics dominant
Complete case	£13,275 (£10,113)	£10,549 (10,371)	£2,727 (£1,473 to £3,980)	0.558 (0.265)	0.535 (0.300)	0.023 (–0.036 to 0.081)	Oral antibiotics dominant
Mean imputation costs	£13,141 (£10,036)	£10,406 (£10,269)	£2,735 (£1,508 to £3,963)	0.537 (0.013)	0.545 (0.015)	-0.007 (-0.045 to 0.031)	Oral antibiotics dominant
District Nurse costs for all missing OPAT types	£13,274 (£448)	£10,657 (£463)	£2,617 (£1,354 to £3,880)	0.537 (0.013)	0.545 (0.015)	-0.007 (-0.045 to 0.031)	Oral antibiotics dominant
Self-administration costs for all missing OPAT types	£13,230 (£442)	£10,343 (£448)	£2,887 (£1,656 to £4,118)	0.537 (0.013)	0.545 (0.015)	-0.007 (-0.045 to 0.031)	Oral antibiotics dominant

QALYs, quality-adjusted life years; SE, standard error; OPAT, outpatient parenteral antimicrobial therapy.

‡Difference between arms was calculated using a generalized linear model

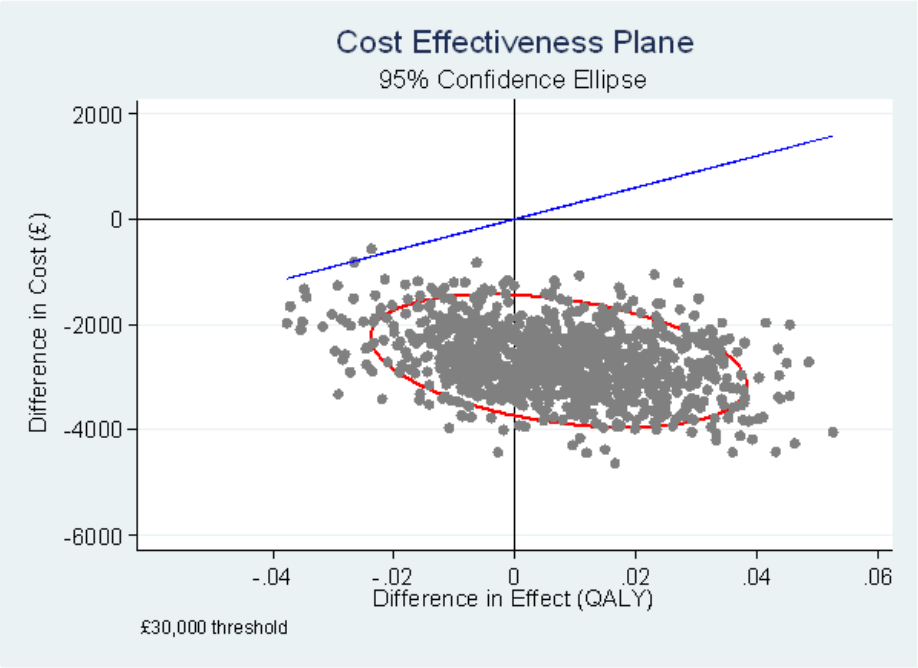

Figure 2. Cost-effectiveness plane.

Some of the limitations arose from the high level of missing data for the EQ-5D-3L questionnaire (from 26.4% at baseline to 45.7% at 365-days). No costs of surgery for treatment of bone and joint infections were included in this study; this was a pre-randomisation procedure. Cost for insertion and removal of the intravenous line were obtained from clinical staff who had previously calculated the costs of insertion and removal, however we did not receive a detailed breakdown of the materials used, only time needed. However, given cost estimates were obtained from a reliable source, we believe that this will not impact our results. The data are likely to be skewed and the complete case results in Table 3, Table 4 and Table 5 should be viewed in this light. However, due to the large sample size the effect of the skewness will be moderate and generalised linear models were used in the main analysis.

