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Langton Hewer, S.C., Smyth, A.R., Brown, M. et al. (11 more authors) (2021) Intravenous or oral antibiotic treatment in adults and children with cystic fibrosis and Pseudomonas aeruginosa infection: the TORPEDO-CF RCT. Health Technology Assessment, 25 (65). ISSN 1366-5278

https://doi.org/10.3310/hta25650

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Health Technology Assessment

Volume 25 • Issue 65 • November 2021

ISSN 1366-5278

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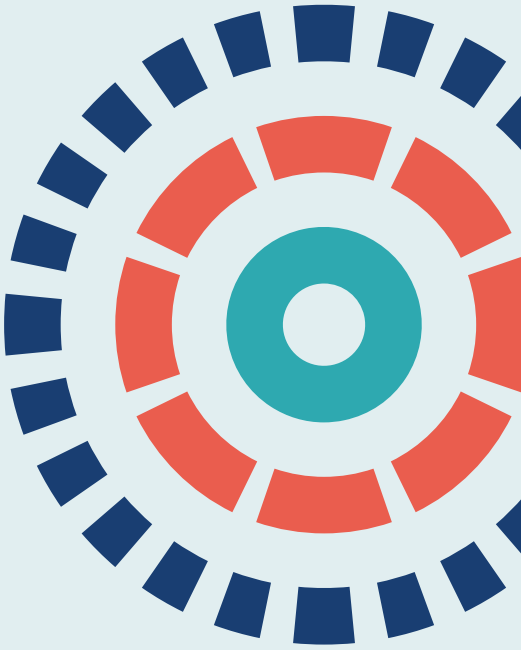

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Intravenous or oral antibiotic treatment in adults and children with cystic fibrosis and *Pseudomonas aeruginosa* infection: the TORPEDO-CF RCT

Simon C Langton Hewer,[1,2*†] Alan R Smyth,[3†] Michaela Brown,[4] Ashley P Jones,[4] Helen Hickey,[4] Dervla Kenna,[5] Deborah Ashby,[6] Alexander Thompson,[7] Laura Sutton,[4] Dannii Clayton,[4] Barbara Arch,[4] Łukasz Tanajewski,[8] Vladislav Berdunov[8] and Paula R Williamson[4] on behalf of the TORPEDO-CF study group

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Declared competing interests of authors: Alan R Smyth reports grants from Vertex Pharmaceuticals, Inc. (Boston, MA, USA), personal fees from Vertex Pharmaceuticals, Inc., non-financial support from Teva Pharmaceuticals (Petah Tikva, Israel) and non-financial support from Novartis International AG (Basel, Switzerland) outside the submitted work. In addition, Alan R Smyth has a patent for alkyl quinolones as biomarkers of *Pseudomonas aeruginosa* infection and uses thereof issued and was a member of the Health Technology Assessment (HTA) Clinical Evaluation and Trials Committee (from 1 April 2011 to 1 April 2016). Deborah Ashby has been a member of various National Institute for Health Research (NIHR) Committees from 2008 to 2018 [HTA Commissioning Sub-Board (Expression of Interest) 1 April 2016 to 31 March 2017; HTA Funding Teleconference Members 31 May 2016 to 1 October 2016; NIHR Clinical Trials Unit Standing Advisory Committee 1 May 2008 to 1 May 2014; HTA Board Recruitment 1 January 2016 to 31 December 2018; HTA Remit and Competitiveness Group 1 May 2018 to 30 November 2018; HTA Funding Committee

Policy Group (formerly Commissioning Strategy Group) 1 November 2015 to 30 November 2018, Imperial College London; and HTA Commissioning Committee, 1 November 2015 to 31 December 2018, all while at Imperial College London]. In additon, Deborah Ashby is supported by NIHR Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. Paula R Williamson was Director of Liverpool Clinical Trials Centre (April 2005–December 2018; formerly Medicines for Children Clinical Trials Unit), which received funding from NIHR (end date 31 August 2021), and reports grants from the University of Liverpool, during the conduct of the study. We would like to thank the European Cystic Fibrosis Society Clinical Trial Network for its help and financial support in setting up the trial in Italy.

Published November 2021
DOI: 10.3310/hta25650

This report should be referenced as follows:

Langton Hewer SC, Smyth AR, Brown M, Jones AP, Hickey H, Kenna D, *et al*. Intravenous or oral antibiotic treatment in adults and children with cystic fibrosis and *Pseudomonas aeruginosa* infection: the TORPEDO-CF RCT. *Health Technol Assess* 2021;**25**(65).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 07/51/01. The contractual start date was in December 2009. The draft report began editorial review in August 2019 and was accepted for publication in December 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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Abstract

Intravenous or oral antibiotic treatment in adults and children with cystic fibrosis and *Pseudomonas aeruginosa* infection: the TORPEDO-CF RCT

Simon C Langton Hewer,[1,2*†] Alan R Smyth,[3†] Michaela Brown,[4] Ashley P Jones,[4] Helen Hickey,[4] Dervla Kenna,[5] Deborah Ashby,[6] Alexander Thompson,[7] Laura Sutton,[4] Dannii Clayton,[4] Barbara Arch,[4] Łukasz Tanajewski,[8] Vladislav Berdunov[8] and Paula R Williamson[4] on behalf of the TORPEDO-CF study group

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Background: People with cystic fibrosis are susceptible to pulmonary infection with *Pseudomonas aeruginosa*. This may become chronic and lead to increased mortality and morbidity. If treatment is commenced promptly, infection may be eradicated through prolonged antibiotic treatment.

Objective: To compare the clinical effectiveness, cost-effectiveness and safety of two eradication regimens.

Design: This was a Phase IV, multicentre, parallel-group, randomised controlled trial.

Setting: Seventy UK and two Italian cystic fibrosis centres.

Participants: Participants were individuals with cystic fibrosis aged > 28 days old who had never had a *P. aeruginosa* infection or who had been infection free for 1 year.

Interventions: Fourteen days of intravenous ceftazidime and tobramycin or 3 months of oral ciprofloxacin. Inhaled colistimethate sodium was included in both regimens over 3 months. Consenting patients were randomly allocated to either treatment arm in a 1 : 1 ratio using simple block randomisation with random variable block length.

Main outcome measures: The primary outcome was eradication of *P. aeruginosa* at 3 months and remaining free of infection to 15 months. Secondary outcomes included time to reoccurrence, spirometry, anthropometrics, pulmonary exacerbations and hospitalisations. Primary analysis used intention to treat (powered for superiority). Safety analysis included patients who had received at least one dose of any of the study drugs. Cost-effectiveness analysis explored the cost per successful eradication and the cost per quality-adjusted life-year.

Results: Between 5 October 2010 and 27 January 2017, 286 patients were randomised: 137 patients to intravenous antibiotics and 149 patients to oral antibiotics. The numbers of participants achieving the primary outcome were 55 out of 125 (44%) in the intravenous group and 68 out of 130 (52%) in the oral group. Participants randomised to the intravenous group were less likely to achieve the primary outcome; although the difference between groups was not statistically significant, the clinically important difference that the trial aimed to detect was not contained within the confidence interval (relative risk 0.84, 95% confidence interval 0.65 to 1.09; $p = 0.184$). Significantly fewer patients in the intravenous group (40/129, 31%) than in the oral group (61/136, 44.9%) were hospitalised in the 12 months following eradication treatment (relative risk 0.69, 95% confidence interval 0.5 to 0.95; $p = 0.02$). There were no clinically important differences in other secondary outcomes. There were 32 serious adverse events in 24 participants [intravenous: 10/126 (7.9%); oral: 14/146 (9.6%)]. Oral therapy led to reductions in costs compared with intravenous therapy (–£5938.50, 95% confidence interval –£7190.30 to –£4686.70). Intravenous therapy usually necessitated hospital admission, which accounted for a large part of this cost.

Limitations: Only 15 out of the 286 participants recruited were adults – partly because of the smaller number of adult centres participating in the trial. The possibility that the trial participants may be different from the rest of the cystic fibrosis population and may have had a better clinical status, and so be more likely to agree to the uncertainty of trial participation, cannot be ruled out.

Conclusions: Intravenous antibiotics did not achieve sustained eradication of *P. aeruginosa* in a greater proportion of cystic fibrosis patients. Although there were fewer hospitalisations in the intravenous group during follow-up, this confers no advantage over the oral therapy group, as intravenous eradication frequently requires hospitalisation. These results do not support the use of intravenous antibiotics to eradicate *P. aeruginosa* in cystic fibrosis.

Future work: Future research studies should combine long-term follow-up with regimens to reduce reoccurrence after eradication.

Trial registration: Current Controlled Trials ISRCTN02734162 and EudraCT 2009-012575-10.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 65. See the NIHR Journals Library website for further project information.

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List of abbreviations

A&E	accident and emergency
AE	adverse event
BMI	body mass index
BNF	*British National Formulary*
CEAC	cost-effectiveness acceptability curve
CF	cystic fibrosis
CFQ	Cystic Fibrosis Questionnaire
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FEF_{25-75}	forced expiratory flow at 25–75% of forced vital capacity
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	good clinical practice
GLM	generalised linear model
GP	general practitioner
HCHS	Hospital and Community Health Service
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IDSMC	Independent Data and Safety Monitoring Committee
IMP	investigational medicinal product
INB	incremental net benefit
IQR	interquartile range
ITT	intention to treat
i.v.	intravenous
LCTC	Liverpool Clinical Trials Centre
MCRN CTU	Medicines for Children Research Network Clinical Trials Unit
MedDRA	Medical Dictionary for Regulatory Activities
MRSA	meticillin-resistant *Staphylococcus aureus*
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PFGE	pulsed-field gel electrophoresis
PHE	Public Health England
PI	principal investigator
PISC	patient information sheet and consent form
PPI	patient and public involvement
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
REC	Research Ethics Committee
SAE	serious adverse event
SAR	serious adverse reaction
SD	standard deviation
SE	standard error
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TMG	Trial Management Group
TORPEDO-CF	Trial of Optimal TheRapy for Pseudomonas EraDicatiOn in Cystic Fibrosis
TSC	Trial Steering Committee
VNTR	variable number tandem repeat

Plain English summary

Cystic fibrosis is a genetic condition that affects mucous glands, causing sticky mucus in the lungs and digestive system. People with cystic fibrosis are prone to lung infection with a bacterium called *Pseudomonas aeruginosa*, which can lead to serious long-term complications and death. It is possible to eradicate *P. aeruginosa* if antibiotics are started promptly and taken for several months.

The Trial of Optimal TheRapy for Pseudomonas EraDicatiOn in Cystic Fibrosis (TORPEDO-CF) was designed to find out if intravenous ceftazidime and tobramycin were better at eradicating *P. aeruginosa* than oral ciprofloxacin.

A total of 286 children, young people and adults with cystic fibrosis joined the study from 70 UK and two Italian centres. Approximately half of the participants received treatment with intravenous antibiotics and half with oral antibiotics. All participants received inhaled colistin for 3 months and were followed up for a minimum of 15 months.

We studied whether or not either treatment eradicated *P. aeruginosa*, and if reinfection happened during follow-up. We also collected data on lung function, other chest infections and hospital admissions, and examined whether or not one treatment was more cost-effective than the other.

In total, 15 adults joined TORPEDO-CF, so the study population may not totally match the wider cystic fibrosis population; however, in TORPEDO-CF, we found that intravenous antibiotics did not achieve persistent eradication of *P. aeruginosa* in a greater proportion of cystic fibrosis patients. We also found that oral antibiotics were more cost-effective than intravenous antibiotics. The intravenous antibiotics group had fewer hospital admissions during follow-up, but, as they were usually admitted for their initial treatment, this was not considered an advantage over the oral antibiotics group.

The TORPEDO-CF results do not support the use of intravenous antibiotics to eradicate *P. aeruginosa* in cystic fibrosis and, when the findings of this trial are applied in routine clinical practice in the NHS, patients will most likely receive oral treatment as an outpatient, avoiding the need for hospital admission.

Scientific summary

Background

Cystic fibrosis is the most common life-limiting recessively inherited condition in white populations. It is a multisystem disorder in which the airways frequently become blocked with mucus, often associated with respiratory infections. These infections may lead to progressive respiratory failure and ultimately to death from breathing failure. *Pseudomonas aeruginosa* is a common infection in the lungs of patients with cystic fibrosis.

However, there is uncertainty about the best method to eradicate *P. aeruginosa* from the lower respiratory tract and several different strategies are used, including oral quinolones such as ciprofloxacin, and intravenous and nebulised antibiotics.

The Trial of Optimal TheRapy for Pseudomonas EraDicatiOn in Cystic Fibrosis (TORPEDO-CF) was conducted to assess the effectiveness and safety of two eradication regimens in children, young people and adults with cystic fibrosis.

Methods

Study design

This was a Phase IV, multicentre, parallel-group, randomised controlled trial that compared the effects of intravenous therapy with oral therapy in participants with cystic fibrosis.

Participants were randomised in a ratio of 1 : 1 to receive up to 3 months of treatment, and, once treatment had stopped, they were then followed up for a minimum of 15 months.

The trial also included an economic evaluation to estimate the incremental cost per quality-adjusted life-year for intravenous therapy compared with oral therapy.

Eligibility criteria

Eligible participants had a confirmed diagnosis of cystic fibrosis and a positive isolation of *P. aeruginosa*, were aged > 28 days, were either *Pseudomonas* naive (i.e. never previously had *P. aeruginosa* isolated from samples) or *Pseudomonas* free (i.e. infection free for at least 1 year), and were able to start allocated treatment within 21 days from the date of the positive microbiology report. Participants were excluded if the *P. aeruginosa* was resistant to one or more of the trial antibiotics, if they had a known hypersensitivity or other contraindication to any of the trial antibiotics, if they were already receiving *P. aeruginosa* suppressive therapy (such as an inhaled antibiotics), if they had received any *P. aeruginosa* eradication therapy within the previous 9 months, or if they were pregnant or breastfeeding. Participants could be randomised into TORPEDO-CF only once and could not be randomised within 4 weeks of taking part in another intervention trial.

Recruitment

Randomisation and blinding

Participants were randomised in a 1 : 1 ratio; randomisation sequences were computer-generated, stratified by centre. Owing to the nature of both therapies, blinding was not possible during the course of the trial.

Outcome measures

Primary outcome

The primary outcome of the trial was defined as successful eradication of *P. aeruginosa* infection 3 months after allocated treatment had started, with the participant remaining infection free through to 15 months after the start of allocated treatment.

Secondary outcomes

The secondary outcomes of the trial were:

- time to reoccurrence of original *P. aeruginosa* infection
- reinfection with a different genotype of *P. aeruginosa*
- lung function (forced expiratory volume in 1 second, forced vital capacity and forced expiratory flow at 25–75% of forced vital capacity)
- oxygen saturation
- growth and nutritional status – height, weight and body mass index
- number of pulmonary exacerbations
- admission to hospital
- number of days spent as an inpatient in hospital during treatment phase, and between 3 and 15 months after randomisation
- quality of life (as measured using the Cystic Fibrosis Questionnaire)
- utility (as measured using the EuroQol-5 Dimensions)
- adverse events
- other sputum/cough microbiology (meticillin-resistant *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Aspergillus* spp., *Candida* spp. infection)
- cost per patient (from an NHS perspective)
- incremental cost-effectiveness ratio (cost per successfully treated patient, cost per quality-adjusted life-year)
- carer burden (absenteeism from education or work)
- participant burden (absenteeism from education or work).

The protocol wording for the outcome 'number of days spent as an inpatient in hospital during treatment phase and between 3 and 15 months after randomisation' is 'Number of days spent as inpatient in hospital over the three-month period after allocated treatment has finished treatment, and between three months and 15 months after eradication treatment has finished (other than 14 days spent on initial intravenous treatment)'. It has been changed in the list of secondary outcomes to aid clarity.

Sample size

The total target number of participants was 286 (143 in each treatment group).

Statistical methods

Primary and secondary outcome data were analysed following the intention-to-treat principle. Safety analyses included participants' data if they had received at least one dose of the randomised treatment.

The statistical analysis plan was developed prior to the final analyses being conducted.

The number and percentage of participants who were classified as a success or a failure for the primary outcome were presented for each treatment arm. The difference between the groups was tested using the chi-squared test, and the relative risk and associated 95% confidence intervals were presented.

The secondary outcomes were analysed using the following methods: binary outcomes were analysed using the chi-squared test, longitudinal data were analysed using mixed models, time-to-event data were analysed using log-rank tests, and continuous data were analysed using a Mann–Whitney *U*-test, as appropriate.

Economic analysis

An economic analysis was conducted that assessed the incremental cost per successful eradication of *P. aeruginosa* infection 3 months after allocated treatment had started, and remaining infection free through to 15 months after the start of allocated treatment, in the oral therapy arm compared with the intravenous therapy arm. The time horizon for the analysis was 15 months post randomisation, and an NHS and Personal Social Services perspective was used for the collection and incorporation of resource use. All costs were calculated in Great British pounds using the price year 2016/17. Where possible, unit costs were sourced from national databases. To account for missingness in the data, multiple imputation was used ($m = 25$). Regression analysis for incremental costs and outcomes was adjusted for baseline utility and age, with the correlation between costs and patient outcomes controlled using bootstrap sampling with replacement ($n = 2000$).

The secondary analysis calculated quality-adjusted life-years by applying preference weights to recorded EuroQol-5 Dimensions, three-level version, scores from patients or carers (on behalf of patients). Using a cost-effectiveness threshold (λ) of £20,000 per quality-adjusted life-year, the incremental net benefit of treating patients with oral therapy compared with intravenous therapy was calculated. Sensitivity analyses explored key drivers of cost-effectiveness identified a priori, including the use of the specialised cystic fibrosis reimbursement tariff for patients, societal costs and using different functional forms for the cost regression-based models.

Results

Participants who were randomised to the intravenous antibiotic therapy group had a reduced likelihood of successful eradication of *P. aeruginosa* 3 months after the start of treatment and remaining infection free through to 15 months after the start of allocated treatment (relative risk 0.84, 95% confidence interval 0.65 to 1.09; $p = 0.184$). The results from the sensitivity analysis were robust to changes that were made. These results did not change the original conclusion.

Owing to the small number of participants with samples available for variable number tandem repeat typing at both time points, the analysis of the outcome 'time to reoccurrence of the original *P. aeruginosa* infection' should be interpreted with caution. This also applies to the results of the analysis of the outcome 'infection with a different and distinct genotype of *P. aeruginosa*'.

The results of the analysis of the secondary outcomes did not show an effect over time on percentage predicted forced expiratory volume in 1 second, percentage predicted forced expiratory flow at 25–75% of forced vital capacity, or oxygen saturation. Forced vital capacity was significantly better in the intravenous antibiotic group than in the oral group (mean difference 3.14, 95% confidence interval 0.15 to 6.14; $p = 0.040$); however, this finding should be interpreted with caution as there was no adjustment for multiple testing. Similarly, body mass index (adults) was significantly lower in the intravenous group than in the oral group (mean difference −0.73, 95% confidence interval −1.39 to −0.08; $p = 0.029$) but this was based on a small number of adults with available data (13 in total). There was no evidence of an effect at 15 months on oxygen saturation or on height for age *z*-score, weight for age *z*-score or body mass index *z*-scores in children.

During 15 months' follow-up, 52 out of 146 (35.6%) participants in the oral antibiotic group and 38 out of 137 (27.7%) participants in the intravenous antibiotic group experienced a pulmonary exacerbation.

The difference was not statistically significant. Significantly fewer participants in the intravenous group [intravenous 40/129 (31%) vs. oral 61/136 (44.9%)] were hospitalised in the 12 months following eradication treatment (relative risk 0.69, 95% confidence interval 0.50 to 0.95; $p = 0.020$). During the same 12-month period, the median hospital stay for participants in both groups was 0 days (interquartile range 0–13 days for the oral group and 0–3 days for the intravenous group; $p = 0.005$). There were no statistically significant differences between study groups for the number of participants who had cough or sputum samples containing meticillin-resistant *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Aspergillus* spp. or *Candida* spp.

There were no statistically significantly differences between the two treatment groups at 15 months across any of the domains in each of the quality-of-life questionnaires.

The median number of days of absenteeism from education or work for carers and participants was not statistically significantly different between the two treatment groups.

There were no significant safety concerns in either of the groups.

Oral therapy led to lower overall costs than intravenous therapy, and had similar or greater clinical effectiveness. For a threshold of £20,000 per quality-adjusted life-year, oral therapy generated £6770.80 (95% confidence interval £5027.40 to £7906.20) benefit per patient compared with intravenous therapy.

Conclusions

Intravenous therapy did not significantly improve the eradication rate of *P. aeruginosa* when compared with oral therapy; the clinically important difference that was set at the beginning of the trial was not contained in the 95% confidence interval, indicating that intravenous therapy is not clinically beneficial when compared with oral therapy in the treatment of *P. aeruginosa*. The health economic analysis also showed that oral therapy was more cost-effective than intravenous therapy, indicating that when the findings of this trial are implemented in routine clinical practice, most patients will receive oral treatment as an outpatient and many admissions will be avoided. This will reduce treatment burden and will reduce health-care costs.

Recommendations for future research

Future research studies should combine long-term follow-up with regimens to reduce reoccurrence after eradication.

Trial registration

This trial is registered as ISRCTN02734162 and EudraCT 2009-012575-10.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 65. See the NIHR Journals Library website for further project information.

Chapter 1 Introduction

Scientific background

Cystic fibrosis (CF) is the most common life-limiting recessively inherited condition in white populations. It is a multisystem disorder in which the airways frequently become blocked with mucus, often associated with respiratory infections. These infections may lead to progressive respiratory failure and ultimately to death from breathing failure. *Pseudomonas aeruginosa* is a common infection in the lungs of patients with CF. The age-specific prevalence of *P. aeruginosa* in pre-school children is 9%, rising to 32% for 10- to 15-year-olds.[1] Early infection can be eradicated in the majority of patients. However, once chronic infection is established, *P. aeruginosa* is virtually impossible to eradicate and is associated with increased morbidity and mortality.[2] Long-term infection is associated with poor outcomes, including more rapid decline in lung function, such as the amount of air expired in 1 second of forced expiration [forced expiratory volume in 1 second (FEV_1)].[3,4] New isolation of *P. aeruginosa* is treated with antibiotics in an attempt to eradicate the infection and to delay acquisition of chronic infection.[5] However, there is uncertainty about the best method to eradicate *P. aeruginosa* from the lower respiratory tract, and several different strategies are used, including oral quinolones such as ciprofloxacin, and intravenous (i.v.) and nebulised antibiotics.[6–10]

There are clear differences between the available treatments in terms of the impact on the patient and their family, the use of resources and the cost of treatment. However, few studies have compared the efficacy and cost-effectiveness of these treatments.

Fourteen days of i.v. treatment will usually necessitate admission to hospital and siting of one or more i.v. lines for drug infusion. The siting of lines can be traumatic, especially for children and their families.

Intravenous aminoglycosides are commonly used and they require further blood tests for monitoring of plasma levels, and can be associated with kidney and inner ear damage.[11] No study has yet been conducted to investigate the therapeutic advantage of i.v. and oral treatment.

In 2005, the NHS National Institute for Health Research (NIHR) commissioned the Medicines for Children Research Network to assess the feasibility of conducting a randomised controlled trial to investigate the prevention of colonisation with *P. aeruginosa* in CF patients. This report was completed in 2007, having surveyed UK clinical practice, surveyed opinions of CF patients and families, and assessed the number of potentially eligible patients for such a trial.[12] The result of this feasibility study was to show that, generally, clinicians treat first or new growth of *P. aeruginosa* in accordance with the UK CF Trust guidelines[13] and 95% of clinicians reported that they would consider i.v. treatment of first isolation of *P. aeruginosa*. In addition, 71% of clinician and 43% of consumer respondents would consider entry for themselves/their patients into a randomised controlled trial comparing oral with i.v. antibiotics. The conclusion of the study stated '[T]he clinical community are in equipoise when considering effectiveness of eradication therapy for treatment of *P. aeruginosa* in patients with cystic fibrosis' and recommended that it is feasible to consider the initiation of a randomised controlled trial investigating eradication therapy to treat *P. aeruginosa* in patients with CF.

This study has been conceived and designed in response to addressing this clinical equipoise and has been commissioned by the NIHR.

Rationale for research

There is equipoise about the best method to eradicate *P. aeruginosa* from the lower respiratory tract. Several strategies exist to treat early infection with *P. aeruginosa*. This includes the use of inhaled antibiotics, such as colistin and tobramycin,[9,14,15] oral quinolones, such as ciprofloxacin,[6,10] and i.v. antibiotics, usually consisting of a combination of an aminoglycoside with a beta-lactam.

Antibiotic strategies for eradication of *P. aeruginosa* in people with CF have been investigated in a systematic review of randomised clinical trials,[16] which concluded that there is an urgent need for well-designed and well-executed trials. The review made the specific recommendation that any future trial should investigate the hypothesis to see if antibiotic treatment of early *P. aeruginosa* infection prevents or delays chronic infection, and whether or not this then results in an appreciable clinical benefit to patients, without causing them harm. The systematic review made the recommendation that the following outcomes be considered for any future randomised controlled trial: spirometric lung function; nutritional status;[11] and socioeconomic outcomes, including quality of life.

The UK CF Trust has published guidance for antibiotic treatment for CF, including treatment for eradication of newly acquired *P. aeruginosa* infection.[11] This guidance recommends energetic treatment for a patient who has isolated *P. aeruginosa* where cultures have previously been negative and the report commented that there is no evidence favouring any particular regimen for eradication. The guidance states that appropriate treatment in this situation will include oral ciprofloxacin for the duration of treatment up to 3 months or i.v. treatment such as a beta-lactam antibiotic (e.g. ceftazidime or meropenem) or an anti-pseudomonal penicillin in combination with i.v. tobramycin.[11] Intravenous antibiotics are usually administered for 10–14 days in patients with CF, although there have been no randomised controlled trials of shorter treatment durations.

The rationale for choosing 14 days of i.v. treatment and for choosing 3 months for oral treatment is that both of these regimens are standard practice in many UK CF centres identified in the feasibility study,[12] both are standard recommendations within the published UK guideline[11] and they are believed to represent current best practice.

Interventions

Participants recruited into the study were randomised to one of the following treatment groups.

Group A

In this treatment group, participants received up to 14 days (recommended treatment duration of 14 days; minimum treatment duration 10 days) of i.v. antibiotics as follows:

- Ceftazidime 150 mg/kg/day, in three divided doses (maximum of 3 g three times daily). Some centres used a once-daily continuous infusion (where the maximum daily dose would usually be 6 g/day) or twice-daily regimen for ceftazidime. These centres were permitted to continue using this regimen for the study and should have followed their local dosing guidelines.
- Tobramycin 10 mg/kg/day once daily (maximum 660 mg/day). Some centres used a twice-daily or thrice-daily regimen for tobramycin. These centres were permitted to continue using their current regimen for the study and should have followed their local dosing guidelines.

Therapeutic drug monitoring was used to guide tobramycin dosing as per national guidelines[11] and usual clinic procedures.

Group B

In this treatment group, participants received 3 months (12 weeks) of treatment oral ciprofloxacin twice daily. Ciprofloxacin dose was 20 mg/kg twice daily (maximum 750 mg twice daily). This was in

line with the *British National Formulary* (BNF) for children.[17] Some clinicians preferred to use a lower dose of 15 mg/kg twice daily for children < 5 years, as used in national CF guidelines.[11]

Both treatment arms received 3 months (12 weeks) of nebulised colistin in conjunction with the randomised treatment. The colistin dose was as recommended by the UK CF Trust: 1,000,000 units twice daily for children aged ≤ 2 years and 2,000,000 units twice daily for children aged > 2 years and adults. If the colistin was administered using an I-neb™ (Philips Respironics, Murrysville, PA, USA), then a lower dose of 1,000,000 units twice daily was used for all ages.

It was considered likely that during the study period a small proportion of participants would develop a further *P. aeruginosa* infection. These participants were treated as per local centre guidelines.

Objective

This study aimed to establish the superiority of 14 days of i.v. therapy compared with 3 months of oral therapy.

Chapter 2 Trial design and methods

Study design

This study was a Phase IV, multicentre, parallel-group, randomised controlled trial comparing 14 days of i.v. antibiotic therapy with 3 months of oral antibiotic therapy for participants with CF (*Figure 1*).

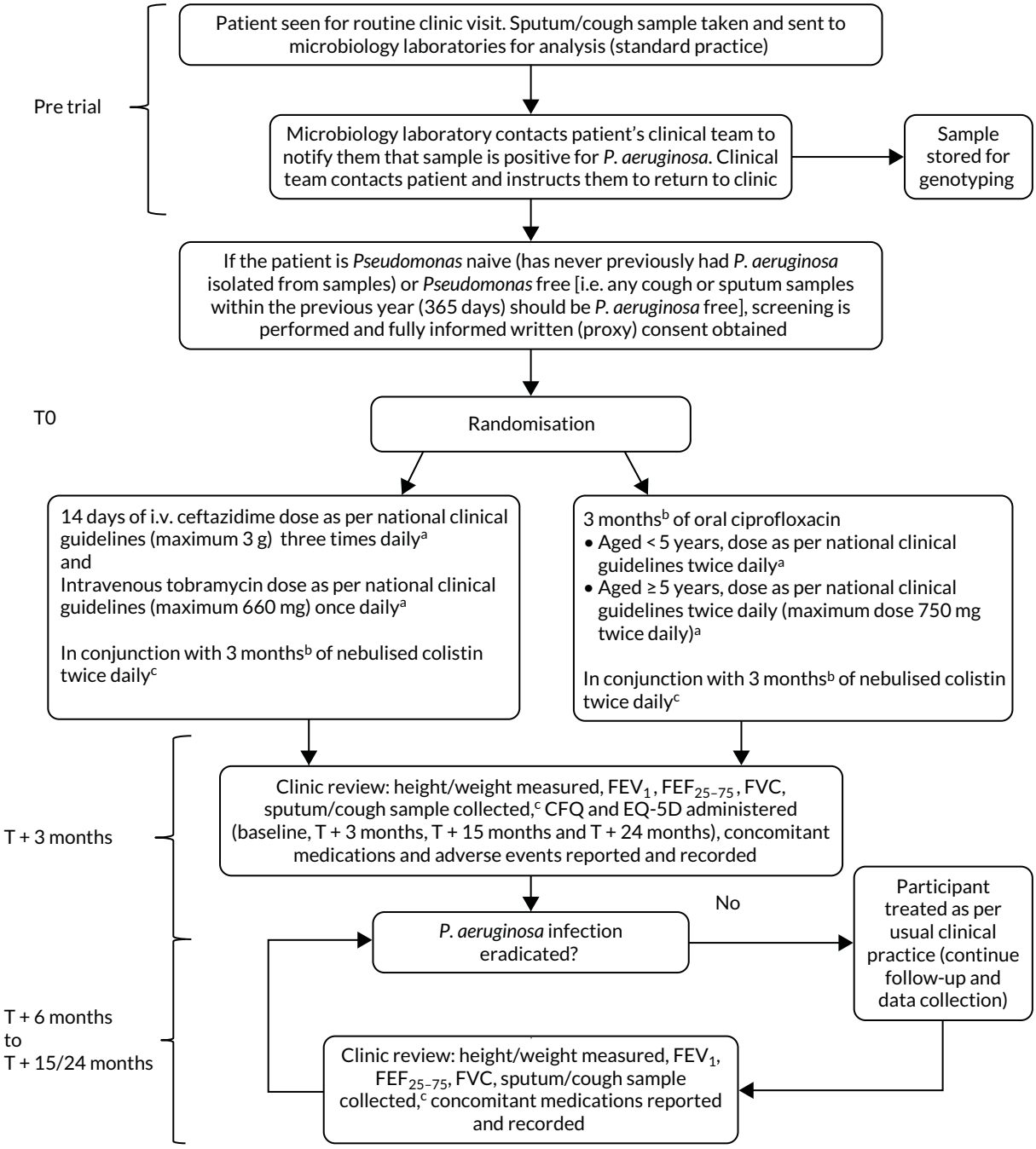

FIGURE 1 The TORPEDO-CF study design. a, Sites that are unable to comply with the trial dosing regimen can use their current dosing regimen as long as the total daily dose administered is within national clinical guidelines; b, 3 months is defined as 12 weeks; and c, sample stored for genotyping.

Trial registration and ethics

The trial was registered on the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database on 5 May 2009 (as EudraCT number 2009-012575-10) and received clinical trials authorisation from the Medicines and Healthcare products Regulatory Agency on 2 November 2009 (clinical trials authorisation reference 12893/0220/001). The trial and all subsequent protocol amendments were reviewed and authorised by the Medicines and Healthcare products Regulatory Agency.

The trial protocol was not initiated until it had received the favourable opinion of the National Research Ethics Committee (REC) (London REC reference 09/H0718/51) on 16 November 2009. It was then reviewed at the research and development offices at participating sites. All subsequent amendments were reviewed and approved by the National Research Ethics Committee, London REC.

The trial was listed on the International Standard Randomised Controlled Trial Number (ISRCTN) registry on 21 May 2009 as ISRCTN02734162.

Participant inclusion and exclusion criteria

Inclusion criteria

- Individuals with a diagnosis of CF.
- Children over the age of 28 days, older children and adult CF participants (i.e. there was no upper age limit).
- Competent adults who had provided fully informed written consent to participate in the trial.
- Minors for whom proxy consent had been given by their parent or legal guardian and who had provided their assent to participate in the trial (where possible).
- Individuals who had isolated *P. aeruginosa* and were either:
    - *P. aeruginosa* naive (i.e. never previously had *P. aeruginosa* isolated from samples) or
    - *P. aeruginosa* free [i.e. any cough or sputum samples within the previous year (365 days) were *P. aeruginosa* free].
- Participants were able to commence treatment no later than 21 days from the date of a *P. aeruginosa*-positive microbiology report.

Exclusion criteria

- Antibiotic resistance of the current *P. aeruginosa* sample to any of ciprofloxacin, ceftazidime, tobramycin or colistin reported by local microbiology laboratory.
- Known participant hypersensitivity to ciprofloxacin, ceftazidime, tobramycin or colistin.
- Other known contraindications to any of ciprofloxacin, ceftazidime, tobramycin or colistin including previous aminoglycoside hearing or renal damage.
- Participants in receipt of *P. aeruginosa*-suppressing treatment, in particular nebulised colistin or tobramycin, or oral ciprofloxacin for the previous 9 calendar months. Short courses of oral ciprofloxacin or i.v. antibiotics (with an anti-pseudomonal spectrum of action) were not a reason for exclusion unless given to treat proven infections with *P. aeruginosa*.
- Treatment with other anti-pseudomonal nebulised antibiotics.
- Pregnant and nursing mothers (women of child-bearing age were counselled on the risks of becoming pregnant during the trial and were offered a pregnancy test).
- Previous randomisation in the Trial of Optimal TheRapy for Pseudomonas EraDicatiOn in Cystic Fibrosis (TORPEDO-CF).
- Previous participation in another related intervention trial within 4 weeks of taking part in TORPEDO-CF.

Recruitment

The trial took place in 70 UK CF centres and two CF centres in Italy.

Recruitment commenced on 5 October 2010 and the final participant was randomised on 27 January 2017.

Informed consent

The trial recruited adults and minors (defined in statutory instrument 2004[18] No. 1031 as aged < 16 years). Informed consent procedures reflected the legal and ethical requirements for obtaining valid written informed consent in these populations.

Prior written informed consent was required for all trial participants. In obtaining and documenting informed consent, the investigator was required to comply with the applicable regulatory requirements, and adhered to the principles of good clinical practice (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki.[19]

Potential participants and their families were provided information regarding the trial both verbally and in writing using the ethics-approved patient information sheets and consent forms (PISCs). They were given the opportunity to discuss the trial with the site team. The PISCs took into account the age of minors and their assent was obtained, where appropriate. Potential participants and their families were provided with a clear overview of the trial and details of the procedures, and the potential risks and benefits of all trial medications were carefully discussed.

Adequate time to consider trial entry (generally 24 hours, although it was acknowledged that some patients/families came to a decision sooner) was allowed and all participants were given the opportunity to ask questions, had the opportunity to discuss the study with their surrogates and had time to consider the information prior to agreeing to participate. All PISCs used in TORPEDO-CF were made available in the native language of the countries participating in the trial (with the exception of Wales, where the majority language was used).

All of the recruiting investigators were experienced CF physicians familiar with imparting information to the relevant trial populations. All investigators requesting consent to participate had attended GCP training. During the screening process, if a potential patient was identified, then they/their parent or the person with parental responsibility were approached by the investigator or a designated member of the investigating team. The trial and its objectives were then described to them, at which point any questions could also be answered. The treatment schedule and trial visits were in line with standard clinical care. The potential risks and benefits of the trial interventions were discussed, as well as what would happen if they chose not to enter the trial or had to withdraw from the trial for any reason.

The right of the patient (non-minors) or parent/legal guardian (for minors) to refuse consent to participate in the trial without giving reasons was respected. After the patient had entered the trial, the clinician remained free to give alternative treatment to that specified in the protocol, at any stage, if they felt that it was in the best interest of the participant. However, the reason for doing so was recorded and the patient remained within the trial for the purpose of follow-up and data analysis according to the treatment option to which they had been allocated. Similarly, the patient remained free to withdraw from the protocol treatment and trial follow-up at any time without giving reasons and without prejudicing their further treatment.

Randomisation

Participants were randomised using a secure (24-hour) web-based randomisation programme, which was controlled centrally by the Liverpool Clinical Trials Centre (LCTC), to ensure allocation concealment. Randomisation lists were generated in a 1 : 1 ratio using simple block randomisation, with random variable blocks of length of two and four after an initial block of length of three to reduce predictability. Randomisation was stratified by site, but this was not disclosed in the protocol to further reduce predictability.

Participant treatment allocation was displayed on a secure web page and an automated e-mail confirmation was sent to the authorised randomiser and the principal investigator (PI) or co-investigator (where applicable) at the randomising site. It was the responsibility of the PI or delegated research staff to inform the pharmacy department at their centre of the potential participant prior to randomisation to ensure that there was a sufficient supply of the study drugs.

In the event of an internet connection failure between the centre and the randomisation system, the centre contacted the LCTC to resolve the problem. In the event that site access could not be promptly reinstated, LCTC would attempt to centrally randomise the patient using the web system. Where this was not possible, LCTC would randomise the participant using a back-up randomisation envelope. Of the 286 participants who were randomised, four were randomised utilising a back-up randomisation envelope.

Interventions

Participants recruited into the study were randomised to one of the following treatment groups.

Group A

Up to 14 days (recommended treatment duration of 14 days; minimum treatment duration 10 days) of i.v. antibiotics as follows:

- Ceftazidime 150 mg/kg/day, in three divided doses (maximum of 3 g three times daily). Some centres used a once-daily continuous infusion (where the maximum daily dose would usually be 6 g/day) or twice-daily regimen for ceftazidime. These centres were permitted to continue using this regimen for the study and should have followed their local dosing guidelines.
- Tobramycin 10 mg/kg/day once daily (maximum 660 mg/day). Some centres used a twice-daily or thrice-daily regimen for tobramycin. These centres were permitted to continue using their current regimen for the study and should have followed their local dosing guidelines.

Therapeutic drug monitoring was used to guide tobramycin dosing as per national guidelines[11] and usual clinic procedures.

Group B

Three months (12 weeks) of oral ciprofloxacin twice daily. Ciprofloxacin dose was 20 mg/kg twice daily (maximum 750 mg twice daily). This was in line with the BNF for children.[17] Some clinicians preferred to use a lower dose of 15 mg/kg twice daily for children < 5 years, as used in national CF guidelines.[11]

Both treatment arms received 3 months (12 weeks) of nebulised colistin in conjunction with the randomised treatment. Colistin dose was as recommended by the UK CF Trust: 1,000,000 units twice daily for children aged ≤ 2 years and 2,000,000 units twice daily for children aged > 2 years and adults. If the colistin was administered using an I-neb™, a lower dose of 1,000,000 units twice daily was used for all ages.

During the study period, it was likely that a small proportion of participants would develop a further *P. aeruginosa* infection. These participants were treated as per local centre guidelines.

Data collection and management

Outcome measures

Primary outcome

The primary outcome is the successful eradication of *P. aeruginosa* infection 3 months after allocated treatment has started, and remaining infection free through to 15 months after the start of allocated treatment.

Secondary outcomes

- Time to reoccurrence of original *P. aeruginosa* infection.
- Reinfection with a different genotype of *P. aeruginosa*.
- Lung function: FEV_1, forced vital capacity (FVC), forced expiratory flow at 25–75% of forced vital capacity (FEF_{25-75}).
- Oxygen saturation.
- Growth and nutritional status: height, weight and body mass index (BMI).
- Number of pulmonary exacerbations. (Definition of pulmonary exacerbation used guidelines by Rosenfeld.[20])
- Admission to hospital.
- Number of days spent as an inpatient in hospital during treatment phase and between 3 and 15 months after randomisation.
- Quality of life [Cystic Fibrosis Questionnaire (CFQ)].
- Utility [EuroQol-5 Dimensions (EQ-5D)].
- Adverse events (AEs).
- Other sputum/cough microbiology [meticillin-resistant *Staphylococcus aureus* (MRSA), *Burkholderia cepacia* complex, *Aspergillus*, *Candida* spp. infection].
- Cost per patient (from an NHS perspective).
- Incremental cost-effectiveness ratio (ICER) [cost per successfully treated patient, cost per quality-adjusted life-year (QALY)].
- Carer burden (absenteeism from education or work).
- Participant burden (absenteeism from education or work).

The protocol wording for the outcome '[N]umber of days spent as an inpatient in hospital during treatment phase and between 3 and 15 months after randomisation' is: '[N]umber of days spent as inpatient in hospital over the three-month period after allocated treatment has finished treatment, and between three months and 15 months after eradication treatment has finished-finished (other than 14 days spent on initial intravenous treatment)'. It has been changed in the list of secondary outcomes to aid clarity.

Data collection tools

Cystic Fibrosis Questionnaire

The CFQ is the only published, disease-specific measure of health-related quality of life (HRQoL) for children (aged 6–13 years), adults and adolescents (aged $\geq$ 14 years) with CF.[21] Twelve domains of HRQoL are covered in a 44-item survey, which includes physical functioning, role functioning, vitality, health perceptions, emotional functioning and social functioning, as well as domains specific to CF: body image, eating disturbances, treatment burden, and respiratory and digestive symptoms.[22] Quality-of-life questionnaires (i.e. CFQs) were completed at baseline, and at 3, 15 and 24 months after the allocated treatment was started. (Note that the 24-month scores were collected for only those trial participants who started allocated treatment before 1 January 2016.)

Health Utility (EuroQol-5 Dimensions)

The EuroQol-5 Dimensions, three-level version (EQ-5D-3L)[23] scores were collected at baseline, and at 3, 15 and 24 months post treatment commencement (24-month scores were collected for only those trial participants who started allocated treatment before 1 January 2016). Participants completed the baseline booklet before their treatment allocation was revealed.

The PI or delegated research staff were required to ensure that the randomisation number and time point at which the questionnaire booklet was administered were recorded and to notify LCTC if a participant was too unwell to complete the questionnaire booklet or missed an assessment. Participants who failed to complete their full treatment allocation were still given the questionnaire booklet to complete at the protocol-defined time points to avoid bias.

Sample size

Original trial sample size calculation

The sample size calculation was based on the primary outcome of initial eradication of *P. aeruginosa* following the start of allocated treatment and continued eradication until 15 months after the start of allocated treatment. Data dating back to 1995 on the eradication of *P. aeruginosa* 3 months after the start of treatment and 12 months following the end of treatment were obtained from an audit conducted on all current CF participants treated according to a standard UK CF trust protocol at Alder Hey Children's Hospital, Liverpool (conducted by Louisa Heaf and Kate Davenport) (Louise Heaf and Kate Davenport, Alder Hey Children's Hospital, 2008, personal communication). The data were treated in accordance with a standard UK CF Trust protocol. Data on 48 children were collected, with infection eradicated in 77% (37/48) of children at 3 months following the start of treatment and 58% (28/48) of children continuing to remain infection free at 12 months after the end of treatment (i.e. equivalent to 15 months after the start of allocated treatment in the proposed trial).

For 90% power, at a 5% level of significance, to detect an absolute difference between the control group (oral ciprofloxacin) and the treatment group (i.v.) of 20% (a difference of between 55% and 75%), 128 participants were required in each group. A 20% difference between the two treatment regimens was regarded to be of clinical importance, since the more intensive i.v. treatment would need to be justified by such a substantial benefit. Based on the experience of the TOPIC trial,[24] in which five out of 244 (2%) participants who were randomised did not provide primary outcome data for the intention-to-treat (ITT) analysis, it was expected that the number of participants who would not provide data for the primary outcome during TORPEDO-CF would be quite small. Every effort was made to follow up all randomised participants, regardless of treatment tolerance, but the sample size was inflated to allow for 10% of participants not providing primary outcome data, increasing the total target sample size to 286 participants.

