National Institute for Health Research

TORPEDO-CF – Trial of Optimal TheRapy for Pseudomonas EraDicatiOn in Cystic Fibrosis

Eudract No. 2009-012575-10

Trial registration: ISRCTN02734162

Statistical Analysis Plan

Version 2.0 21/09/2018

	ORIGINATED BY	QC PERFORMED BY	APPROVED BY
Name	Michaela Brown	Laura Sutton	Paula Williamson
Title	Trial Statistician	CTRC Statistician	Head of department
Date	21/09/2018		
Protocol Version and Date	V9.0 21/10/2016		

1 Change Control

Protocol version	Updated SAP version no.	Section number changed	Description of change	Date changed
9.0	2.0	15.0	Clarification that the protocol deviation relating to treatment non-compliance should be based on a cut-off of 120 doses (out of 168 doses) for the Ciprofloxacin arm to be consistent with the cut-off of 10 out of 14 days of treatment for the IV arm. This was a recommendation from the blind review.	23/08/18
9.0	2.0	17.2	Age removed from the baseline characteristics table as a continuous variable and presented only as a categorical variable. %predicted FEF_{25-75} and O_2 saturation added to the baseline characteristics table. All continuous baseline characteristics to be presented as mean and standard deviations. These were recommendations from the blind review. Also, CFQ quality of life measures removed from baseline characteristics table as it is not possible to combine different domains into a total score. Minor amendments to the presentation of genotyping data consistent with the way data has been captured.	23/08/18
9.0	2.0	17.4.1.1	Clarification added that • For a sample to be classed as the T3 sample for the primary outcome analysis it must be taken within 4 weeks either side of the expected T3 visit date and the patient must have stopped treatment at least 2 days before this • For a sample to be classed as the T15 sample for the primary outcome analysis it must be taken within 4 weeks either side of the expected T15 visit date • Patients who do not have a sample within the T3 window defined above will not be included in the analysis of eradication at 3 months. • Patients who do not have a sample within the T15 window and have not previously grown *P. Aeruginosa* within the primary outcome window will be excluded from the primary outcome analysis. These were recommendations from the blind review.	23/08/18
9.0	2.0	17.4.2.3 .2	Results to be presented at specific time points rather than as change from baseline. This was a recommendation from blind review. Also wording added to say that co-efficients from the model will be presented to be consistent with the report shell document and wording added to clarify that a treatment group*time interaction term would be added to the model.	23/08/18
9.0	2.0	17.4.2.9 .2	Results to be presented at specific time points rather than as change from baseline. This was a recommendation from blind review. Also wording added to clarify that a treatment group*time interaction term would be added to the model.	23/08/18

9.0	2.0	19.1	Sensitivity analyses 1 and 2 amended to include all patients that have been followed up past 3 months but not had a sample taken within the 15 month window Sensitivity analysis 3 amended to include patients that have been followed up longer than 15 months but did not have a sample within the 15 months. These patients will be classified as success or failure dependent on the next sample that was taken following the 15 month window. An additional sensitivity analysis added where a logistic regression model adjusted for centre as a random effect will be fitted to investigate heterogeneity across sites.	23/08/18
9.0	2.0	17.4.2.1.2	Wording added to explain that two analyses will be performed assuming extreme cases for patients who did not have required samples assessed for genotyping. This was a recommendation from blind review.	21/09/18
9.0	2.0	17.4.2.2.2	Wording removed that said analysis would be repeated separately for each genotype. This was a recommendation from blind review.	21/09/18

2 Approval and Agreement

SAP Version Number being approved: 2.0

Trial Statistician

Name _____

Signed _____ Date _____

Senior Statistician* [Senior statistician has seen unblinded data so has not written this SAP. Duty delegated to independent statistician who has not seen unblinded data.]

Name _____

Signed _____ Date _____

Chief Investigator/clinical lead

Name _____

Signed _____ Date _____

Name _____

Signed _____ Date _____

OR Electronic approval attached ☐

3 Roles and Responsibilities

M Brown (CTRC, Department of Biostatistics, University of Liverpool): Trial Statistician; B Arch (CTRC, Department of Biostatistics, University of Liverpool): Statistician; P Williamson (CTRC, Department of Biostatistics, University of Liverpool): Head of Department; S Langton Hewer (Department of Cystic Fibrosis and Paediatric Respiratory Medicine, University Hospitals Bristol NHS Foundation Trust): Chief Investigator; A Smyth (Department of Child Health, Queens Medical Centre Nottingham): Chief Investigator.

Author's contributions

B Arch proposed the statistical analysis plan (SAP) building on the outlined analyses set out in the study protocol. MB updated the SAP in relation to recommendations made during the blind review of the data. P Williamson read and reviewed the SAP and helped with questions relating to the analysis. S Langton Hewer and A Smyth read, reviewed, and approved the SAP.

4 List of Abbreviations and Definitions of Terms

AR	Adverse reaction
BC	*Burkolderia cepacia*
bd	Twice daily
CF	Cystic Fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CRF	Case report form
EoT	End of treatment
IDSMC	Independent Data and Safety Monitoring Committee
IQR	Inter-quartile range
ITT	Intention-to-treat
MP	Monitoring Plan
MRSA	Meticillin-resistant Staphylococcus aureus
od	Once daily
QoL	Quality of Life
SAE	Serious adverse event
SD	Standard deviation
Tds	Three-times daily
IV	Intravenous

Contents

5 Statement of Compliance

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned final analyses for the study TORPEDO-CF: “Trial of Optimal Therapy for Pseudomonas Eradication in Cystic Fibrosis”. The planned statistical analyses described within this document are compliant with those specified in brief within the TORPEDO-CF protocol version 9.0 21/10/2016.

This study is carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, Clinical Trials Research Centre (CTRC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

This SAP comprehensively describes the planned final analyses.

This study is a clinical trial of a medicinal product and is registered on the EudraCT database. The statistical analysis plan has been developed to support the posting of results on the EudraCT system. This is a regulatory requirement which should be fulfilled within 6 months after the end of the study as defined within the clinical trial protocol.

The results of the final analysis described within this statistical analysis plan will be contained within a statistical analysis report. This report will be used as the basis of the primary research publications according to the study publication plan.