Strengths and weaknesses in relation to other studies, discussing important differences in results

Despite the high economic burden of bone and joint infections, economic studies in this area are rare[22] and there is a need for more economic evaluations of joint infections[23]. No previous studies have explored the cost-effectiveness of oral antibiotics to treat bone and joint infections compared to intravenous antibiotics. A cost-effectiveness study, comparing exchange arthroplasty with debridement and prosthetic retention for infected total hip arthroplasty in the elderly, found debridement and retention improved quality-adjusted life expectancy and increased costs in 65- and 80-year-old men and women over a lifetime[24]. The incremental cost-effectiveness ratio ranged from $500 for frail 80 year old men to $21,800 in 65 year old women. In an economic evaluation by Kapadia *et al.*, the authors explored the use of chlorhexidine cloths prior to total knee arthroplasty and found that assuming 1,000 total knee arthroplasty patients a net saving of $2.1 million would occur[25]. The study assumed an estimated cost of $130,000 per revision due to infection, with 22 patients in a cohort of 1,000 without use of the cloth becoming infected, and 6 infections in the cohort using the cloth. Two studies estimated revision costs for infected prostheses; for infected hips, estimated costs are £22,000[4] and for infected knees, £30,000[5]. These costs included the revision surgery and subsequent inpatient stay. A 2013 review summarised the economic literature in the treatment of periprosthetic infections, looking at prevention, treatment and surgical options for periprosthetic infections[26]. Unlike OVIVA, the treatment costs included the cost of revision and a 1993 study estimated an average cost of $50,000 to $60,000 per patient with an infected total hip arthroplasty[22].

Meaning of the study

Annually in the UK, it is conservatively estimated that there are 6,350 post-operative bone and joint infections; if all of these were treated with oral antibiotics during the first six weeks of therapy there is a potential for savings to the NHS of around £17 million annually. The important benefits to patients receiving oral antibiotics compared to receiving intravenous antibiotics include a shorter median inpatient stay as well as decreased indwelling intravenous catheter days with associated reduced inconvenience, discomfort and complications[27]. Ultimately, the savings made by the use of oral antibiotics in half of the trial participants have already exceeded the running costs of the clinical trial.

Unanswered questions and future research

Further savings in the management of bone and joint infection might be possible by defining the optimal duration of therapy. At present, there are few trial data to guide duration and, in the opinion of the authors, there may be considerable redundancy in current standard treatment protocols. The benefits of limiting systemic antimicrobial exposure may well include a reduction in selection for antibiotic resistance and a consequent cost saving in managing treatment failures or transmission events.

What is already known on this topic:

- The 'gold standard' treatment for bone and joint infections is surgery followed by a course of intravenous antibiotics
- There is a growing body of literature showing that oral antibiotics are as effective as intravenous in treating this cohort
- Oral antibiotics are less costly than intravenous antibiotics

What this study adds:

- Oral antibiotics are non-inferior compared to intravenous antibiotics in treating bone and joint antibiotics with regards to definitive treatment failure
- Treating a bone or joint infection with an initial 6 weeks course of oral antibiotics saves an estimated £2,700 over one year, per person, compared to early treatment with intravenous antibiotics

Data availability

Underlying data

The ethical permissions governing this trial limit data sharing to approved studies of antibiotic treatment. Requests for participant level data should be directed to the chief investigator; Dr Matthew Scarborough (email address: Matthew.Scarborough@ouh.nhs.uk). Requests from interested parties will be granted access to the data when there is appropriate approval from their home institution for their analysis and where the purpose of the proposed analysis relates to antibiotic treatment, consistent with our ethical approval for sharing data

ClinicalTrials.gov number – NCT00974493 - ISRCTN91566927

Reporting guidelines

Figshare: CHEERS checklist for "Cost-effectiveness of oral versus intravenous antibiotics (OVIVA) in patients with bone and joint infection: evidence from a non-inferiority trial". https://doi.org/10.6084/m9.figshare.8197682.v1[28].

Author statement

NM, CG and AB conceived the presented idea. AB was co-investigator on the OVIVA project. NM carried out the analysis with input from CG and AB. NM and CG drafted the manuscript and AB, IR, HKL, PB, MM, BA, JF and MS contributed to the final version. MM conceived OVIVA, designed the protocol, obtained funding and recruited patients. PB conceived the OVIVA project, obtained funding, designed the protocol, recruited patients, gathered data and had general oversight of the OVIVA trial. MS was principle investigator of the OVIVA trial.

Acknowledgements

The following individuals make up the OVIVA collaborators: S. Warren, S. Hopkins, J. Folb, E. Moore, N. Jenkins, R.A. Seaton, C.J. Hemsley, J.A.T. Sandoe, I. Aggarwal, S.C. Ellis and R.K. Sutherland.