Based on the results of the feasibility study conducted for the Health Technology Assessment programme,[12] it was found that the median rate per annum for the number of first or new growths of *P. aeruginosa* was 3% (range 1–8%) in adults and was 10% (range 2.5–23%) in children. Applying these estimates to the UK CF population (based on figures from 22 adult centres, 28 paediatric centres and two centres with combined populations) enabled a potential population of eligible adults and children of approximately 122 and 475, respectively, per annum. From the feasibility report, the consent rate was estimated to be 44%; therefore, the anticipated number of eligible participants was approximately 54 adults and 209 children per annum.

Patient and public involvement

TORPEDO-CF was conceived as a NIHR-commissioned call and thus had patient and public involvement (PPI) through this process. In addition, it benefited from a feasibility study that explored

the importance, and acceptability, of the research question for children, young people and their parents, and adults with CF.

In its set-up, TORPEDO-CF profited from PPI involvement through the Young Persons Advisory Group of the Medicines for Children Research Network, which provided input on the design of documentation intended for the use of trial participants (e.g. information sheets and promotional materials).

During its conduct, TORPEDO-CF received support from the CF Trust and PPI representation within the Trial Management Group (TMG) was in the form of ad hoc representation through the CF Trust Special Adviser on Research and Patient Involvement, who advised on activities to enhance engagement with the CF community generally and with potentially eligible individuals in particular.

An important element of PPI involvement was provided by the independent Trial Steering Committee (TSC). PPI representation on the committee provided reassurance that TORPEDO-CF remained of relevance to and in the interests of the CF community.

Changes to the protocol

The first site was opened to recruitment on 18 June 2010 and version 2.0 of the protocol was in operation at this time.

Over the course of the trial, eight substantial amendments were made to the protocol. Each amendment was assessed by the TMG and approved by the REC and by the Medicines and Healthcare products Regulatory Agency. The main corrections to the protocol included changes to the management of the trial and the addition of further guidance for participating sites. The definition of the primary outcome was also amended from '[S]uccessful eradication of *P. aeruginosa* infection at three months post randomisation, remaining infection free through to 15 months post randomisation' to '[S]uccessful eradication of *P. aeruginosa* infection three months after allocated treatment has started, remaining infection free through to 15 months after the start of allocated treatment' to eliminate any systematic bias due to the inevitable delay in starting i.v. treatment compared with oral treatment (caused by the need for the patient to be admitted to hospital to receive i.v. treatment).

The initial changes to the protocol were to provide clarification of the exclusion criteria and the secondary outcomes. Following site set up, several sites raised an issue with regard to differences in site dosing regimens compared with that specified in the protocol. The TMG confirmed that the changes were acceptable clinically and from a trial perspective.

Please refer to the trial protocol for a full list of protocol amendments (see NIHR Journals Library; www.journalslibrary.nihr.ac.uk). A summary of amendments follows.

Protocol version 1.0 (21 August 2009) to version 2.0 (15 February 2010)

- The length of treatment for the i.v. group was changed from 10 to 14 days to reflect clinical practice.
- Inclusion criteria 1 and 3 clarified.
- The inclusion criteria were amended: the text 'has not isolated *P. aeruginosa* from cough, sputum or bronchoalvelolar lavage' was replaced with '[A] minimum number of four consecutive cough or sputum samples should be *P. aeruginosa* free within a 12 month period to satisfy eligibility' and the text 'three weeks after the clinical team has been informed that *P. aeruginosa* has been isolated' was replaced with '21 days'.

- Clarification of text in exclusion criteria 1–5.
- An extra exclusion criterion was added: '[P]revious participation in another intervention trial within four weeks of taking part in TORPEDO-CF'.
- Secondary outcome '[T]ime to reoccurrence of *P. aeruginosa* infection' amended to '[T]ime to reoccurrence of original *P. aeruginosa* infection'.
- Secondary outcome 'time to new *P. aeruginosa* infection' replaced with 're-infection with a different genotype of *P. aeruginosa*'.
- Secondary outcome '[C]arer burden (absenteeism from school or work)' was clarified by changing to '[C]arer burden (absenteeism from education or work)'.
- Clarifications made to section 6, 'Trial treatments'.
- Clarifications made to section 7, 'Assessments and Procedures'.

Protocol version 2.0 (15 February 2010) to version 3.0 (1 September 2010)

- Clarification text added to exclusion criterion 4: '[P]lease note, short courses of oral ciprofloxacin or intravenous antibiotics (with an anti-pseudomonal spectrum of action) are not an exclusion unless they are given to treat proven infections with *P. aeruginosa*'.
- Primary end-point text amended from '[S]uccessful eradication of *P. aeruginosa* infection at three months post randomisation, remaining infection free through to 15 months post randomisation' changed to read '[S]uccessful eradication of *P. aeruginosa* infection three months after allocated treatment has started, remaining infection free through to 15 months after the start of allocated treatment'.
- Secondary end point 8 changed from '[N]umber of days spent as inpatient in hospital over the three-month period post-treatment and between three months and 15 months post-treatment (other than 14 days spent on initial intravenous treatment)' to '[N]umber of days spent as inpatient in hospital over the three-month period post-randomisation and between three months and 15 months post-randomisation (other than 14 days spent on initial intravenous treatment)'.
- In section 8.4 of the protocol, text in sample size calculation changed to reflect change in analysis from post randomisation to post treatment.
- In section 9.7 of the protocol, change in the reporting timelines for AEs/serious adverse events (SAEs), beginning from the time allocation treatment started up to 28 days after treatment cessation.

Protocol version 3.0 (1 September 2010) to version 4.0 (13 December 2011)

- Inclusion criterion 1 changed from '[D]iagnosis of cystic fibrosis (CF) (clinical feature + sweat chloride > 60 mmol/l and/or 2 CFTR [cystic fibrosis transmembrane conductance regulator] mutations)' to '[D]iagnosis of cystic fibrosis (CF)'.
- Trial treatment text (arm A) changed from '[F]ourteen days intravenous ceftazidime 50 mg/kg/dose (maximum three grams) three times daily and intravenous tobramycin 10 mg/kg/d (maximum 660mg) once daily' to '[F]ourteen days intravenous ceftazidime dose as per national clinical guidelines (maximum three grams) three times daily and intravenous tobramycin dose as per national clinical guidelines (maximum 660 mg) once daily'.
- Trial treatment text (arm B) changed from '[T]hree months oral ciprofloxacin < 5 years, 15 mg/kg twice daily, ≥ 5 years, 20 mg/kg twice daily (maximum dose 750 mg twice daily)' to '[T]hree months oral ciprofloxacin, < 5 years, dose as per national clinical guidelines twice daily, ≥ 5 years, dose as per national clinical guidelines twice daily (maximum dose 750 mg twice daily)'.

Protocol version 4.0 (13 December 2011) to version 5.0 (11 January 2012)

- Changes made to section 6, 'Trial Treatments', in relation to the provision of drug by home care companies.

Protocol version 5.0 (11 January 2012) to version 6.0 (17 October 2013)

- Inclusion criterion 5b changed from '*P. aeruginosa* free (i.e. a minimum of four consecutive cough or sputum samples should be *P. aeruginosa* free within a 12 month period to satisfy eligibility.)' to '*P. aeruginosa* free (i.e. any cough or sputum samples within the previous year (365 days) should be *P. aeruginosa* free.)'.
- Exclusion criterion 4 changed from 'previous 9 months' to 'previous 9 calendar months'.
- Removing requirement for all SAEs to be reported on a SAE report form. Replaced with '[A]ll AEs that has been assessed and judged by the investigator to be not serious to be reported on an AE form and returned to MCRN CTU [Medicines for Children Research Network Clinical Trials Unit] as per routine schedule. All SAEs that have been assessed and judged by the investigator to be unrelated or unlikely to be related to be reported on an AE form and returned to MCRN CTU as per routine schedule. All serious adverse reactions (SARs) and Suspected unexpected serious adverse reactions (SUSARs) must be reported immediately by the investigator to the MCRN CTU on a SAR report form.'

Protocol version 6.0 (17 October 2013) to version 7.0 (12 August 2014)

- Addition of University of Liverpool as co-sponsor; it will act as sole sponsor for international sites.

Protocol version 7.0 (12 August 2014) to version 8.0 (23 December 2015)

- Clarifying follow-up period: patients who start randomised treatment before 1 January 2016 will continue follow-up for 24 months, patients who start randomised treatment on or after 1 January 2016 will continue follow-up for 15 months.
- Clarification to section 6, 'Trial Treatments'.

Protocol version 8.0 (23 December 2015) to version 9.0 (12 October 2016)

- Updated number of patients to be enrolled.

Compliance with intervention

Participants' compliance with trial treatment was monitored using participant-completed treatment diaries to record their daily treatment routine.

The majority of the trial treatment for participants in the i.v. antibiotic therapy group was anticipated to be administered during hospital in-patient visits, ensuring accurate monitoring of investigational medicinal product (IMP) compliance. Participants who had experience of administering i.v. antibiotics at home or those who preferred to have home i.v. were allowed to self-administer i.v. antibiotics at the discretion of their local PI. In this event, participants were asked to complete a home i.v. treatment diary each day to ensure compliance with the study medication. Any unused medication and the packaging of all used medication were to be returned at the next scheduled follow-up visit. All returned medication/packaging was destroyed as per local procedures.

Trial management and oversight

University Hospitals Bristol NHS Foundation Trust was the sponsoring organisation, and delegated responsibilities to LCTC, the University of Liverpool and the chief investigator. LCTC was responsible for co-ordination of the trial (see *Appendix 1*).

University of Liverpool was co-sponsor, having no responsibility for the conduct of the trial in the UK, but acting as sole sponsor for non-UK centres (i.e. the University of Liverpool was legally responsible for the non-UK conduct of the trial).

Trial Management Group

The TMG was a multidisciplinary team comprising the chief investigators, scientific co-investigators, PPI representatives, sponsor representative, health economists and members of LCTC (see *Appendix 1*).

The TMG was responsible for the day-to-day clinical and practical aspects of the trial.

Independent Data and Safety Monitoring Committee

The Independent Data and Safety Monitoring Committee (IDSMC) comprised two independent clinicians and a statistician (see *Appendix 2*). The main responsibilities of the IDSMC were to safeguard the interests of the TORPEDO-CF participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall progress and conduct of the trial. The IDSMC met at least annually during the trial and provided recommendations to the TSC. Reports to the IDSMC were produced by the statistical team at LCTC.

Trial Steering Committee

The TSC comprised an independent chairperson, two independent physicians, two PPI representatives, an independent statistician and representatives from the TMG (see *Appendix 2*). An observer from the sponsor and from the funder were also invited to meetings. The TSC met at least annually throughout the trial, both by teleconference and by e-mail, shortly after the IDSMC met and its main role was to provide overall oversight of the trial.

Chapter 3 Statistical methods

General statistical considerations

The analysis and reporting of the study were undertaken in accordance with the Consolidated Standards of Reporting Trials (CONSORT)[25] and the International Conference on Harmonisation E9 Guidelines.[26] The main features of the statistical analysis plan are included here with a full and detailed statistical analysis plan (available at www.uhbristol.nhs.uk/media/3933191/torpedo_final_analysis_statistical_analysis_plan_v2.pdf; accessed 8 October 2021). All statistical analyses were undertaken using SAS® software version 9.3 or later (SAS Institute Inc., Cary, NC, USA).

A two-sided p-value ≤ 0.05 was used to declare statistical significance for all analyses, and all confidence intervals (CIs) were calculated at the 95% level. There were no adjustments for multiple testing; rather, all secondary analyses were treated as hypothesis generating.

The primary analysis followed the ITT principle as far as practically possible; all randomised participants were analysed on the basis of the treatment to which they were randomised, regardless of whether or not they received it. If consent for treatment was withdrawn but the participant was happy to remain in the study for follow-up, then they were followed up until completion. However, if they decided to withdraw consent completely, then the reasons for withdrawal of consent were collected (when possible) and reported for both groups.

Analysis of baseline data

Demographic and baseline characteristics were summarised for each treatment group using descriptive statistics. No formal statistical testing was performed on these data. Descriptive statistics, including the number of observations, mean and standard deviation (SD) for continuous variables, and counts and percentages for discrete variables, were presented, as appropriate.

Analysis of compliance data

For i.v. antibiotic therapy, the number of daily doses that participants received varied by site. The protocol stated that patients should receive at least 10 days of treatment. For these reasons, compliance is presented in terms of the number of days on treatment rather than in terms of the number of doses received.

For oral antibiotic therapy, compliance is presented in terms of the number of doses received and a compliance rate [the percentage of the total doses ($n = 168$: two doses per day for three lots of 28 days) that were received].

For nebulised therapy, compliance is presented in the same way as oral antibiotic therapy. Data are presented split by treatment group.

All compliance data are presented descriptively [total (n), mean, SD, median, interquartile (IQR) range, range, minimum and maximum]. No formal statistical testing was undertaken.

Analysis of primary outcome

The primary outcome, successful eradication of *P. aeruginosa* 3 months after the start of treatment, and remaining infection free through to 15 months after the start of treatment, was a binary outcome. Participants were classified as a success if there was no record of *P. aeruginosa* on their microbiology case report form between 3 and 15 months after treatment commencement, and a failure if there was at least one record of *P. aeruginosa* on their microbiology report during this time.

To determine if a participant had eradicated *P. aeruginosa* at 3 months, they must have had a sample within 28 days on either side of their expected 3-month visit date (treatment commencement date + 84 days), which was at least 2 days after the last date of any anti-pseudomonal treatment. To determine if a patient had remained *P. aeruginosa* free at 15 months, they must have had either a positive sample within the primary outcome window (3–15 months) or a sample within 28 days either side of their expected 15-month visit date (treatment commencement date + 420 days). Participants who had not regrown *P. aeruginosa* and did not have a sample within the 15-month window (defined above) were not included in the primary analysis. If a patient was withdrawn before 15 months of follow-up was completed, they were included in the primary outcome analysis only if they had isolated *P. aeruginosa*; if there was no evidence that they had isolated *P. aeruginosa* prior to being withdrawn they were not included in the primary analysis.

The number and percentage of participants who were classified as a success and a failure for the primary outcome were presented for each treatment group. The difference between the groups was tested using the chi-squared test, and the relative risk and associated 95% CI are presented. The number and percentage of patients who had a positive sample at their 3-month follow-up visit are also presented for each treatment group. As a post hoc analysis, the difference between the groups at 3 months was also tested using the chi-squared test, the relative risk and associated 95% CI were calculated, and a sensitivity analysis was also carried out that extended the 3-month window to – 4 weeks/+ 10 weeks.

Six sensitivity analyses were conducted to determine the robustness of the results of the primary analysis:

1. All participants followed up past 3 months, but with no 15-month sample were classified as successes.
2. All participants followed up past 3 months, but with no 15-month sample were classified as failures.
3. All patients followed up past 3 months, but with no 15-month sample were classified as successes/failures according to the next sample taken after the end of the 15-month window.
4. Primary analysis adjusted for centre effect – a logistic regression model was fitted to investigate heterogeneity across centres and adjusted for centre as a random effect.
5. Analysis as per the primary analysis, but 3- and 15-month windows extended to 10 weeks either side of the expected visit dates: post hoc analysis.
6. Analysis as per the primary analysis, but 15-month window removed (any sample after 3-month window included): post hoc analysis.

Analysis of secondary outcomes

Time to reoccurrence of the original *P. aeruginosa* infection was presented graphically using Kaplan–Meier curves stratified by treatment. The difference between the two treatment groups was tested using the log-rank test. Two analyses of this outcome were performed as a result of blind review. The first assumed that all patients who had had a reoccurrence of *P. aeruginosa* but did not have both a baseline and a follow-up sample (between 3 and 24 months) sent for genotyping did not have a reoccurrence of the original *P. aeruginosa* strain. The second assumed that these patients did have a reoccurence of the original *P. aeruginosa* strain.

Reinfection with a different genotype of *P. aeruginosa* and admission to hospital were analysed using the chi-squared test. The relative risk and 95% CI are also presented.

Lung function [percentage predicted FEV_1, percentage predicted FVC and percentage predicted $FEF_{25–75}$ (not measured in participants < 5 years)], oxygen saturation and growth and nutritional status [height *z*-scores (children only), weight *z*-scores (children only), BMI *z*-scores (children only) and BMI (adults only)] were analysed using a repeated-measures random effects model with a special power covariance structure. The baseline measurement, treatment group and time were included in the model as coefficients and a treatment-by-time interaction was also fitted. The treatment difference at 15 months and 95% CI are presented.

For the number of pulmonary exacerbations and the number of days spent in hospital, a Mann–Whitney *U*-test was used to test whether or not the distribution was the same in each treatment arm.

Quality of life (as measured by the CFQ – Revised) was analysed using a mixed-effects model for repeated measures with an unstructured covariance matrix. The baseline measurement, treatment group and time were included in the model as coefficients and a treatment-by-time interaction was also fitted. The treatment difference at 15 months and 95% CI are presented.

Whether or not participants had grown at least one positive culture of MRSA, *Burkholderia cepacia* complex, *Aspergillus* or *Candida* was analysed using the chi-squared test (where there were sufficient events), and the relative risk and 95% CI are presented. Other sputum microbiology was presented descriptively; no formal analysis was undertaken.

Carer and participant burden was analysed in two ways. Whether or not carers/participants had been absent from work/education was analysed using the chi-squared test and presented with a relative risk and 95% CI. The Mann–Whitney *U*-test was used to determine whether or not there was a difference in the distributions of the number of days carers/participants were absent from work/education in each treatment group.

Analysis of safety data

The safety analysis data set contained all participants who were randomised and had commenced treatment. All events were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The number of occurrences of each AE [at the preferred term and System Organ Class (SOC) levels] and the number (and percentage) of patients experiencing each AE are presented for each treatment arm and overall. A similar table was produced for all SAEs reported under all versions of the protocol.

Each SAE reported under versions 1.0–5.0 of the protocol and each SAR reported under version 6.0 of the protocol onwards is presented in the form of line listings detailing:

- SAE number
- treatment
- preferred term
- SOC
- date of onset
- serious criteria (reporting of all that apply from seven possible options) (PI and chief investigator assessment)
- severity (mild/moderate/severe) (PI assessment)
- relationship to study drug (PI and chief investigator assessment)

- expectedness (chief investigator assessment)
- most likely cause (disease under study/other illness/prior or concomitant treatment/protocol procedure/lack of efficacy) (PI assessment)
- outcome.

There was no formal statistical analysis of any safety data.

Post hoc analyses

Time to *P. aeruginosa* reoccurrence is presented graphically using Kaplan–Meier curves stratified by treatment. The difference between the two treatment groups was tested using the log-rank test. Two analyses of this outcome were performed; the first included all positive samples after 3 months and the second included samples post 3 months and prior to 15 months. The hazard ratio (HR) and 95% CI were also calculated for the second analysis.

Additional analyses were performed on the lung function, oxygen saturation, growth and nutritional status, and quality-of-life outcomes. Where the interaction term was not significant in the original model, it was removed and an overall treatment difference and 95% CI are presented. Treatment differences at 3 and 24 months and the associated 95% CIs were also presented from the original model.

Chapter 4 Genotyping of *Pseudomonas aeruginosa* isolates

Variable number tandem repeats (VNTRs) are short nucleotide sequences that vary in copy number in bacterial genomes and are thought to occur through deoxyribonucleic acid (DNA) strand slippage during replication. This variation in copy number may be exploited to generate a VNTR typing scheme comprising between 9 and 15 selected 'loci', or regions of the bacterial genome. Variation in the number of repeats at each locus generates a numerical code (representing the number of repeat units at each locus) that may be used to correlate with a bacterial strain type. This method of bacterial strain typing has been widely used for a range of different bacterial organisms such as *Mycobacterium tuberculosis*, *Mycobacteroides abscessus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *P. aeruginosa*.[27–31]

Selecting suitable loci for a VNTR typing scheme is critical for defining the scheme's capacity for strain discrimination. Usually, loci are selected following specialised computer software analysis of whole-genome sequence(s) of isolate(s) of the species of interest.[32] Factors such as a small repeat size, choosing non-coding parts of the genome as well as areas that are not likely to contain insertions or deletions, and whole-genome coverage are important when choosing potential loci.

Use of variable number tandem repeat in a reference laboratory setting

Public Health England (PHE) has used VNTR analysis at nine loci as a method for *P. aeruginosa* strain typing since 2010 and, to date (May 2019), PHE has a national database of 31,028 profiles comprising CF, non-CF and environmental isolates from hospitals across the UK, providing a good national picture. Good concordance of this methodology was found on comparison with the gold standard, pulsed-field gel electrophoresis (PFGE).[31] In addition, as it is a polymerase chain reaction-based method, results can be generated rapidly and are portable between laboratories, making it preferable to PFGE, which is more laborious and not easily comparable between laboratories. Of the nine loci chosen for this scheme, the ninth is particularly discriminatory and may be used to evaluate relatedness between isolates from hospital outbreaks and in other settings among non-CF patients,[33–36] but this locus is not always useful for CF isolate discrimination, as variation in copy number may be found in different colonies from the same sputum sample.

Examining the UK *Pseudomonas aeruginosa* population structure using variable number tandem repeat analysis

A study conducted by PHE in 2013 used VNTR analysis to examine the population structure of *P. aeruginosa* among UK CF patients, non-CF patients and hospital environmental isolates over a 2-year period.[37] In total, 3870 isolates were examined, comprising 726 environmental isolates from 47 hospitals and 2325 isolates from 2230 patients (of whom approximately 54% were CF patients) from 143 centres. The study highlighted the existence of VNTR profiles representing common clones present in both patient and environmental specimens, submitted from hospitals across the UK. Fourteen common types, each found in more than 24 patients within this 2-year period, were described. Among these were three well-characterised strains associated with transmissibility, which have been isolated almost exclusively from CF patients, namely the Liverpool, Manchester and Midlands 1 strains.[38,39] These were isolated from 6%, 1.7% and 1.5%, respectively, of 1204 CF patient isolates in the above-named study.[37]

Four of the most common profiles were examined in more detail. Two of these correlated with previously well-established international clonal lineages, namely 'PA14' (VNTR profile: 12, 2, 1, 5, 5, 2, 4, 5, x, where the ninth locus is variable) and 'clone C' (VNTR profile: 11, 6, 2, 2, 1, 3, 7/8, 2/3, x, where the seventh, eighth and ninth loci may vary in copy number),[40,41] which correspond to multilocus sequence types ST253 and 17, respectively. The other two types were 'cluster A' (VNTR profile: 8, 3, 4, 5, 2, 3, 5, 2, x), corresponding to ST27, and 'cluster D' (VNTR profile: 10, 3, 5, 5, 4, 1, 3, 7, x), where 'x' is variable (ST395). These four types were isolated from 6%, 5%, 3% and 2% of patients, respectively, and were geographically widespread, although they were not always isolated in large numbers in individual hospitals. PFGE analysis of representatives of each of these VNTR types from multiple hospitals separated the isolates into four broad clusters corresponding to their VNTR type with an overall similarity of approximately 70%. This led to the hypothesis that in most cases patients acquired these strains independently rather than by patient-to-patient transmission. Further evidence for the clonal nature of these four common profiles was found by examining the sequences for the intrinsic $bla_{\text{OXA-50-like}}$ gene.

To examine the hypothesis that these strains were often acquired independently, whole-genome sequences for 12 isolates of 'cluster A' from nine hospitals comprising six CF, five non-CF and one environmental isolate from geographically distant sites and separated in time were examined. The presence and absence of genes from the accessory genome detected 9454 variable sequences across the 12 isolates and the six reference genomes that were compared. A set of seven accessory genes were chosen from these, which were found to be variably present among a larger set of 'cluster A' isolates. Representatives from patients within a single centre mostly had distinct accessory gene profiles, suggesting that these patients acquired the strain independently, whereas those with clear epidemiological links shared the same profile. Profiles also varied between representatives from different centres.

Challenges in variable number tandem repeat analysis of cystic fibrosis isolates

Variable number tandem repeat analysis of CF isolates often poses additional challenges compared with the analysis of non-CF outbreaks, particularly, although not exclusively, among chronically infected patients. In addition to the variation at the last locus found between different colony types from the same sputum, variation of up to two repeats at one out of the first eight loci may also be found in some patient samples. There may also be variation between sequential isolates over time. Caution needs to be applied when inferring strain relatedness solely using VNTR analysis in certain cases. For example, it is unlikely to be sufficiently discriminatory when assessing whether isolates with similar profiles pre and post antibiotic therapy represent reinfection from an environmental/other source or therapeutic failure. In these cases, the greater discrimination provided through whole-genome sequencing of isolates may be required. Despite these drawbacks, this method has been successfully used by PHE to type *P. aeruginosa* isolates from hospitals throughout the UK since 2010, and has proved invaluable for highlighting outbreaks and aiding cross-infection decisions in CF clinics.

Chapter 5 Clinical effectiveness results

Participant recruitment

The first participant was randomised on 5 October 2010 and the final participant was randomised on 27 January 2017, when the recruitment target was met. The last follow-up visit occurred on 10 April 2018.

Sixty-one out of the 72 sites (see *Appendix 3*) that screened patients randomised at least one participant. Twenty-two sites randomised at least five participants.

The flow of participants through the trial is presented in the CONSORT flow diagram (*Figure 2*). A total of 1308 patients screened for eligibility (patients could be screened on multiple occasions); 1022 did

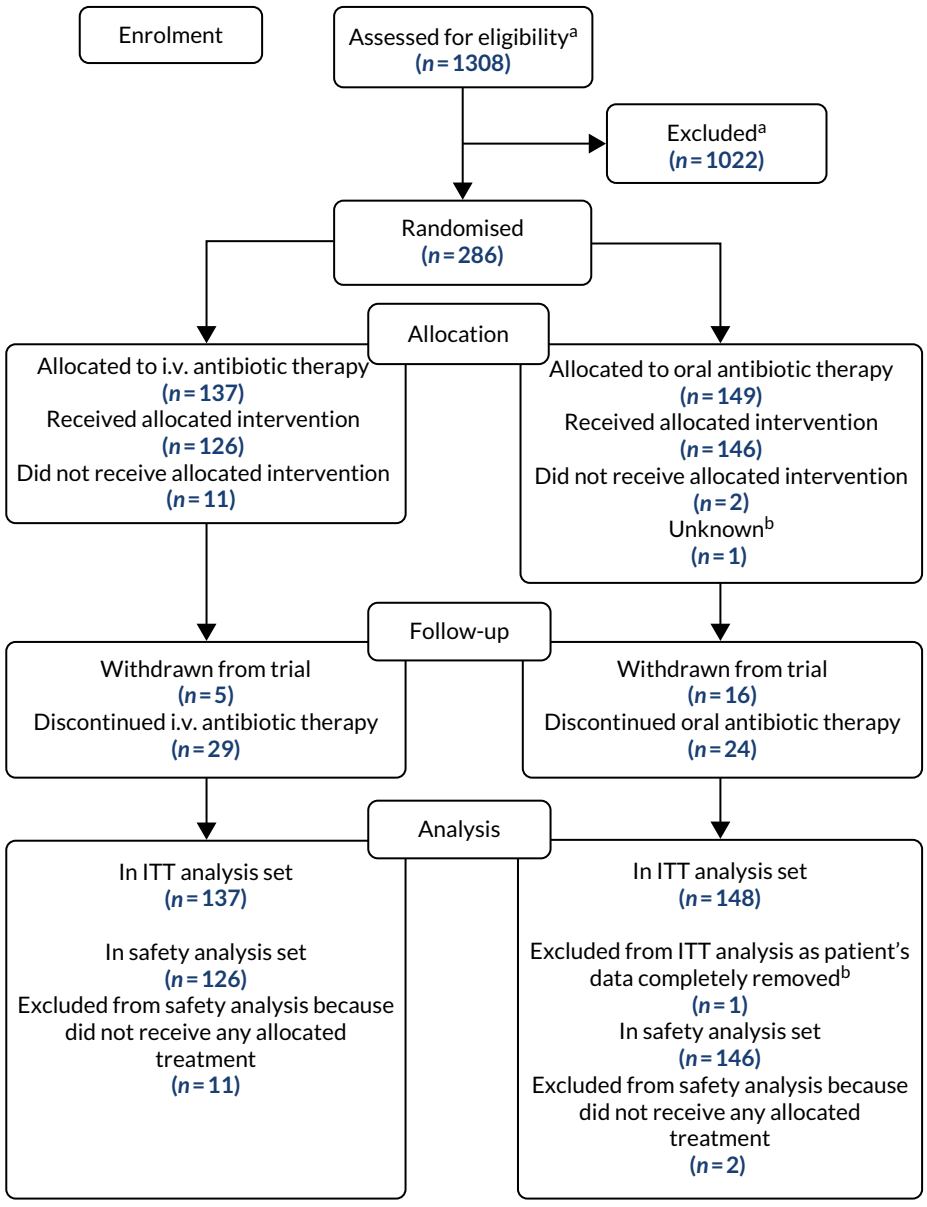

FIGURE 2 The CONSORT flow diagram for all trial participants. a, Multiple screenings allowed; b, Patient randomised by all data completely removed as PI sign off could not be obtained.

not undergo randomisation because they did not meet the eligibility criteria and 286 patients were randomised (137 to i.v. antibiotic therapy and 149 to oral antibiotic therapy). Detailed information on recruitment is provided in *Appendix 4*, *Tables 28–32*.

Analysis populations

The ITT analysis population included 285 of the 286 participants (99.7%) who were randomised; one participant's data could not be included as PI approval could not be obtained despite every effort being made by the TMG to do so. The safety population included 272 of the 286 randomised participants (95.1%); 13 patients did not receive any of their allocated treatment and one participant's data could not be included as PI approval could not be obtained. The analysis set for the primary outcome included 255 participants: 125 in the i.v. antibiotic therapy group and 130 in the oral antibiotic therapy group.

All participants who withdrew consent for trial continuation contributed outcome data up until the point of withdrawal.

Premature discontinuations

Premature discontinuation of treatment (either IMP or non-IMP) occurred in 40 of the 137 participants in the i.v. antibiotic therapy group (29.2%) and 26 of the 148 participants in the oral antibiotic therapy group (17.6%). The most common reasons for premature discontinuation of treatment in the i.v. antibiotic therapy group were withdrawal of consent ($n = 9$; 22.5%), venous access problem ($n = 7$; 17.5%) and long-line failure ($n = 5$; 12.5%), and in the oral antibiotic therapy group the reasons were AE ($n = 13$; 50%) and withdrawal of consent ($n = 4$; 15.4%). Reasons for premature discontinuation of treatment are summarised in *Table 1*.

TABLE 1 Reasons for premature discontinuation of treatment

Reason	Treatment group, *n* (%)		Total, *n* (%)
	i.v. antibiotic therapy	Oral antibiotic therapy	
AE	1 (2.5)	13 (50.0)	14 (21.2)
Withdrawn consent	9 (22.5)	4 (15.4)	13 (19.7)
Venous access problem	7 (17.5)	0 (0.0)	7 (10.6)
Long-line failure	5 (12.5)	0 (0.0)	5 (7.6)
Missing	4 (10.0)	1 (3.8)	5 (7.6)
Clinician decision	3 (7.5)	1 (3.8)	4 (6.1)
Other[a]	3 (7.5)	1 (3.8)	4 (6.1)
SAE/reaction	1 (2.5)	3 (11.5)	4 (6.1)
Error[b]	3 (7.5)	0 (0.0)	3 (4.5)
Bed not available	2 (5.0)	0 (0.0)	2 (3.0)
Insufficient medication supplied	0 (0.0)	2 (7.7)	2 (3.0)
Lost to follow-up	1 (2.5)	0 (0.0)	1 (1.5)
Poor adherence	0 (0.0)	1 (3.8)	1 (1.5)
Unknown	1 (2.5)	0 (0.0)	1 (1.5)
Total	40	26	66

a Child behaviour, bacteraemia reclassified, regrew *P. aeruginosa* so changed treatment, and a few bottles exploded on mixing.
b Mix-up with dates in pharmacy, clinician not aware that patient needed further medication, and participant forgot to take nebuliser on holiday.

Withdrawal from follow-up occurred in 5 of the 137 participants in the i.v. antibiotic therapy group (3.6%) and 16 of the 148 participants in the oral antibiotic therapy group (10.8%). The most common reason in both groups was that participants were lost to follow-up [three participants in the i.v. antibiotic therapy group (60%); nine participants in the oral antibiotic therapy group (56.3%)]. Reasons for withdrawals from follow-up are summarised in *Table 2*.

Baseline characteristics

The demographic baseline data of the 285 randomised participants were comparable between the two groups. The proportion of infants and toddlers was slightly larger in the i.v. antibiotic therapy group (30.7%, compared with 18.9% in the oral antibiotic therapy group). The proportions of male and female participants were approximately the same across the two treatment groups, with slightly more female than male participants (*Table 3*).

Body mass index, lung function and oxygen saturation were similar across the two treatment groups. The proportions of patients who were naive or free from *P. aeruginosa* for the preceding 12 months and who had experienced a pulmonary exacerbation were also comparable across the two groups. There were fewer patients in the i.v. antibiotic therapy that had a diagnosis based on a homozygous delta f508 mutation (60.8%, compared with 51.1% in the oral antibiotic therapy group). Similar numbers of participants in each treatment group had other microorganisms detected at baseline (see *Table 3*).

TABLE 2 Reasons for withdrawal from follow-up

	Treatment group, *n* (%)		
Reason	**i.v. antibiotic therapy**	**Oral antibiotic therapy**	**Total, *n* (%)**
AE	0 (0.0)	1 (6.3)	1 (4.8)
Lost to follow-up	3 (60.0)	9 (56.3)	12 (57.1)
Other[a]	1 (20.0)	2 (12.5)	3 (14.3)
Withdrawn consent	1 (20.0)	4 (25.0)	5 (23.8)
Total	5	16	21

a Complex family issues, travel problems, and change in family circumstances.

TABLE 3 Demographic baseline data: individual level (all centres)

	Treatment group, *n* (%)	
Baseline characteristic	**i.v. antibiotic therapy (*N* = 137)**	**Oral antibiotic therapy (*N* = 148)**
Age group[a]		
Infants and toddlers (28 days–23 months)	42 (30.7)	28 (18.9)
Children (2–11 years)	71 (51.8)	92 (62.2)
Adolescents (12–17 years)	18 (13.1)	19 (12.8)
Adults (18–64 years)	6 (4.4)	9 (6.1)
Sex		
Male	63 (46)	67 (45.3)
Female	74 (54)	81 (54.7)

continued

TABLE 3 Demographic baseline data: individual level (all centres) (*continued*)

Baseline characteristic	Treatment group, *n* (%)	
	i.v. antibiotic therapy (*N* = 137)	Oral antibiotic therapy (*N* = 148)
P. aeruginosa		
Naive	81 (59.1)	93 (62.8)
Free	56 (40.9)	55 (37.2)
Other micro-organisms detected		
Candida albicans	11 (8)	17 (11.5)
MRSA	0 (0.0)	2 (1.4)
Burkholderia cepacia complex	0 (0.0)	0 (0.0)
Aspergillus fumigatus	2 (1.5)	2 (1.4)
Other organisms	26 (19)	31 (20.9)
Genotype		
p.Phe508del/p.Phe508del	70 (51.1)	90 (60.8)
p.Phe508del/other	40 (29.2)	43 (29.1)
p.Phe508del/unknown	4 (2.9)	5 (3.4)
Other/other	12 (8.8)	7 (4.7)
Unknown	11 (8.0)	3 (2)
Pulmonary exacerbation present	18 (13.1)	17 (11.5)
BMI *z*-score (paediatric), *n*, mean (SD)	125, 0.3 (1)	131, 0.3 (0.9)
BMI (adults) (kg/m^2), *n*, mean (SD)	6, 24.6 (1.8)	9, 23.2 (2.3)
Time from *P. aeruginosa* isolation to treatment initiation (days), *n*, mean (SD)	126, 8.8 (5.3)	145, 6.8 (5.3)
FEV_1% predicted (l), *n*, mean (SD)	67, 86.6 (15.8)	70, 85.7 (16)
FVC% predicted (l), *n*, mean (SD)	67, 92.2 (15.5)	70, 95.1 (14.5)
FEF_{25-75}% predicted (l), *n*, mean (SD)	44, 72.7 (26.6)	53, 70.6 (30.3)
Oxygen saturation (%), *n*, mean (SD)	118, 97.7 (1.4)	133, 97.7 (1.7)

a Date of birth was not provided for two participants to allow age to be calculated. Age at randomisation was provided after database lock and analysis, and was added to the baseline table manually.

Protocol deviations

Protocol deviations were monitored centrally by evaluating inclusion/exclusion criteria at trial entry and throughout the trial. A total of 284 participants (99.6%) had at least one major protocol deviation. The most common protocol deviations related to visits occurring outside the protocol-specified visit windows; 282 participants (98.9%) had a visit outside the window at 3 or 15 months (major deviation) and 280 participants (98.2%) had a visit outside the window at 6, 9, 12, 18, 21 or 24 months (minor deviation). All protocol deviations were agreed with the co-chief investigators prior to them seeing any unblinded results (*Table 4*).

TABLE 4 Protocol deviations

Deviation	Treatment group, *n* (%)		Total, *n* (%) (*N* = 285)
	i.v. antibiotic therapy (*N* = 137)	Oral antibiotic therapy (*N* = 148)	
Any protocol deviation	137 (100.0)	148 (100.0)	285 (100.0)
At least one major deviation	137 (100.0)	147 (99.3)	284 (99.6)
Consent not obtained	0 (0.0)	0 (0.0)	0 (0.0)
Inclusion of patient previously randomised into TORPEDO-CF	0 (0.0)	0 (0.0)	0 (0.0)
Treatment non-compliance (< 10 days of i.v. treatment or 120 doses of ciprofloxacin)	35 (25.5)	6 (4.1)	41 (14.4)
Premature discontinuation of randomised treatment because of safety	2 (1.5)	16 (10.8)	18 (6.3)
Premature discontinuation of randomised treatment because of patient preference	15 (10.9)	5 (3.4)	20 (7.0)
Scheduled visits at 3 and 15 months occurring outside appropriate time frame (3 months should be more than 48 hours after and no more than 14 days after; 15 months should be no more than 7 days before and 14 days after)	136 (99.3)	146 (98.6)	282 (98.9)
At least one minor deviation	134 (97.8)	146 (98.6)	280 (98.2)
Outside age range	0 (0.0)	0 (0.0)	0 (0.0)
Patient starting treatment > 21 days after a positive microbiology report	1 (0.7)	3 (2.0)	4 (1.4)
Inclusion of patient who has not been clear of *P. aeruginosa* for 12 months	1 (0.7)	0 (0.0)	1 (0.4)
Scheduled visits at 6, 9, 12, 18, 21 and 24 months occurring outside appropriate time frame (no more than 7 days either side)	134 (97.8)	146 (98.6)	280 (98.2)

Compliance

Intravenous antibiotic therapy

Serum creatinine levels prior to the administration of the first dose of tobramycin are presented in *Table 5*, along with tobramycin serum concentrations prior to the administration of the second dose and after 1 week. *Table 6* provides summary statistics for the number of days that participants received i.v. treatment.

TABLE 5 Serum creatinine (mmol/l) and tobramycin (mg/l) serum levels

Summary statistic	Serum creatinine level (mmol/l) prior to first tobramycin dose administration	Tobramycin serum levels (mg/l)	
		Prior to second dose administration	After 1 week
n	109	112	102
Mean	35.6	0.7	1.2
SD	17.7	1.3	4.3
Minimum	0	0	0
Median	33	0.4	0.4
Maximum	132.6	8.7	41
Missing (*n*)	28	25	35

TABLE 6 Ceftazidime and tobramycin compliance

Summary statistic	Number of days on treatment	
	Ceftazidime	Tobramycin
n	137	137
Mean	11.5	11.0
SD	5.3	5.1
Minimum	0	0
Median	14	14
Maximum	16	16
Missing (*n*)	0	0

Oral antibiotic therapy

Table 7 provides summary statistics for the number of doses that participants received along with a compliance rate based on a denominator of 168 doses [two doses per day for 84 days (3 × 28 days)]. As some participants remained on treatment for longer than the required 84 days, this information was updated (post hoc) to include only those doses taken in the first 84 days.

Colistin therapy

Table 8 provides summary statistics for the compliance rate based on a denominator of 168 doses [two doses per day for 84 days (3 × 28 days)]. As some participants remained on treatment for longer than the required 84 days, this information was updated (post hoc) to include only those doses taken in the first 84 days.

TABLE 7 Ciprofloxacin compliance

Summary statistic	All doses		Doses from first 84 days	
	Number of doses	Compliance rate (%)	Number of doses	Compliance rate (%)
n	105	105	105	105
Mean	167.1	99.5	156.6	93.2
SD	32.8	19.5	29	17.27
Minimum	0	0.0	0	0.0
Median	173	103.0	166	98.8
Maximum	230	136.9	168	100
Missing (*n*)	43	43	43	43

TABLE 8 Colistin compliance

Summary statistic	Compliance rate (%) using all doses		Compliance rate (%) using doses from the first 84 days	
	i.v. antibiotic therapy	Oral antibiotic therapy	i.v. antibiotic therapy	Oral antibiotic therapy
n	97	105	97	105
Mean	87.8	97.7	82.1	91.6
SD	34.4	21.4	31.5	19.0
Minimum	0.0	0.0	0.0	0.0
Median	100.6	101.2	98.2	98.2
Maximum	125	136.9	100	100
Missing (*n*)	40	43	40	43

Time from randomisation to treatment commencement

The median (IQR) time from randomisation to treatment commencement was 3 (1–6) days in the i.v. antibiotic therapy group and 0 (0–1) days in the oral antibiotic therapy group.

Primary outcome

The primary outcome (successful eradication of *P. aeruginosa* infection 3 months after allocated treatment has started and remaining infection free through to 15 months after the start of allocated treatment) was achieved by 55 of the 125 participants (44.0%) in the i.v. antibiotic therapy group and by 68 of the 130 participants (52.3%) in the oral antibiotic therapy group. Participants who were randomised to the i.v. antibiotic therapy group had a reduced chance of having successful eradication of *P. aeruginosa* 3 months after the start of treatment and remaining infection free through to 15 months (relative risk 0.84, 95% CI 0.65 to 1.09; $p = 0.184$). Results from five of the six sensitivity analyses to address missing data can be found in *Table 9*, which details the number of patients included in each analysis, the number in each treatment group in whom eradication was or was not observed, the relative risk, 95% CI and the *p*-value from the chi-squared test. The results from all five sensitivity analyses are consistent with the results from the primary analysis, indicating that the original results

TABLE 9 Primary outcome results

Analysis	Treatment group, *n/N* (%)		Relative risk (95% CI)	*p*-value
	i.v. antibiotic therapy	Oral antibiotic therapy		
Primary outcome: successful eradication of* P. aeruginosa *infection 3 months after allocated treatment has started, remaining infection free through to 15 months after the start of allocated treatment				
Primary analysis	55/125 (44)	68/130 (52.3)	0.84 (0.65 to 1.09)	0.184
Sensitivity analysis 1: all participants followed up past 3 months with no 15-month sample classified as success	66/136 (48.5)	85/144 (56.9)	0.85 (0.68 to 1.07)	0.159
Sensitivity analysis 2: all participants followed up past 3 months with no 15-month sample classified as failure	55/136 (40.4)	68/144 (47.2)	0.86 (0.66 to 1.12)	0.253
Sensitivity analysis 3: all participants followed up past 3 months with no 15-month sample classified as success/failure in accordance with the next sample taken after 15-month window	66/136 (48.5)	81/144 (56.3)	0.86 (0.69 to 1.08)	0.196
Sensitivity analysis 4: as primary analysis, but 3- and 15-month windows extended to – 4 weeks/ + 10 weeks of the expected visit dates	61/132 (46.2)[a]	73/139 (52.5)[a]	0.88 (0.69 to 1.12)[a]	0.299[a]
Sensitivity analysis 5: as per primary analysis, but 15-month window removed (any sample after 3-month window included)	58/136 (42.7)[a]	70/144 (48.6)[a]	0.88 (0.68 to 1.13)[a]	0.317[a]
Subgroup analysis 1: *P. aeruginosa* free participants	23/49 (46.9)	21/50 (42.0)	1.12 (0.72 to 1.74)	NR
Subgroup analysis 2: *P. aeruginosa* naive participants	32/76 (42.1)	47/80 (58.8)	0.72 (0.53 to 0.99)	NR
Unsuccessful eradication of* P. aeruginosa *3 months after allocated treatment has started				
Primary analysis	13/110 (11.8)	5/116 (4.3)	2.74 (1.01 to 7.44)[a]	0.037[a]
Sensitivity analysis: as primary analysis, but 3-month window extended to –4 weeks/ +10 weeks of the expected visit date	22/124 (17.7)[a]	12/135 (8.9)[a]	2.00 (1.03 to 3.86)[a]	0.035[a]

NR, not reported.
a Post hoc analysis.

are robust with regard to the assumptions that were made. The additional sensitivity analysis not reported in *Table 9* applied all of the same assumptions as the primary analysis, but used a logistic regression model to adjust for centre as a random effect. The adjustment to the model for centre did not significantly affect the results ($p = 0.218$), indicating that there was no statistically significant effect of centre on the primary results. Results from a post hoc subgroup analyses in *P. aeruginosa* naive and *P. aeruginosa* free patients are also reported in *Table 9*. A Mantel–Haenszel test for interaction was conducted and the relative risks were not significantly different in the two subgroups ($p = 0.19$).