All analyses are performed with standard statistical software (SAS v9.3 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and SOP TM021 Archiving procedure in CTRC. The testing and validation of the statistical analysis programs will be performed following SOP ST001.

6 Background and Rationale

The full rationale for undertaking the trial and trial background are explained in detail in the protocol. To summarise, there is equipoise about the best method to eradicate *P.aeruginosa* from the lower respiratory tract. Antibiotic strategies for eradication of *P.aeruginosa* in people with cystic fibrosis (CF) have been investigated in a systematic review of randomised clinical trials which concluded that there is an urgent need for well-designed and well-executed trials which are specifically designed to examine whether antibiotic treatment of early *P.aeruginosa* infection will prevent or delay chronic infection, and result in appreciable clinical benefit to patients, without causing them harm. Additionally, the CF trust has published guidance for antibiotic treatment of CF, including treatment for eradication of newly acquired *P. aeruginosa*. This report has recommended energetic treatment for a patient who has isolated *P.aeruginosa* where cultures have previously been negative and has commented that there is no evidence favouring any particular regimen for eradication. See Section 1 of protocol for full details.

7 TORPEDO-CF Study Objectives

The primary objective of this trial is to establish whether fourteen days' intravenous ceftazidime with tobramycin is superior to three months' oral ciprofloxacin in eradicating *P.aeruginosa* in CF patients.

The primary null hypothesis is: no difference between the two treatment arms in terms of number of patients that successfully eradicate *P.aeruginosa* three months after commencing treatment and remain infection free through to 15 months after commencing treatment.

There are several secondary objectives, comparing the two treatments on a number of outcomes (see Section 9.2 below for a complete list).

8 Investigational Plan and Study Design

8.1 Overall study design and plan - description

This study is an open label phase IV, multi-centre, parallel group, 2-arm randomised controlled trial comparing fourteen days of intravenous antibiotic therapy to three months of oral antibiotic therapy for participants with CF.

8.2 Treatments studied

Full descriptions of the treatments and dose guidelines can be found in Section 6.1 of the protocol. In brief:

Arm A: 14 days* intravenous (IV) antibiotics as follows:

- Ceftazidime in 3 divided doses three-times daily (tds) (or alternatively a once/twice daily continuous infusion)
- Tobramycin once daily (od) (maximum 660mg /day) (or alternatively a two/three-times daily regimen)

**Recommended treatment duration should be 14 days, minimum treatment duration should be no less than 10 days*

Arm B: 3 months** oral ciprofloxacin twice daily (bd).

Both treatment arms will also receive 3 months** of nebulised colistin in conjunction with the randomised treatments.

***Three months is defined as 12 weeks*

8.3 Treatment compliance

For Arm A, *Treatment CRF – Ceftazidime/Tobramycin* records information on serum creatinine concentration prior to first tobramycin dose administration and tobramycin serum trough concentration prior to second dose administration and after one week of treatment.

- For patients that receive IV treatment as an inpatient, duration of IV treatment and amount of drug given is recorded on *Treatment CRF – Ceftazidime/Tobramycin*. The CRF: *Treatment diary 1* records whether each colistin dose was taken.
- For patients that receive IV treatment at home, *Treatment diary 2* records whether each dose of each treatment (ceftazidime, tobramycin and colistin) was taken.
- For patients that receive IV treatment in hospital and then at home, data will be a combination of both diary 1 and 2 so will need to be extracted from both CRFs and then combined.

For Arm B, *Treatment diary 3* records whether each ciprofloxacin and colistin dose was taken.

Patients on both arms are asked to return any unused drugs; this is captured on the CRFs: *Treatment compliance Arm A* and *Treatment compliance Arm B*. Full details of how treatment compliance is monitored is given in the protocol, Section 6.8.

8.4 Patient population studied

8.4.1 Inclusion criteria

The inclusion criteria can be found in Section 4.1 of the protocol.

8.4.2 Exclusion criteria

The exclusion criteria can be found in Section 4.2 of the protocol.

8.4.3 Removal of patients from therapy or assessment

Patients are free to withdraw from trial follow-up at any point, patients who do so will have data collected up to the point of withdrawal included in analyses unless they explicitly state that this is not their wish. Reasons for withdrawal will be captured where provided. See Section 14.2 below.

8.5 Consent process

Prospective consent is taken prior to patients being randomised into the trial. Further information on the consent process can be found in the Section 10.3 of the protocol.

8.6 Blinding

This is an open label trial due to the differences in the administrations of drugs in the different treatment arms.

8.7 Method of assignment to treatment

Patients are allocated to a treatment group based on a 1:1 randomisation procedure. Randomisation is stratified by clinic (adults/paediatrics) within centre but because of the low recruitment targets at sites, small block sizes were required to ensure balance across treatment groups. To ensure allocation concealment the sites are not aware that the randomisation lists are stratified and therefore the randomisation number is sequential across all sites rather than within sites. Randomisation lists were generated in STATA using block randomisation with random variable block length. To further reduce predictability of allocations, all lists used an initial block size of 3. A secure 24-hour web based randomisation programme controlled centrally by the Medicines for Children Clinical Trials Unit (MC CTU) is used to ensure allocation concealment.

8.8 Sequence and duration of all study periods

Figure 1 in the protocol provides a schematic of the trial design.

8.9 Schedule of assessments

Table 3 in Section 7 of the protocol outlines the schedule of assessments.

Note that for the purpose of this trial, a 'month' is defined as 28 days. Visits should have occurred as follows:

	Scheduled study visit	**Time after treatment start**
T_3	3 months	12 weeks
T_6	6 months	24 weeks
T_9	9 months	36 weeks
T_{12}	12 months	48 weeks
T_{15}	15 months	60 weeks
T_{18}	18 months	72 weeks
T_{21}	21 months	84 weeks
T_{24}	24 months	96 weeks

Due to large numbers of visits occurring outside of appropriate visit windows and not consistently being captured on scheduled or unscheduled visit CRFs; where outcomes refer to specific time points, data will be included based on dates of assessments rather than CRF names. For an assessment to be associated with a particular time-point it must have occurred within 1 week either side of the expected visit date, apart from T_{15} which may be minus 1 week or plus 2 weeks of the expected visit date.