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 3

Reviewer Report 03 January 2020

https://doi.org/10.21956/wellcomeopenres.17138.r37435

✔ **Simon Dixon**
Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, UK

Thank you for the changes.

Please note that the text relating to the cost-effectiveness plane needs amending as it still refers to confidence intervals. Also, the threshold is now missing from the Figure; it would be preferred if this were included.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health Economics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 07 Jan 2020

Nicola McMeekin, University of Glasgow, Glasgow, UK

Thank you for your helpful comments and suggestions during the reviewing process, we appreciate the time you have taken to read and review this manuscript. In the latest version of the manuscript we have amended Figure 2 by including the £30,000 threshold line and updated the text so the 95% confidence intervals are now described as an ellipse.

Competing Interests: No competing interests were disclosed.

Version 2

Reviewer Report 26 November 2019

https://doi.org/10.21956/wellcomeopenres.17023.r36921

Diarmuid Coughlan
Health Economics and Evidence Synthesis Group, Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK

I am happy with the updates. I note that in Table 5 - you have N(%) and then you are inconsistent with the use of % in the table. Please correct formatting.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health Economics; Hospital pharmacy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 10 Dec 2019

Nicola McMeekin, University of Glasgow, Glasgow, UK

Thank you for spotting the formatting inconsistency in Table 5, this has been corrected.

Competing Interests: No competing interests were disclosed.

Reviewer Report 21 November 2019

https://doi.org/10.21956/wellcomeopenres.17023.r36922

Simon Dixon
Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, UK

Thank you for making amendments in response to my comments. There are a few points that require a little more work.

In relation to point 5, your comments suggest that you do not know the full details of how the unit costs for insertion and removal were generated. This needs to be recognised as a limitation of the research;

whether you consider this uncertainty to be important should also be stated and explained/justified.

In relation to point 6, you have clarified that the bootstrapping did not account for covariate adjustment (and presumably the imputation of missing data). This needs to be clarified by saying that the bootstrapping is based on the unadjusted, non-imputed data. This is important as the adjustment and imputation can have a marked impact on the results, leading to a discrepancy between the bootstrapped and regression-based results.

In relation to point 7, you have stated the type of test undertaken, but you have not justified this. The cost data are likely to be heavily skew (e.g. Table 4), the EQ-5D data are likely to be bimodal (e.g. Table 5) and the prescription data are likely to be count data (e.g. Table 3). Consequently, the appropriateness of the t-test is open debate.

In relation to point 14, you very politely point out my incorrect interpretation of the 95% intervals on the ICER; thank you for that. What confused me is that it is very unusual for confidence intervals to be plotted on the cost-effectiveness plane. The use of confidence ellipses is the preferred method for summarising uncertainty in relation to a joint density function; this approach should be used here.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health Economics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 Dec 2019

Nicola McMeekin, University of Glasgow, Glasgow, UK

Many thanks for your useful comments, we feel that they have improved our paper. In response to your comments we have made the following amendments to our manuscript:

We have added two points to the Limitation section: units costs for insertion and removal, and the use of t-tests for comparing complete case results.
We have made it clear in the Methods section that the bootstrapping iterations are based on unadjusted, non-imputed data.
And finally we have revised the cost-effectiveness plane to include a confidence eclipse.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 23 August 2019

https://doi.org/10.21956/wellcomeopenres.16715.r36165

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Diarmuid Coughlan
Health Economics and Evidence Synthesis Group, Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK

General Comments:
This is an important paper on the cost-effectiveness of oral versus intravenous antibiotics in patients with bone and joint infection. This is a very important clinical question as proven with the results of the trial published in the NEJM. It is also a very broad clinical question with nuance regarding types of infections, health status of patients and antibiotics used in the trial.

Some minor edits:

1. Table 1: be consistent with decimal point use (£190 vs £34.00).

2. Table 2: Not sure you need the Total column.

3. Table 3 & 4: Labelling could be better. Place N beside Intravenous N=515 (97.7%) Oral N=513 (97.3%).
   Also, label days: Intervention period (Day 1-42) and post-intervention period (Day 43 -360)

4. Discussion section, paragraph: strengths and weaknesses in relation to other studies, discussing important differences in results.
   Typo: No previous studies have explored the cost-effectiveness of oral antibiotics to treat bone and joint infections compared to **oral (Should be intravenous?)** antibiotics.