The number of participants who did not eradicate *P. aeruginosa* 3 months after the start of treatment was 13 (11.8%) in the i.v. antibiotic therapy group and five (4.3%) in the oral antibiotic therapy group. Participants who were randomised to the i.v. antibiotic therapy had an increased risk of unsuccessful eradication of *P. aeruginosa* 3 months after the start of treatment (relative risk 2.74, 95% CI 1.01 to 7.44; $p = 0.037$) (post hoc analysis). The results of this analysis were supported by a sensitivity analysis in which the 3-month window was widened to – 4 weeks/+ 10 weeks of the expected 3-month visit date (relative risk 2.00, 95% CI 1.03 to 3.86; $p = 0.035$).

A post hoc analysis was performed on time to *P. aeruginosa* reoccurrence. *Figure 3* is the Kaplan–Meier plot for time to *P. aeruginosa* reoccurrence up until the end of the 15-month window. This analysis included the 255 participants included in the primary analysis. Oral antibiotic therapy delayed time to *P. aeruginosa* reoccurrence compared with i.v. antibiotic therapy; however, the effect was not statistically significant (HR 1.31, 95% CI 0.93 to 1.85; $p = 0.119$). *Figure 4* is the Kaplan–Meier plot for time to *P. aeruginosa* reoccurrence up until the end of the 24-month follow-up period.

Following database lock and the unblinding of the treatment allocations, it was found that one participant (who had withdrawn from the trial and was not included in the primary analysis) had a positive sample for *P. aeruginosa* on the day that they had stopped treatment. The definition in the statistical analysis plan stated that any samples taken in the 48-hour window following treatment cessation should be excluded and this was executed for the primary analysis shown above; however, this should have stated that only samples that were negative for isolation of *P. aeruginosa* in this period should be excluded – positive samples should have been included. Further investigation identified no other occurrences of this; in a post hoc analysis that included this participant, there was no impact on the primary analysis.

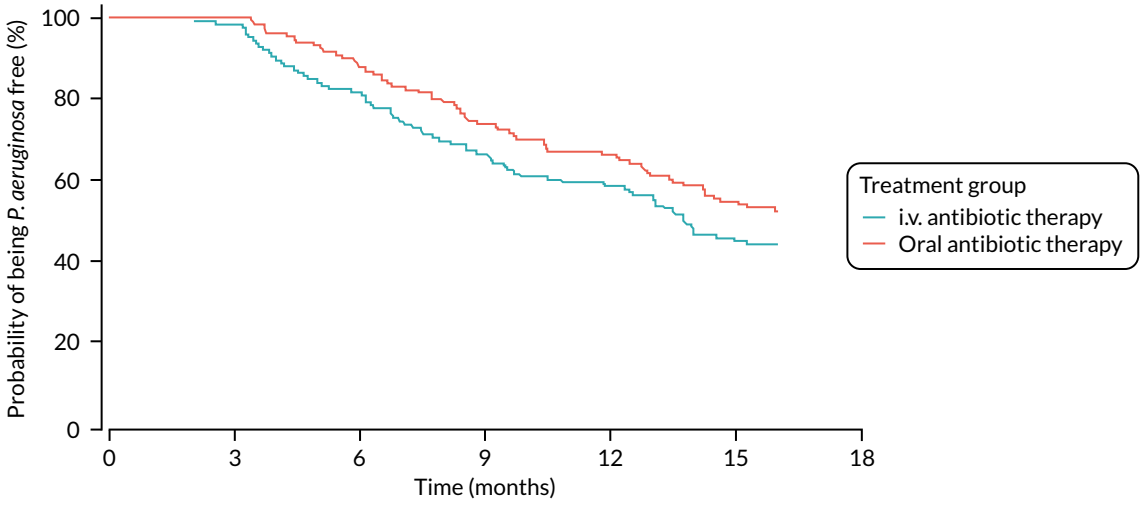

FIGURE 3 Time to reoccurrence of *P. aeruginosa* infection (any strain) up to the end of the 15-month window.

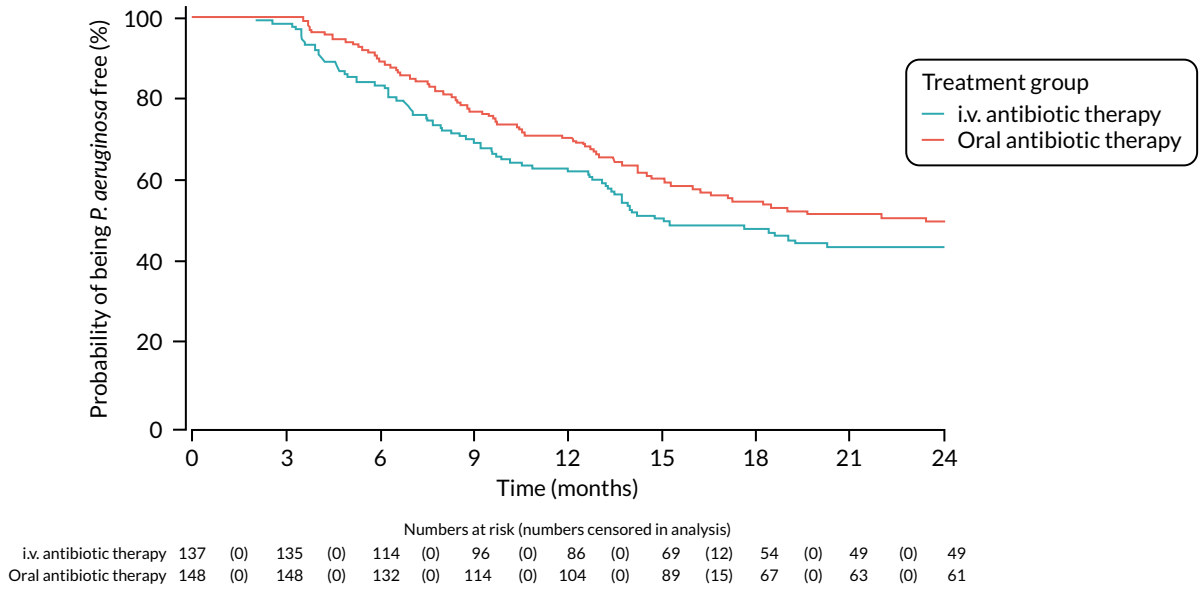

FIGURE 4 Time to reoccurrence of *P. aeruginosa* infection (any strain) up to the end of the 24-month follow-up period.

Secondary outcomes

Time to reoccurrence of original Pseudomonas aeruginosa *infection*

A total of 50 participants ($n = 28$ in the i.v. antibiotic therapy group; $n = 22$ in the oral antibiotic therapy group) had *P. aeruginosa* genotyping performed on both a baseline and a follow-up sample over the course of the trial. Owing to the limited numbers of participants with genotyping results, two analyses were performed on this outcome, in which assumptions were made around whether any reoccurring *P. aeruginosa* infections were the same strain or different. Both analyses included all 285 participants.

In the first analysis, in which participants who had regrown *P. aeruginosa* but did not have genotyping performed were assumed to have regrown the same strain, there was no statistically significant difference between oral antibiotic and i.v. antibiotic therapy treatment groups in time to reoccurrence of infection with the original *P. aeruginosa* strain (HR 1.37, 95% CI 0.99 to 1.91; $p = 0.061$) (*Table 10*, and *Appendix 4*, *Figure 6*). The results from a sensitivity analysis using time from treatment commencement, rather than time from randomisation, confirmed this finding (HR 1.38, 95% CI 0.99 to 1.92; $p = 0.060$) (see *Table 10* and *Appendix 4*, *Figure 7*).

TABLE 10 Secondary outcome: time to reoccurrence of original *P. aeruginosa* infection

Analysis	Treatment group, *n* (%)		HR (95% CI)	*p*-value
	i.v. antibiotic therapy (*N* = 137)	Oral antibiotic therapy (*N* = 148)		
Unknown strains assumed to be the same as baseline				
Time from randomisation	74 (54.0%)	66 (44.6%)	1.37 (0.99 to 1.91)	0.061
Time from treatment commencement	74 (54.0%)	66 (44.6%)	1.38 (0.99 to 1.92)	0.060
Unknown strains assumed to be different from baseline				
Time from randomisation	21 (15.3%)	14 (9.5%)	1.85 (0.94 to 3.64)	0.075
Time from treatment commencement	21 (15.3%)	14 (9.5%)	1.85 (0.94 to 3.64)	0.074

Similarly, in the second analysis, in which participants who had regrown *P. aeruginosa* but did not have genotyping performed were assumed to have regrown a different strain, oral antibiotic therapy delayed time to reoccurrence of the original *P. aeruginosa* compared with i.v. antibiotic therapy, but, again, this was not statistically significant (HR 1.85, 95% CI 0.94 to 3.64; $p = 0.075$) (see *Table 6* and *Appendix 4*, *Figure 8*). The results from a sensitivity analysis using time from treatment commencement rather than time from randomisation confirmed this finding (HR 1.85, 95% CI 0.94 to 3.64; $p = 0.074$) (see *Table 6* and *Appendix 4*, *Figure 9*).

Reinfection with a different strain of Pseudomonas aeruginosa

A total of 42 participants ($n = 25$ in i.v. antibiotic therapy group; $n = 17$ in oral antibiotic therapy group) had genotyping performed on both a baseline and a follow-up sample in the first 15 months of follow-up. In the i.v. antibiotic therapy group, 19 participants (76%) regrew the same strain and six participants (24%) regrew a different strain. In the oral antibiotic therapy group, 12 participants (70.6%) regrew the same strain and five participants (29.4%) regrew a different strain. The risk of regrowing a different strain was slightly lower in the i.v. antibiotic therapy group than in the oral antibiotic therapy group, but the difference was not statistically significant (relative risk 0.82, 95% CI 0.30 to 2.25; $p = 0.733$).

Lung function

Lung function analyses were undertaken on patients aged ≥ 5 years (157/285 randomised patients: 76 in the i.v. antibiotic therapy group and 81 in the oral antibiotic therapy group).

A total of 134 participants had a baseline measurement and at least one follow-up measurement of FEV_1 and FVC, and 96 participants had a baseline and at least one follow-up measurement of $FEF_{25–75}$ and were therefore included in the models. *Table 11* provides the mean and standard error (SE) in each treatment group predicted by the random effects model that fitted a time-by-treatment interaction and also those from the model when no time-by-treatment interaction was included (post hoc), along with the mean treatment difference, 95% CI and the *p*-value for the model with no interaction term (overall) and for each time point for the model with the interaction term. All three measures of lung function were very slightly higher in the i.v. antibiotic therapy than in the oral antibiotic therapy group across all estimates.

Oxygen saturation

A total of 241 participants had a baseline measurement of oxygen saturation and at least one follow-up measurement, and these participants were therefore included in the models. *Table 11* provides the mean and SE in each treatment group predicted by the random effects model that fitted a time-by-treatment interaction and also those from the model when no time-by-treatment interaction was included (post hoc), along with the mean treatment difference, 95% CI and the *p*-value for the model with no interaction term (overall) and for each time point for the model with the interaction term. There was no difference between the two treatment groups.

Growth and nutritional status

Of the 268 children (recruited at a paediatric centre), 256 were included in the analyses of height and BMI, as they had a baseline measurement and at least one follow-up measurement. The analysis of weight was restricted to participants aged ≤ 10 years, so included only 211 children. *Table 11* provides the mean and SE in each treatment group predicted by the random effects model that fitted a time-by-treatment interaction and also those from the model when no time-by-treatment interaction was included (post hoc), along with the mean treatment difference, 95% CI and the *p*-value for the model with no interaction term (overall) and for each time point for the model with the interaction term. There was very little difference between the two treatment groups in terms of the height, weight and BMI *z*-scores that were measured in children. BMI (measured in adults) was slightly lower in the i.v. antibiotic therapy group than in the oral antibiotic therapy group, but only 13 participants were included in this model.

TABLE 11 Secondary outcomes: lung function, oxygen saturation and growth and nutritional status. Estimates predicted by random effects models

Outcome	*n*	Time point	Treatment group, mean (SE)		Mean treatment difference (95% CI)	*p*-value
			i.v. antibiotic therapy	Oral antibiotic therapy		
Lung function						
% predicted FEV_1	134	3 months	85.68 (1.02)	81.93 (0.98)	3.75 (0.97 to 6.53)[a]	0.008[a]
		15 months	86.19 (1.1)	84.11 (1.1)	2.08 (−0.99 to 5.14)	0.184
		24 months	86.57 (1.55)	85.75 (1.54)	0.82 (−3.45 to 5.1)[a]	0.705[a]
		Overall	86.32 (0.99)[a]	83.16 (0.98)[a]	3.16 (0.51 to 5.8)[a]	0.019[a]
% predicted FVC	134	3 months	91.87 (1.04)	88.01 (0.99)	3.86 (1.03 to 6.69)[a]	0.008[a]
		15 months	94.08 (1.08)	90.94 (1.08)	3.14 (0.15 to 6.14)	0.039
		24 months	95.74 (1.5)	93.13 (1.47)	2.61 (−1.52 to 6.73)[a]	0.216[a]
		Overall	93.53 (0.97)[a]	89.98 (0.97)[a]	3.56 (0.9 to 6.21)[a]	0.009[a]
% predicted FEF_{25-75}	96	3 months	74.14 (2.62)	70.38 (2.23)	3.76 (−2.99 to 10.52)[a]	0.274[a]
		15 months	72.39 (2.73)	68.93 (2.45)	3.46 (−3.74 to 10.66)	0.345
		24 months	71.07 (3.63)	67.84 (3.22)	3.23 (−6.29 to 12.76)[a]	0.505[a]
		Overall	73.36 (2.5)[a]	69.71 (2.22)[a]	3.64 (−2.82 to 10.11)[a]	0.269[a]
Oxygen saturation (%)	241	3 months	97.81 (0.1)	97.76 (0.09)	0.05 (−0.21 to 0.3)[a]	0.728[a]
		15 months	97.83 (0.09)	97.78 (0.09)	0.05 (−0.2 to 0.29)	0.709
		24 months	97.84 (0.13)	97.79 (0.12)	0.05 (−0.3 to 0.4)[a]	0.79[a]
		Overall	97.82 (0.08)[a]	97.77 (0.08)[a]	0.05 (−0.18 to 0.27)[a]	0.686[a]
Growth and nutritional status						
Height *z*-score	256	3 months	−0.34 (0.02)	−0.34 (0.02)	0 (−0.06 to 0.05)[a]	0.952[a]
		15 months	−0.34 (0.04)	−0.31 (0.04)	−0.03 (−0.13 to 0.07)	0.572
		24 months	−0.34 (0.06)	−0.29 (0.06)	−0.05 (−0.21 to 0.11)[a]	0.543[a]
		Overall	−0.33 (0.02)[a]	−0.33 (0.02)[a]	0 (−0.06 to 0.05)[a]	0.939[a]
Weight *z*-score	211	3 months	0.06 (0.02)	0.06 (0.02)	0 (−0.06 to 0.06)[a]	0.988[a]
		15 months	0.11 (0.05)	0.13 (0.05)	−0.02 (−0.15 to 0.11)	0.794
		24 months	0.15 (0.08)	0.18 (0.08)	−0.03 (−0.24 to 0.18)[a]	0.78[a]
		Overall	0.09 (0.03)[a]	0.09 (0.03)[a]	0 (−0.06 to 0.06)[a]	0.987[a]
BMI *z*-score	256	3 months	0.31 (0.03)	0.32 (0.02)	−0.01 (−0.08 to 0.06)[a]	0.767[a]
		15 months	0.34 (0.05)	0.33 (0.05)	0.01 (−0.14 to 0.16)	0.912
		24 months	0.36 (0.09)	0.33 (0.08)	0.02 (−0.22 to 0.26)[a]	0.854[a]
		Overall	0.32 (0.03)[a]	0.33 (0.03)[a]	−0.01 (−0.08 to 0.06)[a]	0.774[a]
BMI (kg/m^2)	13	3 months	23.56 (0.18)	24.04 (0.18)	−0.48 (−1.0 to 0.03)[a]	0.067[a]
		15 months	23.51 (0.22)	24.25 (0.24)	−0.73 (−1.39 to −0.08)	0.029
		24 months	23.47 (0.37)	24.4 (0.39)	−0.92 (−2.01 to 0.16)[a]	0.093[a]
		Overall	23.58 (0.18)[a]	24.14 (0.19)[a]	−0.56 (−1.03 to -0.09)[a]	0.02[a]

a Post hoc analysis.

Number of pulmonary exacerbations

A total of 283 participants were included in the analysis of the number of pulmonary exacerbations within the first 15 months of follow-up. In both treatment groups, most participants did not experience any pulmonary exacerbations (i.v. 72.3%; oral 64.4%) during this time, but the risk of experiencing at least one pulmonary exacerbation was lower in the i.v. antibiotic therapy group than in the oral antibiotic therapy group (relative risk 0.78, 95% CI 0.55 to 1.10; $p = 0.155$). The median (IQR) number of exacerbations experienced in each group was 0 (0–1). The distributions of the number of exacerbations experienced in each treatment group were not significantly different ($p = 0.090$). *Table 12* provides the results of the additional analyses of this outcome over different time periods of interest. The results of these analyses were all consistent with the results over the first 15 months of follow-up. The analysis investigating the time to first pulmonary exacerbation found no significant difference between the two treatment groups (HR 0.73, 95% CI 0.50 to 1.06; $p = 0.1$); the Kaplan–Meier plot can be seen in *Figure 5*.

TABLE 12 Secondary outcomes: number of pulmonary exacerbations and admissions to hospital

Outcome	Time period	Treatment group, *n/N* (%)[a]		Relative risk (95% CI)	*p*-value
		i.v. antibiotic therapy	Oral antibiotic therapy		
Number of pulmonary exacerbations	Up to 15 months	38/137 (27.7)	52/146 (35.6)	0.78 (0.55 to 1.10)	0.155
	Up to 3 months	8/135 (5.9)	15/144 (10.4)	0.57 (0.25 to 1.3)	0.173
	3–15 months	31/131 (23.7)	46/136 (33.8)	0.7 (0.48 to 1.03)	0.067
	15–24 months	14/99 (14.1)	26/103 (25.2)	0.56 (0.31 to 1.01)	0.048
Admission to hospital	Up to 3 months	25/135 (18.5)	15/143 (10.5)	1.77 (0.97 to 3.2)	0.057
	3–15 months	40/129 (31.0)	61/136 (44.9)	0.69 (0.5 to 0.95)	0.02
	15–24 months	33/105 (31.4)	41/107 (38.3)	0.82 (0.57 to 1.19)	0.293
Admission to hospital: sensitivity analysis	Up to 3 months	24/135 (17.8)	9/143 (6.3)	2.82 (1.36 to 5.86)	0.003
	3–15 months	39/129 (30.2)	63/136 (46.3)	0.65 (0.47 to 0.9)	0.007
	15–24 months	34/104 (32.7)	41/108 (38.0)	0.86 (0.6 to 1.24)	0.422

a Data are *n/N* (%) for participants experiencing at least one occurrence.

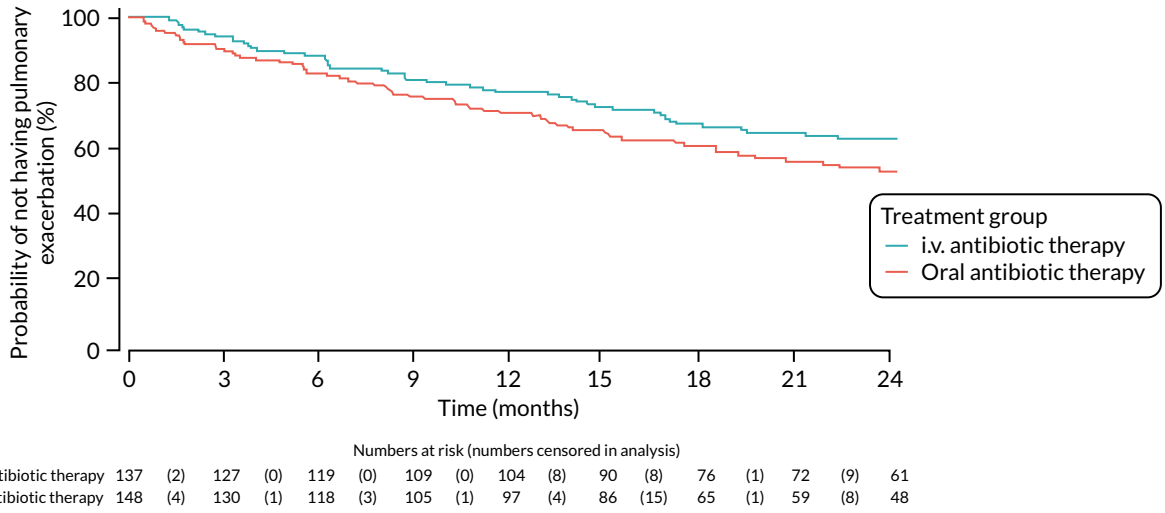

FIGURE 5 Time to first pulmonary exacerbation.

Admission to hospital

A total of 278 participants were included in the analysis over the 3-month treatment period. During this time, most participants were not admitted to hospital (i.v. antibiotic therapy, 81.5%; oral antibiotic therapy, 89.5%). However, the risk of being admitted to hospital (not including admission for the i.v. treatment if randomised to the i.v. antibiotic therapy group) was higher for participants randomised to i.v. antibiotic therapy than for participants randomised to oral antibiotic therapy (relative risk 1.77, 95% CI 0.97 to 3.2; $p = 0.057$). After this time, the risk of being admitted to hospital was reduced for the i.v. antibiotic therapy group compared with the oral antibiotic therapy group. There were 265 participants included in the analysis from 3 to 15 months (relative risk 0.69, 95% CI 0.5 to 0.95; $p =$ value 0.02) and 212 participants included in the analysis from 15 to 24 months (relative risk 0.82, 95% CI 0.57 to 1.19; $p = 0.293$); the reduced number of patients post 15 months was mainly because of the fact that only those participants randomised prior to 1 January 2016 were followed up for 24 months. All results are presented in *Table 12*, along with information on the proportions of participants with no admissions or at least one admission. Results from the sensitivity analysis are also presented in *Table 13* and are consistent with the primary analysis of this outcome.

Number of days spent as an inpatient in hospital

A total of 278 participants were included in the analysis over the 3-month treatment period, 265 participants were included over the period from 3 to 15 months' follow-up and 201 participants were included from 15 to 24 months' follow-up. The median number of days spent as an inpatient in hospital was zero in both treatment groups across all time periods. The distributions of the number of days in hospital in each group were significantly different over the time period from 3 to 15 months' follow-up ($p = 0.005$), but not at the other time points (a p-value of 0.066 for the 3-month treatment period; a p-value of 0.261 for the 15–24 months' follow-up). The results from sensitivity analyses were consistent with these results. All results are provided in *Table 13*.

Quality of life (Cystic Fibrosis Questionnaire)

For this outcome, the analyses were undertaken on patients aged ≥ 6 years (134/285 patients randomised: 62 patients to i.v. antibiotic therapy and 72 patients to oral antibiotic therapy). Of these, 62 patients were expected to be in the self-report analyses and 46 patients were expected to be in the parent analyses for i.v. antibiotic therapy. For oral antibiotic therapy, 72 patients were expected to be in the self-report analyses and 51 patients were expected to be in the parent analyses.

TABLE 13 Secondary outcomes: number of pulmonary exacerbations and number of days spent in hospital

		Treatment group				
		i.v. antibiotic therapy		Oral antibiotic therapy		
Outcome	Time period	*n*	Median (range)	*n*	Median (range)	*p*-value
Number of pulmonary exacerbations	Up to 15 months	137	0 (0–1)	146	0 (0–1)	0.087
Number of days spent in hospital	Up to 3 months	135	0 (0–29)	143	0 (0–14.8)	0.066
	3–15 months	129	0 (0–69)	136	0 (0–64)	0.005
	15–24 months	99	0 (0–33)	102	0 (0–28)	0.261
Number of days spent in hospital: sensitivity analysis 1	Up to 3 months	135	0 (0–29)	143	0 (0–16)	0.050
	3–15 months	129	0 (0–69)	136	0 (0–64)	0.007
	15–24 months	99	0 (0–28)	102	0 (0–28)	0.273
Number of days spent in hospital: sensitivity analysis 2	Up to 3 months	135	0 (0–29)	143	0 (0–10)	0.003
	3–15 months	129	0 (0–69)	136	0 (0–66)	0.004
	15–24 months	99	0 (0–42)	102	0 (0–28)	0.574

A total of 106 participants were included in the analysis of the majority of domains in the self-report questionnaire (some domains included 105 participants because of missing data). The analysis of the domains that were completed by participants aged ≥ 14 years included 27 participants. A total of 73 participants (or 72 participants when missing data occurred) were included in the analyses of the domains in the parent/carer questionnaire. There were no statistically significant differences between the two treatment groups at 15 months across any of the domains in each questionnaire (*Table 14* shows the treatment difference, associated CI and *p*-value from the model). The mean score for each treatment group at each time point for each of the domains is shown in *Appendix 4*, *Figures 10–32*.

Other sputum/cough microbiology

Different numbers of participants were included in the analyses of the different organisms, as, if patients had withdrawn prior to the end of the time point, they were included only if they had previously had an occurrence of the organism of interest. There were no statistically significant differences between the two treatment groups in terms of the occurrence of the four organisms of interest at any time point.

TABLE 14 Secondary outcome: quality of life

Domain	Participants (*n*)	Mean treatment difference at 15 months (95% CI)	*p*-value
Self-report questionnaire			
Physical functioning	106	−3.63 (−10.41 to 3.16)	0.292
Role/school functioning[a]	27	7.66 (−6.21 to 21.52)	0.267
Vitality[a]	27	5.4 (−6.88 to 17.69)	0.373
Emotional functioning	106	−1.59 (−7.39 to 4.22)	0.589
Social functioning	106	2.11 (−4.03 to 8.25)	0.498
Body image	105	−4.01 (−11.78 to 3.77)	0.309
Eating problems	106	−0.39 (−6.78 to 6)	0.903
Treatment burden	105	2.86 (−6.19 to 11.92)	0.532
Health perceptions[a]	27	5.06 (−13.72 to 23.84)	0.583
Weight[a]	27	1.4 (−19.02 to 21.83)	0.725
Respiratory symptoms	106	2.82 (−3.44 to 9.08)	0.374
Digestive symptoms	106	−0.01 (−9.95 to 9.93)	0.998
Parent/carer questionnaire			
Physical functioning	73	−5.17 (−13.55 to 3.22)	0.223
Role/school functioning	72	−1.47 (−10.22 to 7.28)	0.738
Vitality	72	−0.44 (−9.36 to 8.48)	0.923
Emotional functioning	72	3.32 (−3.56 to 10.2)	0.339
Body image	72	−0.56 (12.03 to 10.9)	0.922
Eating problems	72	6.15 (−2.78 to 15.08)	0.174
Treatment burden	73	−0.28 (−11.25 to 10.69)	0.96
Health perceptions	72	−7.25 (−15.09 to 0.6)	0.07
Weight	73	−1.19 (−17.63 to 15.26)	0.886
Respiratory symptoms	73	−3.33 (−11.71 to 9.93)	0.432
Digestive symptoms	72	3.54 (−4.9 to 11.98)	0.405

a Domain completed by participants aged ≥ 14 years.

Table 15 shows the numbers of participants in each treatment group who did/did not have cough or sputum samples containing each organism, the relative risks and 95% CIs and the *p*-values from the chi-squared tests for each organism over each time period of interest.

The number of participants who had cough or sputum samples containing additional organisms of interest is reported in *Appendix 5*, *Table 34*.

Carer and participant burden (absenteeism from education or work)

A total of 270 carers were included in the analysis of absenteeism from education or work during the 15 months following randomisation. Approximately one-third of carers had at least one episode of absence (i.v. antibiotic therapy group, 33.6%; oral antibiotic therapy group, 35.3%), but the risk of absence was not significantly greater in either treatment group (*Table 16*). The median (IQR) number of days of absence experienced in each group for carers was 0 (0–1) and the distributions of the number of days of absence experienced in each group were not significantly different ($p = 0.616$).

A total of 271 participants were included in the analysis of absenteeism from education or work during the 15 months following randomisation. Approximately half of the participants had at least one episode of absence (i.v. antibiotic therapy group, 49.6%; oral antibiotic therapy group, 54.3%), but the risk of absence was not significantly greater in either treatment group (see *Table 16*). The median number of days of absence for participants in the i.v. antibiotic therapy group was 0 (IQR 0–6.2) and the median was 1 (IQR 0–10) in the oral antibiotic therapy group, and the distributions of the number of days absence experienced in each group were not significantly different ($p = 0.263$).

TABLE 15 Secondary outcome: other sputum/cough microbiology

Outcome	Time period	Treatment group, *n/N* (%)		Relative risk (95% CI)	*p*-value
		i.v. antibiotic therapy	Oral antibiotic therapy		
MRSA	Up to 3 months	0/136 (0.0)	1/145 (0.7)	–	–
	Up to 15 months	4/135 (3.0)	2/140 (1.4)	2.07 (0.39 to 11.14)	0.441
	Up to 24 months	4/132 (3.0)	4/133 (3.0)	1.01 (0.26 to 3.94)	0.999
Burkholderia cepacia complex	Up to 3 months	1/136 (0.7)	0/144 (0.0)	–	–
	Up to 15 months	2/135 (1.5)	4/139 (2.9)	0.51 (0.10 to 2.76)	0.684
	Up to 24 months	2/132 (1.5)	4/133 (3.0)	0.50 (0.09 to 2.70)	0.684
Candida infection	Up to 3 months	26/137 (19.0)	27/146 (18.5)	1.03 (0.63 to 1.67)	0.917
	Up to 15 months	55/136 (40.4)	55/142 (38.7)	1.04 (0.78 to 1.40)	0.771
	Up to 24 months	66/135 (48.9)	63/137 (45.7)	1.07 (0.83 to 1.38)	0.592
Aspergillus	Up to 3 months	6/130 (4.4)	5/144 (3.5)	1.27 (0.40 to 4.07)	0.686
	Up to 15 months	14/121 (10.4)	20/139 (14.4)	0.72 (0.38 to 1.37)	0.313
	Up to 24 months	21/113 (15.7)	25/134 (18.7)	0.84 (0.50 to 1.42)	0.517

TABLE 16 Number of carers/participants experiencing at least one episode of absence from education or work during the 15 months following randomisation

Outcome	Time period	Treatment group, *n/N* (%)		Relative risk (95% CI)	*p*-value
		i.v. antibiotic therapy	Oral antibiotic therapy		
Carer burden	Up to 15 months	44/131 (33.6)	49/139 (35.3)	1.03 (0.86 to 1.22)	0.774
Participant burden	Up to 15 months	65/131 (49.6)	76/140 (54.3)	1.10 (0.86 to 1.41)	0.442

Safety

Safety reporting at database lock

A complete list of AEs (verbatim) and the original MedDRA code (preferred term and SOC) that was agreed by the chief investigator prior to the database being locked are shown in *Appendix 5*, *Table 35*.

The non-serious AEs and SAEs that were recorded on the locked database are shown, grouped by the SOC and preferred term, in *Appendix 5*, *Tables 36* and *37*, respectively. Line listings of the SAEs are shown in *Appendix 5*, *Table 38*.

Changes made to safety reporting post hoc

After the database was locked and the blind was broken, it was found that there had been several instances where *P. aeruginosa* and pulmonary exacerbations had been reported both as an AE and also as a primary or secondary outcome, respectively.

There were four SAEs reported as both an outcome and a SAE: three SAEs (reported from three participants in the oral antibiotic therapy group) were included as events for the primary outcome and one SAE (reported from one participant in the oral antibiotic therapy group) was included as both a SAE and a secondary outcome. These events have not been included in *Table 17* and have been reported only in each of the secondary outcome analyses.

There were 17 non-serious AEs reported as both an outcome and an AE: 14 AEs (nine AEs reported from nine participants in the i.v. antibiotic therapy group and five AEs from five participants in the oral antibiotic therapy group) met the definition of the primary outcome and three AEs (reported from three participants in the oral antibiotic therapy group) met the definition of the secondary outcome pulmonary exacerbation. These non-serious AEs have not been included in *Table 18*.

On reflection, the chief investigator and co-chief investigator also felt that there were descriptions of non-serious AEs that could be clarified to aid the reader. The original classifications as recorded on the locked trial database and the clarified classifications (as agreed by both the chief investigator and co-chief investigator) are shown in *Appendix 5*, *Table 39*.

Table 18 uses the clarified classifications.

Safety population

A total of 272 participants received at least one dose of their allocated treatment and were included in the safety population: 126 participants (91.9%) in the i.v. antibiotic therapy group and 146 participants (98.6%) in the oral antibiotic therapy group.

Serious adverse events/reactions

In the i.v. antibiotic therapy group, 11 SAEs/SARs were reported from 10 participants (7.9%) and, in the oral antibiotic therapy group, 21 SAEs/SARs were reported from 14 participants (9.6%). None of the SARs that was reported met the criteria for SUSAR reporting.

Table 17 indicates the number of events reported for each SOC and the number of participants who experienced the event.

Non-serious adverse events

In the i.v. antibiotic therapy arm, 126 non-serious AEs were reported from 60 participants (47.6%) and, in the oral antibiotic therapy group, 136 non-serious AEs were reported from 72 participants (49.3%). The most common SOCs in which events were reported for both treatment groups were respiratory, thoracic and mediastinal disorders; infections and infestations; and gastrointestinal disorders. A complete list of all non-serious AEs [excluding events counted in the analyses of primary and secondary outcomes, and using clarified terms (*Table 39*)] can be found in *Table 18*.

TABLE 17 Serious adverse events/reactions grouped by SOC and preferred term

		Treatment group, *n* (%)					
		i.v. antibiotic therapy (*N* = 126)		Oral antibiotic therapy (*N* = 146)		Total (*N* = 272), *n* (%)	
SOC	Preferred term	Events	Patients	Events	Patients	Events	Patients
Gastrointestinal disorders	Distal intestinal obstruction syndrome	2	2 (1.6)	1	1 (0.7)	3	3 (1.1)
General disorders and administration site conditions	Chest pain	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	General physical health deterioration	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pyrexia	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Hepatobiliary disorders	Hepatic failure	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Infections and infestations[a,b]	Bronchiolitis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Croup infectious	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Gastroenteritis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Infective pulmonary exacerbation of cystic fibrosis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Lower respiratory tract infection[b]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Rhinitis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Upper respiratory tract infection	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Viral infection	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Nervous system disorders	Headache	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Psychiatric disorders	Anxiety[c]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Renal and urinary disorders	Haematuria	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Lung consolidation	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pneumothorax	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Productive cough	0	0 (0.0)	3	3 (2.1)	3	3 (1.1)
Skin and subcutaneous tissue disorders	Rash pruritic	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Surgical and medical procedures	Catheter management	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Vascular disorders	Deep-vein thrombosis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Thrombophlebitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Total[a,b,d]		11	10 (7.9)	17	12 (8.2)	28	22 (8.1)

a Three additional SAEs were reported by three participants in the oral antibiotic therapy group but have not been included here as they were the event of interest for the primary outcome so should not have been reported as a SAE.
b One additional AE was reported by one participant in the oral antibiotic therapy group but has not been included here as it contributed to the analysis of the outcome 'Number of pulmonary exacerbations'.
c Event was that after 5 weeks on trial, participant developed voices in their head, obsessive behaviours and anxiety at night.
d Total number of events may exceed the total number of patients as a patient may report more than one event.

TABLE 18 All non-SAEs grouped by SOC and preferred term

		Treatment group, *n* (%)					
		i.v. antibiotic therapy (*N* = 126)		Oral antibiotic therapy (*N* = 146)		Total (*N* = 272), *n* (%)	
SOC	Preferred term	Events	Patients	Events	Patients	Events	Patients
Ear and labyrinth disorders	Ear discomfort	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Ear pain	0	0 (0.0)	2	2 (1.4)	2	2 (0.7)
Gastrointestinal disorders	Abdominal pain	1	1 (0.8)	2	2 (1.4)	3	3 (1.1)
	Abdominal pain upper	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Constipation	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Diarrhoea	6	5 (4)	3	3 (2.1)	9	8 (2.9)
	Distal intestinal obstruction syndrome	2	2 (1.6)	3	3 (2.1)	5	5 (1.8)
	Haematemesis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Nausea	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Pancreatitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Paraesthesia oral	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Rectal haemorrhage	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Tongue discolouration	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Vomiting	3	3 (2.4)	0	0 (0.0)	3	3 (1.1)
General disorders and administration site conditions	Administration site bruise	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Administration site pain	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Adverse drug reaction	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Catheter site-related reaction	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Chest pain	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Influenza-like illness	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Malaise	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pain	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Pyrexia	2	2 (1.6)	7	7 (4.8)	9	9 (3.3)
	Nasal swelling[a]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Immune system disorders	Seasonal allergy	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
Infections and infestations	Allergic bronchopulmonary aspergillosis[a]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Candida infection	1	1 (0.8)	5	5 (3.4)	6	6 (2.2)
	Chest infection[a]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Conjunctivitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Eczema infected	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)

TABLE 18 All non-SAEs grouped by SOC and preferred term (*continued*)

		Treatment group, *n* (%)					
		i.v. antibiotic therapy (*N* = 126)		Oral antibiotic therapy (*N* = 146)		Total (*N* = 272), *n* (%)	
SOC	Preferred term	Events	Patients	Events	Patients	Events	Patients
	Enterobacter cloacae respiratory infection[a]	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Eye infection	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Hand, foot and mouth disease[a]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Hand, foot and mouth disease (recorded as foot and mouth disease)[a,b]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Gastroenteritis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Haemophilus influenzae respiratory infection	3	3 (2.4)	0	0 (0.0)	3	3 (1.1)
	Haemophilus parainfluenzae respiratory infection	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Infectious mononucleosis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Infective pulmonary exacerbation of cystic fibrosis[c]	4	3 (2.4)	3	3 (2.1)	7	6 (2.2)
	Klebsiella pneumoniae respiratory infection[a]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Mycobacterium avium complex infection	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Nasal vestibulitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Nasopharyngitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Oral candidiasis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Otitis media	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Pneumonia	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Respiratory tract infection	1	1 (0.8)	2	2 (1.4)	3	3 (1.1)
	Sinusitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Stenotrophomonas maltophilia respiratory infection[a]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Streptococcus pyogenes respiratory infection[a]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Upper respiratory tract infection	15	11 (8.7)	3	2 (1.4)	18	13 (4.8)
	Urinary tract infection	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)

continued

TABLE 18 All non-SAEs grouped by SOC and preferred term (*continued*)

		Treatment group, *n* (%)					
		i.v. antibiotic therapy (*N* = 126)		Oral antibiotic therapy (*N* = 146)		Total (*N* = 272), *n* (%)	
SOC	Preferred term	Events	Patients	Events	Patients	Events	Patients
	Varicella	3	3 (2.4)	1	1 (0.7)	4	4 (1.5)
	Viral infection	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Vulvovaginal candidiasis	2	2 (1.6)	0	0 (0.0)	2	2 (0.7)
Injury, poisoning and procedural complications	Fall	1	1 (0.8)	2	2 (1.4)	3	3 (1.1)
	Skull fracture	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Sunburn	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Wrist fracture	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Investigations	Alanine aminotransferase increased	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Blood glucose increased	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Chest X-ray abnormal	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Metabolism and nutrition disorders	Decreased appetite	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Vitamin A deficiency	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Vitamin D deficiency	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Vitamin E deficiency	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Musculoskeletal and connective tissue disorders	Arthralgia	0	0 (0.0)	3	3 (2.1)	3	3 (1.1)
	Back pain	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Flank pain	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Limb discomfort	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Musculoskeletal chest pain	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Musculoskeletal stiffness	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Myalgia	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pain in extremity	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Tendonitis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Malignant melanoma	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Nervous system disorders	Dizziness	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Febrile convulsion	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Headache	3	2 (1.6)	0	0 (0.0)	3	2 (0.7)
	Lethargy	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Migraine	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)

TABLE 18 All non-SAEs grouped by SOC and preferred term (*continued*)

		Treatment group, *n* (%)					
		i.v. antibiotic therapy (*N* = 126)		Oral antibiotic therapy (*N* = 146)		Total (*N* = 272), *n* (%)	
SOC	Preferred term	Events	Patients	Events	Patients	Events	Patients
Product issues	Device occlusion	2	2 (1.6)	0	0 (0.0)	2	2 (0.7)
Psychiatric disorders	Enuresis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Renal and urinary disorders	Dysuria	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Polyuria	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Respiratory, thoracic and mediastinal disorders	Bronchospasm	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Cough	26	22 (17.5)	28	23 (15.8)	54	45 (16.5)
	Epistaxis	1	1 (0.8)	2	2 (1.4)	3	3 (1.1)
	Haemoptysis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Nasal congestion	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Pharyngeal oedema	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pulmonary function decreased[a]	1	1 (0.8)	2	2 (1.4)	3	3 (1.1)
	Productive cough	5	5 (4)	8	8 (5.5)	13	13 (4.8)
	Sputum increased	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Wheezing	3	3 (2.4)	6	6 (4.1)	9	9 (3.3)
Skin and subcutaneous tissue disorders	Dermatitis diaper	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Dry skin	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Eczema	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Onychoclasis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Petechiae	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Photosensitivity reaction	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Rash	2	2 (1.6)	1	1 (0.7)	3	3 (1.1)
	Skin discolouration	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Urticaria	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Total[c,d]		126	60 (47.6)	136	72 (49.3)	262	132 (48.5)

a Wording not consistent with 'preferred term' recorded on database; amended based on additional data available.
b Not confirmed in medical notes.
c Three additional AEs were reported by three participants in the oral antibiotic therapy group, but have not been included here as they contributed to the analysis of the outcome '[N]umber of pulmonary exacerbations'.
d Nine additional AEs were reported by nine participants in the i.v. antibiotic therapy group and five AEs were reported by five participants in the oral antibiotic therapy group, but they have not been included here as they were the event of interest for the primary outcome so should not have been reported as an AE.

Chapter 6 Economic evaluation

Overview

A prospective economic evaluation was conducted alongside the randomised controlled trial to assess the cost-effectiveness of oral antibiotic therapy compared with i.v. antibiotic therapy. The primary analysis used an NHS and Personal Social Services (PSS) perspective for the collection and incorporation of resource use, as recommended by the National Institute for Health and Care Excellence (NICE).[42] The time horizon for the primary analysis was 15 months from randomisation.

The primary outcome within the economic evaluation was the same as that in the clinical study and measured the percentage of patients with successful eradication of *P. aeruginosa* 3 months after the start of treatment and who remained infection free through 15 months after the start of treatment. Analysis for the economic evaluation was based on the population with data for the primary outcome; missing health economic data within that population were multiply imputed.

The primary cost-effectiveness analysis measured the incremental cost per successful eradication of *P. aeruginosa* infection 3 months after allocated treatment had started, and of remaining infection free through to 15 months after the start of allocated treatment, in the oral antibiotic therapy group and the i.v. antibiotic therapy group. Regression analysis controlled for baseline differences between groups.

Secondary cost-effectiveness analyses were carried out and used the EQ-5D-3L (completed by a mixture of patients/carers, as appropriate) and QALYs to value health outcomes.

Where the EQ-5D-3L and QALYs were used to value health outcomes, cost–utility analysis was conducted to measure the incremental net benefit (INB) of treating patients in the oral antibiotic therapy group and the i.v. antibiotic therapy group. Sensitivity analyses explored factors that were identified a priori as likely to be key drivers of cost-effectiveness, including assumptions regarding the incorporation of costs for the intervention.