Not all patients were followed up after T_{15}. T_{18}, T_{21} and T_{24} were proposed in the protocol up to and including version 7. Patients randomised after 1st January 2016 were required to complete up to and including T_{15} only.

9 Listing of Outcomes

9.1 Primary outcome

Successful eradication of *P.aeruginosa infection* three months after allocated treatment has started, and remaining infection free through to 15 months after the start of allocated treatment.

9.2 Secondary outcomes

1. Time to reoccurrence of original *P.aeruginosa* infection
2. Re-infection with a different genotype of *P.aeruginosa*
3. Lung function - FEV_1 , FVC, FEF_{25-75} ,
4. O_2 saturation
5. Growth and nutritional status – height, weight and body mass index
6. Number of pulmonary exacerbations[1]
7. Admission to hospital
8. Number of days spent as an inpatient in hospital during treatment phase and between three and fifteen months after randomisation[2].
9. Quality of life (CFQ)
10. Utility (EQ-5D)
11. Adverse events
12. Other sputum/cough Microbiology (Methicillin resistant *Staphylococcus aureus* (MRSA), *Burkholderia cepacia* complex, Aspergillus, Candida Infection)
13. Cost per patient (from NHS perspective)
14. Incremental cost effectiveness ratio (cost per successfully treated patient, cost per QALY)
15. Carer burden (absenteeism from education or work)
16. Participant burden (absenteeism from education or work)

[1] Defined according to Rosenfeld criterion [4]

[2] Protocol wording for this outcome 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-finished (other than 14 days spent on initial IV treatment)". Changed above to aid clarity.

10 Determination of Sample Size

Section 8.4 of the protocol provides further details on the sample size considerations.

11 Study Framework

The overall objective for each of the study outcomes (primary and secondary) is to test the superiority of fourteen days intravenous ceftazidime with tobramycin compared with three months oral ciprofloxacin.

12 Confidence Intervals, p-values and Multiplicity

All applicable statistical tests will be two-sided and will be performed using a 5% significance level; confidence intervals presented will be 95%. No adjustment will be made for multiplicity for the secondary outcomes.

13 Timing and Objectives of Interim and Final Analyses

13.1 Interim monitoring and analyses

No formal interim analyses of primary or secondary outcomes will be performed but analyses of the accumulating data (recruitment, protocol deviations, baseline characteristics, compliance, withdrawals, missing data and safety data) will be performed at regular intervals (at least annually) for review by an IDSMC, as outlined in the IDSMC charter.

13.2 Final analysis

The final analysis for all outcomes will take place after the end of the trial, which is defined in Section 7.6 of the protocol as the date of final database lock. At this point, data for all participants is frozen and data entry privileges are withdrawn from the trial database.

14 Disposition of Participants

A CONSORT flow diagram [5] will be used to summarise the number of patients who were:

- assessed for eligibility at screening
  - eligible at screening
  - ineligible at screening*
- eligible and randomised
- eligible but not randomised*
- received the randomised allocation
- did not receive the randomised allocation*
- lost to follow-up*
- discontinued the intervention*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

See Figure 1 below.

*reasons will be provided.

14.1 Screening, eligibility and recruitment

Screening logs will be summarised by site in a table detailing:

(i) the number of patients who were assessed for eligibility at the screening visit;

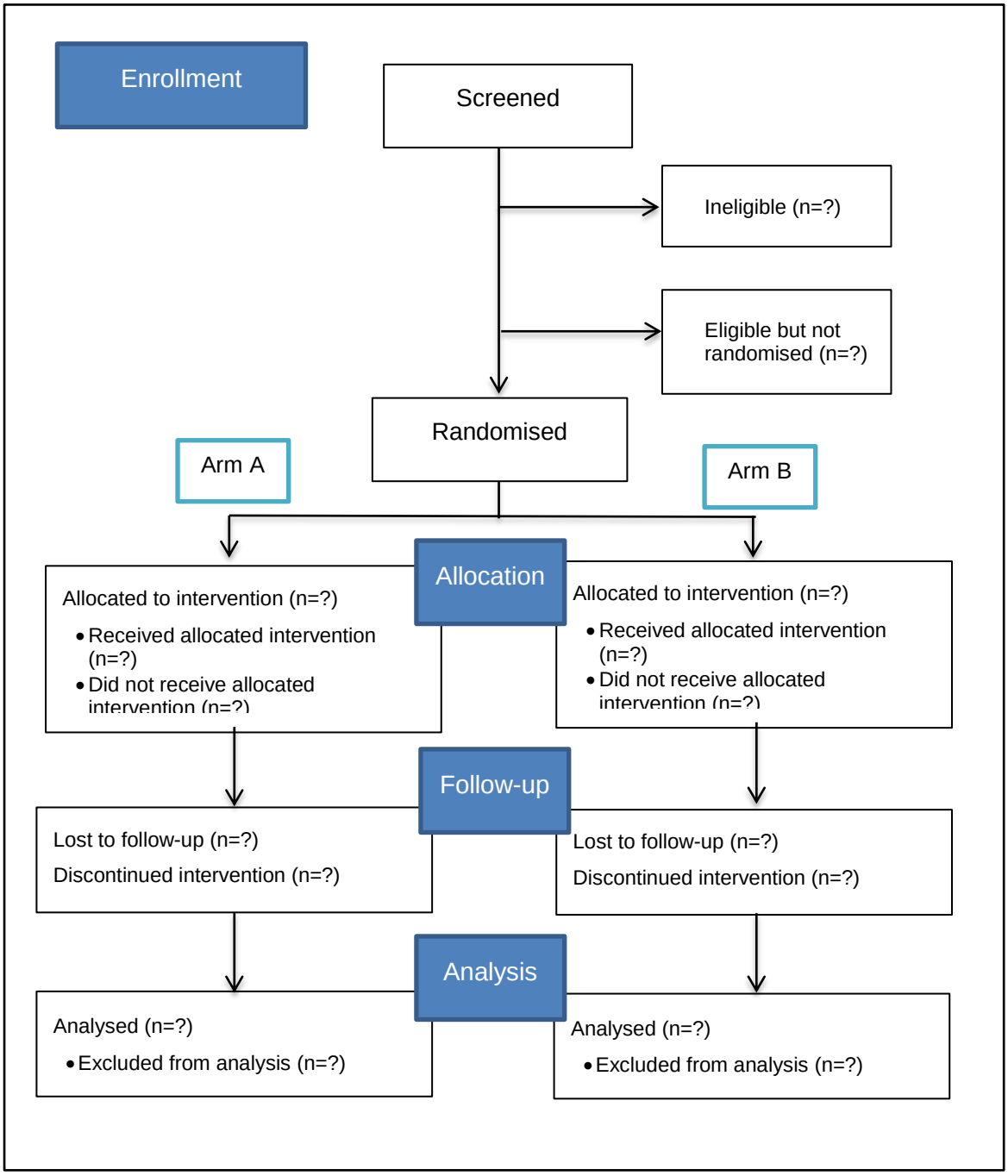
(ii) those who did not meet the study inclusion criteria at screening (expressed as a frequency and a % with the denominator being all patients screened [(i)];