5. Meaning of study - I would like to see a formal budget impact analysis. However, I realise that this would be a lot of additional work.

6. I was confused by this statement:
   The important non-financial benefits to patients receiving oral antibiotics i**nclude a shorter median inpatient stay as well as decreased indwelling intravenous catheter days** with its associated inconvenience, discomfort and r**educed complications.**

   a) Table 3 reports non no difference in mean inpatient stays during the intervention and post-intervention period. Why mention median?
   b) Indwelling IV catheter complications - was this is an issue in the clinical trial? If so, please elaborate.

7. Please add the original trial registration information in the data availability section:
   - ClinicalTrials.gov number
   - NCT00974493
   - ISRCTN91566927

8. I agree with many of the comments made by the other reviewer (Simon Dixon). Don't think Table 5 is necessary. I would try to cut down on some of the details in the other tables and put into a supplemental appendix. (e.g. 'Total' section of Table 3). Table 4 could be more parsimonious using a 'Landscape' table with 3 rows for the cost category and columns for intervention and post-intervention period stratified by IV and oral. Table 9 needs a better label.

9. Statement on Covariate adjustment is a good point made by Simon.

Overall, it's a good paper. I think 9 Tables and 2 Figures in the main manuscript is too much and distracting for a broad clinical/scientific audience.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health Economics; Hospital pharmacy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 29 Oct 2019

Nicola McMeekin, University of Glasgow, Glasgow, UK

Thank you for taking the time to review this manuscript. We address your comments below:
1) Thank you, we have changed this in the table.
2) We are happy to delete the Total column if the reviewer deems this necessary.
3) Thank you, we have changed this in both tables.
4) Changed, thanks you!
5) Whilst we agree that this might add value to our study, we feel that this would be beyond the scope of our study and would require substantial additional data collection and analysis and almost merit a stand-alone paper. We hope that the reviewer might agree with us on this point.
6) Thank you, we have made this sentence clearer and added a reference.
6a) Median was mentioned in the NEJM paper, so we have included it to be consistent with that.

6b) No, this issue was not added as a result of the trial, but a discussion into the benefits of oral antibiotics, a reference has been added to clarify this.
7) We have added this, thank you.
8) Table 5 has been removed and tables 6 and 7 (EQ-5D and QALY results) have been combined in Table 5. If necessary we could put the unit cost table – Table 1 in an a supplementary appendix, if that is possible with Wellcome Open Research. We have changed the label for Table 9 (now Table 7).
9) Thank you, we have included more detail in the manuscript - please see the reply to Simon's comment.

Competing Interests: No competing interests were disclosed.

Reviewer Report 12 August 2019

https://doi.org/10.21956/wellcomeopenres.16715.r36050

?

Simon Dixon
Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, UK

General comment
The work is undertaken to a high standard, is clearly written and produces robust conclusions. The research is very important.
Some relatively minor details are omitted and need to be added. Some methods deviate from the 'standard approach', and as such, need to be justified more clearly.

Specific comments

1. An undefined personal communication is used for an important estimate. Either something should be said about its source (e.g. opinion or audit) or a published estimate should be used [first paragraph, p3].

2. "Missing resource and quality of life data was imputed….", should be "…were imputed" [middle paragraph, second column, p3].

3. More should be said in the Introduction or Methods about how IV and oral antibiotics are administered and the role of the OPAT team. This is important for readers to assess the generalisability of findings. It is also unclear how you can have an "inpatient" OPAT type [p4]; I thought OPAT was outpatient.

4. "…an appropriate method to replace missing data utilised". On what basis was appropriateness assessed? Just giving a reference is insufficient. Also, I would have thought that Reference 11 would have been used for this assessment, but it is not referenced at this point. [p4]

5. In Table 1, simply saying that “insertion” and “Removal” costs were based on expert opinion is insufficient. Presumably, the experts didn’t come up with the cost; they provided timings, staff grades and consumables, which were then costed up. Those resource estimates should be provided, possibly as notes to the table. [p4]

6. It is stated that QALYs were adjusted for baseline utility, but not how this was done; providing a reference is insufficient. If this was done statistically, which is implied by the reference, how did you then generate the bootstrapped estimates? [p4]

7. The statistical tests used to compare groups in all the tables are not described. These need to be justified.

8. The inpatient duration for oral therapy is almost identical to that for IV. An explanation of this needs to be given. A lay reader may equate oral therapy to home treatment and IV therapy to inpatient treatment, therefore inpatient duration may be expected to be similar to number of days of IV therapy. [p6]

9. The sentence starting “Table 4 presents….” should be the first sentence of the next paragraph.

10. An exploratory analysis appears in the middle of the results, would this be better framed as a sensitivity analysis? The way it is presented suggest that it is unplanned/post-hoc.