Resource use and costs

Total resource use and costs for each patient in the clinical trial were calculated. The main resource use and cost components for both the oral antibiotic therapy and i.v. antibiotic therapy arm comprised (1) the different modes of antibiotic intervention, information on which was collected through the use of case report forms and (2) any follow-up interactions with the health and social care system, which information was captured through patient diaries and collected at 3, 6, 9, 12 and 15 months. All costs were calculated in Great British pounds with the price year of 2016/17 used. Where possible, unit costs were sourced from national databases including the BNF[43] for medicines; NHS reference costs[44] for inpatient, outpatient and accident and emergency (A&E) visits; and Personal Social Services Research Unit (PSSRU)[45] for primary care consultations (*Tables 19* and *20* present the complete list of unit costs). Where relevant unit costs were not available for the correct price year of 2016/17, unit costs from other price years were inflated using the Hospital and Community Health Service (HCHS) pay and price inflation index.[45]

Interventions

Oral antibiotic therapy and intravenous antibiotic therapy drug costs

In both the oral antibiotic therapy arm and i.v. antibiotic therapy arm, the antibiotic dosage and quantity of all antibiotics prescribed were recorded through data collected in case report forms to

TABLE 19 Unit costs in primary care or community care

Resource	Measurement	Unit cost (£)	Source	Detail
Primary care				
GP visit in surgery	Per visit	38	PSSRU 2017[45]	With qualification and including direct care costs
Nurse visit in surgery	Per visit	14	PSSRU 2017[45]	With qualification and including direct care costs. Assuming a 20-minute consultation
Doctor in walk-in centre	Per visit	44	NHS reference costs 2016–17[44]	Weighted average of non-admitted, type 4 A&E visits
Nurse in walk-in centre	Per visit	44	NHS reference costs 2016–17[44]	Weighted average of non-admitted, type 4 A&E visits
Other	Per visit	35		Average of above
Home visits				
GP visit	Per home visit	161	PSSRU 2017[45]	With qualification and including direct care costs, assuming 40 minutes with travel
District nurse	Per home visit	29	PSSRU 2010[46]	With qualification and including direct care costs, inflated to 2016–17 using HCHS index[45]
Health visitor	Per home visit	58	PSSRU 2010[46]	With qualification and including direct care costs, inflated to 2016–17 using HCHS index[45]
Nurse	Per home visit	44	PSSRU 2010[46]	With qualification and including direct care costs, inflated to 2016–17 using HCHS index[45]
Physiotherapist	Per home visit	61	PSSRU 2010[46]	With qualification and including direct care costs, inflated to 2016–17 using HCHS index[45]
Occupational therapy	Per home visit	45	PSSRU 2017[45]	With qualification and including direct care costs
Other	Per home visit	47		Average of all apart from GP visit
Community-based professional				
Home care worker	Per visit	21	PSSRU 2017[45]	With qualification and including direct care costs, 1 hour
Nurse	Per visit	44	PSSRU 2017[45]	Same as nurse home visit
Physiotherapist	Per visit	49	PSSRU 2017[45]	Same as physiotherapist home visit
Social worker	Per visit	57	PSSRU 2017[45]	With qualification and including direct care costs

GP, general practitioner.

TABLE 20 Secondary care unit costs within the analysis

Resource	Measurement	Unit cost (£)	Source	Detail
Outpatients				
Non-consultant led, adult	Per visit	75	NHS reference costs 2016–17[44]	Any non-paediatric outpatient, weighted average
Non-consultant led, child	Per visit	149	NHS reference costs 2016–17[44]	Any paediatric outpatient, weighted average
Consultant led, adult	Per visit	136	NHS reference costs 2016–17[44]	Any non-paediatric outpatient, weighted average
Consultant led, child	Per visit	196	NHS reference costs 2016–17[44]	Any paediatric outpatient, weighted average
Dietitian	Per visit	37	PSSRU 2010[46]	With qualification and including direct care costs, inflated to 2016–17 using HCHS index[45]
Physiotherapist	Per visit	49	NHS reference costs 2016–17[44]	
MDT, adult	Per visit	1541	NICE 2017[47]	MDT clinic, based on 250 adult patients per year, six visits per person per year
MDT, child	Per visit	1254	NICE 2017[47]	MDT clinic, based on 250 child patients per year, six visits per person per year
Radiology	Per visit	135	NHS reference costs 2016–17[44]	Interventional radiology
Pharmacy	Per visit		PSSRU 2010[46]	With qualification and including direct care costs, inflated to 2016–17 using HCHS index[45]
A&E, discharged	Per visit	128	NHS reference costs 2016–17[44]	Any A&E discharged, weighted average
A&E, admitted	Per visit	221	NHS reference costs 2016–17[44]	Any A&E admitted, weighted average
Intervention				
Ceftazidime	Per vial	4.25–17.59	BNF 2017[43]	
Tobramycin	Per vial	19	BNF 2017[43]	
Ciprofloxacin	Per tablet	0.80–1.20	BNF 2017[43]	
Home i.v.				
Fixed cost	Per course	159	James Sutton, Nottingham University Hospitals, 2019, personal communication	Dispensing fee, delivery fee and ancillaries
Tobramycin	Per day	20–27	James Sutton, Nottingham University Hospitals, 2019, personal communication	Eclipse or intermate (once per day infusions)
Ceftazidime	Per day	22.70–36.30	James Sutton, Nottingham University Hospitals, 2019, personal communication	Eclipse or intermate (once per day infusions)
Inpatient ward stays				
General ward, adult	Per day	380	NHS reference costs 2016–17[44]	Excess bed-days, weighted average for adults
General ward, child	Per day	595	NHS reference costs 2016–17[44]	Excess bed-day, weighted average for paediatrics

MDT, multidisciplinary team.

calculate a cost per course. Drug resource use was calculated assuming that whole vials or ampoules were used for each dose. Unit costs for the drug resource use were sourced from the BNF for i.v. antibiotic therapy within hospital and for the oral antibiotic therapy arm. For i.v. antibiotic therapy within hospital and for oral antibiotic therapy, no dispensing fees or disposable equipment were included in the cost, as this was assumed to be an overhead for the inpatient stay or outpatient visit and incorporated within the reference cost.

For patients who started i.v. antibiotic therapy in hospital and then completed treatment at home, the dose and quantity of drugs prescribed for home i.v. antibiotic therapy were calculated. Dispensing fees, delivery fees and ancillaries were included for home i.v. antibiotic therapy, with unit costs sourced from local pharmacy tariffs. Any unused medicines were assumed to become waste.

Inpatient stay for intravenous antibiotic therapy

For the i.v. antibiotic therapy arm, the length of stay in hospital was recorded. A per diem unit cost, a weighted average of all general ward stays in NHS Reference Costs, stratified by adult or child, was multiplied by the length of stay in days to generate an inpatient stay cost for i.v. antibiotic therapy treatment.

Follow-up resource use and costs

Patient diaries collected follow-up resource use for 15 months following randomisation. Resource use was recorded in diaries when patients interacted with primary care [in general practitioner (GP) practices and home visits], interacted with secondary care (inpatients, outpatients, A&E, walk-in centres), had a diagnostic test in primary or secondary care, or met with a community-based professional (e.g. physiotherapists or social workers). Patients also recorded any medications prescribed through the NHS, as well as any aids or home modifications.

For patients who had recorded an inpatient stay, the length of stay was calculated. A per diem unit cost, stratified by adult or child, was multiplied by the length of stay to generate an inpatient stay cost. The number of visits to A&E and whether the patient was admitted or discharged was calculated with appropriate unit costs attached. For each patient, the number of outpatient visits, stratified by whether the consultation was consultant led or non-consultant led, was calculated and unit costs were attached based on a weighted average of outpatient visits from NHS Reference Costs.[48] Any costs associated with interactions with primary care were based on whether the consultation was with a GP or nurse, and whether the consultation took place within the practice or at home. The number of visits with community-based professionals were recorded and costed. Where patients recorded that they had visited a multidisciplinary team as part of a CF clinic, an appropriate unit cost was attached based on a previously conducted micro-costing study.[47]

The dosage and quantity of all drugs prescribed for patients were recorded and unit costs from the BNF were attached. Drug resource use was calculated assuming that all medications prescribed were used or became waste.

Wider resource use and costs

To record wider societal costs, patient diaries also recorded:

- out-of-pocket costs for transport to consultations using car, bus or taxi
- out-of-pocket costs for over-the-counter medicines
- out-of-pocket costs for aids and appliances
- time from work lost by the carer or patient.

For patients reporting car, bus or taxi travel, the total travel time in minutes was calculated and multiplied by appropriate unit costs per minute of travel. Lost productivity was estimated as the number of minutes lost to work by the care giver or patient multiplied by mean hourly earnings

reported by the Office for National Statistics.[49] Out-of-pocket costs for over-the-counter medicines, as well as aids and appliances, were calculated using currently available prices.

Outcomes

The primary outcome measure was the percentage of patients with successful eradication of *P. aeruginosa* 3 months after the start of treatment and who remained infection free through 15 months after the start of treatment and this was calculated for both the i.v. antibiotic therapy arm and the oral antibiotic therapy arm.

The secondary outcome was the QALY, which is a composite of HRQoL, as measured by the EQ-5D-3L, and length of life. The EQ-5D-3L questionnaire has five domains (i.e. mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) and three levels (i.e. no problems, some problems and extreme problems) and was completed by either patients or their carers (if < 13 years) at baseline, and at 3, 15 and 24 months. It is still unclear what the most appropriate method is to elicit HRQoL for very young children.[50,51] The EQ-5D-3L was selected in this study as it was available at the time of study design and provides consistency with measures of HRQoL frequently used in economic evaluations within adult populations. However, although there are now specific measures of HRQoL developed for children, none of the new measures has a robust evidence base for performance yet.[50] In the primary analysis, the time horizon of 15 months was used to match the collection of resource use data. In sensitivity analysis, the long-term 24-month horizon for QALYs was assessed. The EQ-5D-3L utility tariff was applied to the EQ-5D-3L questionnaire responses to generate utility scores for each time point for each patient. To calculate the QALYs, linear interpolation was assumed between the time points and the area under the curve method was applied.[52]

Statistical analysis: bootstrapping and missing data

Missing data were multiply imputed ($m = 25$) through the use of chained equations.[53] The data were assumed to be missing at random. To account for non-normality in the distributions of costs and HRQoL, predictive mean matching was used. Missing cost data were imputed at the level of the category (inpatient care, outpatient visits, A&E visits, primary care, etc.) and total costs were passively imputed as a sum of the individual cost domains for those with missing data. For HRQoL, missing data were imputed for the utility score for each of the time points and QALYs were passively calculated. Predictors in both the cost and HRQoL multiple imputation models were patients' age, sex, treatment arm, and costs at baseline. Owing to the large numbers of patients with missing data for wider resource use, missing data were not imputed and, instead, individuals were assumed to have zero use.

To account for statistical uncertainty and the correlation between costs and patient outcomes, the data were bootstrap sampled with replacement 2000 times.[54] For each bootstrap sample, missing data were imputed[55] and incremental measures of cost and outcome were calculated using regression analysis, controlling for baseline HRQoL, age and treatment arm. The regression analysis used ordinary least squares, accounting for the multiply imputed data through the use of Rubin's rules.[56] All regression analysis, including bootstrapping and multiple imputation, was conducted using Stata® v14 (StatCorp LP, College Station, TX, USA).

Cost-effectiveness

In the primary analysis, mean incremental costs and outcomes were calculated using the binary treatment arm variable within the linear regression models. To calculate the uncertainty around mean incremental costs and outcomes, the percentile method was used, with the 97.5th and 2.5th percentile

bootstrap iterations representing the 95% CIs. Each of the 2000 bootstrap iterations were plotted on a cost-effectiveness plane. If feasible, an ICER was calculated:

$$\text{ICER} = \frac{\text{cost}_{\text{OT}} - \text{cost}_{\text{IVT}}}{\%\ \text{infection free}_{\text{OT}} - \%\ \text{infection free}_{\text{IVT}}}, \quad (1)$$

where OT is oral therapy and IVT is i.v. therapy.

A cost-effectiveness acceptability curve (CEAC) reflecting the likelihood of either technology being cost-effective for a decision-maker's willingness to pay for the outcome variable was also plotted.

In the secondary analysis, mean incremental costs and QALYs were calculated, with 95% CIs estimated through the percentile method. The INB was estimated from the incremental costs and QALYs for i.v. antibiotic therapy compared with oral antibiotic therapy using the following formula:

$$\text{INB} = \lambda \times (\text{QALY}_{\text{OT}} - \text{QALY}_{\text{IVT}}) - (\text{cost}_{\text{OT}} - \text{cost}_{\text{IVT}}), \quad (2)$$

with λ representing the opportunity cost of health-care resources used in the NHS, otherwise known as the cost-effectiveness threshold. NICE uses a threshold range between £20,000 and £30,000 per QALY.[57] A positive INB suggests that i.v. antibiotic therapy is the cost-effective option and a negative INB suggests oral antibiotic therapy is the cost-effective option. Cost-effectiveness planes and CEACs were also plotted for the secondary analyses.

Sensitivity analysis

A series of assumptions used in the economic evaluation were explored through one-way sensitivity analysis. Separate analyses explored:

1. full time horizon of QALYs (24 months) alongside the collection of resource use data (15 months)
2. using generalised linear models (GLMs) for the cost analysis with different link and family functions
3. using yearly health-care resource use codes for CF instead of treatment costs and inpatient stay per diem
4. using a societal perspective for the collection and incorporation of costs.

Generalised linear models

Owing to the skewed and zero-centred nature of costing data, some analysts have recommended using more complex models such as GLMs to assess incremental differences.[58] GLMs have an associated link function and family function. The base-case approach for both primary and secondary analyses involved using an identity link with Gaussian family, equivalent to ordinary least squares regression. For sensitivity analysis, a range of different family functions were also explored alongside an identity link and log-link, including inverse Gaussian, Poisson and gamma. The method of recycled predictions was used to estimate the incremental difference in costs.

Using cystic fibrosis Healthcare Resource Groups

Since 2013–14, the NHS has used specialised tariffs for patients with CF.[59] The CF currency uses a risk-adjusted banding system with seven bands of increasing complexity, with providers reimbursed on a yearly basis according to the risk-adjusted bands. The CF currency is intended to include all direct medical costs associated with treatment and bandings are split according to whether patients are adults (≥ 17 years) or children.

Patients were placed in bands according to their age, any length of stay associated with the initial intervention and the recorded length of stay for further hospitalisation.

Appendix 6, *Table 40* includes the banding algorithm and *Table 41* provides the unit costs for the bandings. Inpatient costs were then replaced in totality with banding costs for 1 year. All other costing estimates were included within this separate Healthcare Resource Group (HRG) analysis to calculate a total NHS and PSS cost.

Societal perspective for the inclusion of costs

A societal perspective included patients' purchase of home aids or over-the-counter medicines, and the cost of transport to attend outpatient visits or inpatient stays, as well as work lost by patients or caregivers during the trial. Unit costs were attached to resource use using costs reported in *Appendix 6*. The total societal costs were calculated by adding these wider costs to the NHS and PSS costs.

Results

The analysis for health economics was based on a total of 255 patients, of whom 130 patients were randomised to the oral antibiotic therapy arm and 125 patients were randomised to the i.v. antibiotic therapy arm.

Tables 21 and *22* present resource utilisation and levels of missingness for NHS and societal resource use data, respectively. Most resource use was balanced between the arms. However, the resource use in the oral antibiotic therapy arm was suggestive of having a larger proportion of inpatient stays than the i.v. antibiotic therapy arm.

Table 23 presents data for the completion of the EQ-5D-3L for the different time points recorded. The domains most affected by CF were pain and discomfort, and self-care, with fewer patients having 'no problems' in these domains. There was no clear difference between EQ-5D-3L levels between arms of the trial or over the duration of the trial.

TABLE 21 Mean NHS and PSS resource use and missingness data

	Treatment group, *n* (SD)	
Resource use	**i.v. antibiotic therapy (*N* = 125)**	**Oral antibiotic therapy (*N* = 130)**
Secondary care		
≥ 3 visits	0.12 (0.42)	0.12 (0.42)
Missing	66	61
A&E attendance, discharged	0.05 (0.29)	0.06 (0.29)
Missing	66	61
Inpatient stay	0.27 (0.61)	0.38 (0.71)
Missing	43	40
Outpatient (visits)	1.57 (0.77)	1.58 (0.79)
Missing	78	82

continued

TABLE 21 Mean NHS and PSS resource use and missingness data (*continued*)

Resource use	Treatment group, *n* (SD)	
	i.v. antibiotic therapy (*N* = 125)	Oral antibiotic therapy (*N* = 130)
Primary care		
GP at surgery	0.25 (0.62)	0.30 (0.71)
Missing	40	34
Doctor at walk-in centre	0.00 (0.00)	0.05 (0.27)
Missing	40	34
Nurse at surgery	0.09 (0.29)	0.13 (0.42)
Missing	40	34
Nurse at walk-in centre	0.00 (0.00)	0.00 (0.00)
Missing	40	34
Other	0.16 (0.55)	0.14 (0.54)
Missing	40	34
Number of prescriptions	2.02 (2.79)	2.18 (3.02)
Missing	41	39
Home visits		
GP	0.39 (0.49)	0.30 (0.46)
Missing	66	57
District nurse	0.44 (0.62)	0.32 (0.50)
Missing	66	57
Health visitor	0.44 (0.62)	0.36 (0.63)
Missing	66	57
Nurse	0.56 (0.82)	0.44 (0.78)
Missing	66	57
Physiotherapy	0.49 (0.73)	0.34 (0.58)
Missing	66	57
Occupational therapy	0.39 (0.49)	0.30 (0.46)
Missing	66	57
Other	0.39 (0.49)	0.30 (0.46)
Missing	66	57
Home care worker	0.07 (0.37)	0.20 (0.60)
Missing	68	60
Community-based professionals		
Social worker	0.07 (0.37)	0.20 (0.60)
Missing	68	60
Nurse	0.11 (0.49)	0.06 (0.29)
Missing	68	60
Physiotherapist	0.00 (0.00)	0.07 (0.39)
Missing	68	60

TABLE 22 Societal resource utilisation and missingness

Resource use	Treatment group, *n* (%)	
	i.v. antibiotic therapy (*N* = 125)	Oral antibiotic therapy (*N* = 130)
Patient aids		
Missing	67	61
Transport car		
No trips	1 (0.8)	5 (4.0)
1–5 trips	51 (41.5)	49 (39.2)
6–10 trips	7 (5.7)	13 (10.4)
> 10 trips	64 (52.0)	58 (46.4)
Missing	2	5
Transport bus		
No trips	29 (23.2)	39 (30.0)
0–5 trips	2 (1.6)	3 (2.3)
6–10 trips	0 (0.0)	1 (0.8)
> 10 trips	94 (75.2)	87 (66.9)
Transport taxi		
No trips	26 (20.8)	37 (28.5)
0–5 trips	9 (7.2)	10 (7.7)
6–10 trips	1 (0.8)	0 (0.0)
> 10 trips	89 (71.2)	83 (63.8)
Transport other		
No trips	21 (16.8)	30 (23.3)
0–5 trips	20 (16.0)	14 (10.9)
6–10 trips	0 (0.0)	2 (1.6)
> 10 trips	84 (67.2)	83 (64.3)
Missing	0	1
Over-the-counter medicines		
0 purchases	110 (88.0)	102 (78.5)
1 purchase	7 (5.6)	19 (14.6)
2 purchases	6 (4.8)	8 (6.2)
3 purchases	2 (1.6)	1 (0.8)
Reported as losing time from work (patient)		
No	116 (99.1)	124 (100.0)
Yes	1 (0.9)	0 (0.0)
Reported as losing time from work (carer)		
No	106 (90.6)	115 (92.7)
Yes	11 (9.4)	9 (7.3)

TABLE 23 The EQ-5D-3L reporting by time point

EQ-5D-3L domain and level	Time point (%)							
	Baseline		3 months		15 months		24 months	
	i.v. antibiotic therapy ($n = 89$)	Oral antibiotic therapy ($n = 103$)	i.v. antibiotic therapy ($n = 86$)	Oral antibiotic therapy ($n = 97$)	i.v. antibiotic therapy ($n = 71$)	Oral antibiotic therapy ($n = 89$)	i.v. antibiotic therapy ($n = 57$)	Oral antibiotic therapy ($n = 65$)
Mobility								
No problems	93.8	95.4	93.3	94.1	82.2	93.7	89.8	94.1
Some problems	6.3	4.6	6.7	5.9	17.8	6.3	10.2	5.9
Extreme problems	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Self-care								
No problems	73.6	84.5	77.9	84.8	75.3	86.7	84.2	89.7
Some problems	14.3	4.9	11.6	6.1	16.4	8.9	12.3	5.9
Extreme problems	12.1	10.7	10.5	9.1	8.2	4.4	3.5	4.4
Usual activities								
No problems	84.4	93.5	91.0	89.9	80.3	89.4	91.4	93.9
Some problems	13.5	6.5	7.9	10.1	18.3	10.6	6.9	6.1
Extreme problems	2.1	0.0	1.1	0.0	1.4	0.0	1.7	0.0
Pain and discomfort								
No problems	80.0	81.7	82.0	82.0	74.0	81.9	75.9	86.8
Some problems	20.0	17.4	18.0	18.0	23.3	18.1	24.1	13.2
Extreme problems	0.0	0.9	0.0	0.0	2.7	0.0	0.0	0.0
Anxiety and depression								
No problems	86.3	88.9	85.2	88.9	80.6	87.2	84.7	95.5
Some problems	12.6	11.1	12.5	11.1	18.1	11.7	15.3	3.0
Extreme problems	1.1	0.0	2.3	0.0	1.4	1.1	0.0	1.5

Incremental costs and outcomes

Unit costs used in the analysis are shown in *Appendix 6*.

In *Table 24*, mean costs and outcomes are calculated for the arms of the trial. The mean costs for the intervention were far higher for the i.v. antibiotic therapy arm (£7284.40) than for the oral antibiotic therapy arm (£264.30). Follow-up inpatient costs and outpatient costs were higher for the oral

TABLE 24 Costs and outcomes between treatment groups (based on multiply imputed data, $m = 25$)

	Treatment group		Incremental difference (95% CI)	
Cost and outcome	Oral antibiotic therapy ($N = 130$)	i.v. antibiotic therapy ($N = 125$)	Oral – i.v.	Baseline adjusted[a]
NHS resource use (£)				
A&E	23.79	24.15		
Inpatients	1682.40	1027.00		
Outpatients	1414.00	1221.50		
Primary care	25.13	28.42		
Home visits	172.00	185.10		
Intervention cost	264.30	7284.40		
Prescribed medicines	248.20	124.30		
Total costs	3565.40	2610.50	954.90 (−132.10 to 2041.90)	1018.50 (−91.60 to 2128.70)
Intervention cost	264.30	7284.40	−7020.20 (−7548.50 to −6491.80)	−6957.00 (−7492.80 to −6421.20)
Total NHS costs (plus intervention)	3829.70	9895.00	−6065.30 (−7287.10 to −4843.40)	−5938.50 (−7190.30 to −4686.70)
Wider resource use (£)				
Patient/carer lost work	1.88	7.67		
Aids and appliances	11.13	8.77		
Over-the-counter medicine	1.04	1.01		
Travel costs	90.49	86.05		
Total societal costs (plus intervention)	3934.30	9998.50	−6064.20 (−7296.20 to −4832.20)	−5937.00 (−7120.80 to −4659.10)
Outcomes				
Primary outcome (% successfully eradicated)	0.52	0.44	0.083 (−0.040 to 0.21)	0.091 (−0.034 to 0.22)
HRQoL				
EQ-5D baseline	0.873	0.820		
EQ-5D 3 months	0.893	0.854		
EQ-5D 15 months	0.893	0.829		
EQ-5D 24 months	0.923	0.895		
QALYs (over 15 months)	1.114	1.050	0.063 (0.0074 to 0.12)	0.035 (−0.007 to 0.088)
QALYs (over 24 months)	1.795	1.697	0.098 (0.013 to 0.18)	0.058 (−0.004 to 0.140)

a Baseline EQ-5D, age.

antibiotic therapy arm than for the i.v. antibiotic therapy arm. Overall, oral antibiotic therapy was less costly than i.v. antibiotic therapy, with the incremental difference in mean costs between the arms being –£5938.50 (95% CI –£7190.30 to –£4686.70) after adjusting for baseline covariates. Most of the total cost difference reflects the difference in intervention costs, with i.v. antibiotic therapy being associated with high inpatient stay costs. The inclusion of societal costs had a trivial impact on overall incremental cost differences between the arms of the trial, with the incremental societal cost, after adjusting for baseline covariates, being –£5938.50 (95% CI –£7190.30 to –£4686.70) for the oral antibiotic therapy arm compared with the i.v. antibiotic therapy group.

The primary outcome measure showed that the oral antibiotic therapy arm had a larger proportion of successful eradications of *P. aeruginosa* 3 months after the start of treatment and remaining infection free through 15 months after start of treatment than the i.v. antibiotic therapy arm. The incremental difference in effect after adjusting for baseline covariates was 0.091 (95% CI –0.034 to 0.22).

For a 15-month time horizon, patients in the oral antibiotic therapy arm gained 1.14 QALYs, with patients in the i.v. antibiotic therapy arm gaining only 1.05 QALYs. There was an overall unadjusted incremental difference in QALYs of 0.063 (95% CI 0.0074 to 0.12) after 15 months, with an adjusted incremental difference in QALYs of 0.035 (95% CI –0.015 to 0.086). After 24 months, patients in the oral antibiotic therapy arm gained 1.8 QALYs and patients in the i.v. antibiotic therapy arm gained 1.7 QALYs. There was an unadjusted incremental difference in QALYs of 0.098 (95% CI 0.013 to 0.18) and an adjusted incremental difference in QALYs of 0.058 (95% CI –0.020 to 0.14) for the oral antibiotic therapy arm compared with the i.v. antibiotic therapy arm.

Cost-effectiveness analysis

Table 25 shows incremental cost-effectiveness for the primary and secondary analysis, as well as the impact of sensitivity analyses on cost-effectiveness. In all scenarios, oral antibiotic therapy was associated with lower costs than i.v. antibiotic therapy, and was also more effective. Consequently, oral antibiotic therapy dominated i.v. antibiotic therapy in both the primary and the secondary analyses. In the secondary analysis, for a threshold of £20,000 per QALY, oral antibiotic therapy generated £6770.80 (95% CI £5027.40 to £7906.20) benefit per patient, compared with i.v. antibiotic therapy.

The use of specialised HRG costs led to a smaller difference in costs between the two arms, but the oral antibiotic therapy arm still had a lower incremental cost of –£653.08 (95% CI–£1197.80 to –£79.80) compared with the i.v. antibiotic therapy arm. *Table 26* shows how patients were grouped into HRG bands. Patients in the oral antibiotic therapy arm were more likely to be in band 1 than patients in the i.v. antibiotic therapy arm, in which patients tended to be clustered in higher-risk/higher-cost bands. However, the highest band reported in the data (band 3) included a larger proportion of patients in the oral antibiotic therapy arm than in the i.v. antibiotic therapy arm as a result of a small number of patients in the oral antibiotic therapy arm having a long inpatient stay in the follow-up period. In the secondary analysis with CF HRG costs, the oral antibiotic therapy arm generated £653.10 (95% CI £79.80 to £1197.80) benefit per patient for a cost-effectiveness threshold of £20,000 per QALY.

Changes in model function for the cost data and the inclusion of societal costs led to only small changes in the incremental cost differences between the arms of the trial. The INB was large for oral antibiotic therapy compared with i.v. antibiotic therapy in each scenario.

Incremental cost-effectiveness planes and CEACs for the primary analysis, secondary analysis and associated sensitivity analyses are shown in *Appendix 6*, *Figures 33–45*.

TABLE 25 Incremental costs, outcomes, ICERs and INB between treatment groups

Analysis	Incremental cost (£) (95% CI)	Incremental outcome (95% CI)	ICER	INB (95% CI)
Primary analysis: proportion infection free, NHS and PSS perspective costs, 15-month horizon, adjusted	−5938.50 (−7107.40 to −4666.30)	0.091 (−0.034 to 0.22)	Oral dominates	N/A
Sensitivity analysis				
Primary analysis: proportion infection free, NHS and PSS perspective costs, 15-month horizon, covariate adjusted, CF HRG costs used	−653.08 (−1197.80 to −79.80)	0.091 (−0.034 to 0.22)	Oral dominates	N/A
Primary analysis: clinical effect, societal perspective costs, 15-month horizon, adjusted	−5937.00 (−7120.80 to −4659.10)	0.091 (−0.034 to 0.22)	Oral dominates	N/A
Primary analysis: proportion infection free, NHS and PSS perspective costs, covariate adjusted, GLM cost model [link(log); family (Gaussian)]	−5942.40 (−7054.90 to −4713.10)	0.091 (−0.034 to 0.22)	Oral dominates	N/A
Primary analysis: proportion infection free, NHS and PSS perspective costs, covariate adjusted, GLM cost model [link(log); family (Gaussian)]	−6625.50 (−8574.80 to −5196.60)	0.091 (−0.034 to 0.22)	Oral dominates	N/A
Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, covariate	−5938.50 (−7107.40 to −4666.30)	0.035 (−0.007 to 0.088)	Oral dominates	6770.8 (5027.4 to 7906.2)
Sensitivity analysis				
Secondary analysis: 24-month horizon QALYs, NHS and PSS perspective costs, covariate adjusted	−5938.50 (−7107.40 to −4666.30)	0.058 (−0.004 to 0.140)	Oral dominates	7229.8 (5411.8 to 8553.1)
Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, covariate, CF HRG costs used	−653.08 (−1197.80 to −79.80)	0.035 (−0.007 to 0.088)	Oral dominates	653.1 (79.8 to 1197.8)
Secondary analysis: 15-month horizon QALYs, societal perspective costs, covariate	−5937.00 (−7052.60 to −4713.20)	0.035 (−0.007 to 0.088)	Oral dominates	6755.7 (4977.4 to 8409.3)
Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, covariate adjusted, GLM cost model [link(log); family (Gaussian)]	−5942.40 (−7054.90 to −4713.10)	0.035 (−0.007 to 0.088)	Oral dominates	6684.4 (5057.0 to 8406.9)
Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, covariate adjusted, GLM cost model [link(log); family (inverse Gaussian)]	−6625.50 (−8574.80 to −5196.60)	0.035 (−0.007 to 0.088)	Oral dominates	7343.0 (5586.8 to 9756.2)
Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, CF HRG, covariate adjusted, GLM cost model [link(log); family (Gaussian)]	−656.60 (−1231.00 to −75.33)	0.035 (−0.007 to 0.088)	Oral dominates	1518.9 (251.8 to 2678.9)
Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, CF HRG, covariate adjusted, GLM cost model [link(log); family (inverse Gaussian)]	−636.70 (−1238.40 to −45.30)	0.035 (−0.007 to 0.088)	Oral dominates	1499.1 (224.2 to 2666.1)

N/A, not applicable.

TABLE 26 Cystic fibrosis HRG bands and mean band costs

	Treatment group (%)		Incremental difference (95% CI)	
HRG band	Oral antibiotic therapy (*N* = 130)	i.v. antibiotic therapy (*N* = 125)	Oral – i.v.	Baseline adjusted[a]
1	81	0		
1a	8	38		
2	0	50		
2a	8	9		
3	4	2		
Mean cost, £ (SE)	6263.10 (205.80)	7154.60 (164.30)	843.80 (–1369.30 to –318.30)	894.40 (–1412.60 to –370.20)

a Age, baseline HRQoL.

For each scenario, oral antibiotic therapy was highly likely to be cost-effective, with virtually all of the bootstrap replicates falling within the south-east quadrant, demonstrating that the oral antibiotic therapy was both more effective and less costly than i.v. antibiotic therapy. For the secondary analysis involving a cost-effectiveness threshold of £20,000 per QALY, oral antibiotic therapy had a 100% chance of being cost-effective compared with i.v. antibiotic therapy in the base-case analysis, and findings were robust to assumptions regarding the use of CF HRG codes, costing model specification and inclusion of societal costs.

Chapter 7 Discussion

We tested the hypothesis that, for eradicating a new infection with *P. aeruginosa* in people with CF, an i.v. antibiotic regimen (2 weeks of i.v. ceftazidime and tobramycin) is more effective than an oral antibiotic (12 weeks of oral ciprofloxacin). In line with UK CF antibiotic guidelines,[11] inhaled colistimethate sodium was included in both regimens. We found that the i.v. regimen was not superior in achieving the primary outcome – eradication of *P. aeruginosa* at 3 months and remaining free of infection to 15 months. The clinically important difference that was set at the beginning of the trial, was not contained in the 95% CI. In the 12 months following completion of the eradication regimen, there was a statistically significant difference in the length of hospital stay in favour of the i.v. antibiotic therapy group. However, this is unlikely to be clinically important as the median length of stay was 0 days in both groups. The proportion of patients who had at least one hospital stay was significantly lower in the i.v. antibiotic therapy group (30.2%) than in the oral antibiotic therapy group (46.3%). A possible explanation of this finding is that patients who already had one hospital admission for eradication might be less likely to be offered or to accept a further admission in the subsequent 12-month period. We found significant differences in percentage predicted FVC and adult BMI in favour of the i.v. regimen; however, these differences were based on small numbers, were numerically small and are unlikely to be clinically important. There were no other significant differences in secondary outcome measures, AEs or acquisition of new organisms between the two groups.

A recent systematic review pointed out that, although *P. aeruginosa* infection carries an adverse prognosis and eradication is an effective approach, there is no evidence to favour one eradication regimen over another.[16] Uncontrolled studies have advocated an i.v. eradication regimen.[60] However, i.v. treatment often entails hospital admission, requires i.v. access (which may be traumatic)[61] and carries the risk of side effects such as nephrotoxicity and, in the case of aminoglycosides such as tobramycin, ototoxicity.[62] Regardless of which regimen is used, regular collection of airways' specimens is advised to detect *P. aeruginosa* early.[11] Furthermore, eradication treatment should be initiated as soon as possible after *P. aeruginosa* is detected in respiratory secretions.[63] A recent crossover trial of eradication in young children demonstrated a much lower eradication rate in those who received the placebo in the initial 28-day treatment period.[64] The TORPEDO-CF protocol mandated that the eradication regimen should start no more than 21 days from the report demonstrating *P. aeruginosa* in the airways.

The TORPEDO-CF used a pragmatic design which aimed to minimise the burden of participation. Respiratory specimens for microbiology were collected at routine clinic visits, which meant that not all specimens were obtained in the 3-week time window at the end of the 15-month follow-up period. To address this, we extended the window to include patients with samples 4 weeks on either side of 15 months and conducted a sensitivity analysis using the next sample collected after the 15-month window. We collected sputum and (where this was not possible) a cough swab. Bronchoscopy has been used to collect samples for microbiological outcomes in previous eradication trials,[9] but it is not used for this purpose in routine clinical practice, and, hence, was not mandated in TORPEDO-CF.

A strength of our study is the large sample size and the length of follow-up. In the first generation of placebo-controlled eradication trials, sample size was often small and microbiological eradication was reported immediately after the end of eradication treatment.[9] More recently, a large randomised controlled trial, evaluating two 28-day eradication regimens, found that > 60% of participants had further infection with *P. aeruginosa* during a median follow-up period of 16 months.[65] Arguably, with longer periods of follow-up, reoccurrence of *P. aeruginosa* will be influenced to a lesser degree by a single course of eradication treatment. Hence, the 12 months of post-eradication follow-up used in our study is a reasonable period over which to evaluate the effect of treatment in achieving sustained eradication of *P. aeruginosa*.

There were several limitations of TORPEDO-CF. It took longer than expected to recruit the required sample size for the trial. Feasibility data suggested that 25% of eligible patients would be adults.[12] However, we recruited only 15 adults out of a total sample size of 286 participants, partly because of a smaller number of adult centres participating in the trial. We advise caution in applying these trial findings to the adult CF population.

Many patients and families had a strong preference for one eradication regimen; 324 patients/families declined to participate because they did not want i.v. treatment and 34 patients/families declined because they did not want an oral regimen. Our feasibility study suggested that 45% of parents and patients would consider participation. The consent rates achieved in TORPEDO-CF were a little lower: 286 out of 772 (37%) eligible patients approached. A total of 1308 patients were screened for eligibility for the trial; 1022 patients did not meet the eligibility criteria and we randomised 286 patients.

The possibility that the trial participants may be different from the rest of the CF population and may have had a better clinical status and, therefore, be more likely to agree to the uncertainty of trial participation cannot be ruled out. Thirty participants were excluded from the primary analysis (12 participants in the i.v. antibiotic treatment group and 18 participants in the oral antibiotic treatment group). These were participants in whom *P. aeruginosa* was not detected following completion of eradication, but who did not have a sample taken at the 15-month time window. These exclusions will diminish the power of the study to show superiority of one regimen over another.

Not all participants received their allocated treatment, and a further group did not receive the prescribed course in full. Of the 137 participants in the i.v. antibiotic therapy group, 11 (8.0%) participants did not receive treatment (either allocated intervention or colistimethate sodium) and 29 (21.2%) participants stopped treatment early. In the oral antibiotic therapy group, 2 out of 148 participants (1.4%) did not start treatment and 24 (16.1%) participants stopped treatment early. The most common reason for not completing allocated treatment was difficulty with i.v. access. Lack of complete fidelity to allocated treatment will also reduce the trial's power to demonstrate superiority.

Recent engagement work from the UK has identified 'the best way of eradicating pseudomonas' as one of the top 10 research priorities for the patient community.[66] In the USA, 'respiratory microorganism detection and treatment was the top priority'.[67] Future research studies should combine long-term follow-up with regimens to reduce reoccurrence after eradication. The recent OPTIMIZE (Optimizing Treatment for Early Pseudomonas aeruginosa Infection in Cystic Fibrosis) trial[68] used 18 months of oral azithromycin as an adjunct to eradication with inhaled tobramycin, but found no difference in time to reoccurrence. In future, a randomised registry design such as used in the ongoing cystic fibrosis (CF) anti-staphylococcal antibiotic prophylaxis trial (CF-START); ISRCTN18130649] may be applied to *Pseudomonas* eradication trials to allow long-term follow-up and to reduce both the cost of trials and the inconvenience to trial participants.

Engagement work with the CF community both in the UK[66] and in the USA[67] has highlighted research to reduce the treatment burden in CF as a priority. When a treatment (such as i.v. antibiotics) is burdensome, but no more effective, it follows that patients should be offered an eradication regimen that is appropriate to their clinical condition and personal circumstances. *P. aeruginosa* may be identified at the time of a pulmonary exacerbation when i.v. antibiotics are clinically indicated. In other cases, when the patient is asymptomatic, oral eradication is appropriate. In our trial, only 13.1% of patients in the i.v. group and 11.5% in the oral group had an exacerbation at baseline. If the findings of this trial are implemented in routine clinical practice, most patients will receive oral treatment as an outpatient and many admissions will be avoided. This will reduce treatment burden and will reduce health-care costs.

The health economic analysis was partially limited by difficulties associated with gathering HRQoL data in young children. Although the EQ-5D-3L was selected for consistency and practical reasons, its completion by young patients or by carers is subject to great uncertainty. Measures of HRQoL in young

patients have been developed since the inception of this trial, but evidence of their validity is still at an early stage. As a consequence of the challenges associated with eliciting HRQoL, the health economics analysis for cost-effectiveness primarily relied on the results that similar proportions of individuals had a repeat infection over the duration of the trial, while oral antibiotics were considerably cheaper to administer. Oral therapy was clearly shown to be less expensive than i.v. therapy, with a cost saving of £5938.50 (equivalent to US$7543.00). Consequently, the most cost-effective strategy was the use of oral antibiotics. If the trial had found significant clinical benefit from i.v. eradication therapy over oral therapy, then some additional cost for i.v. therapy could be balanced against this to assist decision-making. However, there were no important clinical benefits to the use of i.v. over oral therapy and the large difference in cost suggests that oral therapy should usually be recommended for eradication of early infection with *P. aeruginosa* in CF.

Our trial found that, even in the oral arm (which had the better result for our primary outcome), only around half of participants were free of infection 15 months after randomisation. Future research should aim to improve rates of eradication through approaches such as earlier detection of *P. aeruginosa* and salvage therapy for failed eradication. It should also be a priority to evaluate the effects of *CFTR* modulators on acquisition and eradication of *P. aeruginosa*.

Acknowledgements

This project was funded by the UK NIHR Health Technology Assessment programme, project number 07/51/01 and trial registration number EudraCT 2009-012575-10. The trial sponsor was University Hospitals Bristol NHS Foundation Trust and co-sponsor for the Italian sites was the University of Liverpool, a member of Liverpool Health Partners.

We would like to thank all the participants and their families who took part in this trial and the staff from all participating centres (see *Appendix 3*, *Table 28*). We would also like to give thanks for the contributions of the independent members of the TSC [Professor Jonathan Grigg (chairperson), Dr Ranjit Lall, Mrs Jennifer Wederell, Ms Sophie Lewis, Mr Dominic Kavanagh, Dr David Stableforth and Professor Duncan Geddes (until November 2011)] and to the IDSMC [Dr Robert Dinwiddie (chairperson), Professor Christiane De Boeck and Mrs Enid Hennessy].

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Publications

Smith CT, Williamson P, Jones A, Smyth A, Langton Hewer S, Gamble C. Risk-proportionate clinical trial monitoring: an example approach from a non-commercial trials unit. *Trials* 2014;**15**:127.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review and appropriate agreements being in place.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Clinical Trials Unit team

The trial was conducted by the LCTC, University of Liverpool, Liverpool, UK.

TABLE 27 Roles of Clinical Trials Unit team

Role	Team member
Director	Professor Paula Williamson[a]
Senior statistician	Dr Ashley Jones
Senior trial manager	Ms Helen Hickey
Senior data managers	Ms Sue Howlin
	Ms Clare Jackson
	Ms Joanne Eatock
Information systems managers	Dr Duncan Appelbe
	Ms Marie Connor
Trial statistician	Mrs Michaela Brown
Trial co-ordinator(s)	Dr Christopher Smith
	Ms Hannah Short
	Ms Claire Taylor
	Mr Tom Kearns
	Ms Farhiya Ashoor
Trial co-ordinator assistant	Ms Sarah Olsen
Contributing statisticians	Professor Carrol Gamble
	Mrs Barbara Arch
	Ms Dannii Clayton
	Mr Andrew McKay
	Dr Laura Sutton
Data managers	Ms Michelle Girvan
	Mr Paul Tate
Database developers	Mrs Janet Harrison
	Mr Meirion Thomas

a Professor Paula Williamson was the director of the Clinical Trials Research Centre, University of Liverpool at the time that the work was carried out. The unit has since been rebranded as LCTC and is now directed by Professor Carrol Gamble.

Appendix 2 Trial oversight committees

Trial Steering Committee

Independent members: Professor Jonathan Grigg, Dr David Stableforth, Professor Barry Plant, Professor Duncan Geddes, Mrs Jennifer Wederell, Dr Ranjit Lall, Ms Sophie Lewis and Mr Dominic Kavanagh.

Non-independent members: Dr Simon Langton Hewer and Professor Alan Smyth.

Independent Data and Safety Monitoring Committee

Dr Robert Dinwiddie, Professor Christiane De Boeck and Mrs Enid Hennessy.

Trial Management Group

Dr Simon Langton Hewer, Professor Alan Smyth, Professor Deborah Ashby, Professor Paula Williamson, Ms Jessica Bissett, Dr Ashley Jones, Mrs Michaela Brown, Ms Helen Hickey, Ms Sue Howlin, Ms Farhiya Ashoor and Dr Dervla Kenna.