(iii) those who were eligible at screening and were not approached for consent, (expressed as a frequency and a % with the denominator being all eligibles [(i) - (ii)];

(iv) those who were approached and consent not obtained, (expressed as a frequency and a % with the denominator being all eligible that were approached for consent [(i) - (ii) - (iii)];

(v) those randomised (expressed as a frequency and a % with the denominator being the total that consented [(i) – (ii) – (iii) – (iv)].

Figure 1: Consort Diagram



Reasons for ineligibility will be summarised overall in a table with the following categories:

- Younger than 28 days of age
- Known to be pregnant
- Not *P.aeruginosa* free
- Not able to commence treatment within 21 days from the date of a *P.aeruginosa* positive microbiology report
- Antibiotic resistance of the current *P.aeruginosa* sample to any of: ciprofloxacin, ceftazidime, tobramycin or colistin reported by local microbiology laboratory
- Receiving *P.aeruginosa* suppressing treatment for the treatment of *P. aeruginosa*, in particular: nebulised colistin or tobramycin, or oral ciprofloxacin for the previous 9 months
- Known hypersensitivity to either ciprofloxacin, ceftazidime, tobramycin or colistin
- Other known contraindications to any of ciprofloxacin, ceftazidime, tobramycin or colistin including previous aminoglycoside hearing or renal damage
- Had treatment with other anti-pseudomonal nebulisers
- Previously randomised into TORPEDO-CF study
- Participated in another intervention trial within the last four weeks
- Poor compliance with previous medication/s
- Other reason

Frequencies will be presented.

Reasons for patients not being approached will be summarised overall in a table with the following categories:

- Clinician decision
- Family circumstances
- No bed available
- Patient missed
- Patient transferred
- Social concerns
- No one available to consent
- Didn’t understand English
- Other reason
- No reason given

Frequencies will be presented.

Reasons for consent declined will be summarised overall in a table with the following categories:

- Didn’t want IV treatment
- Didn’t want oral treatment
- Didn’t want to attend follow-up
- Didn’t want to be involved in research
- Didn’t want to be randomised
- Didn’t want to receive the eradication therapy

- Family circumstances
- Other reason
- No reason given

Frequencies will be presented.

A recruitment summary table will be presented showing the following for each centre: centre code, hospital name, dates site opened/closed to recruitment, dates of first/last randomisation and total number randomised.

14.2 Post randomisation discontinuations

The *End of Treatment* (EoT) CRF will capture patients that discontinue treatment prematurely. These patients will still be followed up and have data collected unless they withdraw consent for this.

Patients with an EoT CRF will have reasons for discontinuing treatment recorded. These will be summarised overall within treatment arm with the following categories:

- Adverse event
- Serious adverse event
- Pregnancy
- Lost to follow-up
- Death
- Withdrawn consent
- Other

Frequencies will be presented along with percentages using the number of patients that prematurely discontinued treatment as the denominator. Information will also be presented on who took the decision for the patient to discontinue treatment prematurely.

Patients who withdraw from the trial will be captured in *Withdrawal* CRFs. Reasons for withdrawal, where known, will be summarised overall and within treatment arm with the following categories:

- Adverse event
- Serious adverse event
- Pregnancy
- Lost to follow-up
- Death
- Withdrawn consent
- Other

Frequencies will be presented along with percentages using the number of patients that were withdrawn as the denominator. Information will also be presented on who took the decision for the patient to withdraw.

A blind review of withdrawals will be carried out: information on patients who do not have complete primary outcome data will be provided to reviewers: days to withdrawal (from randomisation), and reasons for withdrawal; and also patients who have a 15 month visit out of the specified T_{15} window. A decision will be made as to whether these patient can either be included in the primary analysis or could be included in a further sensitivity analysis based on the data that they have available. Other outcomes may also be presented for blind review, especially where time of withdrawal may potential lead to a bias in results.
Following blind review, this SAP will be adapted if necessary to apply additional sensitivity analyses modelling longitudinal outcomes jointly with time-to-withdrawal.

15 Protocol Deviations

Protocol deviations that will be reported will be defined in the monitoring plan for the trial. Protocol deviations are classified prior to unblinding of treatment to the statistical team. All protocol deviations will be defined and signed-off using ST001TEM04 Protocol deviations and population exclusions template prior to unblinding. Protocol deviation classifications are taken from the Monitoring Plan (MP) V2.0 (date 05/05/2015). For the protocol deviation 'Treatment non-compliance', patients will be classified as deviating if they have received less than 10 days of IV treatment or less than 120 doses of Ciprofloxacin (equivalent compliance rate to IV arm).

For each treatment arm, the number (and percentage) of patients with each separate protocol deviation will be presented in this analysis report along with the number (and percentage) of patients with (i) at least one major protocol deviation; (ii) at least one minor protocol deviation; and (iii) at least one protocol deviation of any classification (minor or major). No formal statistical testing will be undertaken.

16 Unblinding

This section is not applicable as TORPEDO is an open-label trial.