11. Is Table 5 necessary? The results are given in the text anyway (except for the estimates of variation, which could be added). [p8]

12. The post-hoc regression of QALYs on failure is not a result; it should be part of the discussion about the perceived weakness of the EQ-5D for this condition/study. [p9]

13. The description of the bootstrapped replications in cost-effectiveness plane on [p9] and [p11] don’t seem to match the figure, for example 82.8% fall into the south east quadrant. Do you mean, fall to right of the cost-effectiveness threshold line? You also say that 17.2% of the sample result in higher QALYs, really?

14. The threshold line in the SE quadrant is not necessary. [p10]

15. The statement starting “There is a 100% probability that...” includes an ‘and statement’ which makes interpretation confusing/difficult. This needs to be re-written. You may also want to consider qualifying the statement by saying that it relates to this particular set of bootstrapped samples, another set may produce a lower probability. [p11]

16. Something needs to be said about covariate adjustment within the economics analysis. Whilst an adjustment has been made for baseline utility (but not described sufficiently), it is common in economic evaluation for other covariates to be included in a regression based analysis, sometimes in the form of a related regression on QALYs. Whilst I don’t consider this to be a big issue in this instance, the authors should describe this alternative approach and explain the appropriateness their approach, this is methodological uncertainty.

17. Something needs to be said about the truncation of data. Alternative methods would be to take account of this within a regression analysis of costs and QALYs using appropriate specifications,

or to extrapolate the costs/QALYs. Again, whilst I don't consider this to be a big issue in this instance, the authors should describe this alternative approach and explain the appropriateness of their approach, this is methodological uncertainty.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health economics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 29 Oct 2019

Nicola McMeekin, University of Glasgow, Glasgow, UK

Thank you for taking the time to comment on our manuscript. We address each of your points in our response below:

1) Thank you - we have added 'opinion' to clarify this point.
2) Thank you, we have changed this.
3) We have expanded on this on the information in paragraph 3 on the administration of IV and oral antibiotics.
The different types of OPAT collected on the CRF were:

- Self-administering
- District nurse administering
- Attending clinic for administration
- In intermediate or long-term care facility administering antibiotics
- Completed IVs as inpatient
- Not on IVs, PO on discharge only

That is why there is an 'inpatient' OPAT type.
4) Thank you, we have moved reference 11 to the sentence before in the manuscript as suggested

and rewritten this sentence.
5) Thank you – we have added more detail to the table. The expert had already computed the cost for other purposes so we didn't get a full breakdown to include.
6) Thank you, this has been clarified in the manuscript, there was no adjustment for baseline utilities in the bootstrapping sample.
7) T-tests were used to compare differences for continuous measures between groups in complete case analysis. For MI results we used a glm model. This is now being mentioned in the manuscript.

8) The median difference is different from the mean, the median difference is 14 v 11 days, this was a statistically significant difference, and mentioned in the Discussion section. Also, the trial protocol allowed for participants to have an initial maximum of 7 days treatment before being randomised so many were on IV antibiotics initially. The standard deviation for the mean in the oral arm was larger than that for the IV arm showing wider variability in this arm compared to the IV arm. Finally, there is likely to be a number of reasons that a participant would require an inpatient stay other than IV antibiotics.
9) Thank you, we have changed this.
10) Thank you, this analysis was carried out to confirm that a course of 42 days intravenous antibiotics is more expensive than 42 days oral antibiotics, and has been moved to the Discussion section as a post-hoc analysis.
11) This has been deleted, thank you.
12) Thank you, this has been deleted from results and moved to the Discussion section.
13) Thank you – we have amended the paper.
14) Thank you, this is not a threshold line, it is a line that depicts the upper 95% confidence interval.
15) Thanks, this sentence has been amended.
16) We have amended the 'Data analysis' section to include the covariates used in the adjustment.
17) Censored but not dead participants had costs and QALYs extrapolated in the MI adjustment, we have included a sentence to explain this in the Methods section.

Competing Interests: No competing interests were disclosed.