Appendix 3 Recruiting centres in centre number order

TABLE 28 Participating sites and PIs

Centre and clinic	Investigators
Addenbrooke's Hospital – Paediatrics	Dr Robert Ross-Russell
Alder Hey Children's Hospital – Paediatrics	Professor Kevin Southern
Barts and The London Children's Hospital – Paediatrics	Dr Chinedu Nwokoro
Belfast City Hospital – Adults	Dr Damian Downey
Birmingham Children's Hospital – Paediatrics	Dr Maya Desai
Birmingham Heartlands Hospital – Adults	Dr Joanna L Whitehouse
Birmingham Heartlands Hospital – Paediatrics	Dr Sarah Denniston
Bradford Royal Infirmary – Paediatrics	Dr Eduardo Moya
Bristol Royal Hospital for Children – Paediatrics	Dr Simon Langton Hewer
Bristol Royal Infirmary – Adults	Dr Simon Langton Hewer
Chesterfield Royal Hospital – Paediatrics	Professor Jim Crossley
Conquest Hospital – Paediatrics	Dr Geeta Gopal
Countess of Chester Hospital – Paediatrics	Dr Ravi Jayaram
Darlington Memorial Hospital – Paediatrics	Dr John Furness
Derriford Hospital – Adults	Dr David Derry
Derriford Hospital – Paediatrics	Dr Alan Cade
Eastbourne District General Hospital – Paediatrics	Dr. Geeta Gopal
Genoa CF Centre – Adults	Dr Laura Minicucci
Genoa CF Centre – Paediatrics	Dr Laura Minicucci
Gloucestershire Royal Hospital – Paediatrics	Dr Mike Webb
Great Ormond Street Hospital – Paediatrics	Dr Colin Wallis
Hillingdon Hospital – Paediatrics	Dr Stephen Goldring
Hull Royal Infirmary – Paediatrics	Dr Ashwini Kotwal
James Cook University Hospital – Paediatrics	Dr Rajamanickam Jayaraj
James Paget University Hospital – Paediatrics	Dr Caroline Kavanagh
Kettering General Hospital – Paediatrics	Dr Patti Rao
King's College Hospital – Paediatrics	Dr Gary Ruiz
King's Mill Hospital – Paediatrics	Dr Mike Yanney
Leicester Children's Hospital – Paediatrics	Dr Erol Gaillard
Leighton Hospital – Paediatrics	Dr Julie Ellison
Lincoln County Hospital – Paediatrics	Dr Amol Chingale
Macclesfield District General Hospital – Paediatrics	Dr Surendran Chandrasekaran
Musgrove Park Hospital – Paediatrics	Dr Alexandra Powell
New Cross Hospital – Paediatrics	Dr Rosie Rayner

continued

TABLE 28 Participating sites and PIs (*continued*)

Centre and clinic	Investigators
Norfolk and Norwich University Hospital – Paediatrics	Dr Caroline Kavanagh
North Devon District Hospital – Paediatrics	Dr Dermot Dalton
Nottingham City Hospital – Adults	Dr Jane Dewar
Nottingham Children's Hospital – Paediatrics	Professor Alan Smyth
Oxford Children's Hospital – Paediatrics	Dr Jeremy Hull
Pilgrim Hospital – Paediatrics	Dr Margaret Crawford
Queen Alexandra Hospital – Paediatrics	Dr Hannah Buckley
Royal Alexandra Children's Hospital – Paediatrics	Dr Paul Seddon
Royal Berkshire Hospital – Paediatrics	Dr Claire Holt
Royal Brompton Hospital – Adults	Dr Nick Simmonds
Royal Brompton Hospital – Paediatrics	Professor Andrew Bush
Royal Cornwall Hospital – Paediatrics	Dr Anne Prendiville
Royal Derby Hospital – Paediatrics	Dr Nigel Ruggins
Royal Devon and Exeter Hospital – Adults	Dr Patrick Oades
Royal Devon and Exeter Hospital – Paediatrics	Dr Patrick Oades
Royal Hospital for Sick Children – Paediatrics	Professor Steve Cunningham
Royal Preston Hospital – Paediatrics	Dr Karnam Sugumar
Royal Shrewsbury Hospital – Paediatrics	Dr Martyn Rees
Royal United Hospital – Paediatrics	Dr Rebecca Winterson
Royal Victoria Infirmary – Adults	Dr Simon Doe
Royal Victoria Infirmary – Paediatrics	Dr Malcolm Brodie
Salisbury District Hospital – Paediatrics	Dr Robert Scott-Jupp
Sheffield Children's Hospital – Paediatrics	Dr Christopher Taylor
Southampton General Hospital – Adults	Dr Mary Carroll
Southampton General Hospital – Paediatrics	Dr Julian Legg
St James's University Hospital – Paediatrics	Dr Tim Lee
Torbay Hospital – Adults	Dr Lee Dobson
Torbay Hospital – Paediatrics	Dr Atanu Mukherjee
University Hospital North Staffordshire – Adults	Professor Warren Lenny
University Hospital North Staffordshire – Paediatrics	Professor Warren Lenny
University Hospital of Wales – Adults	Dr Ian Ketchell
University Hospital of Wales – Paediatrics	Dr Julian Forton
Walsgrave Hospitals NHS Trust – Paediatrics	Dr Edward Simmonds
Warrington Hospital – Paediatrics	Dr Christopher Bedford
William Harvey Hospital – Paediatrics	Dr Ola Smith
Wythenshawe Hospital – Adults	Dr Naveen Rao
Wythenshawe Hospital – Paediatrics	Dr Naveen Rao
York Teaching Hospital – Paediatrics	Dr Murray Wheeler

Appendix 4 Additional results

TABLE 29 Patients screened by site

Centre and clinic	Total patients screened, *n*	Total screening assessments,[a] *n*	Ineligible		Not approached for consent		Consent not obtained		Randomised		Consent rate, %
			n	%	*n*	%	*n*	%	*n*	%	
Addenbrooke's Hospital – Paediatrics	22	23	1	4.3	1	4.3	16	69.6	5	21.7	23.8
Alder Hey Children's Hospital – Paediatrics	53	55	12	21.8	2	3.6	19	34.5	22	40	53.7
Barts and The London Children's Hospital – Paediatrics	25	26	3	11.5	3	11.5	17	65.4	3	11.5	15
Belfast City Hospital – Adults	3	3	2	66.7	0	0.0	0	0.0	1	33.3	100
Birmingham Children's Hospital – Paediatrics	75	76	17	22.4	14	18.4	30	39.5	15	19.7	33.3
Birmingham Heartlands Hospital – Adults	4	4	0	0.0	0	0.0	0	0.0	4	100	100
Birmingham Heartlands Hospital – Paediatrics	13	13	5	38.5	1	7.7	6	46.2	1	7.7	14.3
Bradford Royal Infirmary – Paediatrics	2	2	1	50	1	50	0	0.0	0	0.0	–
Bristol Royal Hospital for Children – Paediatrics	48	48	4	8.3	7	14.6	15	31.3	22	45.8	59.5
Bristol Royal Infirmary – Adults	1	1	0	0.0	0	0.0	0	0.0	1	100	100
Chesterfield Royal Hospital – Paediatrics	4	5	0	0.0	0	0.0	3	60	2	40	40
Conquest Hospital – Paediatrics	5	6	1	16.7	0	0.0	2	33.3	3	50	60
Countess of Chester Hospital – Paediatrics	6	6	1	16.7	1	16.7	4	66.7	0	0.0	0.0
Darlington Memorial Hospital – Paediatrics	2	2	1	50	1	50	0	0.0	0	0.0	–
Derriford Hospital – Adults	29	49	39	79.6	1	2	5	10.2	4	8.2	44.4
Derriford Hospital – Paediatrics	17	19	1	5.3	0	0.0	15	78.9	3	15.8	16.7
Eastbourne District General Hospital – Paediatrics	2	2	0	0.0	0	0.0	0	0.0	2	100	100
Genoa CF Centre – Adults	1	1	0	0.0	0	0.0	0	0.0	1	100	100
Genoa CF Centre – Paediatrics	1	1	0	0.0	0	0.0	0	0.00	1	100	100
Gloucestershire Royal Hospital – Paediatrics	37	54	32	59.3	5	9.3	16	29.6	1	1.9	5.9
Great Ormond Street Hospital – Paediatrics	46	46	9	19.6	12	26.1	18	39.1	7	15.2	28
Hillingdon Hospital – Paediatrics	1	1	0	0.0	0	0.0	0	0.0	1	100	100
Hull Royal Infirmary – Paediatrics	13	14	3	21.4	1	7.1	4	28.6	6	42.9	60
James Cook University Hospital – Paediatrics	23	39	26	66.7	1	2.6	5	12.8	7	17.9	58.3
James Paget Univeristy Hospital – Paediatrics	3	3	3	100	0	0.0	0	0.0	0	0.0	–

Centre and clinic	Total patients screened, *n*	Total screening assessments,[a] *n*	Ineligible		Not approached for consent		Consent not obtained		Randomised		Consent rate, %
			n	%	*n*	%	*n*	%	*n*	%	
Kettering General Hospital – Paediatrics	7	7	1	14.3	0	0.0	2	28.6	4	57.1	66.7
King's College Hospital – Paediatrics	14	14	1	7.1	1	7.1	1	7.1	11	78.6	91.7
King's Mill Hospital – Paediatrics	9	9	1	11.1	0	0.0	3	33.3	5	55.6	62.5
Leicester Children's Hospital – Paediatrics	56	79	48	60.8	10	12.7	13	16.5	8	10.1	38.1
Leighton Hospital – Paediatrics	6	6	0	0.0	3	50	1	16.7	2	33.3	66.7
Lincoln County Hospital – Paediatrics	15	15	1	6.7	0	0.0	9	60	5	33.3	35.7
Macclesfield District General Hospital – Paediatrics	2	3	1	33.3	2	66.7	0	0.0	0	0.0	–
Musgrove Park Hospital – Paediatrics	10	10	3	30	0	0.0	2	20	5	50	71.4
New Cross Hospital – Paediatrics	20	21	6	28.6	2	9.5	10	47.6	3	14.3	23.1
Norfolk and Norwich University Hospital – Paediatrics	18	25	9	36	3	12	9	36	4	16	30.8
North Devon District Hospital – Paediatrics	2	2	0	0.0	0	0.0	0	0.0	2	100	100
Nottingham City Hospital – Adults	9	9	6	66.7	0	0.0	3	33.3	0	0.0	0.0
Nottingham Children's Hospital – Paediatrics	44	52	12	23.1	3	5.8	24	46.2	13	25	35.1
Oxford Children's Hospital – Paediatrics	6	6	1	16.7	0	0.0	3	50	2	33.3	40
Pilgrim Hospital – Paediatrics	5	6	1	16.7	0	0.0	2	33.3	3	50	60
Queen Alexandra Hospital – Paediatrics	15	22	9	40.9	1	4.5	3	13.6	9	40.9	75
Royal Alexandra Children's Hospital – Paediatrics	12	13	0	0.0	0	0.0	8	61.5	5	38.5	38.5
Royal Berkshire Hospital – Paediatrics	3	3	0	0.0	0	0.0	0	0.0	3	100	100
Royal Brompton Hospital – Adults	31	31	19	61.3	3	9.7	8	25.8	1	3.2	11.1
Royal Brompton Hospital – Paediatrics	78	79	4	5.1	14	17.7	55	69.6	6	7.6	9.8
Royal Cornwall Hospital – Paediatrics	25	38	20	52.6	1	2.6	14	36.8	3	7.9	17.6
Royal Derby Hospital – Paediatrics	13	14	3	21.4	2	14.3	9	64.3	0	0.0	0.0
Royal Devon and Exeter Hospital – Adults	11	12	7	58.3	2	16.7	1	8.3	2	16.7	66.7
Royal Devon and Exeter Hospital – Paediatrics	33	33	13	39.4	2	6.1	8	24.2	10	30.3	55.6
Royal Hospital for Sick Children – Paediatrics	24	24	4	16.7	3	12.5	12	50	5	20.8	29.4

continued

TABLE 29 Patients screened by site (*continued*)

Centre and clinic	Total patients screened, *n*	Total screening assessments,[a] *n*	Ineligible		Not approached for consent		Consent not obtained		Randomised		Consent rate, %
			n	%	*n*	%	*n*	%	*n*	%	
Royal Preston Hospital – Paediatrics	14	14	3	21.4	1	7.1	6	42.9	4	28.6	40
Royal Shrewsbury Hospital – Paediatrics	10	13	3	23.1	0	0.0	1	7.7	9	69.2	90
Royal United Hospital – Paediatrics	17	19	10	52.6	0	0.0	5	26.3	4	21.1	44.4
Royal Victoria Infirmary – Adults	3	3	0	0.0	1	33.3	1	33.3	1	33.3	50
Royal Victoria Infirmary – Paediatrics	11	11	3	27.3	2	18.2	4	36.4	2	18.2	33.3
Salisbury District Hospital – Paediatrics	2	2	0	0.0	0	0.0	0	0.0	2	100	100
Sheffield Children's Hospital – Paediatrics	43	52	18	34.6	3	5.8	25	48.1	6	11.5	19.4
Southampton General Hospital – Adults	2	2	0	0.0	0	0.0	1	50	1	50	50
Southampton General Hospital – Paediatrics	4	4	0	0.0	0	0.0	2	50	2	50	50
St James's University Hospital – Paediatrics	197	264[b]	154	58.3	71	26.9	32	12.1	4	1.5	11.1
Torbay Hospital – Adults	1	1	0	0.0	0	0.0	0	0.0	1	100	100
Torbay Hospital – Paediatrics	13	15	13	86.7	0	0.0	2	13.3	0	0.0	0.0
University Hospital North Staffordshire – Adults	6	7	2	28.6	1	14.3	4	57.1	0	0.0	0.0
University Hospital North Staffordshire – Paediatrics	20	20	1	5	2	10	4	20	13	65	76.5
University Hospital of Wales – Adults	2	2	0	0.0	0	0.0	1	50	1	50	50
University Hospital of Wales – Paediatrics	8	8	1	12.5	2	25	2	25	3	37.5	60
Walsgrave Hospitals NHS Trust – Paediatrics	16	18	3	16.7	2	11.1	8	44.4	5	27.8	38.5
Warrington Hospital – Paediatrics	3	3	1	33.3	0	0.0	1	33.3	1	33.3	50
William Harvey Hospital – Paediatrics	3	3	0	0.0	0	0.0	2	66.7	1	33.3	33.3
Wythenshawe Hospital – Adults	12	12	7	58.3	3	25	2	16.7	0	0.0	0.0
Wythenshawe Hospital – Paediatrics	10	10	4	40	1	10	2	20	3	30	60
York Teaching Hospital – Paediatrics	7	7	0	0.0	1	14.3	6	85.7	0	0.0	0.0

a Multiple screenings allowed.
b There were three patients with their reason missing.

TABLE 30 Reasons for ineligibility

Reason for ineligibility	Number of patients[a]
Aged ≤ 28 days	4
Known to be pregnant	5
Not *P. aeruginosa* free	168
Not able to commence treatment within 21 days from the date of a *P. aeruginosa*-positive microbiology report	20
Antibiotic resistance of the current *P. aeruginosa* sample to any of the study drugs	49
Has been receiving *P. aeruginosa*-suppressing treatment	211
Known hypersensitivity to any of the study drugs	29
Other known contraindications to any of the study drugs	7
Had treatment with other anti-pseudomonal nebulisers	47
Previously randomised into TORPEDO-CF	22
Participated in another interventional trial within last 4 weeks	14
Poor compliance	22
Did not identify *P. aeruginosa*	18
Unknown whether patient is *P. aeruginosa* free/naive	1

a Multiple screenings allowed.

TABLE 31 Reasons patients not approached

Reason patient not approached	Number of patients[a]
Clinician decision	113
Family circumstances	11
No bed available	2
Patient missed	25
Patient transferred	4
Social concerns	12
Did not understand English	8
Other reason	4
No reason given	14

a Multiple screenings allowed.

TABLE 32 Reasons consent not provided

Reason patient not consented	Number of patients[a]
Did not want i.v. treatment	324
Did not want oral treatment	34
Did not want to attend follow-up	7
Did not want to be involved in research	3
Did not want to be randomised	7
Did not want to receive the eradication therapy	4
Family circumstances	22
Leaving country	1
Unclear	4
No reason given	80

a Multiple screenings allowed.

TABLE 33 Recruitment summary table

Centre and clinic	Date site opened to recruitment	Date site closed to recruitment	Date of first randomisation	Date of last randomisation	Total randomised (*n*)
Addenbrooke's Hospital – Paediatrics	22 September 2011	27 January 2017	10 May 2012	29 September 2015	5
Alder Hey Children's Hospital – Paediatrics	21 February 2011	27 January 2017	5 October 2011	24 November 2016	22
Barts and The London Children's Hospital – Paediatrics	21 September 2012	27 January 2017	6 October 2014	9 November 2015	3
Belfast City Hospital – Adults	22 January 2013	27 January 2017	4 March 2014	4 March 2014	1
Birmingham Children's Hospital – Paediatrics	1 September 2010	27 January 2017	5 October 2010	6 December 2016	15
Birmingham Heartlands Hospital – Adults	1 June 2012	27 January 2017	21 May 2013	26 February 2014	4
Birmingham Heartlands Hospital – Paediatrics	25 May 2012	27 January 2017	20 November 2014	20 November 2014	1
Bristol Royal Hospital for Children – Paediatrics	18 June 2010	27 January 2017	18 November 2010	18 January 2017	22
Bristol Royal Infirmary – Adults	13 September 2011	27 January 2017	3 June 2014	3 June 2014	1
Chesterfield Royal Hospital – Paediatrics	19 January 2011	27 January 2017	20 January 2011	24 March 2011	2
Conquest Hospital – Paediatrics	27 February 2012	27 January 2017	13 April 2012	24 March 2014	3
Derriford Hospital – Adults	30 July 2010	27 January 2017	16 April 2013	24 February 2015	4
Derriford Hospital – Paediatrics	30 July 2010	27 January 2017	12 October 2010	7 October 2016	3
Eastbourne District General Hospital – Paediatrics	25 January 2012	27 January 2017	1 February 2012	3 October 2013	2

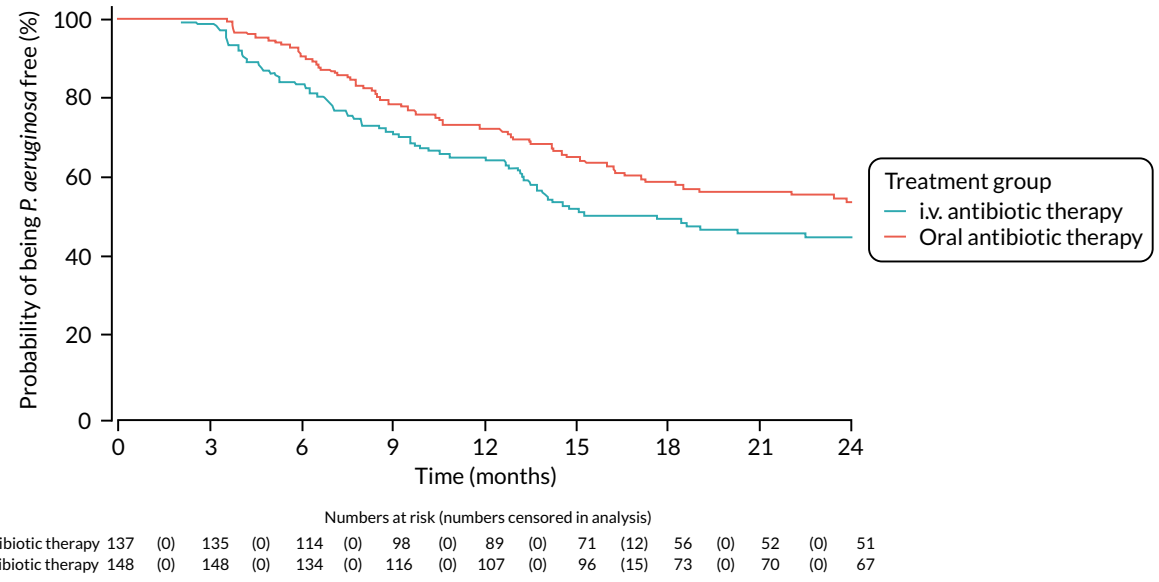
TABLE 33 Recruitment summary table (*continued*)

Centre and clinic	Date site opened to recruitment	Date site closed to recruitment	Date of first randomisation	Date of last randomisation	Total randomised (*n*)
Genoa CF Centre – Adults	6 October 2016	27 January 2017	11 October 2016	11 October 2016	1
Genoa CF Centre – Paediatrics	6 October 2016	27 January 2017	25 October 2016	25 October 2016	1
Gloucestershire Royal Hospital – Paediatrics	21 October 2010	27 January 2017	7 January 2011	7 January 2011	1
Great Ormond Street Hospital – Paediatrics	1 November 2011	27 January 2017	19 March 2012	28 November 2013	7
Hillingdon Hospital – Paediatrics	21 August 2012	27 January 2017	21 August 2012	21 August 2012	1
Hull Royal Infirmary – Paediatrics	26 January 2012	27 January 2017	3 February 2014	16 February 2016	6
James Cook University Hospital – Paediatrics	28 March 2012	27 January 2017	23 July 2012	21 January 2015	7
Kettering General Hospital – Paediatrics	11 April 2012	27 January 2017	31 August 2012	15 February 2016	4
King's College Hospital – Paediatrics	26 October 2011	27 January 2017	18 January 2012	17 October 2016	11
King's Mill Hospital – Paediatrics	2 November 2011	27 January 2017	20 April 2012	22 November 2016	5
Leicester Children's Hospital – Paediatrics	28 June 2011	27 January 2017	5 January 2012	11 November 2016	8
Leighton Hospital – Paediatrics	6 September 2011	27 January 2017	3 January 2012	7 August 2014	2
Lincoln County Hospital – Paediatrics	29 July 2011	27 January 2017	16 December 2011	19 November 2014	5
Musgrove Park Hospital – Paediatrics	21 July 2010	27 January 2017	11 March 2011	20 November 2015	5
New Cross Hospital – Paediatrics	15 March 2011	27 January 2017	24 May 2011	30 December 2014	3
Norfolk and Norwich University Hospital – Paediatrics	10 February 2012	27 January 2017	30 April 2012	28 July 2016	4
North Devon District Hospital – Paediatrics	26 April 2013	27 January 2017	24 September 2013	9 September 2014	2
Nottingham Children's Hospital – Paediatrics	12 July 2010	27 January 2017	22 February 2011	6 September 2016	13
Oxford Children's Hospital – Paediatrics	17 May 2011	27 January 2017	18 October 2012	7 November 2014	2
Pilgrim Hospital – Paediatrics	6 February 2012	27 January 2017	7 February 2012	25 August 2015	3
Queen Alexandra Hospital – Paediatrics	24 April 2012	27 January 2017	9 August 2012	30 September 2016	9
Royal Alexandra Children's Hospital – Paediatrics	11 May 2012	27 January 2017	31 July 2012	12 February 2016	5
Royal Berkshire Hospital – Paediatrics	10 December 2013	27 January 2017	24 February 2015	5 October 2016	3

continued

TABLE 33 Recruitment summary table (*continued*)

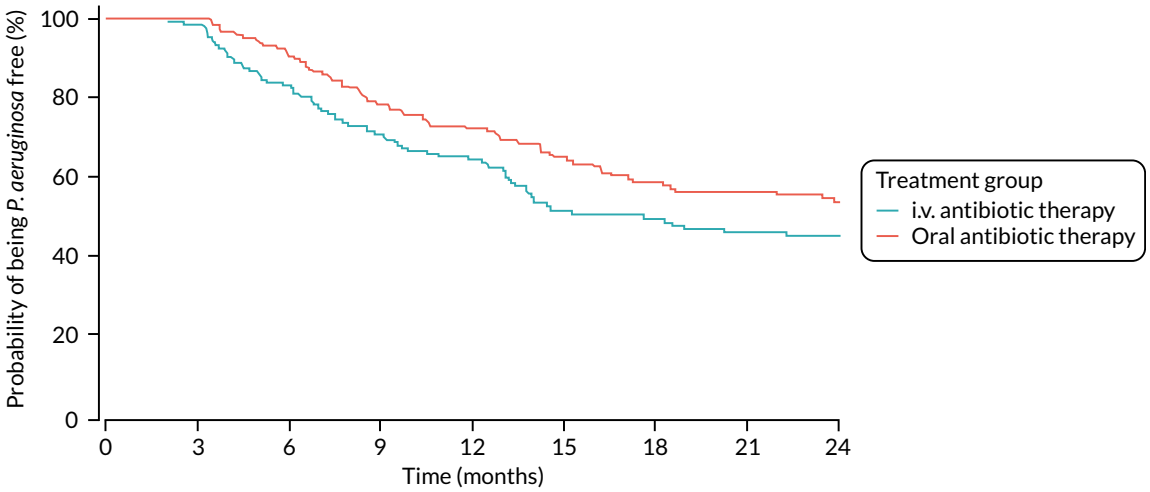
Centre and clinic	Date site opened to recruitment	Date site closed to recruitment	Date of first randomisation	Date of last randomisation	Total randomised (*n*)
Royal Brompton Hospital – Adults	6 January 2015	27 January 2017	2 February 2015	2 February 2015	1
Royal Brompton Hospital – Paediatrics	20 July 2011	27 January 2017	2 July 2012	18 September 2015	6
Royal Cornwall Hospital – Paediatrics	20 December 2010	27 January 2017	26 January 2011	25 June 2013	3
Royal Devon and Exeter Hospital – Adults	4 August 2010	27 January 2017	31 October 2012	30 April 2014	2
Royal Devon and Exeter Hospital – Paediatrics	4 August 2010	27 January 2017	4 January 2011	30 December 2015	10
Royal Hospital for Sick Children – Paediatrics	25 July 2012	27 January 2017	10 April 2013	8 January 2016	5
Royal Preston Hospital – Paediatrics	25 October 2011	27 January 2017	15 November 2011	13 February 2014	4
Royal Shrewsbury Hospital – Paediatrics	6 December 2012	27 January 2017	3 October 2013	27 January 2017	9
Royal United Hospital – Paediatrics	2 March 2011	27 January 2017	27 March 2013	26 January 2017	4
Royal Victoria Infirmary – Adults	22 March 2016	27 January 2017	18 May 2016	18 May 2016	1
Royal Victoria Infirmary – Paediatrics	22 March 2016	27 January 2017	1 September 2016	19 September 2016	2
Salisbury District Hospital – Paediatrics	23 April 2013	27 January 2017	13 October 2015	6 December 2016	2
Sheffield Children's Hospital – Paediatrics	23 February 2011	27 January 2017	03 October 2012	7 December 2016	6
Southampton General Hospital – Adults	19 February 2013	27 January 2017	12 February 2015	12 February 2015	1
Southampton General Hospital – Paediatrics	4 February 2013	27 January 2017	22 April 2013	24 March 2014	2
St James's University Hospital – Paediatrics	20 April 2011	27 January 2017	30 April 2012	17 October 2014	4
Torbay Hospital – Adults	17 November 2011	27 January 2017	15 December 2011	15 December 2011	1
University Hospital North Staffordshire – Paediatrics	26 January 2011	27 January 2017	30 January 2012	9 September 2015	13
University Hospital of Wales – Adults	24 October 2012	27 January 2017	29 September 2014	29 September 2014	1
University Hospital of Wales – Paediatrics	20 February 2013	27 January 2017	16 January 2014	2 October 2014	3
Walsgrave Hospitals NHS Trust – Paediatrics	26 August 2011	27 January 2017	20 October 2011	11 March 2015	5
Warrington Hospital – Paediatrics	6 November 2012	27 January 2017	20 September 2013	20 September 2013	1
William Harvey Hospital – Paediatrics	25 May 2012	27 January 2017	15 November 2013	15 November 2013	1
Wythenshawe Hospital – Paediatrics	20 November 2012	27 January 2017	5 August 2013	7 October 2013	3



Numbers at risk (numbers censored in analysis)

i.v. antibiotic therapy	137	(0)	135	(0)	114	(0)	98	(0)	89	(0)	71	(12)	56	(0)	52	(0)	51
Oral antibiotic therapy	148	(0)	148	(0)	134	(0)	116	(0)	107	(0)	96	(15)	73	(0)	70	(0)	67

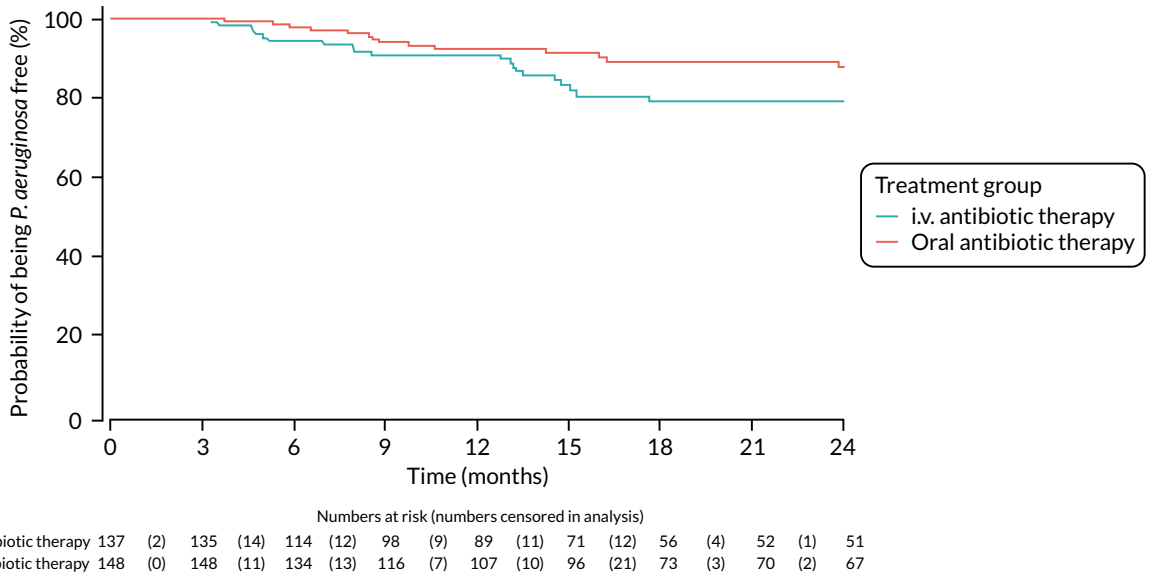
FIGURE 6 Time to reoccurrence of original *P. aeruginosa* infection: unknown strains assumed to be same as baseline.



Numbers at risk (numbers censored in analysis)

i.v. antibiotic therapy	137	(0)	135	(0)	114	(0)	97	(0)	88	(0)	70	(12)	56	(0)	52	(0)	51
Oral antibiotic therapy	148	(0)	148	(0)	134	(0)	116	(0)	107	(0)	96	(15)	73	(0)	70	(0)	67

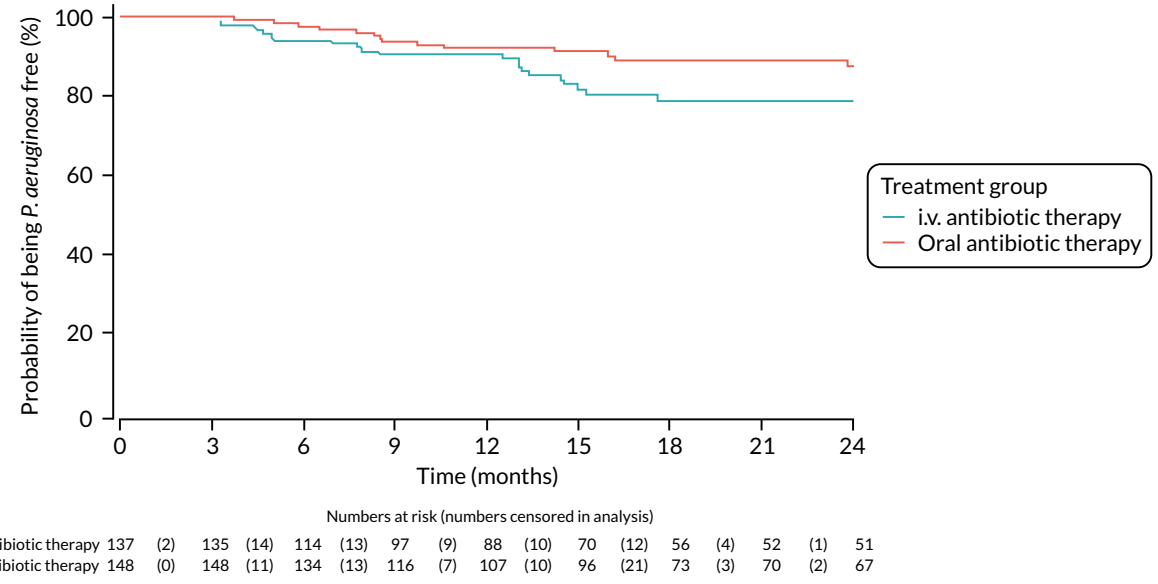
FIGURE 7 Time to reoccurrence of original *P. aeruginosa* infection: unknown strains assumed to be same as baseline (sensitivity analysis using date of treatment commencement rather than date of randomisation).



Numbers at risk (numbers censored in analysis)

i.v. antibiotic therapy	137	(2)	135	(14)	114	(12)	98	(9)	89	(11)	71	(12)	56	(4)	52	(1)	51
Oral antibiotic therapy	148	(0)	148	(11)	134	(13)	116	(7)	107	(10)	96	(21)	73	(3)	70	(2)	67

FIGURE 8 Time to reoccurrence of original *P. aeruginosa* infection: unknown strains assumed to be different from baseline.



Numbers at risk (numbers censored in analysis)

i.v. antibiotic therapy	137	(2)	135	(14)	114	(13)	97	(9)	88	(10)	70	(12)	56	(4)	52	(1)	51
Oral antibiotic therapy	148	(0)	148	(11)	134	(13)	116	(7)	107	(10)	96	(21)	73	(3)	70	(2)	67

FIGURE 9 Time to reoccurrence of original *P. aeruginosa* infection: unknown strains assumed to be different from baseline (sensitivity analysis using date of treatment commencement rather than date of randomisation).

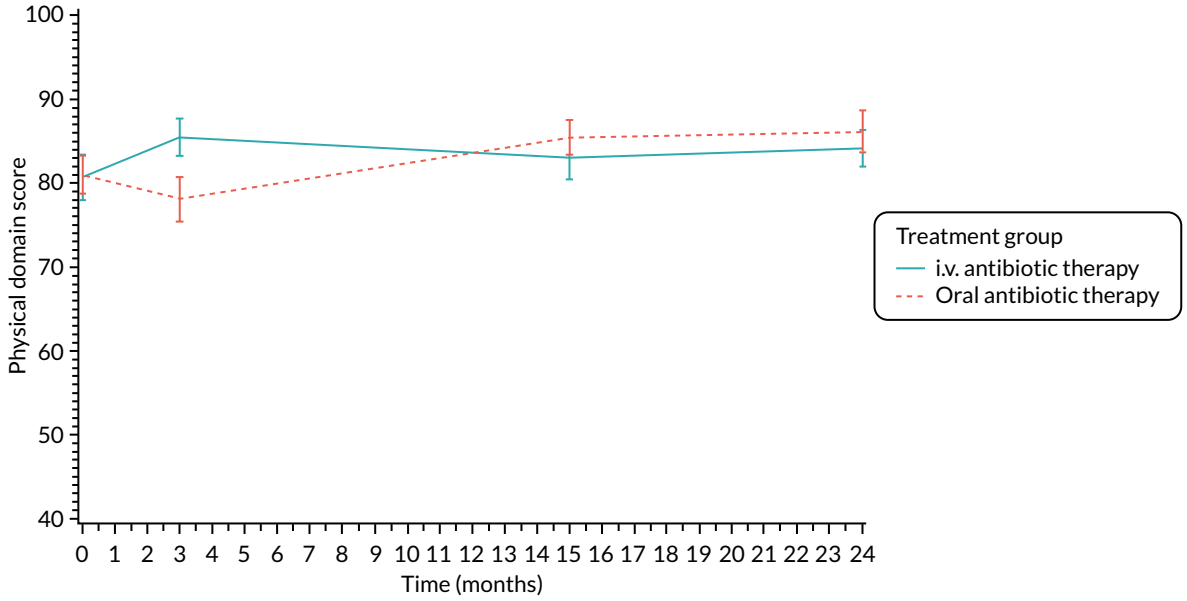


FIGURE 10 Physical functioning (self-report): mean scores over time by treatment group.

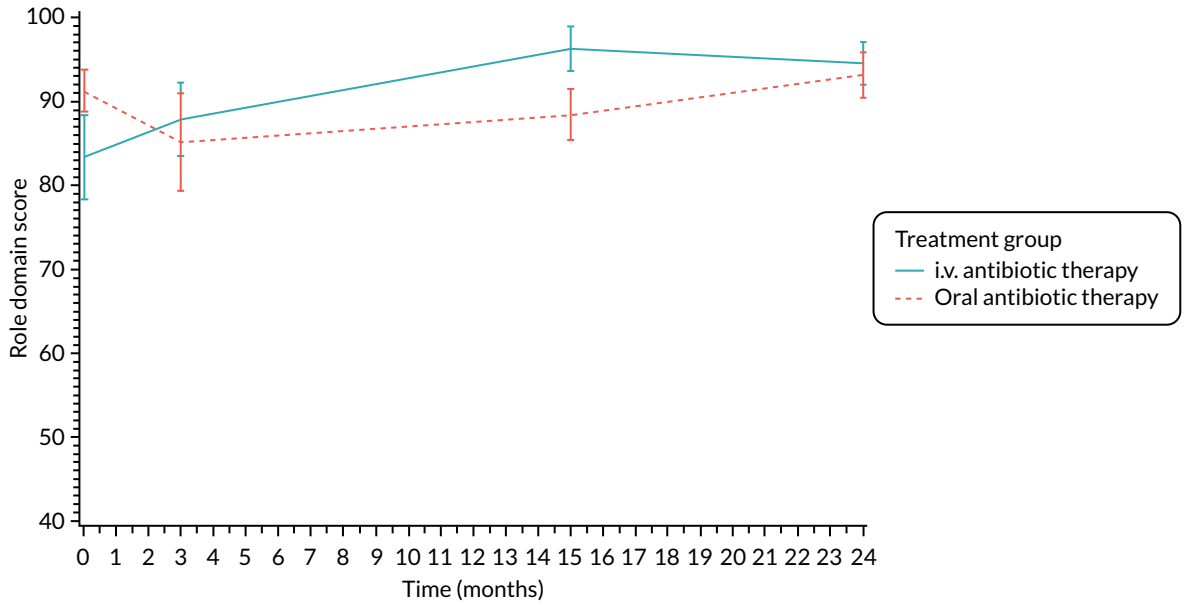


FIGURE 11 Role/school functioning (self-report): mean scores over time by treatment group.

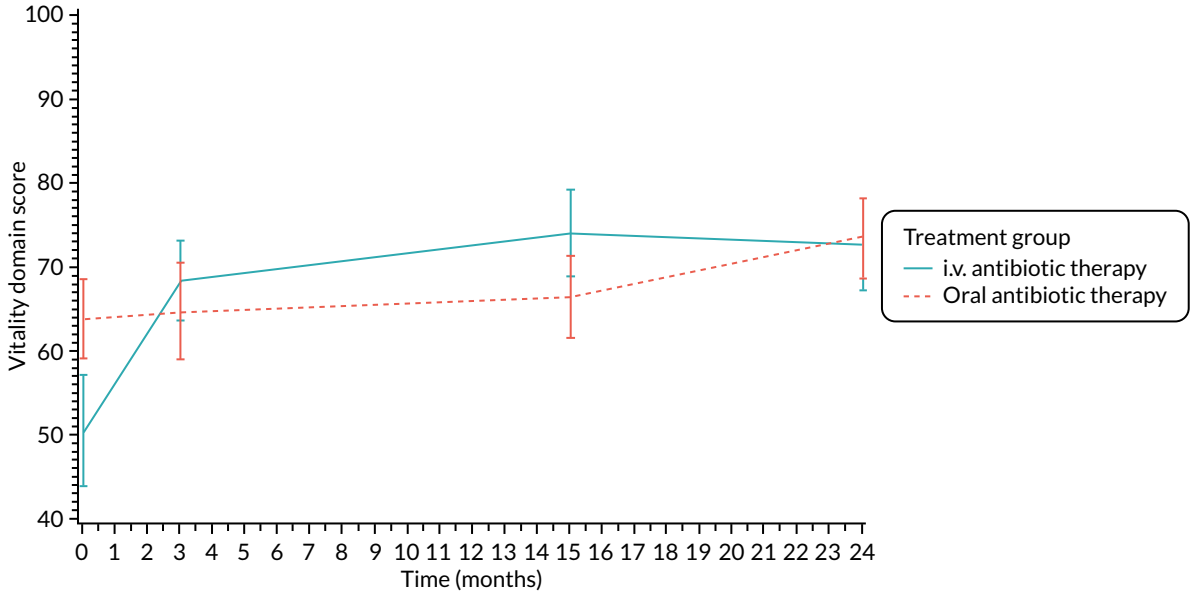


FIGURE 12 Vitality (self-report): mean scores over time by treatment group.

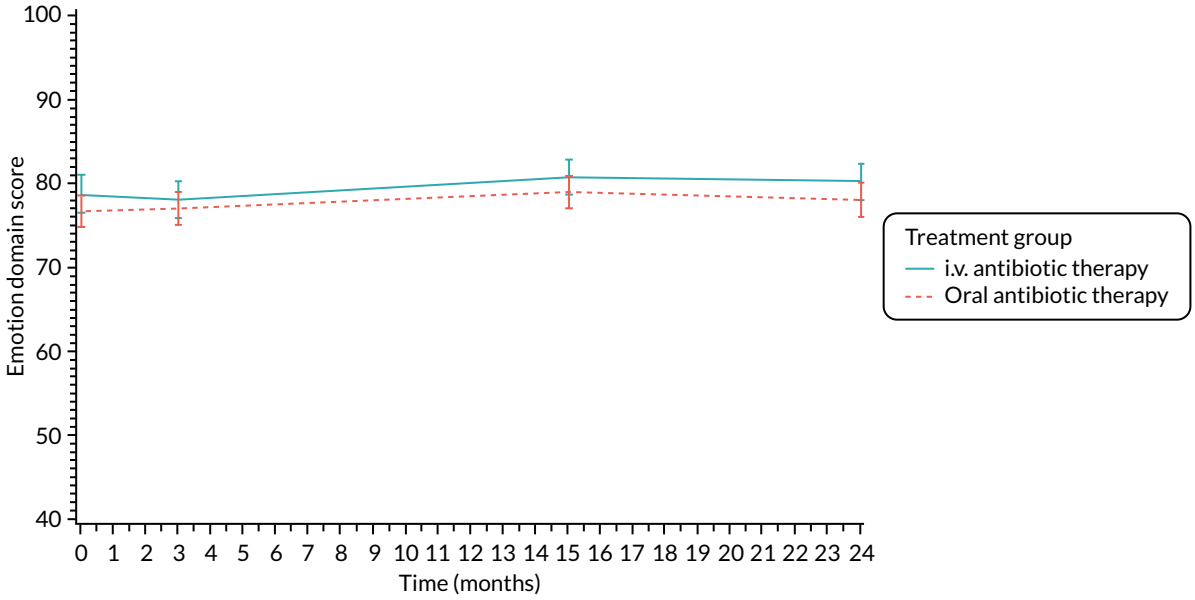


FIGURE 13 Emotional functioning (self-report): mean scores over time by treatment group.

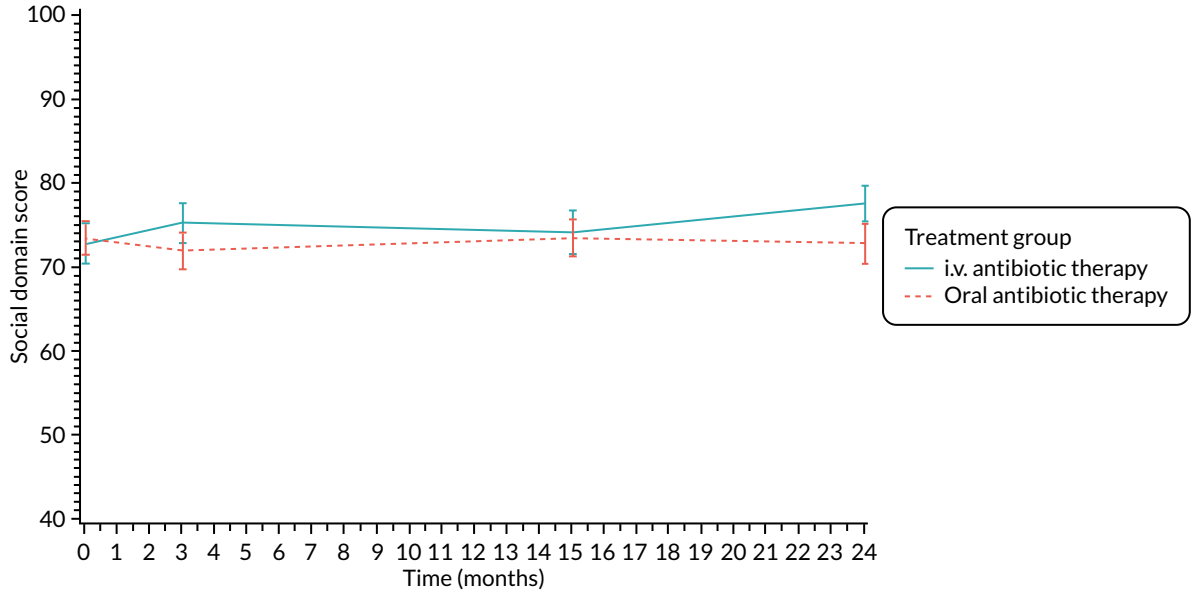


FIGURE 14 Social functioning (self-report): mean scores over time by treatment group.