17 Efficacy Evaluations

17.1 Data sets analysed

The principle of intention-to-treat, as far as practically possible, will be the main strategy of the analysis adopted for the primary outcome and all the secondary outcomes. These analyses will be conducted on all randomised participants, in the group to which they were allocated, and for whom the outcome(s) of interest have been observed/measured. No imputations will be made.

The membership of the analysis set for each outcome will be determined and documented and reasons for participant exclusion will be given prior to the blind being broken and the randomisation lists being requested. Reasons may include missing data, loss to follow up.

Participants to be excluded from analysis populations will be defined in template ST001TEM04: Protocol deviations and data set definitions, agreed and approved prior to any release of randomisation code.

17.2 Demographic and other baseline characteristics

Summary statistics for baseline variables will be calculated for the ITT dataset, split by treatment group to check that randomisation has worked – i.e. that the treatment groups are balanced. Baseline characteristics to be summarised are described in Tables 1 and 2. Table 1 details continuous baseline variables to be reported, and Table 2 details categorical baseline variables.

Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by total (n), mean and SD. Tests of statistical significance will not be undertaken; rather the clinical importance of any imbalance will be noted.

Note: Known reasons for missingness of baseline data will be summarised.

Table 1: Continuous baseline variables to be reported

Variable	Unit of measurement	Precision (decimal places)	CRF where data are recorded
BMI z-score (participants registered at paediatric centres)	-	2	Derived from height and weight data contained in Baseline CRF. See Section 17.4.2.5.1 below for derivation.
BMI (participants registered at centres treating adults)	m/kg^2	1	Derived from height and weight data contained in Baseline CRF. See Section 17.4.2.5.1 below for derivation.
Time from Pseudomonas isolation to treatment initiation*	days	0	Baseline – Section 3: date of report confirming *P.aeruginosa* isolation. Treatment CRFs, Section 1: date started treatment / date started.
%predicted FEV_1 (participants aged 5 or older only)	litres	2	Raw FEV_1 data contained in Baseline CRF. See Section 17.4.2.3.1 below for derivation.
%predicted FVC (participants aged 5 or older only)	litres	2	Raw FVC data contained in Baseline CRF. See Section 17.4.2.3.1 below for derivation.
%predicted FVC_{25-75} (participants aged 5 or older only)	litres	2	Raw FVC data contained in Baseline CRF. See Section 17.4.2.3.1 below for derivation.
O_2 Saturation	%	2	Baseline

*Calculated as the number of days from the date of report confirming *P.aeruginosa* isolation to the date of treatment commencement.

Table 2: Categorical baseline variables to be reported

Variable	Categories	CRF where data are recorded
Age-group[(a)]	Infants and toddlers (28 days – 23 mths) Children (2-11 yrs) Adolescents (12-17 yrs) Adult: 18-64 yrs Elderly adult: ≥ 65 yrs	*Derived from continuous value obtained from* Baseline CRF
Gender	Male Female	Baseline
Pseudomonas status	Naïve Free	Baseline
Other microorganisms detected	Candida MRSA Burkholderia cepacia Aspergillus Other organisms	Microbiology (see Section 17.4.2.12.1 below for derivation)
Genotype	F508/F508 F508/other F508/unknown other/other Diagnosis not based on genetics	Baseline
Pulmonary Exacerbation	Yes No	Baseline (see Section 17.4.2.6.1 below for derivation)

[(a)] EudraCT defined age-groups – these are different to the categorisations/definitions used in the rest of the study

17.3 Compliance with treatment

Arm A: Serum creatinine concentration prior to first tobramycin dose administration and tobramycin serum trough concentration prior to second dose administration and after one week of treatment will be presented. Reasons for any tests not being done will be summarised if provided.

The number of doses of ceftazidime that patients receive varies as some sites offer three times daily dosing and others twice daily dosing. The number of doses of tobramycin also varies as some sites offer once daily dosing, some offer twice daily dosing and some offer three times daily dosing. For this reason and because it is stated in the protocol that patients should receive at least 10 days of treatment, compliance for these drugs will be presented in terms of the number of days on treatment rather than the number of doses received.

Arm B: The protocol defines treatment duration for Ciprofloxacin as 3 months. This may be interpreted by clinicians as 3x28 days or 3x30 days. For the purposes of calculating compliance, the Chief Investigator has defined this as 3x28 days. This means that each patient should receive 168 doses (based on them receiving two doses daily). The number of doses patients actually received is recorded in the treatment diary. The compliance rate is calculated by dividing number of doses actually received by the number of doses that a patient should have received (168).

All: To calculate the number of Colistin doses a patient should have received, the number of days between treatment commencement date and the three month visit date will be calculated and multiplied by 2 (based on them receiving two doses daily). The number of doses patients actually received is recorded in the treatment diary. The compliance rate is calculated by dividing number of doses actually received by the number of doses that a patient should have received.

All compliance data will be summarised by total (n), mean, SD, median, interquartile range, range, minimum and maximum regardless of whether the data are normal or skewed. No formal statistical testing will be undertaken.

17.4 Analysis of outcomes

17.4.1 Primary outcome

The primary outcome is successful eradication of *P. aeruginosa* three months after the start of treatment, remaining infection free through to 15 months after the start of treatment (Yes/No).

17.4.1.1 Derivation

The CRF: *Microbiology Form* captures information on samples taken at all attended visits (scheduled and unscheduled). The variable MBDSTD gives the date the sample was taken, and the variable MBOC6C indicates that *P. aeruginosa* was cultured if it is selected (MBOC6C =”Pseudomonas aeruginosa”).

Success: If there is no record of *P. aeruginosa* on a patient’s microbiology CRF between 3 months and 15 months after treatment commencement.
Failure: If there is at least one record of *P. aeruginosa* on a patient’s microbiology CRF between 3 months and 15 months after treatment commencement.

Any positive sample (MBOC6C =”Pseudomonas aeruginosa”)			**Outcome**
<3 months	**3-15 months**	**>15 months**	
×	×	×	Success
×	×	✓	Success
✓	×	×	Success
✓	×	✓	Success
×	✓	×	Fail
×	✓	✓	Fail
✓	✓	×	Fail
✓	✓	✓	Fail

To determine if a patient has eradicated *P. Aeruginosa* at 3 months, they must have a sample within 28 days either side of the expected 3 month visit date (treatment commencement date + 84 days) which is at least 2 days after the last date of any anti-pseudomonal treatment.