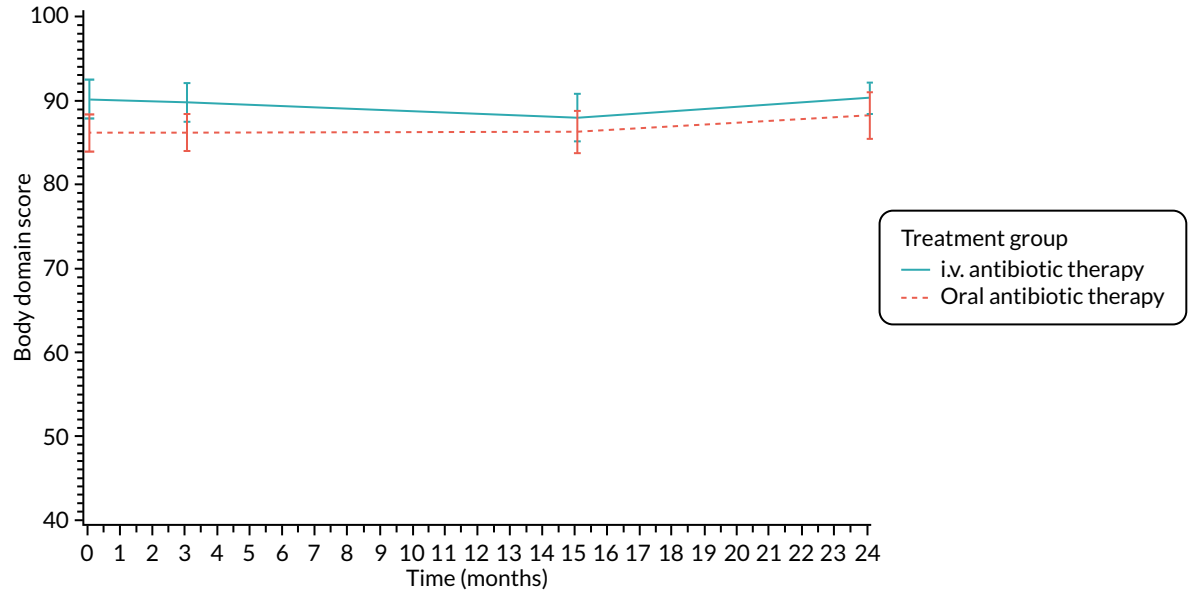


FIGURE 15 Body image (self-report): mean scores over time by treatment group.

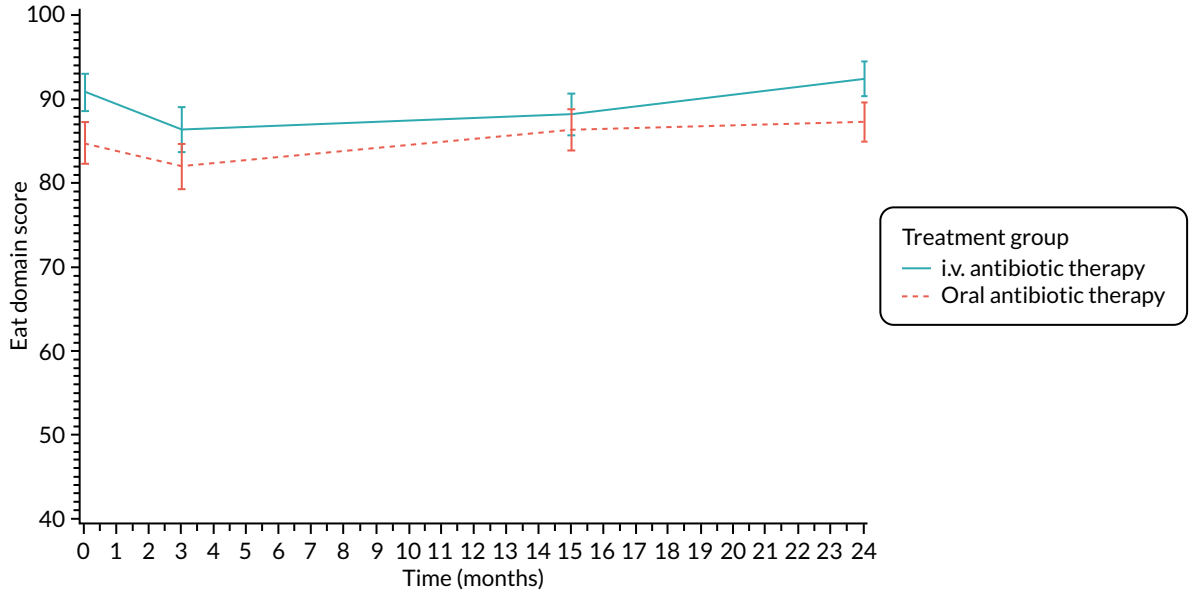


FIGURE 16 Eating problems (self-report): mean scores over time by treatment group.

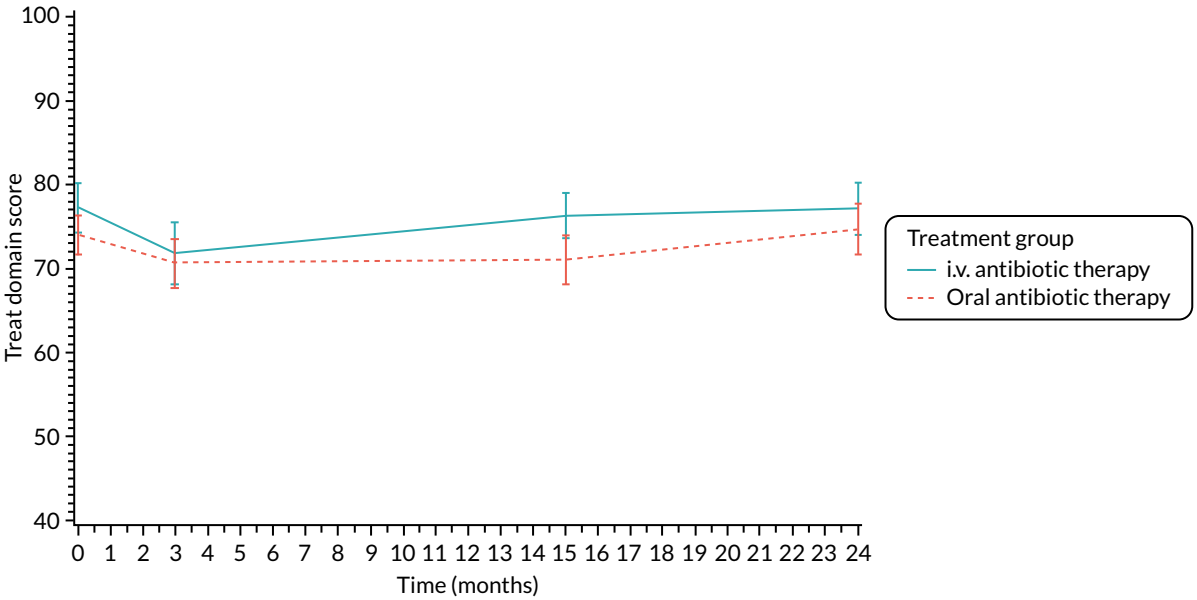


FIGURE 17 Treatment burden (self-report): mean scores over time by treatment group.

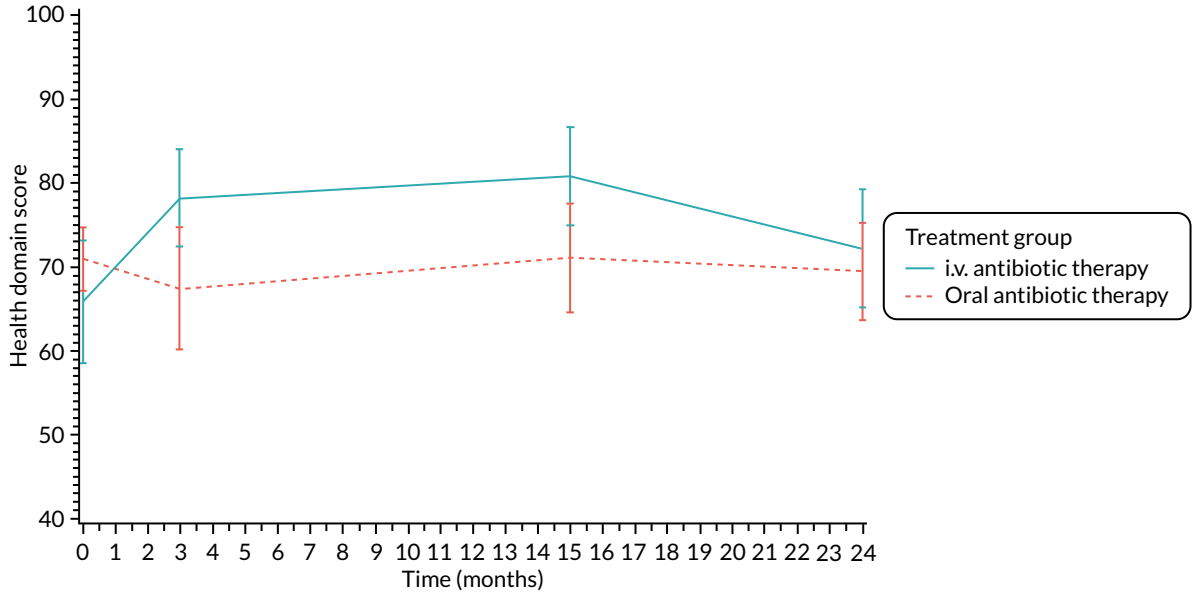


FIGURE 18 Health perceptions (self-report): mean scores over time by treatment group.

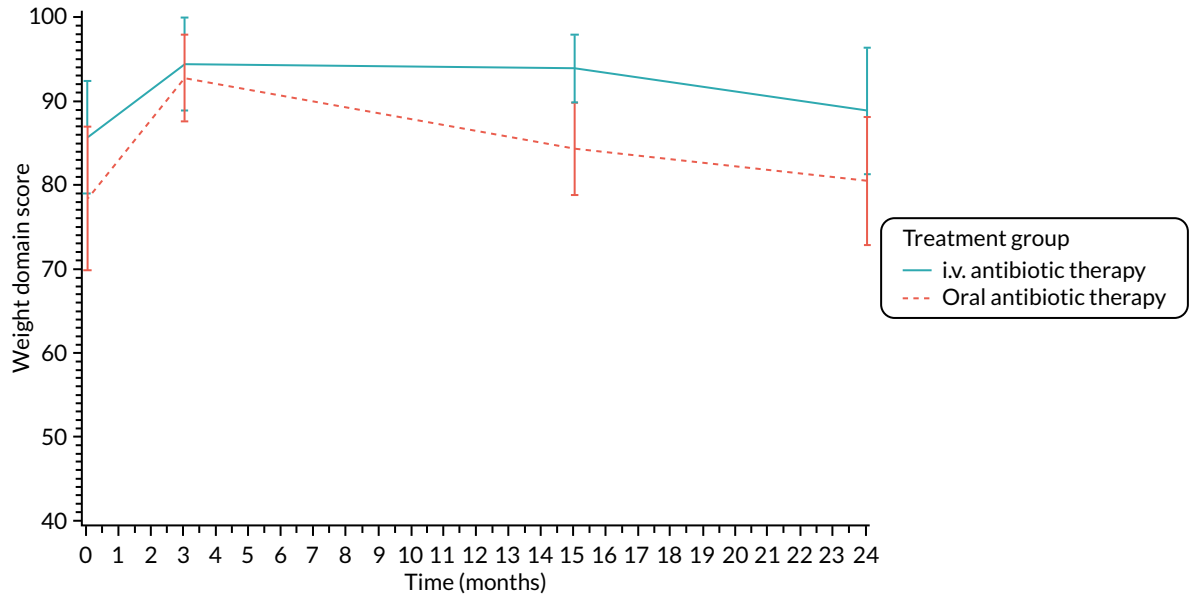


FIGURE 19 Weight (self-report): mean scores over time by treatment group.

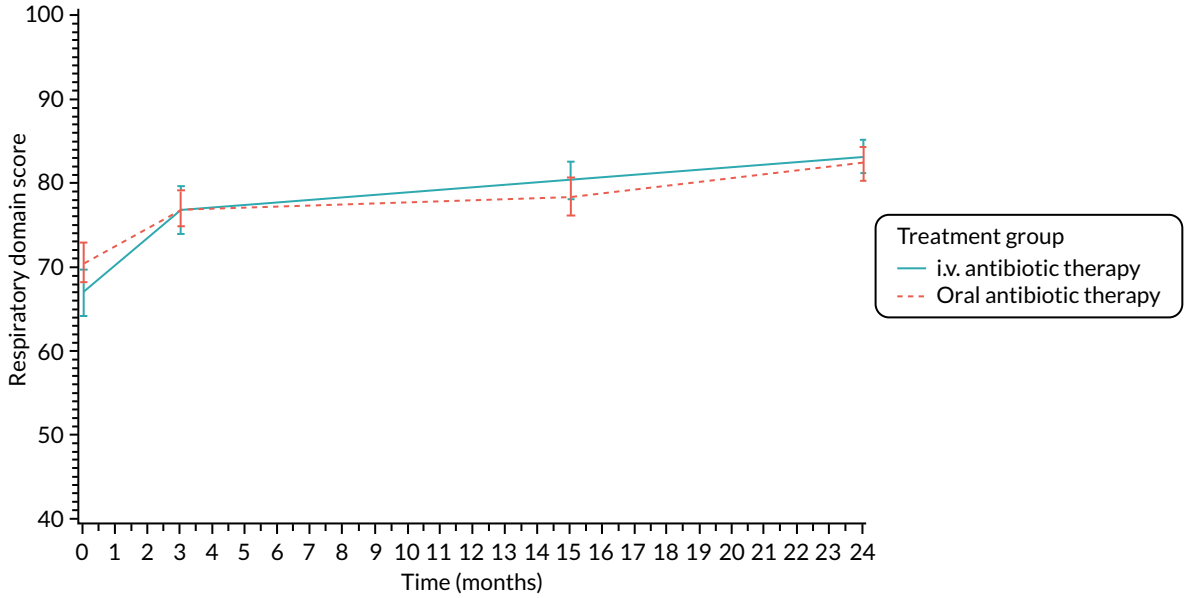


FIGURE 20 Respiratory symptoms (self-report): mean scores over time by treatment group.

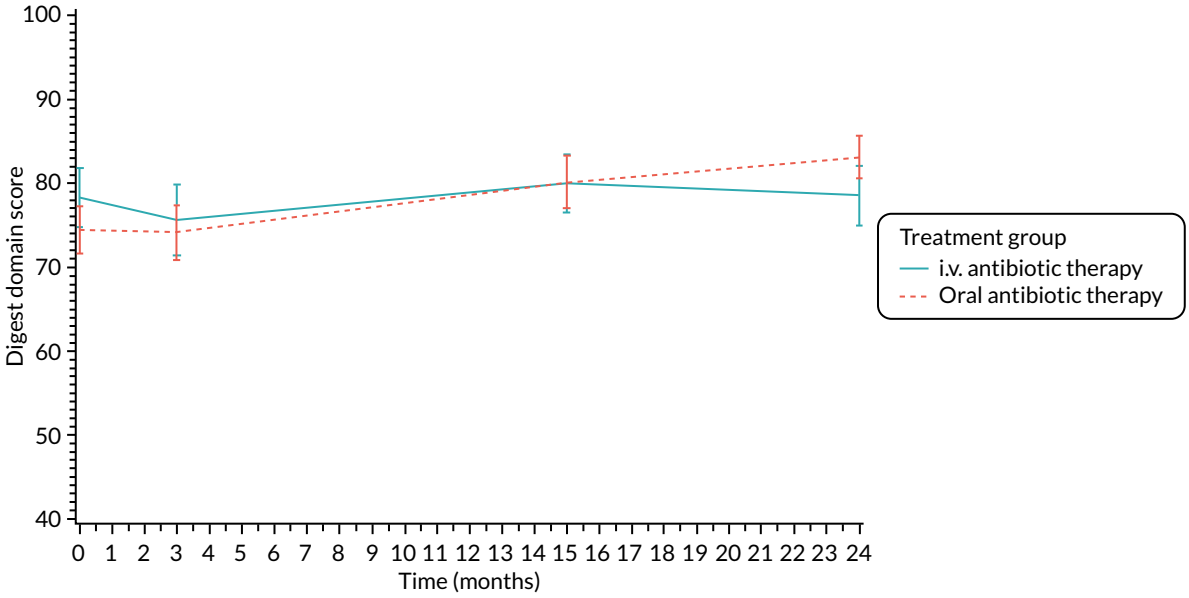


FIGURE 21 Digestive symptoms (self-report): mean scores over time by treatment group.

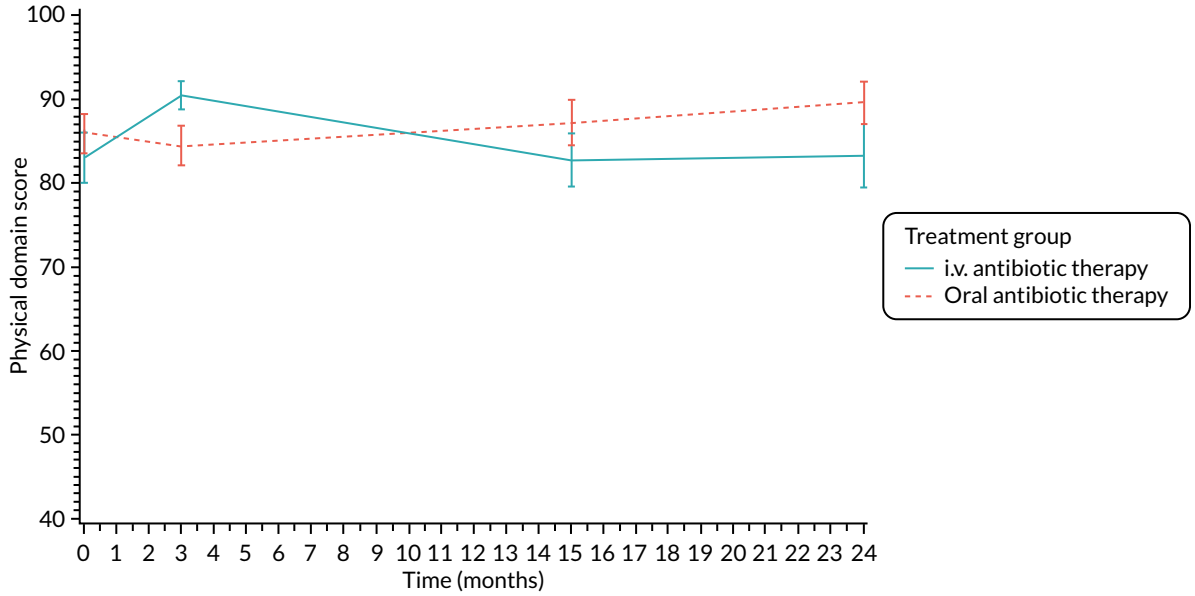


FIGURE 22 Physical functioning (parent/carer): mean scores over time by treatment group.

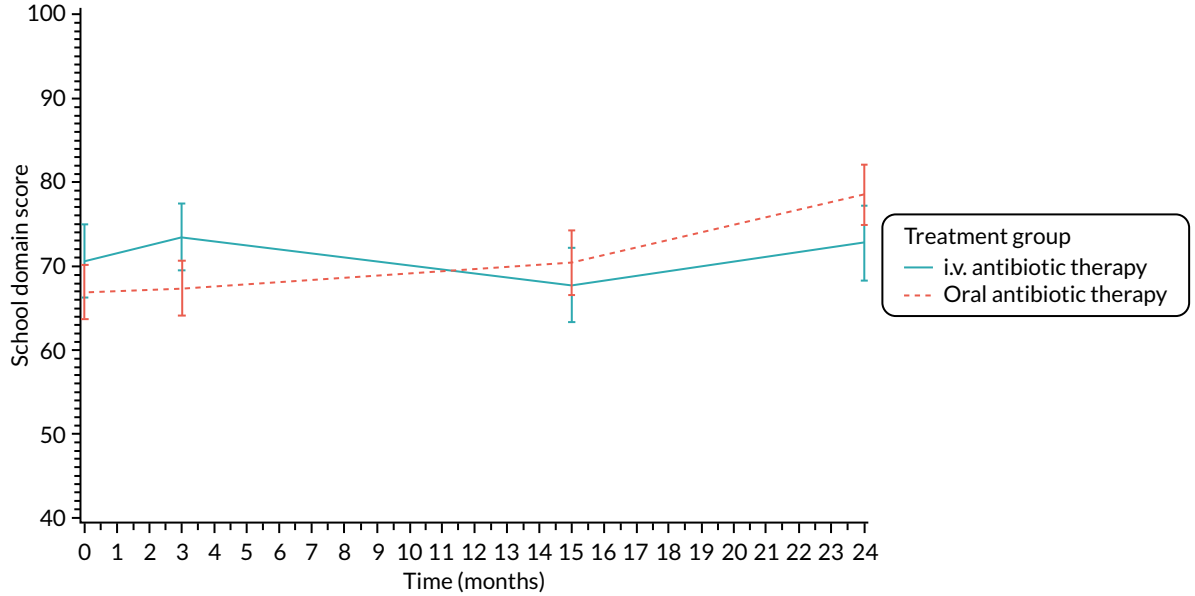


FIGURE 23 Role/school functioning (parent/carer): mean scores over time by treatment group.

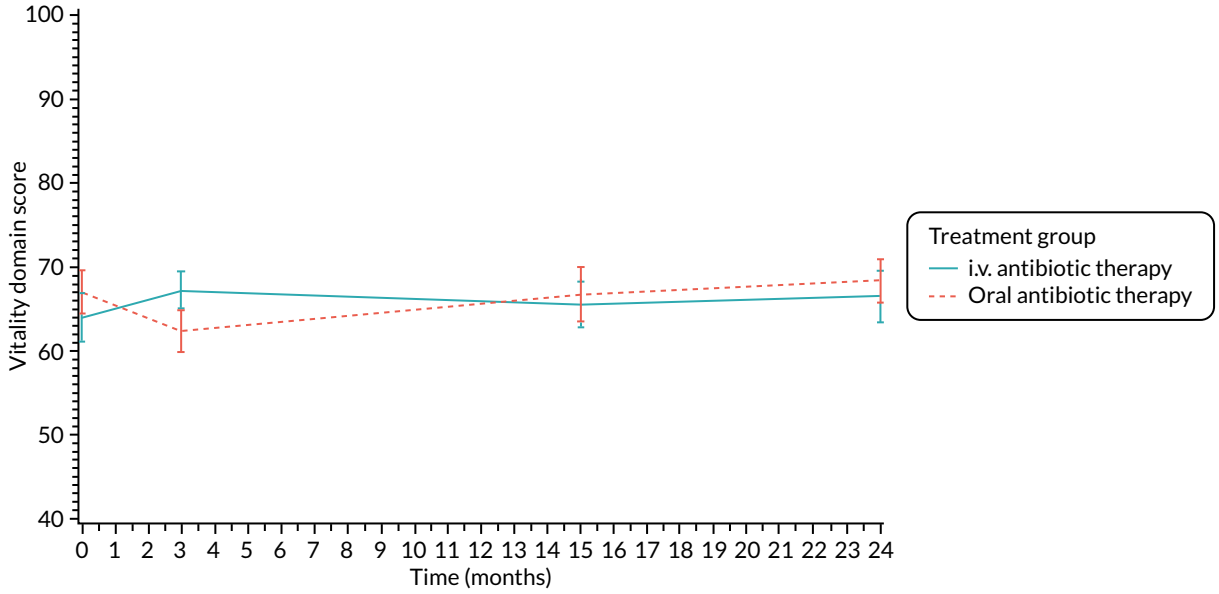


FIGURE 24 Vitality (parent/carer): mean scores over time by treatment group.

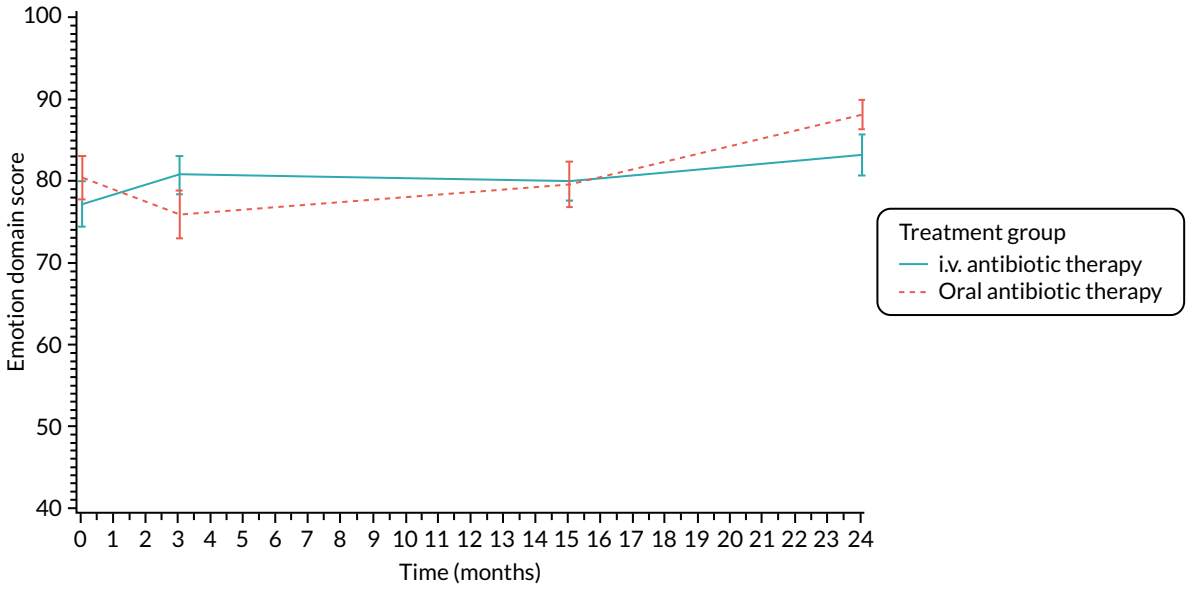


FIGURE 25 Emotional functioning (parent/carer): mean scores over time by treatment group.

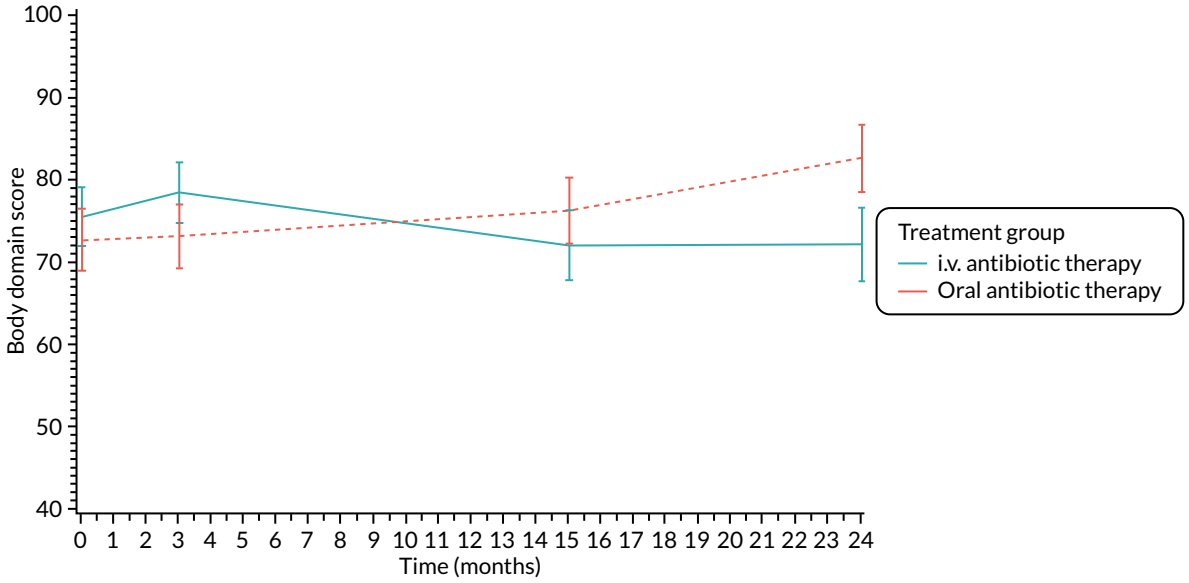


FIGURE 26 Body image (parent/carer): mean scores over time by treatment group.

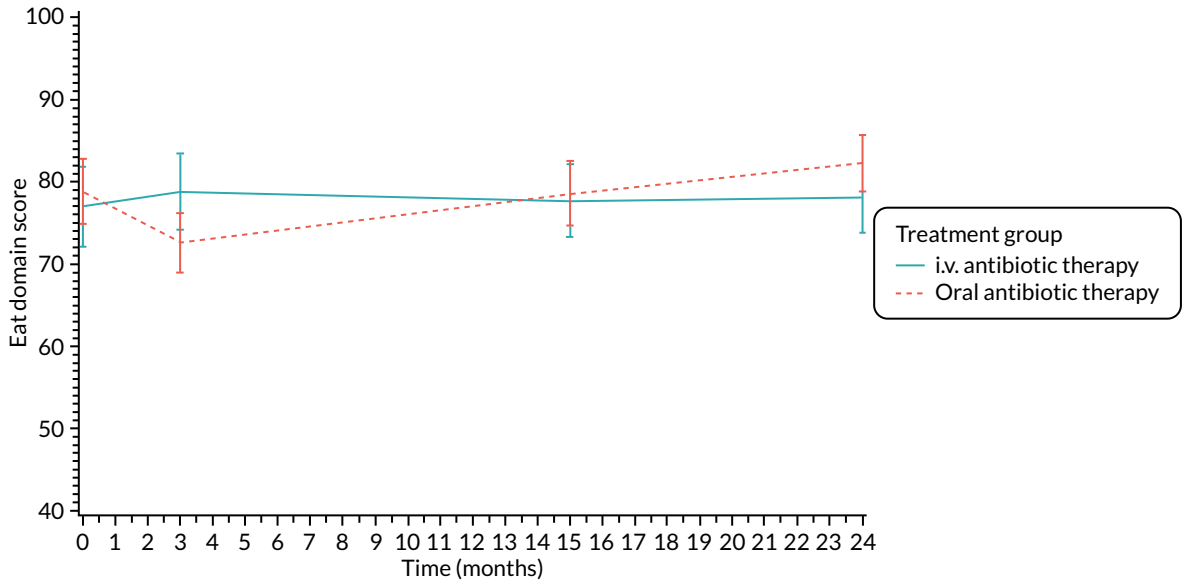


FIGURE 27 Eating problems (parent/carer): mean scores over time by treatment group.

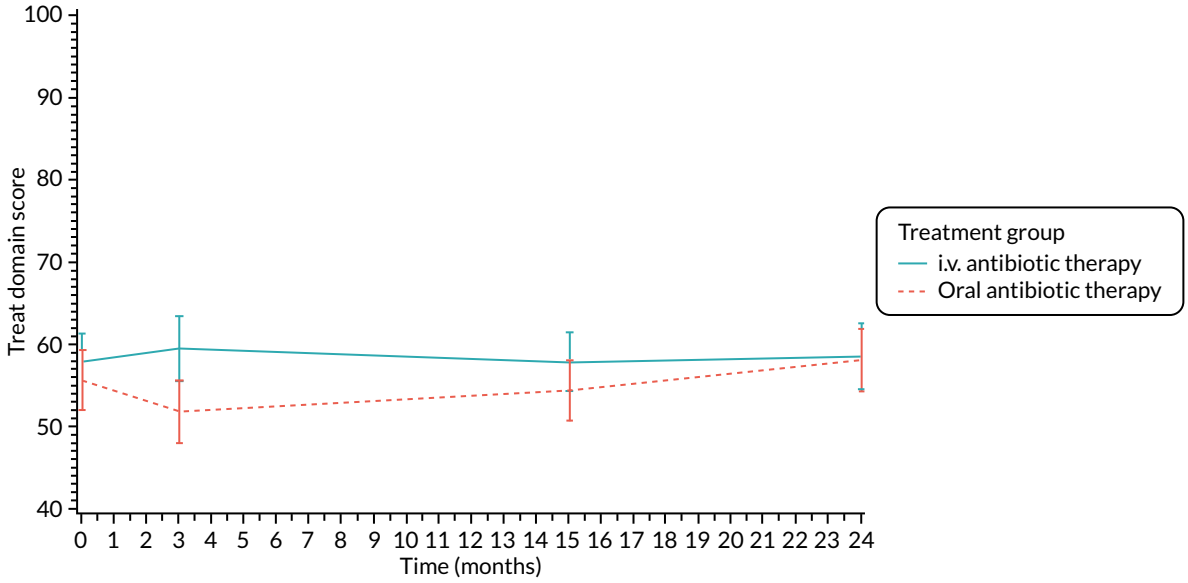


FIGURE 28 Treatment burden (parent/carer): mean scores over time by treatment group.

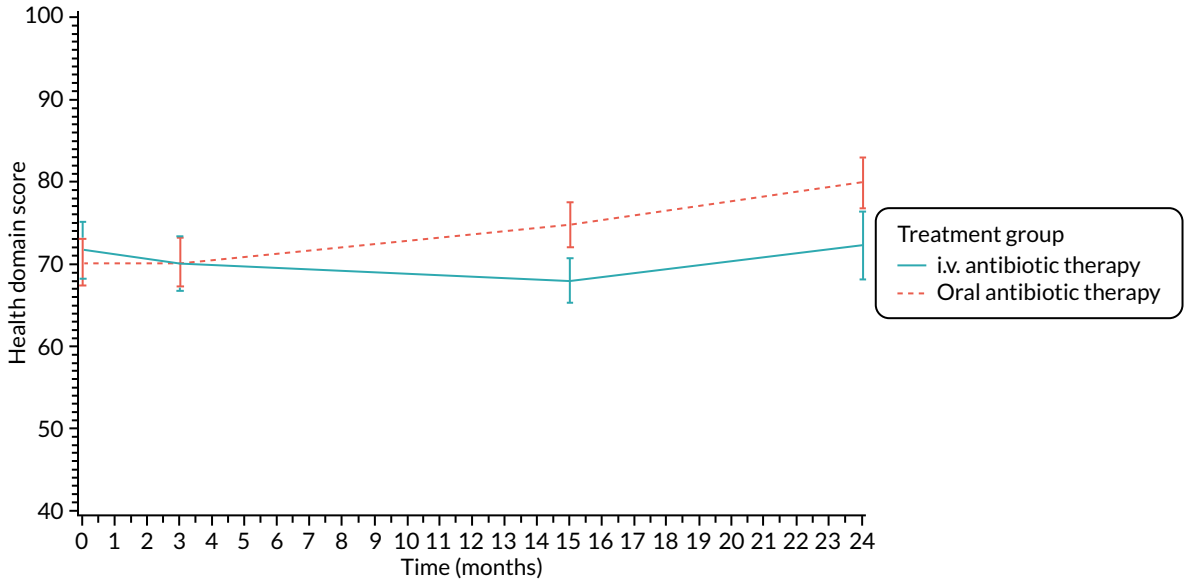


FIGURE 29 Health perceptions (parent/carer): mean scores over time by treatment group.

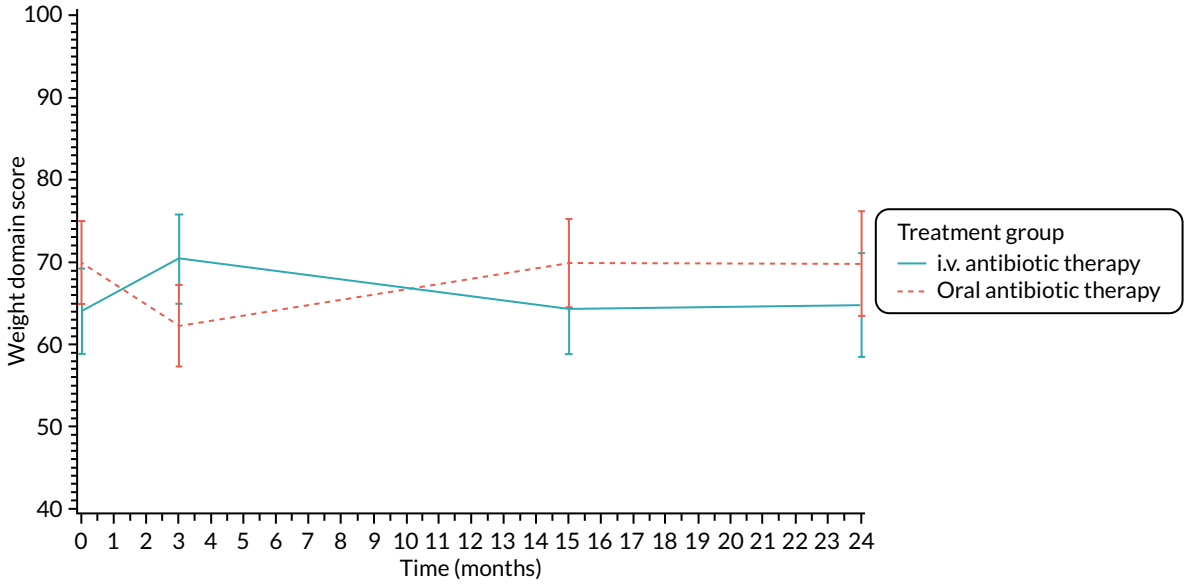


FIGURE 30 Weight (parent/carer): mean scores over time by treatment group.

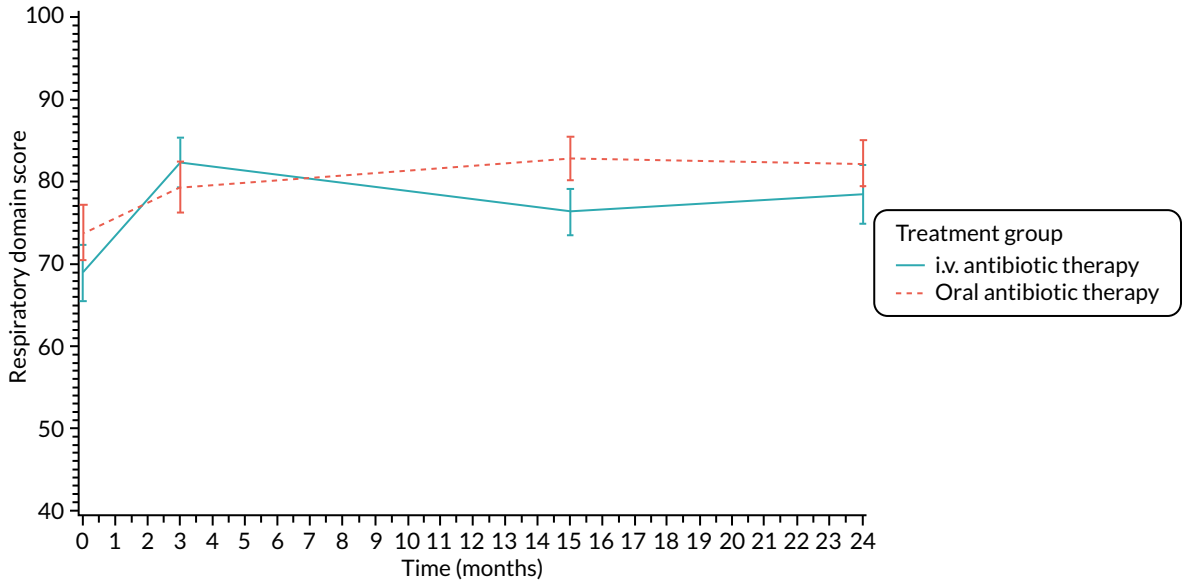


FIGURE 31 Respiratory symptoms (parent/carer): mean scores over time by treatment group.

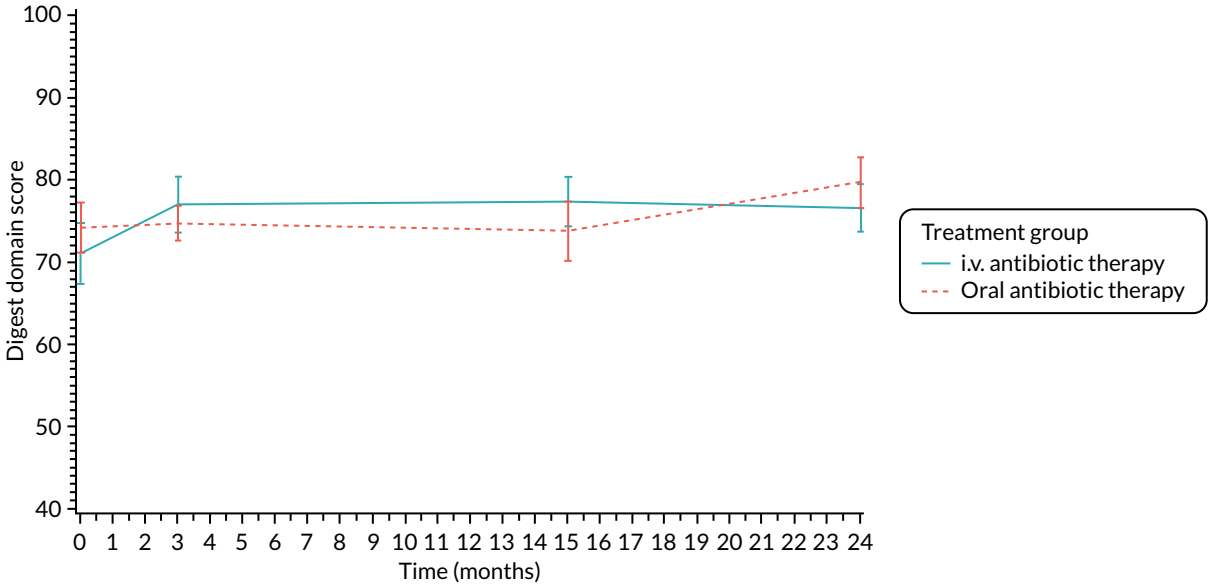


FIGURE 32 Digestive symptoms (parent/carer): mean scores over time by treatment group.

TABLE 34 Number of participants with additional organisms of interest during the 15 months post randomisation

	Treatment group, *n* (%)	
Organism	**i.v. antibiotic therapy (*N* = 137)**	**Oral antibiotic therapy (*N* = 148)**
Staphylococcus aureus	51 (37.2)	53 (35.8)
Haemophilus influenzae	36 (26.3)	32 (21.6)
Mycobacterium abscessus	0 (0)	1 (0.7)
Mycobacterium avium–intracellulare complex	0 (0)	0 (0)
Other non-tuberculous mycobacteria	0 (0)	0 (0)
Stenotrophomonas maltophilia	6 (4.4)	9 (6.1)
Achromobacter xylosoxidans	1 (0.7)	3 (20.0)

Appendix 5 Additional safety data

TABLE 35 The MedDRA classifications for all AEs

AE description (verbatim)	Preferred term	SOC
48 hours of spiking temperatures	Pyrexia	General disorders and administration site conditions
?DIOS-Distal Intestinal Obstruction Syndrome	Distal intestinal obstruction syndrome	Gastrointestinal disorders
A and E admission corzal illness	Upper respiratory tract infection	Infections and infestations
Abdominal pain	Abdominal pain	Gastrointestinal disorders
Abdominal pain? distal intestinal obstruction syndrome	Distal intestinal obstruction syndrome	Gastrointestinal disorders
Abnormal CXR	Chest X-ray abnormal	Investigations
Achilles tendonitis	Tendonitis	Musculoskeletal and connective tissue disorders
Adverse drug reaction to colomycin (i.v.)	Adverse drug reaction	General disorders and administration site conditions
Allergic broncho pulmonary aspergillosis (ABPA)	Bronchopulmonary aspergillosis allergic	Infections and infestations
Bed wetting	Enuresis	Psychiatric disorders
Bilateral knee pain	Arthralgia	Musculoskeletal and connective tissue disorders
Black tongue	Tongue discolouration	Gastrointestinal disorders
Bronchospasm caused by colistin	Bronchospasm	Respiratory, thoracic and mediastinal disorders
CF exacerbation	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
Candidiasis of nappy area	*Candida infection*	Infections and infestations
Chest pain	Chest pain	General disorders and administration site conditions
Chest infection	Lower respiratory tract infection	Infections and infestations
Chicken pox	Varicella	Infections and infestations
Cold productive cough	Productive cough	Respiratory, thoracic and mediastinal disorders
Corza	Rhinitis	Infections and infestations
Cough	Cough	Respiratory, thoracic and mediastinal disorders
Croup, runny nose	Cough	Respiratory, thoracic and mediastinal disorders
DIOS	Distal intestinal obstruction syndrome	Gastrointestinal disorders
Deterioration over 1 month	General physical health deterioration	General disorders and administration site conditions
Diarrhoea	Diarrhoea	Gastrointestinal disorders

continued

TABLE 35 The MedDRA classifications for all AEs (*continued*)

AE description (verbatim)	Preferred term	SOC
Diarrhoea started 3 days after starting cipro	Diarrhoea	Gastrointestinal disorders
Diarrhoea	Diarrhoea	Gastrointestinal disorders
Dizzy episodes	Dizziness	Nervous system disorders
Eczema under dressing	Eczema	Skin and subcutaneous tissue disorders
Episode of ciprofloxacin-resistant P. aeruginosa colonisation	*Pseudomonas* infection	Infections and infestations
Exacerbation of cystic fibrosis	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
Fall from cot on ward	Fall	Injury, poisoning and procedural complications
Fall whilst at school – painful neck	Fall	Injury, poisoning and procedural complications
Fell whilst sledging and hit back of head on road	Fall	Injury, poisoning and procedural complications
Fever/high temperature	Pyrexia	General disorders and administration site conditions
Foot and mount disease	Foot and mouth disease	Infections and infestations
Fractured skull	Skull fracture	Injury, poisoning and procedural complications
Gastroenteritis	Gastroenteritis	Infections and infestations
Glandular fever	Infectious mononucleosis	Infections and infestations
H. influenza on cough swab	*Haemophilus* test positive	Investigations
H. influenza infection	*Haemophilus* infection	Infections and infestations
Hay fever	Seasonal allergy	Immune system disorders
Headache	Headache	Nervous system disorders
High temperature	Pyrexia	General disorders and administration site conditions
Hospital admission with croup	Croup infectious	Infections and infestations
i.v. cannula tissued	Catheter site-related reaction	General disorders and administration site conditions
Increase cough + sputum production	Pyrexia	General disorders and administration site conditions
Increased cough	Cough	Respiratory, thoracic and mediastinal disorders
Increased cough and sputum production	Productive cough	Respiratory, thoracic and mediastinal disorders
Increased cough and sputum production prior to surgery	Productive cough	Respiratory, thoracic and mediastinal disorders
Increased cough at night	Cough	Respiratory, thoracic and mediastinal disorders
Increased faecal loading	Constipation	Gastrointestinal disorders
Increased temperature	Pyrexia	General disorders and administration site conditions
Increased wet cough	Productive cough	Respiratory, thoracic and mediastinal disorders
Infected eczema	Eczema infected	Infections and infestations

TABLE 35 The MedDRA classifications for all AEs (*continued*)

AE description (verbatim)	Preferred term	SOC
Infective exacerbation	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
Isolate of Pseudomonas	*Pseudomonas* infection	Infections and infestations
Isolate of Pseudomonas aeruginosa	*Pseudomonas* infection	Infections and infestations
Itchy rash	Rash pruritic	Skin and subcutaneous tissue disorders
Long line removed as thrombophlebitis evident	Thrombophlebitis	Vascular disorders
Loose stool	Diarrhoea	Gastrointestinal disorders
Loose stools	Diarrhoea	Gastrointestinal disorders
MAI in sputum	*Mycobacterium avium* complex infection	Infections and infestations
Manifestation of anxiety	Anxiety	Psychiatric disorders
Migraine	Migraine	Nervous system disorders
Mild epistaxis	Epistaxis	Respiratory, thoracic and mediastinal disorders
Nausea	Nausea	Gastrointestinal disorders
Neck ache/stiffness	Pain	General disorders and administration site conditions
New growth of pseudomonas	*Pseudomonas* infection	Infections and infestations
Nosebleed	Epistaxis	Respiratory, thoracic and mediastinal disorders
Oral thrush	Oral candidiasis	Infections and infestations
P. aeruginosa at 3-month follow-up	*Pseudomonas* infection	Infections and infestations
PR bleed	Rectal haemorrhage	Gastrointestinal disorders
Pain in knees	Arthralgia	Musculoskeletal and connective tissue disorders
Pain in legs	Pain in extremity	Musculoskeletal and connective tissue disorders
Pancreatitis	Pancreatitis	Gastrointestinal disorders
Petechial rash to trunk	Petechiae	Skin and subcutaneous tissue disorders
Photosensitive rash	Photosensitivity reaction	Skin and subcutaneous tissue disorders
Positive pseudomonas aeruginosa	*Pseudomonas* infection	Infections and infestations
Productive cough	Productive cough	Respiratory, thoracic and mediastinal disorders
Prolonged cough	Productive cough	Respiratory, thoracic and mediastinal disorders
Pulmonary exacerbation	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
Pyrexia (high temp) productive cough	Pyrexia	General disorders and administration site conditions
RTI	Respiratory tract infection	Infections and infestations
Re-growth pseudomonas	*Pseudomonas* infection	Infections and infestations
Respiratory exacerbation bronchiolitis	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations

continued

TABLE 35 The MedDRA classifications for all AEs (*continued*)

AE description (verbatim)	Preferred term	SOC
Respiratory tract infection	Respiratory tract infection	Infections and infestations
Right-sided rib pain	Musculoskeletal chest pain	Musculoskeletal and connective tissue disorders
Short of breath, coughing with exercise/ spontaneous moist cough, considerably reduced air entry R side	Dyspnoea	Respiratory, thoracic and mediastinal disorders
Shoulder ache/stiffness	Musculoskeletal stiffness	Musculoskeletal and connective tissue disorders
Stomach ache	Abdominal pain upper	Gastrointestinal disorders
Swollen throat	Pharyngeal oedema	Respiratory, thoracic and mediastinal disorders
Thrush	*Candida* infection	Infections and infestations
Thrush (nappy area)	*Candida* infection	Infections and infestations
Tingling lips, itchy ears and decreased vision	Paraesthesia oral	Gastrointestinal disorders
Tracheal tug and wheeze	Wheezing	Respiratory, thoracic and mediastinal disorders
Tummy pain	Abdominal pain upper	Gastrointestinal disorders
Tummy pain, loose stools	Diarrhoea	Gastrointestinal disorders
URTI	Upper respiratory tract infection	Infections and infestations
URTI, cough + wheeze	Upper respiratory tract infection	Infections and infestations
UTI	Urinary tract infection	Infections and infestations
Viral infection	Viral infection	Infections and infestations
Viral illness	Viral infection	Infections and infestations
Vitamin A deficiency	Vitamin A deficiency	Metabolism and nutrition disorders
Vitamin D deficiency	Vitamin D deficiency	Metabolism and nutrition disorders
Vitamin E deficiency	Vitamin E deficiency	Metabolism and nutrition disorders
Vomiting starting 3 days after starting Cipro	Vomiting	Gastrointestinal disorders
Vulva candidiasis	Vulvovaginal candidiasis	Infections and infestations
Wet cough	Productive cough	Respiratory, thoracic and mediastinal disorders
Wet cough	Productive cough	Respiratory, thoracic and mediastinal disorders
Wheeze	Wheezing	Respiratory, thoracic and mediastinal disorders
Wheezy 4/52	Wheezing	Respiratory, thoracic and mediastinal disorders
abdominal pain	Abdominal pain	Gastrointestinal disorders
abdominal pain	Abdominal pain	Gastrointestinal disorders
abdominal pain and vomiting – distal intestinal obstruction syndrome	Distal intestinal obstruction syndrome	Gastrointestinal disorders
admission for i.v. antibiotic for chest infection	Lower respiratory tract infection	Infections and infestations
back/side pain	Flank pain	Musculoskeletal and connective tissue disorders

TABLE 35 The MedDRA classifications for all AEs (*continued*)

AE description (verbatim)	Preferred term	SOC
bleeding at site of line insertion	Administration site bruise	General disorders and administration site conditions
blocked feeling in ears	Ear discomfort	Ear and labyrinth disorders
blood in vomit	Haematemesis	Gastrointestinal disorders
bronchospasm	Bronchospasm	Respiratory, thoracic and mediastinal disorders
chest exacerbation	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
chest pain (posteria) pain under rt ribs	Chest pain	General disorders and administration site conditions
chest pain and tiredness	Chest pain	General disorders and administration site conditions
chesty	Cough	Respiratory, thoracic and mediastinal disorders
chicken pox	Varicella	Infections and infestations
cold	Nasopharyngitis	Infections and infestations
conjunctivitis	Conjunctivitis	Infections and infestations
constipation	Constipation	Gastrointestinal disorders
corysal + coughing	Upper respiratory tract infection	Infections and infestations
coryza	Upper respiratory tract infection	Infections and infestations
coryzal illness	Upper respiratory tract infection	Infections and infestations
coryzed and coughing	Upper respiratory tract infection	Infections and infestations
cough	Cough	Respiratory, thoracic and mediastinal disorders
cough, runny nose	Cough	Respiratory, thoracic and mediastinal disorders
cough/wheeze	Cough	Respiratory, thoracic and mediastinal disorders
development of vaginal thrush	Vulvovaginal candidiasis	Infections and infestations
device blockage	Device occlusion	Product issues
diarrhoea	Diarrhoea	Gastrointestinal disorders
distal intestinal obstruction syndrome (DIOS)	Distal intestinal obstruction syndrome	Gastrointestinal disorders
dizzy	Dizziness	Nervous system disorders
dry cough	Cough	Respiratory, thoracic and mediastinal disorders
dry, peeling skin on toes- both feet	Dry skin	Skin and subcutaneous tissue disorders
dvt proximal left calf	Deep vein thrombosis	Vascular disorders
earache	Ear pain	Ear and labyrinth disorders
elevated blood sugars	Blood glucose increased	Investigations
eye infection	Eye infection	Infections and infestations
febrile convulsion	Febrile convulsion	Nervous system disorders

continued

TABLE 35 The MedDRA classifications for all AEs (*continued*)

AE description (verbatim)	Preferred term	SOC
fever	Pyrexia	General disorders and administration site conditions
flu-like symptoms (fever/cough)	Influenza-like illness	General disorders and administration site conditions
fractured left and right wrist	Wrist fracture	Injury, poisoning and procedural complications
gastroenteritis	Gastroenteritis	Infections and infestations
grown pseudomonas	Bacterial disease carrier	Infections and infestations
growth haemophilus on cough swab	*Haemophilus* test positive	Investigations
growth of ent cloacae	*Enterobacter* test positive	Investigations
growth of Klebisella pneumoniae	*Klebsiella* test positive	Investigations
growth of Stenotrophomonas maltophilia in swab	*Stenotrophomonas* test positive	Investigations
haemoptysis (post nasal polyectomy operation)	Haemoptysis	Respiratory, thoracic and mediastinal disorders
hand foot and mouth	Foot and mouth disease	Infections and infestations
headache	Headache	Nervous system disorders
heamophilus influenza infection	*Haemophilus* infection	Infections and infestations
high temperature, hoppy dry cough	Pyrexia	General disorders and administration site conditions
hospital admission due to exacerbation of cf	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
increase cough	Cough	Respiratory, thoracic and mediastinal disorders
increase cough and sputum	Productive cough	Respiratory, thoracic and mediastinal disorders
increased cough	Cough	Respiratory, thoracic and mediastinal disorders
increased cough and sputum and extra oral abs	Cough	Respiratory, thoracic and mediastinal disorders
increased cough since 1st May 2015	Cough	Respiratory, thoracic and mediastinal disorders
increased dry cough	Cough	Respiratory, thoracic and mediastinal disorders
increased frequency passing urine	Polyuria	Renal and urinary disorders
increased sputum	Sputum increased	Respiratory, thoracic and mediastinal disorders
increased sputum congestion	Productive cough	Respiratory, thoracic and mediastinal disorders
increased temperature	Pyrexia	General disorders and administration site conditions
increased wheeze	Wheezing	Respiratory, thoracic and mediastinal disorders
involved in accident injured, bump to abdomen with heamaturic	Haematuria	Renal and urinary disorders
joint pain	Arthralgia	Musculoskeletal and connective tissue disorders
left lower lobe pneumonia	Pneumonia	Infections and infestations

TABLE 35 The MedDRA classifications for all AEs (*continued*)

AE description (verbatim)	Preferred term	SOC
left side intermittent back pain	Back pain	Musculoskeletal and connective tissue disorders
lethargy	Lethargy	Nervous system disorders
liver failure	Hepatic failure	Hepatobiliary disorders
long line blocked	Device occlusion	Product issues
loose stools	Diarrhoea	Gastrointestinal disorders
loss of appetite	Decreased appetite	Metabolism and nutrition disorders
lung consolidation	Lung consolidation	Respiratory, thoracic and mediastinal disorders
lung function not back to normal values	Pulmonary function test	Investigations
malaise	Malaise	General disorders and administration site conditions
meconium ileus equivalent	Distal intestinal obstruction syndrome	Gastrointestinal disorders
mild cough	Cough	Respiratory, thoracic and mediastinal disorders
myalgia	Myalgia	Musculoskeletal and connective tissue disorders
nappy rash	Dermatitis diaper	Skin and subcutaneous tissue disorders
nasal congestion	Nasal congestion	Respiratory, thoracic and mediastinal disorders
nasal vestibulitis	Nasal vestibulitis	Infections and infestations
new diagnosis of melanoma	Malignant melanoma	Neoplasms benign, malignant and unspecified (including cysts and polyps)
no improvement in lung function	Pulmonary function test	Investigations
ongoing respiratory exacerbation	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
onset of productive cough	Cough	Respiratory, thoracic and mediastinal disorders
otitis media	Otitis media	Infections and infestations
p. aeruginosa reoccurred	*Pseudomonas* test positive	Investigations
pain at site of line insertion	Administration site pain	General disorders and administration site conditions
pain and rash from passing urine	Dysuria	Renal and urinary disorders
persistent cough	Cough	Respiratory, thoracic and mediastinal disorders
persisting cough wheeze	Productive cough	Respiratory, thoracic and mediastinal disorders
playground collision – sore arm	Limb discomfort	Musculoskeletal and connective tissue disorders
productive cough	Productive cough	Respiratory, thoracic and mediastinal disorders
pseudomonas aeruginosa – growth on cough swab	*Pseudomonas* infection	Infections and infestations
pseudomonas aeruginosa	*Pseudomonas* test	Investigations
pseudomonas growth	*Pseudomonas* infection	Infections and infestations

continued

TABLE 35 The MedDRA classifications for all AEs (*continued*)

AE description (verbatim)	Preferred term	SOC
pseudomonas isolated on cough swab at end of trial intervention	*Pseudomonas* test positive	Investigations
pseudomonas re occurrence	*Pseudomonas* infection	Infections and infestations
pulmonary exacerbation	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
pulmonary exacerbation	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
pyrexia	Pyrexia	General disorders and administration site conditions
raised alanine transaminase	Alanine aminotransferase increased	Investigations
rash	Rash	Skin and subcutaneous tissue disorders
rash due to ciprofloxacilin	Adverse drug reaction	General disorders and administration site conditions
rash on neck	Rash	Skin and subcutaneous tissue disorders
re growth of pseudomonas aeruginosa	*Pseudomonas* infection	Infections and infestations
re-growth of Pseudomonas – i.v. antibiotics as in-patient	*Pseudomonas* infection	Infections and infestations
recurrent L episaxis for about 2 months	Epistaxis	Respiratory, thoracic and mediastinal disorders
reduction in lung function	Pulmonary function test decreased	Investigations
regrowth of pseudomonas aeruginosa	*Pseudomonas* test positive	Investigations
required added co-amoxiclav for cough	Cough	Respiratory, thoracic and mediastinal disorders
respiratory exacerbation	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
respiratory exacerbation	Infective pulmonary exacerbation of cystic fibrosis	Infections and infestations
respiratory syncytial virus positive	Bronchiolitis	Infections and infestations
segmental right middle lobe collapse/ conslidation consistent with acute plugging or infection	Pneumothorax	Respiratory, thoracic and mediastinal disorders
sinus infection	Sinusitis	Infections and infestations
strep pyogenes – extra oral antibiotics	*Streptococcus* test positive	Investigations
sunburn with skin blistering	Sunburn	Injury, poisoning and procedural complications
swollen nose	Swelling	General disorders and administration site conditions
thrush	*Candida* infection	Infections and infestations
toe nails peeling – both feet	Onychoclasis	Skin and subcutaneous tissue disorders
transient discolouration of arms/legs	Skin discolouration	Skin and subcutaneous tissue disorders
upper arm pain	Pain	General disorders and administration site conditions
upper respiratory tract infection	Upper respiratory tract infection	Infections and infestations

TABLE 35 The MedDRA classifications for all AEs (*continued*)

AE description (verbatim)	Preferred term	SOC
urticrial rash following ciprofloxacin and a mixed nut bar. Subsequent doses of cipro proved to have no adverse reaction	Urticaria	Skin and subcutaneous tissue disorders
venous long line leaking from exit site on flushing	Catheter management	Surgical and medical procedures
viral illness	Viral infection	Infections and infestations
vomits	Vomiting	Gastrointestinal disorders
vomiting	Vomiting	Gastrointestinal disorders
wet cough	Productive cough	Respiratory, thoracic and mediastinal disorders
wet cough increased sputum	Productive cough	Respiratory, thoracic and mediastinal disorders
wheeze	Wheezing	Respiratory, thoracic and mediastinal disorders
wheezy	Wheezing	Respiratory, thoracic and mediastinal disorders
wheezy cough with colomycin	Wheezing	Respiratory, thoracic and mediastinal disorders
wheezy with exercise (montekulast)	Wheezing	Respiratory, thoracic and mediastinal disorders

CXR, chest radiograph; DIOS, distal intestinal obstruction syndrome; L, left; MAI, *Mycobacterium avium* complex infection; PR, per rectum; R, right; RTI, respiratory tract infection; URTI, upper respiratory tract infection; UTI, urinary tract infection.

TABLE 36 Non-SAEs as recorded on the locked database

		Treatment group, *n* (%)					
		i.v. antibiotic therapy (*N* = 126)		Oral antibiotic therapy (*N* = 146)		Total (*N* = 272), *n* (%)	
SOC	Preferred term	Events	Patients	Events	Patients	Events	Patients
Ear and labyrinth disorders	Ear discomfort	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Ear pain	0	0 (0.0)	2	2 (1.4)	2	2 (0.7)
Gastrointestinal disorders	Abdominal pain	1	1 (0.8)	2	2 (1.4)	3	3 (1.1)
	Abdominal pain upper	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Constipation	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Diarrhoea	6	5 (4)	3	3 (2.1)	9	8 (2.9)
	Distal intestinal obstruction syndrome	2	2 (1.6)	3	3 (2.1)	5	5 (1.8)
	Haematemesis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Nausea	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Pancreatitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Paraesthesia oral	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Rectal haemorrhage	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Tongue discolouration	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Vomiting	3	3 (2.4)	0	0 (0.0)	3	3 (1.1)

continued

TABLE 36 Non-SAEs as recorded on the locked database (*continued*)

		Treatment group, *n* (%)					
		i.v. antibiotic therapy (*N* = 126)		Oral antibiotic therapy (*N* = 146)		Total (*N* = 272), *n* (%)	
SOC	Preferred term	Events	Patients	Events	Patients	Events	Patients
General disorders and administration site conditions	Administration site bruise	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Administration site pain	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Adverse drug reaction	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Catheter site-related reaction	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Chest pain	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Influenza-like illness	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Malaise	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pain	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Pyrexia	2	2 (1.6)	7	7 (4.8)	9	9 (3.3)
	Swelling	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Immune system disorders	Seasonal allergy	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
Infections and infestations	Bacterial disease carrier	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Bronchopulmonary aspergillosis allergic	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Candida infection	1	1 (0.8)	5	5 (3.4)	6	6 (2.2)
	Conjunctivitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Eczema infected	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Eye infection	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Foot and mouth disease	0	0 (0.0)	2	2 (1.4)	2	2 (0.7)
	Gastroenteritis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Haemophilus infection	2	1 (0.8)	0	0 (0.0)	2	1 (0.4)
	Infectious mononucleosis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Infective pulmonary exacerbation of cystic fibrosis	4	3 (2.4)	6	6 (4.1)	10	9 (3.3)
	Lower respiratory tract infection	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Mycobacterium avium complex infection	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Nasal vestibulitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Nasopharyngitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Oral candidiasis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Otitis media	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Pneumonia	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Pseudomonas infection	7	7 (5.6)	2	2 (1.4)	9	9 (3.3)
	Respiratory tract infection	1	1 (0.8)	2	2 (1.4)	3	3 (1.1)
	Sinusitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Upper respiratory tract infection	15	11 (8.7)	3	2 (1.4)	18	13 (4.8)

TABLE 36 Non-SAEs as recorded on the locked database (*continued*)

		Treatment group, *n* (%)					
		i.v. antibiotic therapy (*N* = 126)		Oral antibiotic therapy (*N* = 146)		Total (*N* = 272), *n* (%)	
SOC	Preferred term	Events	Patients	Events	Patients	Events	Patients
	Urinary tract infection	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Varicella	3	3 (2.4)	1	1 (0.7)	4	4 (1.5)
	Viral infection	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Vulvovaginal candidiasis	2	2 (1.6)	0	0 (0.0)	2	2 (0.7)
Injury, poisoning and procedural complications	Fall	1	1 (0.8)	2	2 (1.4)	3	3 (1.1)
	Skull fracture	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Sunburn	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Wrist fracture	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Investigations	Alanine aminotransferase increased	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Blood glucose increased	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Chest X-ray abnormal	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Enterobacter test positive	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Haemophilus test positive	2	2 (1.6)	0	0 (0.0)	2	2 (0.7)
	Klebsiella test positive	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pseudomonas test	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Pseudomonas test positive	1	1 (0.8)	2	2 (1.4)	3	3 (1.1)
	Pulmonary function test	0	0 (0.0)	2	2 (1.4)	2	2 (0.7)
	Pulmonary function test decreased	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Stenotrophomonas test positive	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Streptococcus test positive	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Metabolism and nutrition disorders	Decreased appetite	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Vitamin A deficiency	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Vitamin D deficiency	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Vitamin E deficiency	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Musculoskeletal and connective tissue disorders	Arthralgia	0	0 (0.0)	3	3 (2.1)	3	3 (1.1)
	Back pain	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Flank pain	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Limb discomfort	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Musculoskeletal chest pain	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Musculoskeletal stiffness	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Myalgia	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pain in extremity	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Tendonitis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)

continued

TABLE 36 Non-SAEs as recorded on the locked database (*continued*)

		Treatment group, *n* (%)					
		i.v. antibiotic therapy (*N* = 126)		Oral antibiotic therapy (*N* = 146)		Total (*N* = 272), *n* (%)	
SOC	Preferred term	Events	Patients	Events	Patients	Events	Patients
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Malignant melanoma	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Nervous system disorders	Dizziness	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Febrile convulsion	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Headache	3	2 (1.6)	0	0 (0.0)	3	2 (0.7)
	Lethargy	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Migraine	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Product issues	Device occlusion	2	2 (1.6)	0	0 (0.0)	2	2 (0.7)
Psychiatric disorders	Enuresis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Renal and urinary disorders	Dysuria	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Polyuria	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Respiratory, thoracic and mediastinal disorders	Bronchospasm	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Cough	26	22 (17.5)	28	23 (15.8)	54	45 (16.5)
	Epistaxis	1	1 (0.8)	2	2 (1.4)	3	3 (1.1)
	Haemoptysis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Nasal congestion	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Pharyngeal oedema	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Productive cough	5	5 (4)	8	8 (5.5)	13	13 (4.8)
	Sputum increased	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Wheezing	3	3 (2.4)	6	6 (4.1)	9	9 (3.3)
Skin and subcutaneous tissue disorders	Dermatitis diaper	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Dry skin	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Eczema	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Onychoclasis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Petechiae	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Photosensitivity reaction	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Rash	2	2 (1.6)	1	1 (0.7)	3	3 (1.1)
	Skin discolouration	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Urticaria	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Total	135	64 (50.8)	144	75 (51.4)	279	139 (51.1)

TABLE 37 Serious adverse events/SARs as reported in the locked trial database

		Treatment group, *n* (%)					
		i.v. antibiotic therapy (*N* = 126)		Oral antibiotic therapy (*N* = 146)		Total (*N* = 272), *n* (%)	
SOC	Preferred term	Events	Patients	Events	Patients	Events	Patients
Gastrointestinal disorders	Distal intestinal obstruction syndrome	2	2 (1.6)	1	1 (0.7)	3	3 (1.1)
General disorders and administration site conditions	Chest pain	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	General physical health deterioration	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pyrexia	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Hepatobiliary disorders	Hepatic failure	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Infections and infestations	Bronchiolitis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Croup infectious	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Gastroenteritis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Infective pulmonary exacerbation of cystic fibrosis	1	1 (0.8)	1	1 (0.7)	2	2 (0.7)
	Lower respiratory tract infection	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pseudomonas infection	0	0 (0.0)	3	3 (2.1)	3	3 (1.1)
	Rhinitis	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Upper respiratory tract infection	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Viral infection	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Nervous system disorders	Headache	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Psychiatric disorders	Anxiety[a]	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Renal and urinary disorders	Haematuria	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Lung consolidation	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Pneumothorax	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
	Productive cough	0	0 (0.0)	3	3 (2.1)	3	3 (1.1)
Skin and subcutaneous tissue disorders	Rash pruritic	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Surgical and medical procedures	Catheter management	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Vascular disorders	Deep-vein thrombosis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
	Thrombophlebitis	1	1 (0.8)	0	0 (0.0)	1	1 (0.4)
Total		11	10 (7.9)	21	14 (9.6)	32	24 (8.8)

a Event was that, after 5 weeks on the trial, the patient developed voices in their head, obsessive behaviours and anxiety at night.

TABLE 38 Line listings of SAEs/SARs as reported in the locked trial database

SAE number[a]	Allocation	SOC	Preferred term	Onset date	Serious criteria		Severity (PI assessment)	Expectedness (CI assessment)	Relationship		Most likely cause, if unrelated (PI assessment)	Outcome
					PI assessment	CI assessment			PI assessment	CI assessment		
1	Oral	Respiratory, thoracic and mediastinal disorders	Dyspnoea	10 December 2010	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unlikely	Disease under study	Resolved
2	Oral	Infections and infestations	*Pseudomonas* infection	7 March 2011	Required hospitalisation	Required hospitalisation	Mild	Unexpected	Unrelated	Unrelated	Disease under study	Resolved
4	Oral	Infections and infestations	Croup infectious	13 January 2012	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unrelated	Other illness	Resolved
5	Oral	Infections and infestations	*Pseudomonas* infection	26 January 2012	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unrelated	Disease under study	Resolved
6	Oral	Infections and infestations	Bronchiolitis	26 January 2012	Required hospitalisation	Required hospitalisation	Moderate	Expected	Unrelated	Unrelated	Other illness	Resolved
7	i.v.	Skin and subcutaneous tissue disorders	Rash pruritic	5 February 2012	Prolonged existing hospitalisation	Prolonged existing hospitalisation	Moderate	Expected	Possibly	Probably		Resolved
8	Oral	Infections and infestations	Viral infection	23 March 2012	Required hospitalisation	Required hospitalisation	Severe	Unexpected	Unrelated	Unrelated	Other illness	Resolved
9	Oral	Infections and infestations	*Pseudomonas* infection	26 March 2012	Required hospitalisation	Required hospitalisation	Mild	Expected	Probably	Probably		Resolved with sequelae
10	Oral	Infections and infestations	Infective pulmonary exacerbation of cystic fibrosis	3 July 2012	Required hospitalisation	Required hospitalisation	Mild	Unexpected	Unrelated	Unrelated	Disease under study	Resolved
12	Oral	Gastrointestinal disorders	Distal intestinal obstruction syndrome	4 September 2012	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unlikely	Unrelated	Other illness	Resolved
13	Oral	General disorders and administration site conditions	Chest pain	17 August 2012	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unrelated	Other illness	Resolved
14	Oral	Infections and infestations	Lower respiratory tract infection	11 September 2012	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unrelated	Disease under study	Resolved
15	Oral	Respiratory, thoracic and mediastinal disorders	Productive cough	1 October 2012	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unrelated	Disease under study	Resolved with sequelae
16	Oral	Infections and infestations	Gastroenteritis	9 October 2012	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unrelated	Other illness	Resolved
17	i.v.	Gastrointestinal disorders	Distal intestinal obstruction syndrome	13 October 2012	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unrelated	Disease under study	Resolved

SAE number[a]	Allocation	SOC	Preferred term	Onset date	Serious criteria		Severity (PI assessment)	Expectedness (CI assessment)	Relationship		Most likely cause, if unrelated (PI assessment)	Outcome
					PI assessment	CI assessment			PI assessment	CI assessment		
18	i.v.	Gastrointestinal disorders	Distal intestinal obstruction syndrome	25 November 2012	Required hospitalisation	Required hospitalisation	Mild	Unexpected	Unrelated	Unrelated	Disease under study	Resolved
19	i.v.	Vascular disorders	Thrombophlebitis	27 January 2013	Required hospitalisation	Required hospitalisation	Mild	Expected	Probably	Probably		Resolved
20	i.v.	Surgical and medical procedures	Catheter management	12 March 2013	Required hospitalisation	Required hospitalisation	Mild	Unexpected	Unrelated	Unrelated	Protocol procedure	Resolved
21	Oral	Respiratory, thoracic and mediastinal disorders	Pneumothorax	2 May 2013	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unrelated	Disease under study	Resolved
22	i.v.	Renal and urinary disorders	Haematuria	25 May 2013	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unrelated		Resolved
23	i.v.	Hepatobiliary disorders	Hepatic failure	21 August 2013	Required hospitalisation	Immediately life-threatening. Required hospitalisation	Severe	Unexpected	Unrelated	Unrelated	Other illness	Resolved with sequelae
24	Oral	Infections and infestations	Upper respiratory tract infection	18 October 2013	Required hospitalisation	Required hospitalisation	Mild	Unexpected	Unrelated	Unrelated	Other illness	Resolved with sequelae
25	Oral	Respiratory, thoracic and mediastinal disorders	Productive cough	13 October 2013	Required hospitalisation	Required hospitalisation	Mild	Unexpected	Unrelated	Unrelated	Disease under study	Resolved
26	Oral	Respiratory, thoracic and mediastinal disorders	Productive cough	17 December 2013	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unlikely	Unrelated	Lack of efficacy	Resolved
27	Oral	Psychiatric disorders	Anxiety[b]	22 March 2014	Medically significant/ important	Medically significant/ important	Moderate	Expected	Possibly	Possibly	Other illness	Resolved
28	i.v.	Infections and infestations	Infective pulmonary exacerbation of cystic fibrosis	17 December 2013	Required hospitalisation	Required hospitalisation	Moderate	Unexpected	Unrelated	Unrelated	Disease under study	Resolved
29	i.v.	General disorders and administration site conditions	Pyrexia	6 September 2014	Required hospitalisation	Required hospitalisation	Moderate	Expected	Possibly	Unlikely	Other illness	Resolved

CI, chief investigator.

a SAE numbers 3 and 11 were allocated in error to AEs that did not meet the criteria for SAEs.

b Event was that, after 5 weeks on the trial, the patient developed voices in their head, obsessive behaviours and anxiety at night.

Note

There are fewer events reported in *Table 38* than in *Table 37* as from protocol version 6.0 onwards only SARs were reported to this level of detail.

TABLE 39 Clarification of AEs terms made by chief investigator and co-chief investigator

	AE term on locked database	Preferred term on locked database	SOC on locked database	Agreed terminology to be used for preferred term	SOC for agreed terminology
1	Left lower lobe pneumonia	Pneumonia	Infections and infestations	Pneumonia	Infections and infestations
2	Heamophilus influenza infection	*Haemophilus* infection	Infections and infestations	*Haemophilus parainfluenzae* respiratory infection	Infections and infestations
3	H. influenza infection	*Haemophilus* infection	Infections and infestations	*Haemophilus influenzae* respiratory infection	Infections and infestations
4	Swollen nose	Swelling	General disorders and administration site conditions	Nasal swelling	General disorders and administration site conditions
5	Strep pyogenes – extra oral antibiotics	*Streptococcus* test positive	Investigations	*Streptococcus pyogenes* respiratory infection	Infections and infestations
6	Hand foot and mouth	Foot and mouth disease	Infections and infestations	Hand, foot and mouth disease	Infections and infestations
7	Growth haemophilus on cough swab	*Haemophilus* test positive	Investigations	*Haemophilus influenzae* respiratory infection	Infections and infestations
8	Nasal vestibulitis	Nasal vestibulitis	Infections and infestations	Nasal vestibulitis	Infections and infestations
9	Chest infection	Lower respiratory tract infection	Infections and infestations	Chest infection	Infections and infestations
10	Allergic broncho pulmonary aspergillosis (ABPA)	Bronchopulmonary aspergillosis allergic	Infections and infestations	Allergic broncho pulmonary aspergillosis	Infections and infestations
11	Growth of ent cloacae	*Enterobacter* test positive	Investigations	*Enterobacter cloacae* respiratory infection	Infections and infestations
12	H. influenza on cough swab	*Haemophilus* test positive	Investigations	*Haemophilus influenzae* respiratory infection	Infections and infestations
13	Growth of klebsiella pneumoniae	*Klebsiella* test positive	Investigations	*Klebsiella pneumoniae* respiratory infection	Infections and infestations
14	Reduction in lung fuction	Pulmonary function test decreased	Investigations	Pulmonary function decreased	Respiratory, thoracic and mediastinal disorders
15	No improvement in lung function	Pulmonary function test	Investigations	Pulmonary function decreased	Respiratory, thoracic and mediastinal disorders
16	Foot and mount disease	Foot and mouth disease	Infections and infestations	Hand, foot and mouth	Infections and infestations
17	Growth of stenotrophomonas mealtephilia in swab	*Stenotrophomonas* test positive	Investigations	*Stenotrophomonas maltophilia* respiratory infection	Infections and infestations
18	Lung function not back to normal values	Pulmonary function test	Investigations	Pulmonary function decreased	Respiratory, thoracic and mediastinal disorders
19	Admission for i.v. antibiotic for chest infection	Lower respiratory tract infection	Infections and infestations	Chest infection	Infections and infestations

Appendix 6 Additional economic evaluation information

TABLE 40 Logic for banding

Category	Criteria	Band						
		1	1A	2	2A	3	4	5
Therapies	Maximum number of total days of i.v. antibiotics	0	14	28	56	84	112	≥ 113
Hospitalisations	Maximum numbers of days in hospital	0	7	14	14	57	112	≥ 113

TABLE 41 Cystic fibrosis specialty HRG costs

Band	Measurement	Unit cost (£)	Source	Detail
Band 1, adults ≥ 17 years	Per year	3362	NHS reference costs 2016–17[44]	*Table 39*
Band 1A, adults ≥ 17 years	Per year	5380	NHS reference costs 2016–17[44]	*Table 39*
Band 1A, children ≤ 16 years	Per year	5778	NHS reference costs 2016–17[44]	*Table 39*
Band 1, children ≤ 16 years	Per year	5685	NHS reference costs 2016–17[44]	*Table 39*
Band 2, adults ≥ 17 years	Per year	6498	NHS reference costs 2016–17[44]	*Table 39*
Band 2A, adults ≥ 17 years	Per year	8922	NHS reference costs 2016–17[44]	*Table 39*
Band 2A, children ≤ 16 years	Per year	8968	NHS reference costs 2016–17[44]	*Table 39*
Band 2, children ≤ 16 years	Per year	7492	NHS reference costs 2016–17[44]	*Table 39*
Band 3, adults ≥ 17 years	Per year	15,337	NHS reference costs 2016–17[44]	*Table 39*
Band 3, children ≤ 16 years	Per year	16,770	NHS reference costs 2016–17[44]	*Table 39*

Calculation of societal costs

Table 42 provides the societal unit costs used for the sensitivity analysis in the trial. Societal unit costs covered patient aids paid for out of pocket by the carer/patient; any travel time, stratified by mode of transport, recorded during the trial for carers/patients; time lost from work for the carer/patient; and over-the-counter medicines.

Transport

Car

The car travel costs are summarised in *Table 43*. The cost per mile was converted to the cost per minute using the mean speed of 25 miles per hour reported by the Department for Transport in 2018.[71] Speed per minute was 0.42 miles per minute during free flow and 0.23 miles per minute with adjustment for congestion, assuming a mean delay of 47 seconds per minute.

The cost estimates are based on the motoring costs per mile for domestic purposes reported by the AA in 2014.[72] The cost of personal transport did not change between 2014–17 according to the Department for Transport, so the estimates from 2014 were assumed to be applicable to the 2017/18 cost year used in the analysis.[73]

TABLE 42 Societal unit costs

Item	Measurement	Unit cost (£)	Source	Detail
Patient aids				
Anti-allergy pillow	Per item	8.00	Wilko (Wilko Retail Ltd, Worksop, UK)[69]	
Anti-allergy bed covers	Per item	10.00	Wilko[70]	
Peak flow medicine	Per item	5.00	BNF 2017[43]	
Travel costs				
Car	Per minute	0.23	AA plc (Basingstoke, UK)	Based on the motoring costs per mile for domestic purposes
Bus	Per minute	0.08	Department for Transport	Local bus transport statistics reported. 3.5 miles per journey
Taxi	Per minute	0.53	Local authority average	Assumption (based on average of Glasgow, Liverpool, Manchester and Plymouth)
Time lost from work				
Carer/patient time	Per hour	17.00	Office for National Statistics[49]	Work per minute using the mean hourly earnings reported by the Office for National Statistics[49]
Over-the-counter medicines				
Various	Per medicine/pill	Various	BNF 2017[43]	

TABLE 43 Travel costs for car

		Cost per minute (£)	
Item	Cost per mile (£)	Without congestion	With congestion
Standing charges (tax, insurance, capital)	0.35	0.15	0.08
Running costs (fuel, service, parts)	0.20	0.08	0.05
Total running costs	0.56[a]	0.23	0.13

a Rounded up to 0.56.

Bus

The bus travel costs are summarised in *Table 44*. The unit cost of bus transport was based on the operating cost per passenger journey in English metropolitan areas in 2017/18.[74] Given that bus transport is predominantly publicly funded in England, it was assumed that this cost is reflective of the cost paid by the passenger.

TABLE 44 Travel costs for bus

Item	Cost (£)
Cost per passenger journey	1.23
Cost per minute	0.08

The cost per minute was derived from the local bus transport statistics reported by the Department for Transport in 2017/18. There were 4844 million journeys covering 16.9 billion miles, which corresponds to 3.5 miles per journey.[75,76] Assuming a mean speed of 25 miles per hour during free flow and 14 miles per hour adjusting for congestion, the mean duration of a bus journey is 15 minutes.

Taxi

It was assumed that the mean length of a taxi journey is equivalent to the mean length of a bus journey as described above (3.5 miles) lasting 15 minutes.

There is a large variation in regulated taxi fares across the UK. For example, the estimated cost of a 3.5-mile journey (including minimum charge) during daytime hours on a weekday is £6.30 in Glasgow,[77] £8.00 in Liverpool,[78] £8.25 in Plymouth[79] and £8.90 in Manchester.[80] The cost of a 3.5-mile taxi journey was substantially higher in London (£12.40).[81]

The unit cost of a taxi journey depends on whether the journey was taken in or outside London, as presented in *Table 45*.

Lost productivity

Lost productivity was estimated as the lost income from work per minute using the mean hourly earnings reported by the Office for National Statistics,[49] as recorded in *Table 46*.

TABLE 45 Travel costs for taxi

Location	Unit cost per journey (£)	Unit cost per minute (£)	Source
London	12.40	0.83	Transport for London[81]
Outside London	8.00	0.53	Assumption (based on average of Glasgow, Liverpool, Manchester and Plymouth)

TABLE 46 Lost productivity

Category	Per hour (£)	Per minute (£)	Source
Mean hourly earnings excluding overtime	16.76	0.28	Office for National Statistics[49]

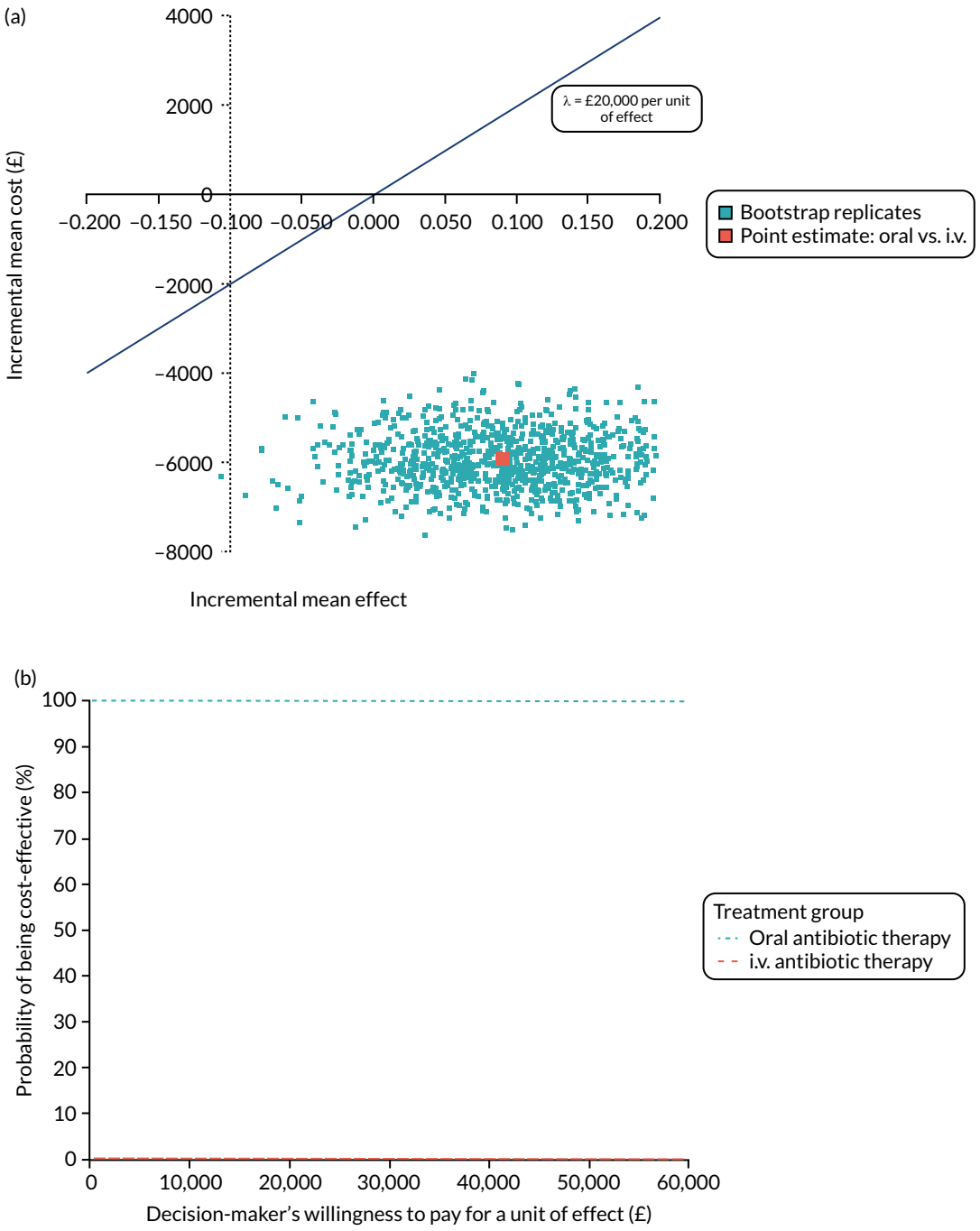


FIGURE 33 Primary analysis: proportion infection free, NHS and PSS perspective costs, 15-month horizon, covariate adjusted. (a) Incremental cost-effectiveness plane; and (b) CEAC.

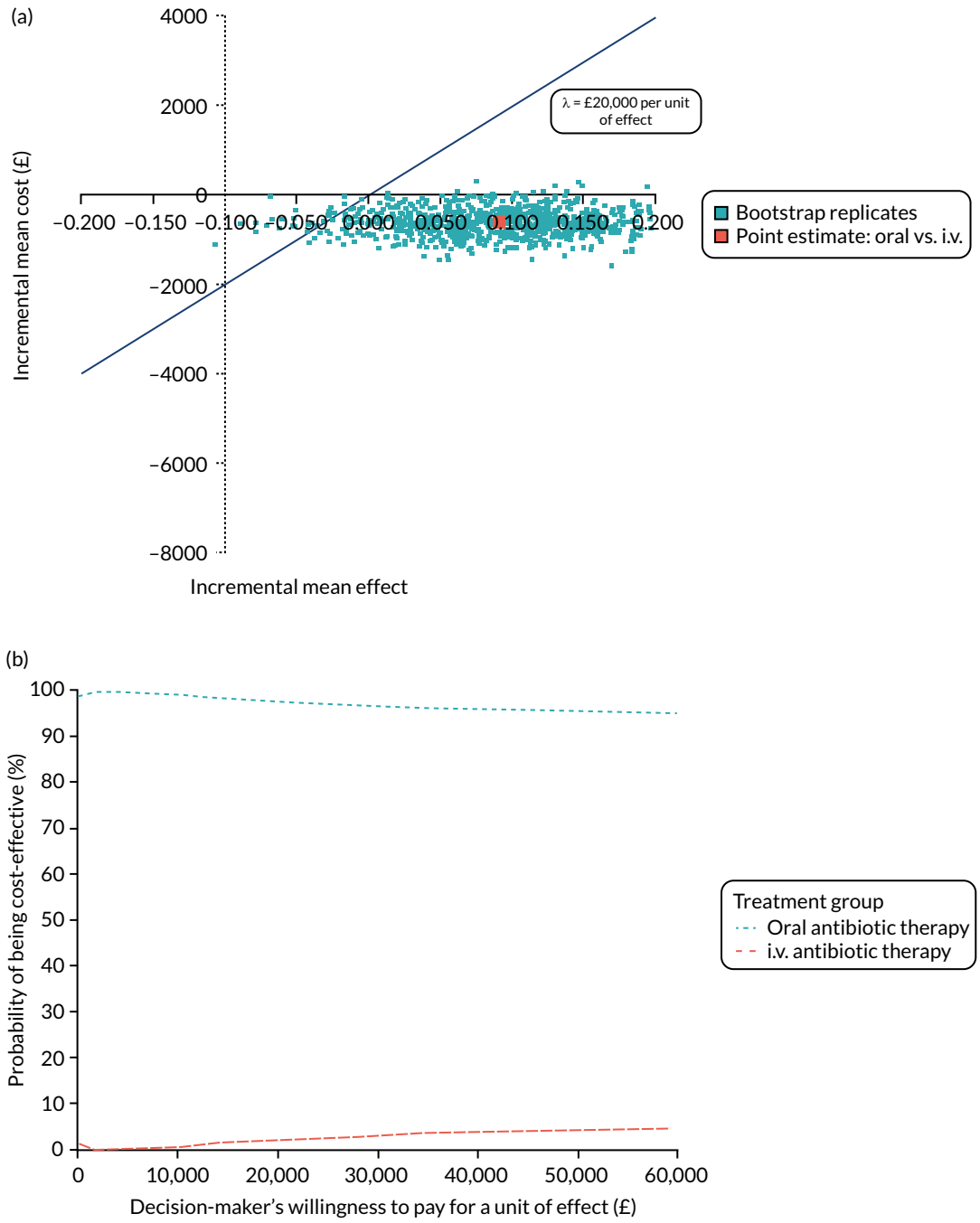


FIGURE 34 Primary analysis with sensitivity test using specialist HRG costs for CF patients. (a) Incremental cost-effectiveness plane; and (b) CEAC.