To determine if a patient has remained *P. Aeruginosa* free at 15 months, they must have either a positive sample within the primary outcome window (3-15 months) or they must have a sample within 28 days either side of the expected 15 month visit date (treatment commencement date + 420 days).

Patients who have not regrown *P. Aeruginosa* and do not have a sample within the 15 month window (defined above) will not be included in the primary analysis. If a patient is withdrawn before 15 months of follow-up is completed, they will only be included in the primary outcome analysis if they have failed. If there is no evidence that they have failed prior to being withdrawn they will not be included in the primary analysis.

17.4.1.2 Analysis

The number of patients who are classified as (a) a success and (b) failure for the primary outcome (and percentages) will be presented for each treatment arm. The relative risk together with 95% confidence interval will be reported along with a two-sided p-value from a chi-squared test. The number and percentage of patients who had a positive sample at their 3-month follow-up visit will also be presented for each treatment arm.

17.4.2 Secondary outcomes

17.4.2.1 Time to reoccurrence of original *P.aeruginosa* infection

Only patients who have a baseline sample and at least one sample post three months will be included in this analysis.

17.4.2.1.1 Derivation

Patients will be categorised with a censoring indicator variable E:

E =

0: no recurrence of original *P.aeruginosa* until last available follow-up date; or

1: *P.aeruginosa* infection has recurred i.e. if and only if genotype of at least one re-infection sample = genotype of baseline infection sample

A time to event (T) in months will be calculated for each patient as $T = T_1 – T_0$, where

T_0 = date of randomisation (CRF: *Treatment CRF*, variable: TATRDTD for patients on IV treatment, OCDTCPSD for patients on oral treatment)

If E=0:

T_1 = date of last available follow-up visit (CRF: *Follow-up*, variable: FUVISITD)

If E=1:

T_1 = date of first sample taken during follow-up which indicates E=1 (CRF: *Microbiology Form*, variable: MBDSTD.

17.4.2.1.2 Analysis

The outcome T will be presented graphically using Kaplan-Meier curves, stratified by treatment group. E=0 denotes a censored observation. Difference between the two treatment arms will be tested using the log-rank test. If there is imbalance in the randomisation, Cox proportional hazards regression may be used to calculate a hazard ratio with 95% CI, comparing the IV treatment group to oral, whilst adjusting for baseline variables for which there is imbalance. From inspection of the Kaplan-Meier plot the separation between the curves should remain proportional across analysis time. If the curves cross again this shows that the proportional hazards assumption has been violated. To put this formally, the proportional hazards assumption is that the ratio of hazards is a constant that does not depend on time:

$$\frac{h_A(t)}{h_B(t)} = r \qquad \text{[Eq1]}$$

When this assumption fails, it is because the hazard ratio changes over time. To test this, we will add predictor for (treatment arm)*time interaction i.e. a time-dependent covariate. Evidence that (treatment arm)*time interaction is not zero is evidence against proportional hazards. In SAS, PROC PHREG provides the p-value of this test. p<0.05 will indicate non-proportional hazards and thus a time-dependent covariate will be included in the Cox model. If p<0.05 it may not be possible to present result from which conclusions may be drawn.

Update following blind review:

Two analyses of this outcome will be performed. The first analysis will assume that all patients who do not have both a baseline sample and a follow up sample in the time window of interest (T3 to T24) sent for genotyping did not have a reoccurrence of the original *P.aeruginosa* strain (E=0). The second analysis will assume that these patients did have the original *P.aeruginosa* strain reoccur (E=1).

17.4.2.2 Re-infection with a different genotype of *P.aeruginosa*

17.4.2.2.1 Derivation

This outcome is derived using the Microbiology CRF, and includes only samples taken at or after T_3 or at or before T_{15}. A binary variable: *P.aeruginosa* infection with a different genotype of *P.aeruginosa* is defined as: genotype of at least one re-infection sample ≠ genotype of baseline infection sample, Yes/No. Where the genotype of the baseline sample is unknown / not available, it will not be possible to derive this outcome.

17.4.2.2.2 Analysis

The number and percentage of patients who are infected with a different type of *P.aeruginosa* during the first 12 months post treatment phase will be presented (from T_3 to T_{15}), split by treatment group. The denominator is the total number of patients within each treatment arm for whom the outcome is derivable. The relative risk together with 95% confidence interval will be reported along with a two-sided p-value from a chi-squared test. The Fisher's exact test may be used if the chi-squared test is not appropriate (counts of <5 within categories).

17.4.2.3 Lung function – FEV_1, FVC, FEF_{25-75}

According to the protocol, spirometry is not routinely carried out in those under 5 years of age although the global lung function initiative states it is valid for patients aged 3-95. To avoid confusion, only participants aged 5 or older will be included in this analysis.

17.4.2.3.1 Derivation

Three raw spirometry measurements FEV_1, FVC, and FEF_{25-75} are taken at each visit. These are recorded at baseline (CRF: *Baseline*, Variables: BLFEV1R, BLFVCR and BLFEV25I); at follow-up (CRF: *Follow-up*, Variables: FUFEV1R, FUFVCR and FUFEV25I); and at unscheduled visits (CRF: *Unscheduled Visit*, Variables: UVFEV1R, UVFVCR and UVFEV25I).

For the purpose of this analysis, all available lung function measurements will be included.

These are converted to clinically useful measures: %predicted FEV_1, %predicted FVC, and %predicted FEF_{25-75} using a SAS macro available from the global lung initiative [7] which requires as input the participants' raw measurements, their age at the visit (derived from date of visit: FUVISITD or UVVISITD and date-of-birth: FUDOBD or UVDOBD), and their height at the visit (for scheduled visits, this is recorded in FUHGHTR; for unscheduled visits height is not recorded – therefore height should be taken from the closest scheduled visit CRF).
A time variable (days from randomisation) will be derived as Visit Date minus Randomisation Date.