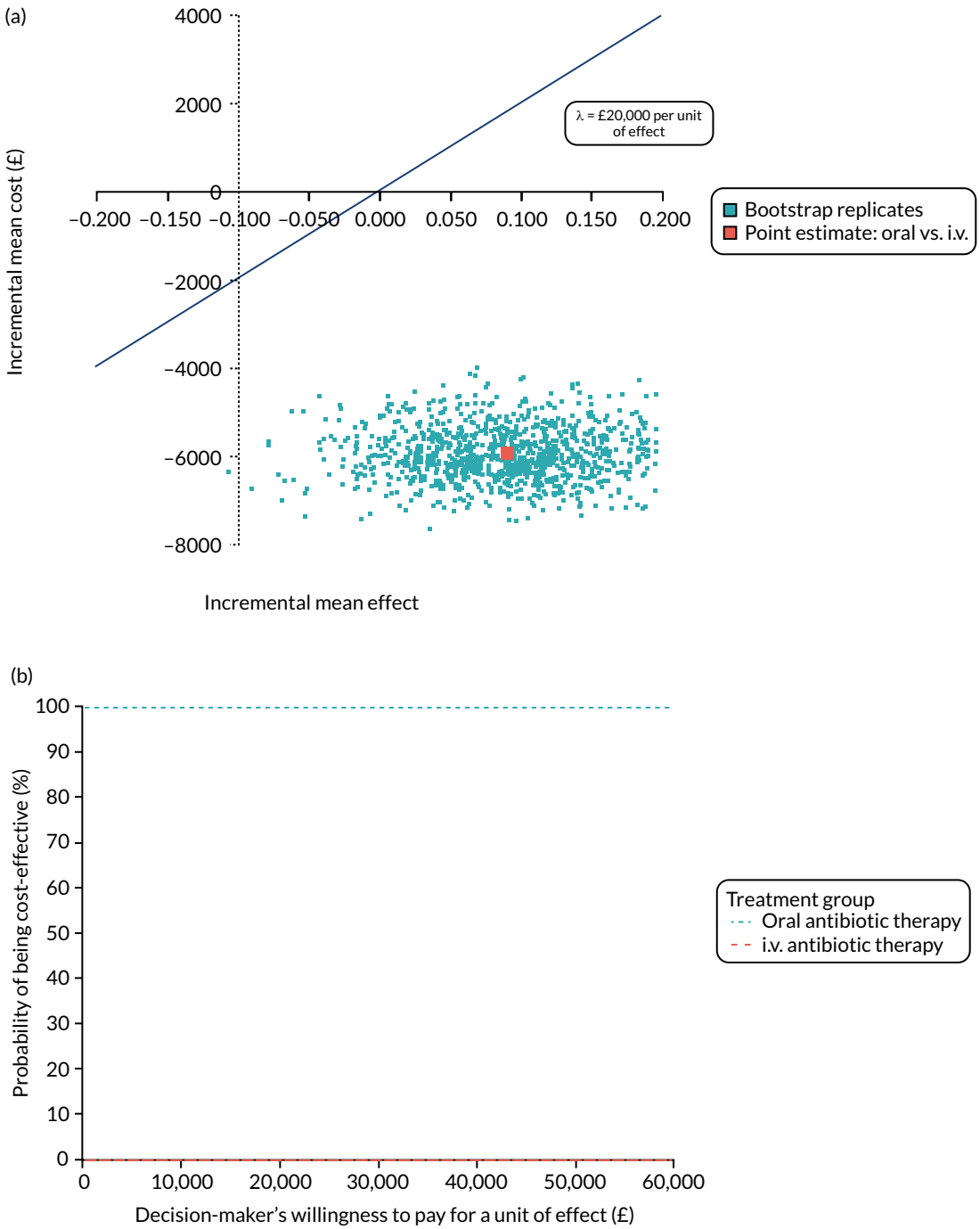


FIGURE 35 Primary analysis: proportion infection free, NHS and PSS perspective costs, covariate adjusted, GLM cost model [link(log); family (Gaussian)]. (a) Incremental cost-effectiveness plane; and (b) CEAC.

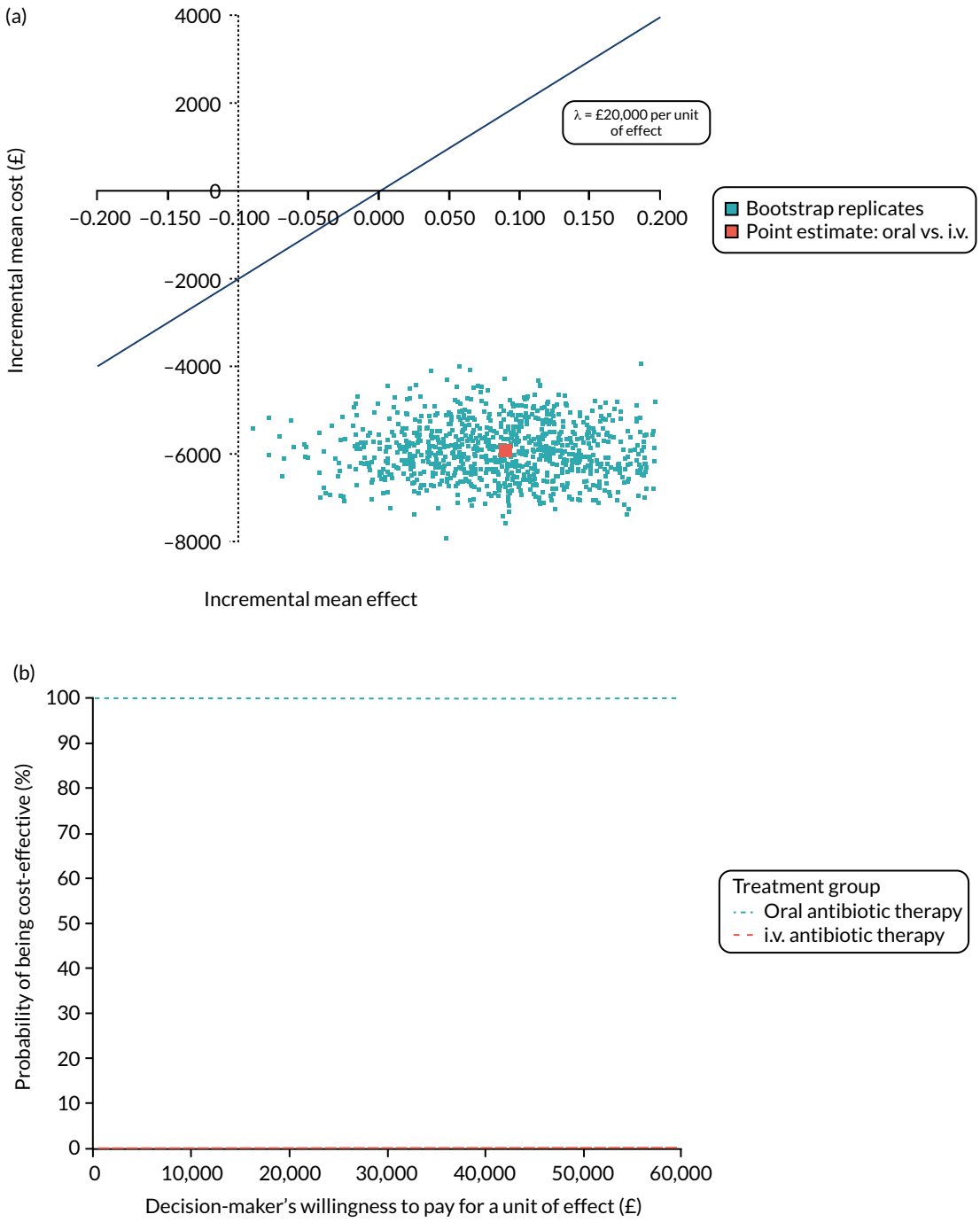


FIGURE 36 Primary analysis: proportion infection free, NHS and PSS perspective costs, covariate adjusted, GLM cost model [link(log); family (Gaussian)]. (a) Incremental cost-effectiveness plane; and (b) CEAC.

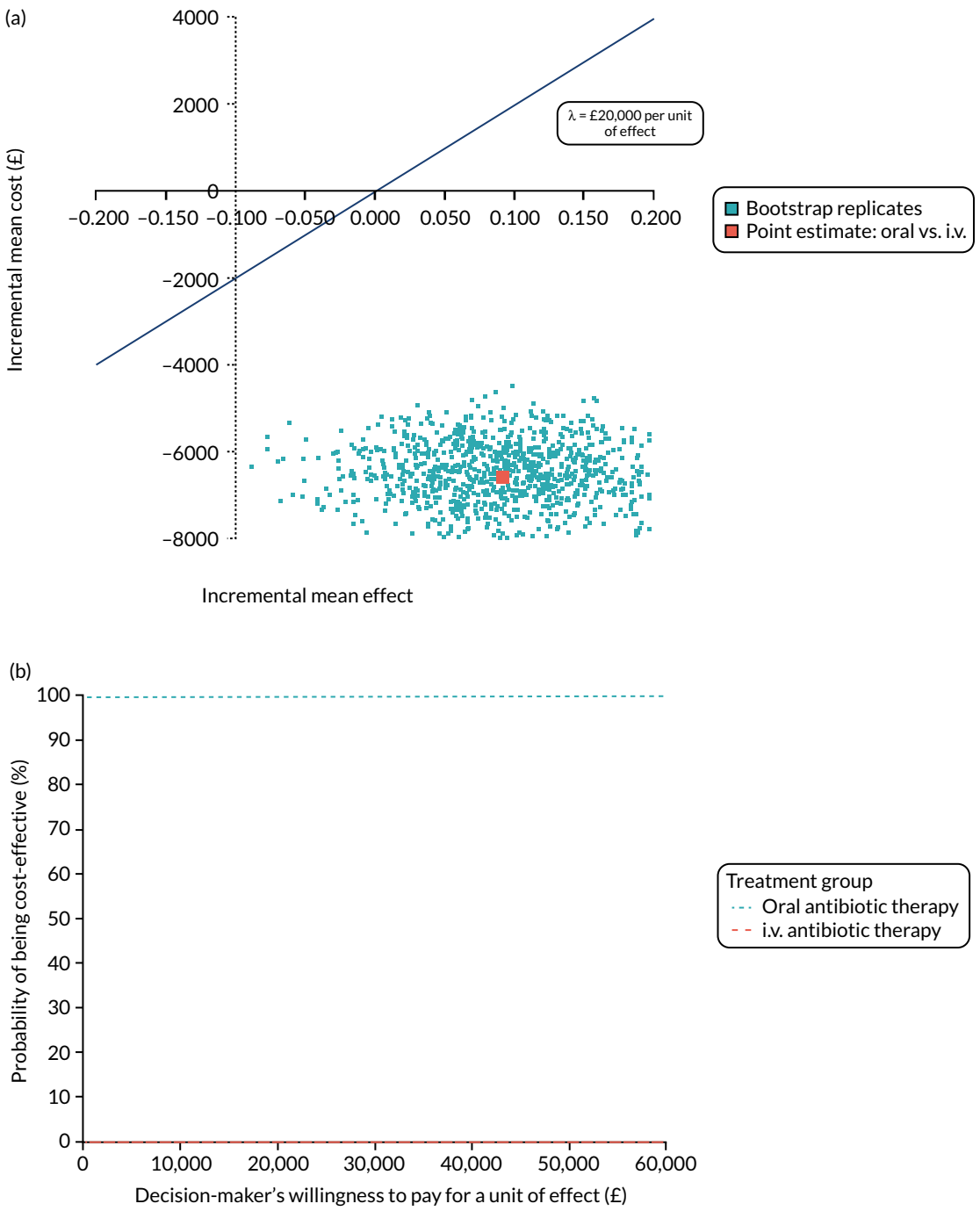


FIGURE 37 Primary analysis: clinical effect, NHS and PSS perspective costs, covariate adjusted, GLM cost model [link(log); family (Gaussian)]. (a) Incremental cost-effectiveness plane; and (b) CEAC.

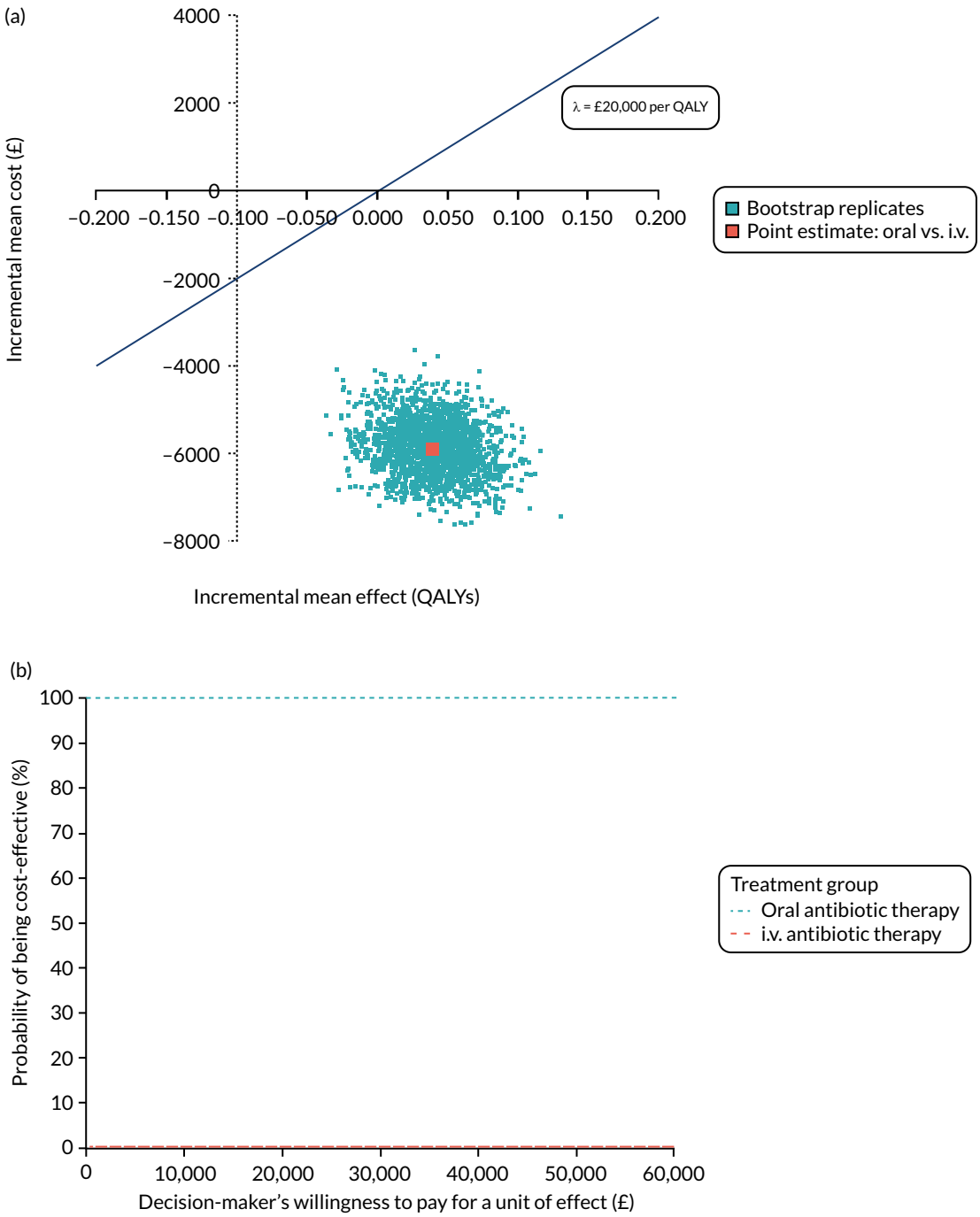


FIGURE 38 Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, covariate. (a) Incremental cost-effectiveness plane; and (b) CEAC.

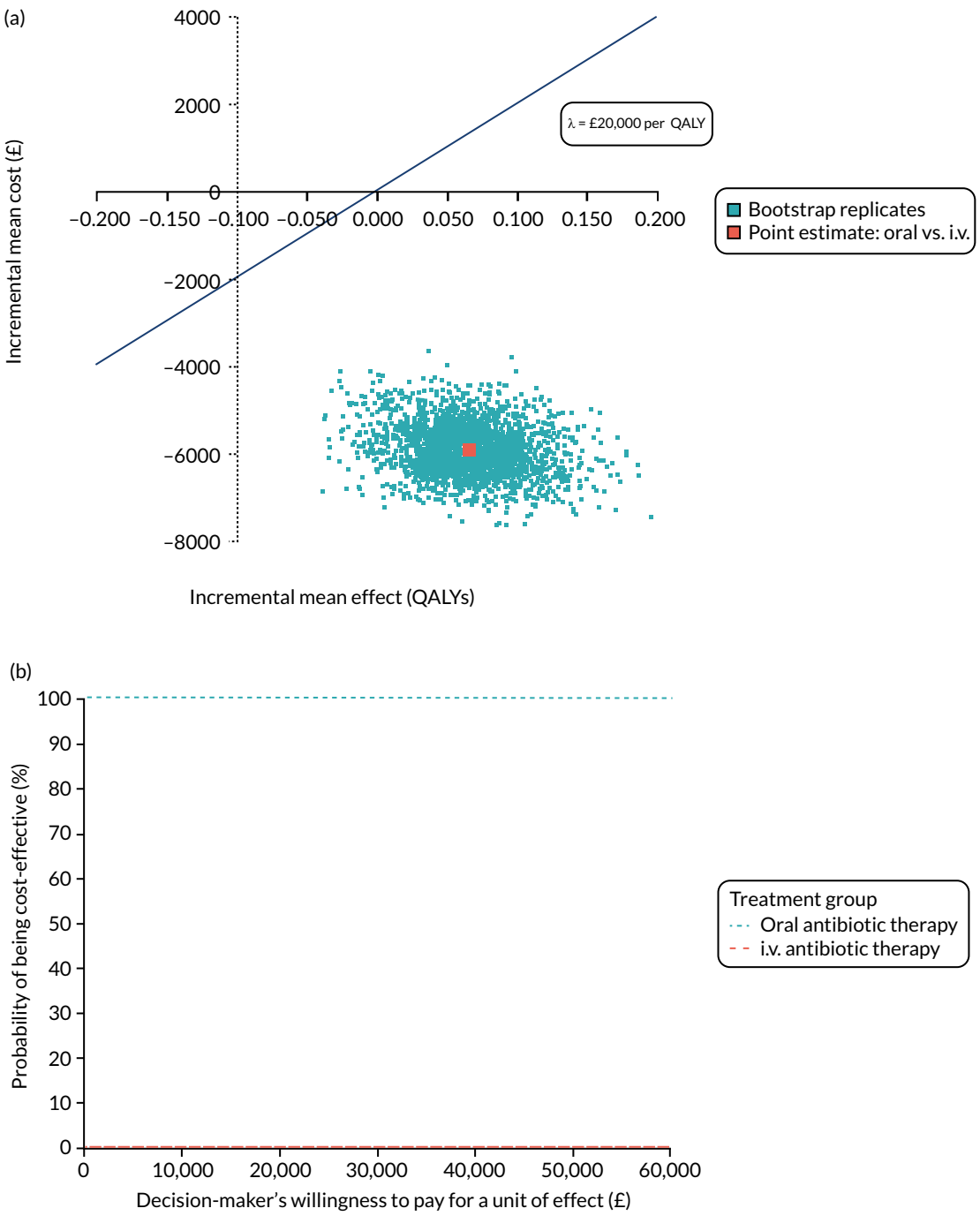


FIGURE 39 Secondary analysis: 24-month horizon QALYs, NHS and PSS perspective costs, covariate adjusted. (a) Incremental cost-effectiveness plane; and (b) CEAC.

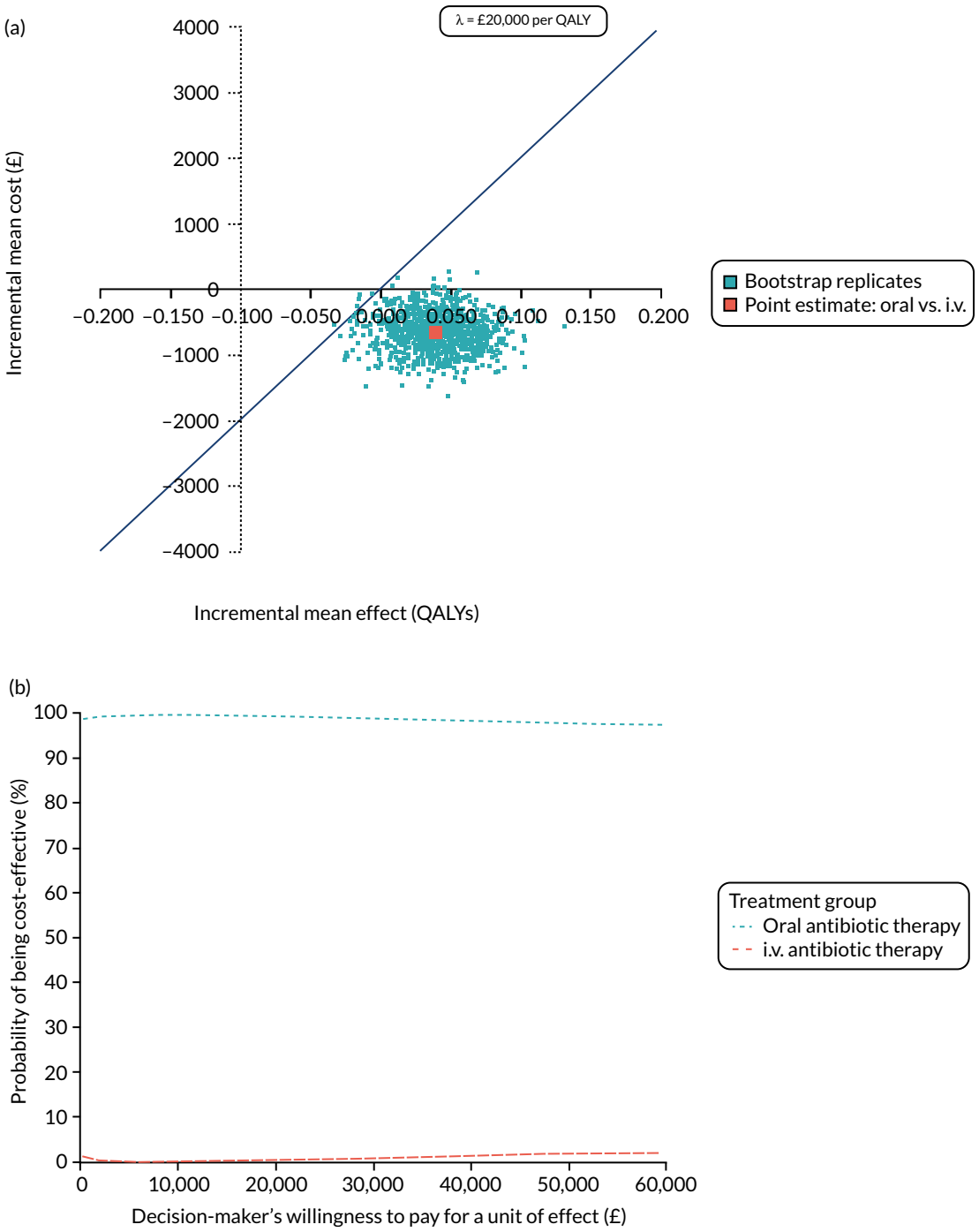


FIGURE 40 Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, covariate adjusted, CF HRG used. (a) Incremental cost-effectiveness plane; and (b) CEAC.

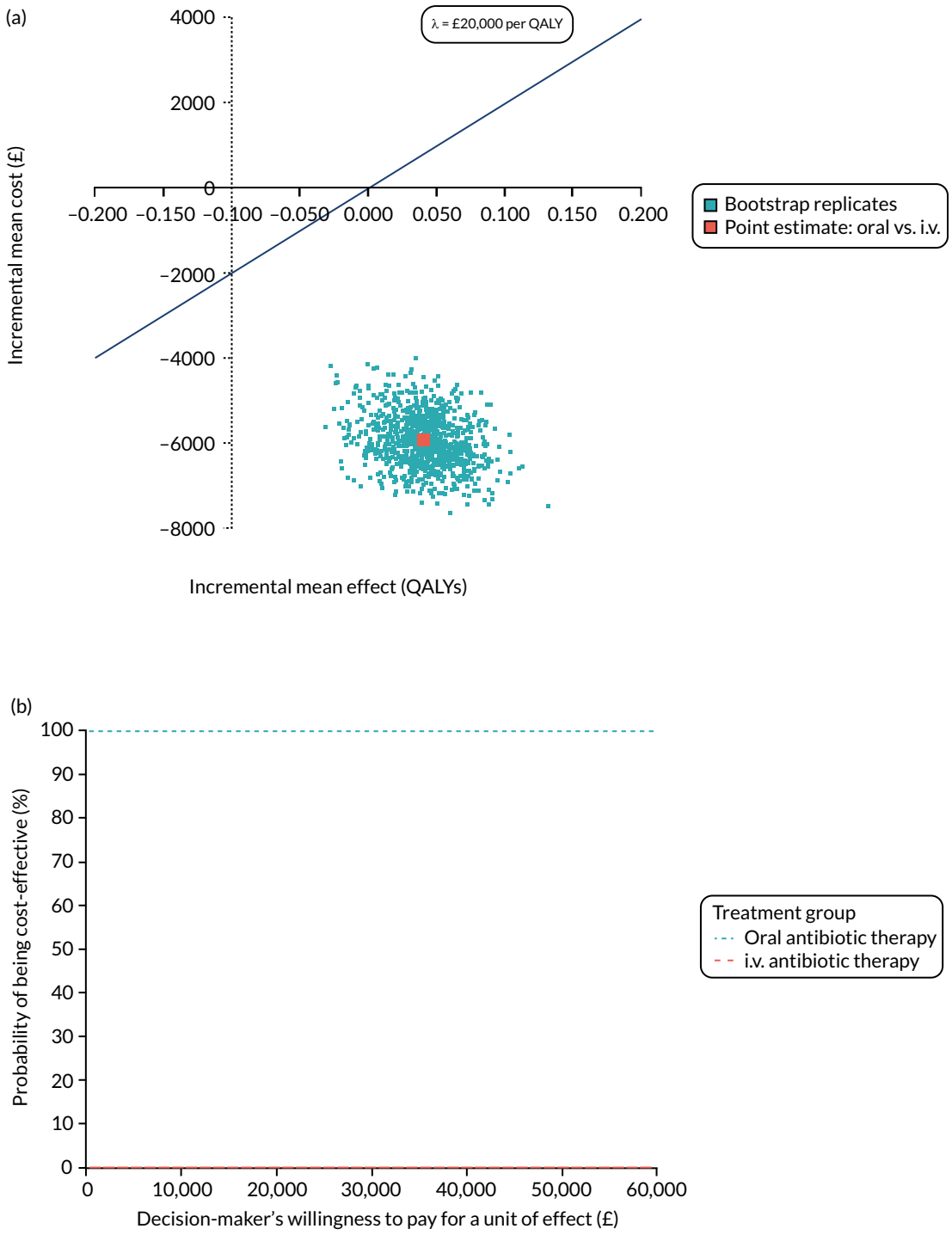


FIGURE 41 Secondary analysis: 15-month horizon QALYs, societal perspective costs, covariate adjusted. (a) Incremental cost-effectiveness plane; and (b) CEAC.

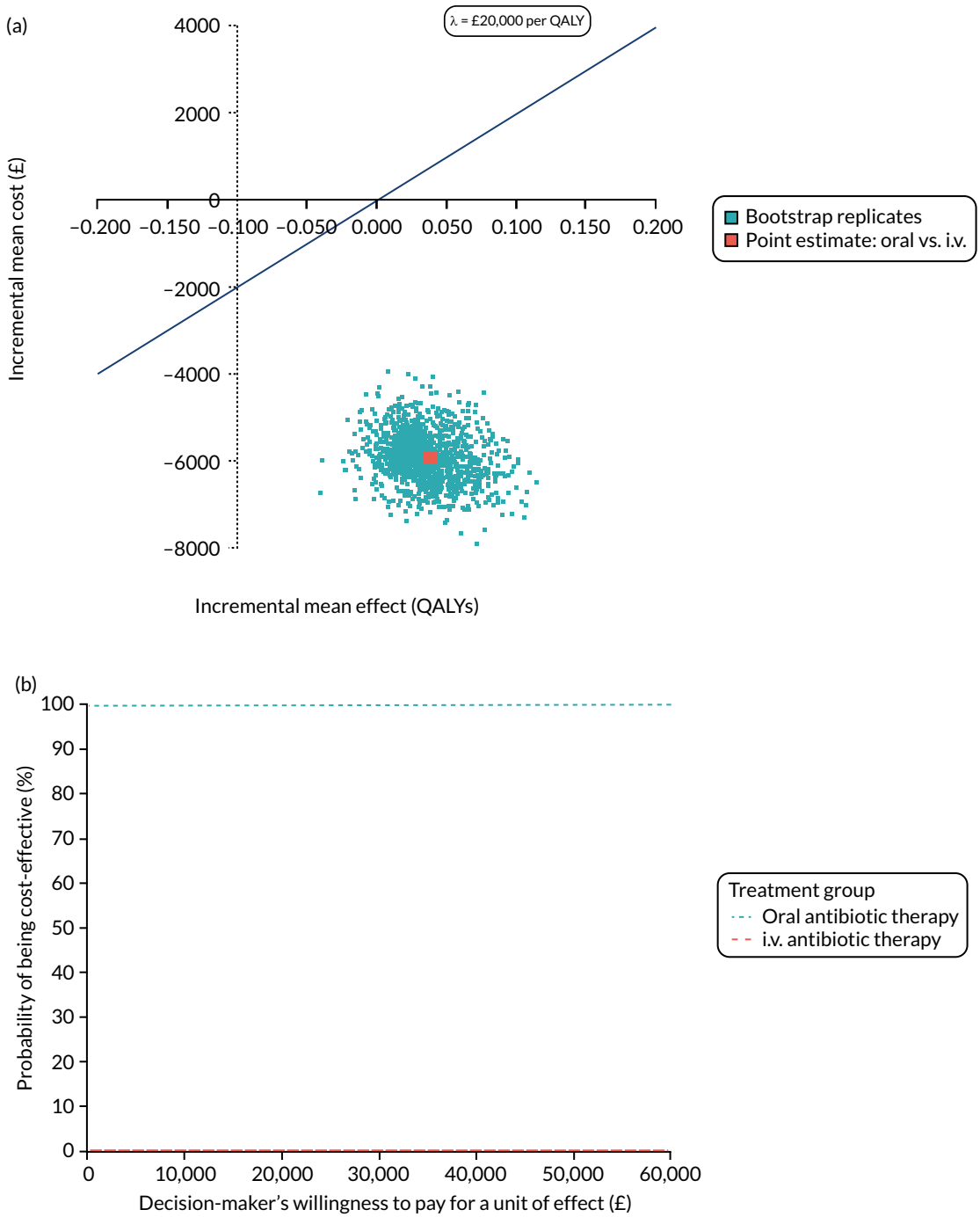


FIGURE 42 Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, covariate adjusted, GLM cost model [link(log); family (Gaussian)]. (a) Incremental cost-effectiveness plane; and (b) CEAC.

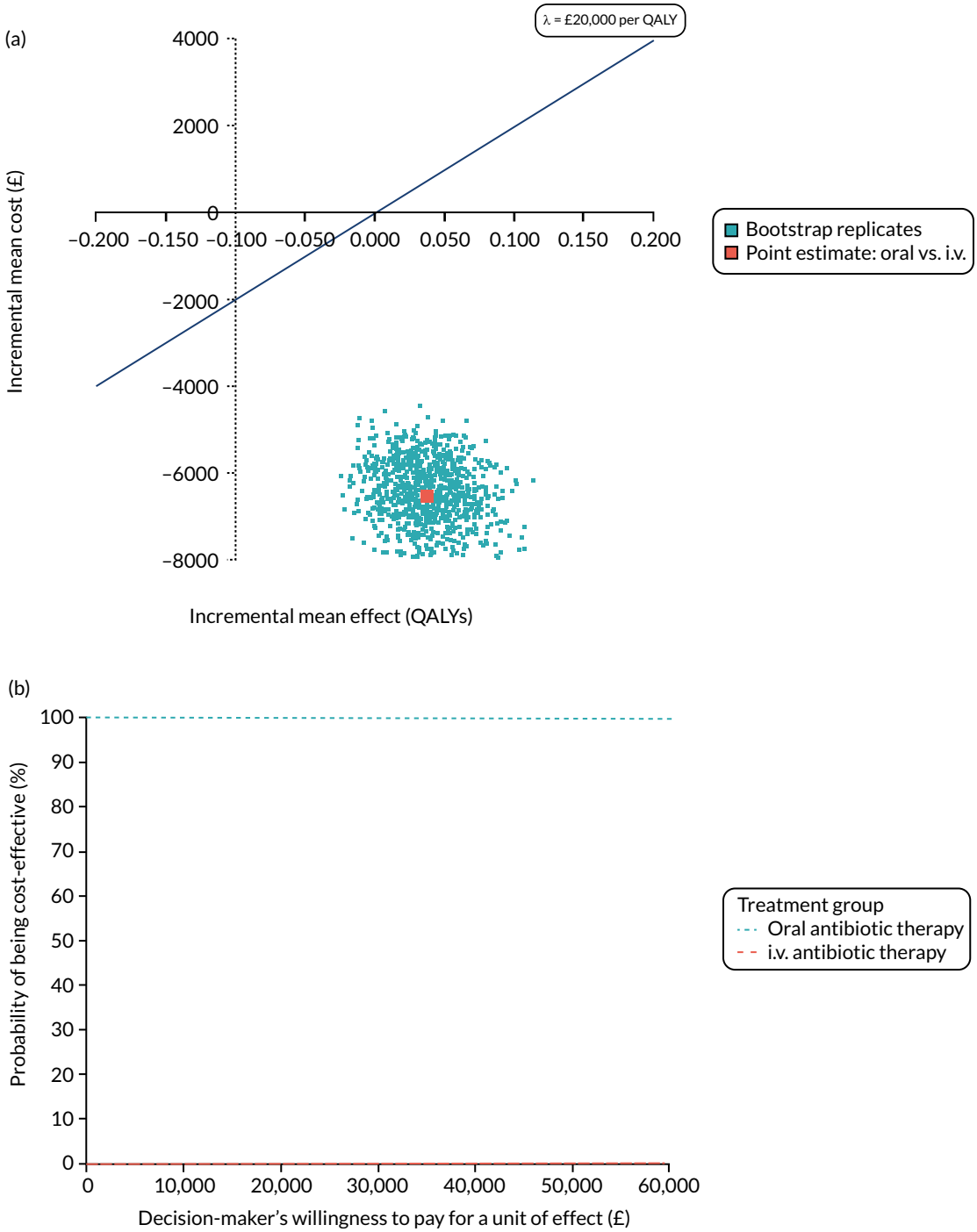


FIGURE 43 Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, covariate adjusted, GLM cost model [link(log); family (inverse Gaussian)]. (a) Incremental cost-effectiveness plane; and (b) CEAC.

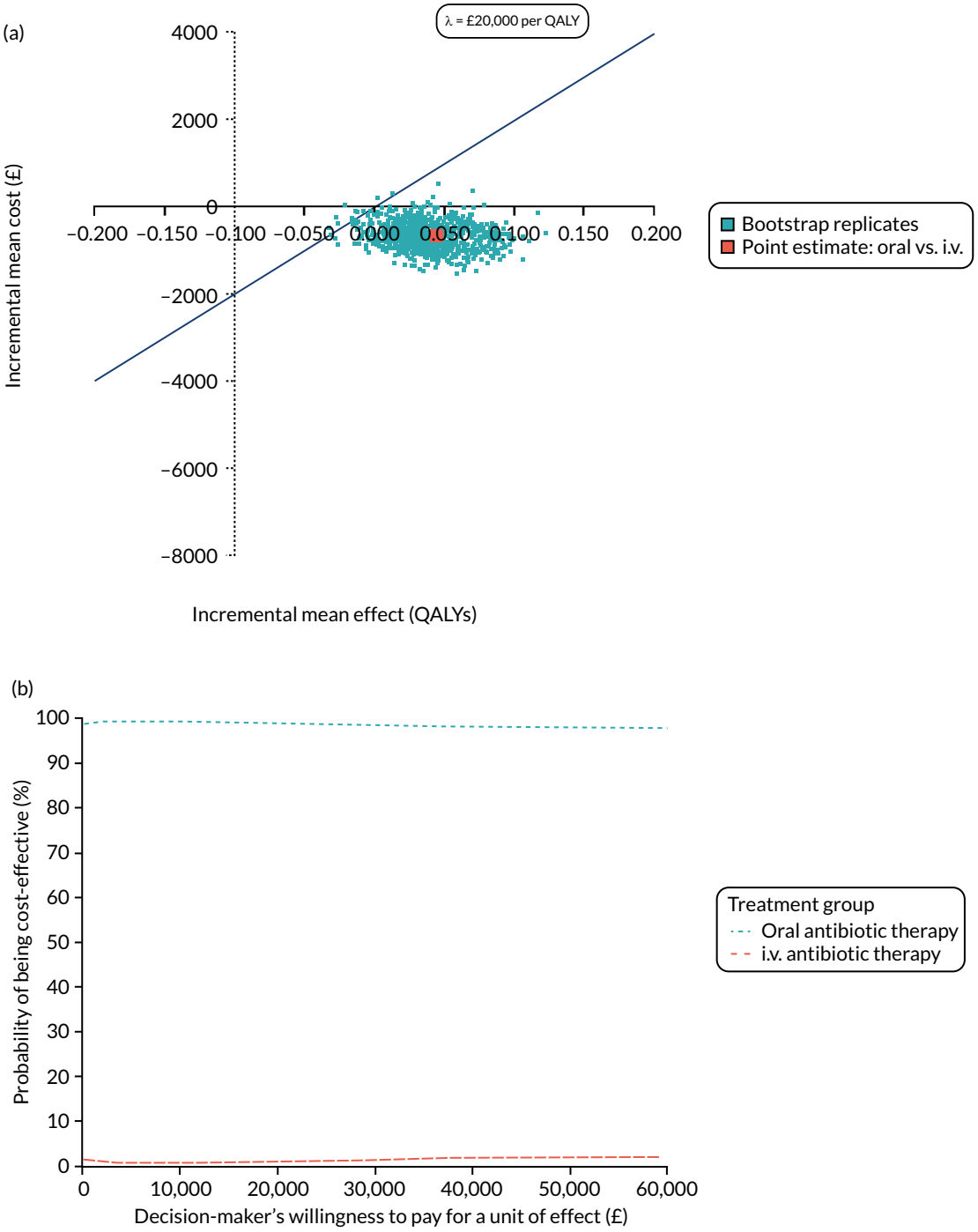


FIGURE 44 Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, CF HRG, covariate adjusted, GLM cost model [link(log); family (Gaussian)]. (a) Incremental cost-effectiveness plane; and (b) CEAC.

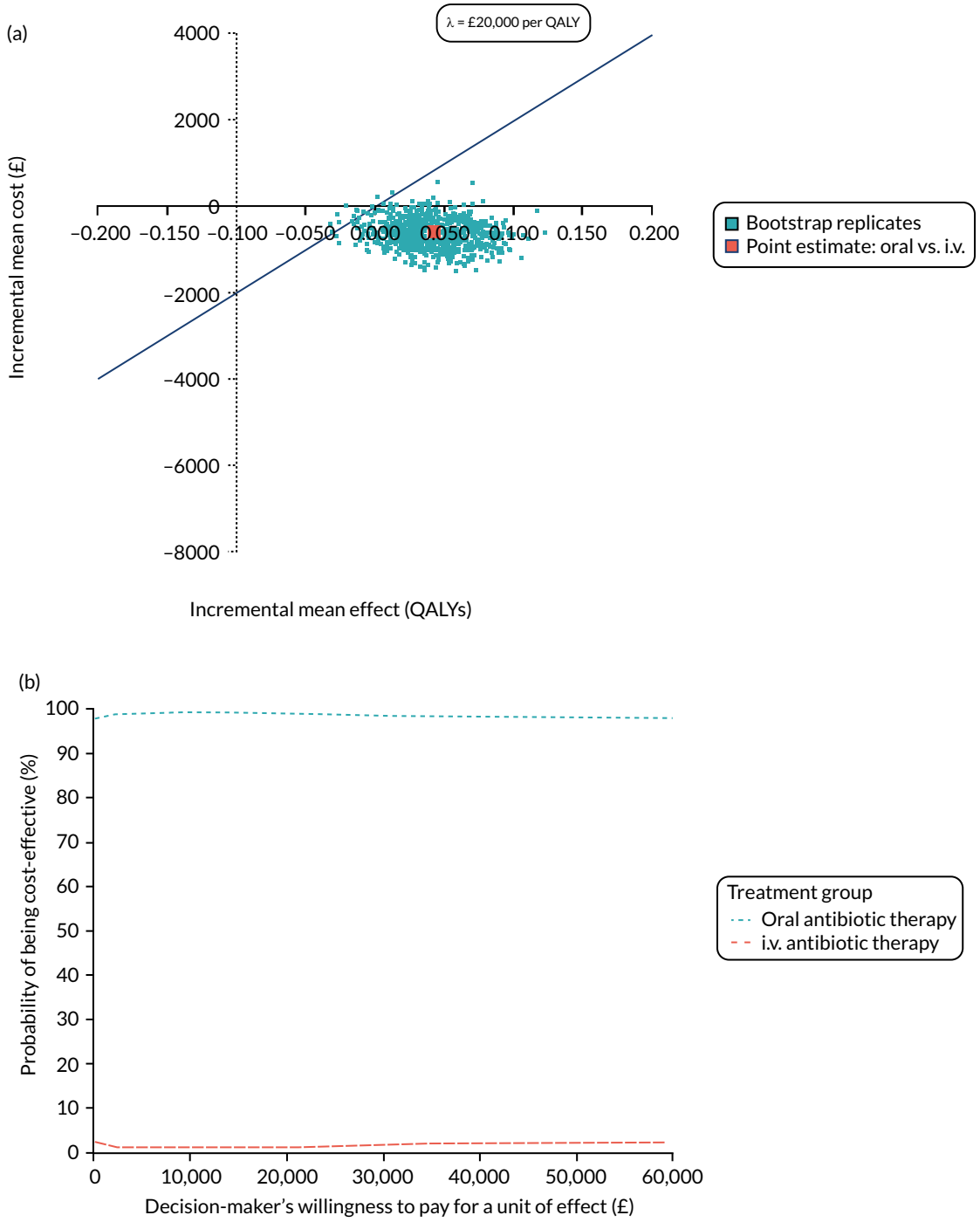


FIGURE 45 Secondary analysis: 15-month horizon QALYs, NHS and PSS perspective costs, CF HRG, covariate adjusted, GLM cost model [link(log); family (inverse Gaussian)]. (a) Incremental cost-effectiveness plane; and (b) CEAC.

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