17.4.2.3.2 Analysis

% predicted FEV_1 (%PredFEV1)

Summary statistics (total [n], mean, SD, median, interquartile range, range, minimum and maximum) will be presented split by treatment at three key time-points: T_3, T_{15} and T_{24}. Only data from scheduled visits at these time-points will be included.
A repeated measures random effects model will be fitted. The dependent variable will be post baseline %PredFEV1. Covariates will be: baseline %PredFEV1, treatment group, time and an interaction term (treatment group*time). A special power covariance structure will be used, under the assumption that the correlation between repeated measurements weakens the greater the time between measurements.
Co-efficients from the model will be presented and a single p-value will be reported testing whether the effect of treatment group is significant over the whole follow-up period.
The mean (SE) %PredFEV1 at 3 months, 15-months and 24 months with 95% confidence intervals as predicted by the fitted model will be reported for each treatment group. The mean

difference between the two treatment groups in %PredFEV1 at 15 months will be presented together with a 95% CI.

% predicted FVC

As for FEV_1 above.

% predicted FEF_{25-75}

As for FEV_1 above.

Reasons for spirometry not being performed will be summarised, where available.

17.4.2.4 O_2 saturation

17.4.2.4.1 Derivation

Oxygen saturation is measured at baseline (BLO2SATI), at each three monthly follow up visit (FLO2SATI) and any unscheduled visits that may occur (UVO2SATI). No manipulation of these variables is required.

17.4.2.4.2 Analysis

The analysis of O_2 saturation is identical to the analysis of %predicted FEV_1 described in 17.4.2.3.2 above.

17.4.2.5 Growth and nutritional status – height, weight and body mass index

Growth is only relevant for children that are still growing, and the age at which children stop growing is different for every child. This study's participants include infants, children, adolescents and adults. For this outcome, it is important to use appropriate measurements for each age-group to capture how growth and nutritional status may have been affected by treatment received. There is no one global measurement that can be used for all ages. For this reason, separate analyses are proposed for children and adults: BMI z-score, height z-score and weight z-score in children; and BMI for adults. The centre type paediatric/adult at randomisation will be used to define child/adult for the purpose of analysis.

17.4.2.5.1 Derivation

Children

Height (cm) (BLHGHTR, FUHGHTR), weight (kg) (BLWGHTR, FUWGHTR) and age (date of visit minus date of birth) are measured at baseline and at each three monthly follow up visit, respectively. Body mass index (BMI) will be calculated using the standard equation:

$$\text{BMI} = \frac{\text{weight}}{(\text{height}/100)^2} \qquad \text{[Eq2]}$$

where height is measured in cm. The WHO 0-60 months of age reference curves [8] will be used to convert BMI to BMI z-scores in children aged less than 5. A SAS macro from WHO [9] will be used for all conversions. The WHO 5-19 years of age reference curves [10] will be used to obtain BMI z-scores for children aged 5-19. A SAS macro from WHO [11] will be used for all conversions. Height and weight reference curves [10] will be used to obtain height and weight z-scores.

Adults

Height (cm) (BLHGHTR, FUHGHTR), weight (kg) (BLWGHTR, FUWGHTR) are measured at baseline and at each three monthly follow up visit, respectively. Body mass index (BMI) will be calculated as in Eq2 above.

17.4.2.5.2 Analysis

Children

The analyses of height, weight and BMI z-scores are identical to the analysis of %predicted FEV_1 described in 17.4.2.3.2 above.

Adults

The analysis of BMI is identical to the analysis of %predicted FEV_1 described in 17.4.2.3.2 above.

17.4.2.6 Number of pulmonary exacerbations

At the design stage of this study, classification of a pulmonary exacerbations (Y/N) was defined using guidelines by Rosenfeld [4] and data collection was designed to enable this classification to be made.

17.4.2.6.1 Derivation

Pulmonary exacerbations are defined using guidelines by Rosenfeld [4]. They propose a score system for deciding whether the patient is experiencing a pulmonary exacerbation. The score is calculated as follows:

$$PE_{score} = 1.8 \times \mathrm{I}_1 + 1.5 \times \mathrm{I}_2 + 1.5 \times \mathrm{I}_3 + 1.6 \times \mathrm{I}_4 + 1.2 \times \mathrm{I}_5 + 1.1 \times \mathrm{I}_6 - 3.1 \quad \text{[Eq3]}$$

where I_1 = 1 if decreased exercise tolerance 'present'; 0 otherwise

I_2 = 1 if increased cough 'present'; 0 otherwise

I_3 = 1 if increased sputum/cough congestion 'present'; 0 otherwise

I_4 = 1 if school or work absenteeism 'present'; 0 otherwise

I_5 = 1 if increased adventitial sounds on lung examination 'present'; 0 otherwise

I_6 = 1 if decreased appetite 'present'; 0 otherwise.

If the PE_{score} > 2.6 then the patient is experiencing a pulmonary exacerbation.

If any indicators I_1 – I_6 are coded as missing for whatever reason, they will be assigned the value 0 on the assumption that if the symptom is absent.

Pulmonary exacerbations criteria are captured at baseline and on all follow up visit CRFs along with any unscheduled visit CRFs that may be completed. They relate to the 2 weeks prior to the follow-up visit.

The total number of exacerbations recorded per child during the first 15 months of follow-up is the number of visits for which PE_{score} > 2.6. Note, we expect that all exacerbations will be measured, as they would usually result in the need for an unscheduled visit.

17.4.2.6.2 Analysis

The number of exacerbations during the first 15 months follow-up will be summarised with median and interquartile range for each treatment arm. A Mann-Whitney U-test will test whether the distribution of number of exacerbations is the same in each treatment arm. The number and percentage of patients experiencing at least one exacerbation in each treatment arm will also be reported. Treatment groups will be compared using the chi-squared test. The Fisher's exact test may be used if the chi-squared test is not appropriate (counts of <5 within categories).

17.4.2.7 Admission to hospital

17.4.2.7.1 Derivation

Each follow-up visit CRF (scheduled and unscheduled) records whether the participant has had any inpatient stays since the last visit. At least one admission to hospital since last follow-up visit is recorded if FUINPTVC='Yes' for scheduled visits, and with UVINPTVC='Yes' for unscheduled visits.

Admission to hospital is split into admission to hospital during three discrete time-periods of interest:

A: During treatment phase (Baseline to T_3)

B: 12 months post treatment phase (T_3 to T_{15})

C: During the remainder of follow-up (T_{15} to T_{24}) [where applicable]

There are therefore three admission to hospital outcomes Y_A, Y_B, and Y_C.

Define Y_A, Y_B, and Y_C:

(1) **Y_A**: There was at least one hospital admission during the treatment phase (not including any relating to IV treatment if in Arm A of trial) (T_0-T_3)

(2) **Y_B**: There was at least one hospital admission during the first 12 months of follow-up (T_3-T_{15})

(3) **Y_C**: There was at least one hospital admission during the remainder of follow-up (T_{15}-T_{24}) [where applicable]

As long as scheduled visits occur at T_3 and T_{15} (and if applicable T_{24}) the following table gives the derivation for each outcome:

Outcome	Success criteria	Failure criteria	Assumption
Y_A	At least one CRF dated at T_3 or earlier reports a hospital admission	No CRFs dated at T_3 or earlier report hospital admission	Scheduled visit at T_3 took place
Y_B	At least one CRF dated after T_3 and at or before T_{15} reports a hospital admission	No CRFs dated after T_3 and at or before T_{15} report hospital admission	Scheduled visits at T_3 and T_{15} took place
Y_C	At least one CRF dated after T_{15} and at or before T_{24} reports a hospital admission	No CRFs dated after T_{15} and at or before T_{24} report hospital admission	Scheduled visits at T_{15} and T_{24} took place

Uncertainty regarding time-period that hospital visit occurred in

Where any of the key scheduled visits are missing (T_3, T_{15}), the next available unscheduled/scheduled visit will act as proxy for the missing visit. However, as dates are not provided for when hospital stays take place, there is uncertainty as to which period of interest to assign reported hospital stay. For the purpose of this analysis, we will assume that all reported hospital stay occurs in the period of interest **most** likely.

Example: an unscheduled visit takes place at 3.5 months reporting inpatient stay. No scheduled visit took place at 3 months. The patient's previous visit took place at 2 months. It is therefore uncertain whether some or all of the reported hospital stay took place during the treatment phase, or in the first 12 months after treatment. The 3.5 month visit data relates to a 1.5 month period, and >50% of this is during the treatment phase. Therefore we will say that the hospital stay is more likely to have occurred in the treatment phase.

17.4.2.7.2 Analysis

The number and percentage of participants having had at least one hospital stay during the first 3 months of treatment, and during the first year after treatment will be reported. The number and percentage of participants who had at least one hospital stay after T_{15} will also be reported – the denominator will be the number of patients within each treatment arm that were followed up until T_{24}.

The relative risk with 95% CI of experiencing at least one hospital stay during each time-period of interest will be presented. A chi-squared test will be used to calculate a p-value for this relative risk. Note that if hospital stays are rare, a Fisher's exact test may be needed to calculate the p-value, or it may be the case that no test is possible.

Sensitivity analysis:

The analysis will be re-run under the assumption that where there is uncertainty about which period hospital stay occurred in, all reported hospital stay occurs in the time-period **least** likely. The results of both analyses will be compared. If the results lead to different conclusions, the limitations of the data collection methodology should be highlighted in any reporting of this outcome.

17.4.2.8 Number of days spent as an inpatient in hospital during treatment phase and between three and fifteen months after randomisation[3].

17.4.2.8.1 Derivation

Each follow-up visit CRF (scheduled and unscheduled) records the number of days the participant has had any inpatient stays since their last visit. Length of time hospitalised since last follow-up visit is recorded in FUINPTWI and FUINPTDI for scheduled visits and UVINPTWI) and UVINPTVI for an unscheduled visit.

Length of time hospitalised is split by three discrete time-periods of interest:

A: During treatment phase (Baseline to T_3)

B: 12 months post treatment phase (T_3 to T_{15})

C: during the remainder of follow-up [if applicable]

There are therefore three length-of-time hospitalised outcomes Y_A, Y_B, and Y_C.

Define Y_A, Y_B, and Y_C:

(1) $\mathbf{Y_A}$: Number of days hospitalised during the treatment phase (not including any relating to IV treatment if in Arm A of trial) (T_0-T_3)

(2) $\mathbf{Y_B}$: Number of days hospitalised during the first 12 months of follow-up (T_3-T_{15})

(3) $\mathbf{Y_C}$: Number of days hospitalised during remainder of follow-up (T_{15}-T_{24}) [if applicable]

As long as scheduled visits occur at T_3 and T_{15} [and if applicable T_{24}] the following table gives the derivation for each outcome:

Outcome	Derivation	Assumption
Y_A	Sum of all weeks and days hospitalised from CRFs dated at T_3 or earlier, expressed in days	Scheduled visit at T_3 took place
Y_B	Sum of all weeks and days hospitalised from CRFs dated after T_3 and at or before T_{15}, expressed in days	Scheduled visits at T_3 and T_{15} took place
Y_C	Sum of all weeks and days hospitalised from CRFs dated after T_{15} and at or before T_{24}, expressed in days	Scheduled visits at T_{15} and T_{24} took place

[3] Protocol wording for this outcome 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-finished (other than 14 days spent on initial IV treatment)". Changed above to aid clarity.

It is possible that some CRF data will span two time-periods due to follow-up visits taking place outside of the per-protocol specified window. In these cases, linear interpolation will be used to estimate the total number of days spent in each time-period. This estimate will be added to the known total number of days from the forms that do not incur uncertainty, to get a total for each time-period.

Example: an unscheduled visit takes place at 3.5 months reporting 5 days of inpatient stay. No scheduled visit took place at 3 months. The patient's previous visit took place at 2 months, where 2 days hospitalisation were recorded. It is therefore uncertain whether some or all of the reported hospital stay reported at 3.5 months took place during the treatment phase, or in the first 12 months after treatment. The 3.5 month visit data relates to a 1.5 month period. Therefore on average, one day of hospital stay took place every 0.3 months. So we interpolate that 3.3 visits took place during the treatment phase, and 1.7 took place during the first 0.5 months of follow-up. Adding to the data from the 2-month visit, we have an estimated total of 5.3 days stay for the treatment phase.

17.4.2.8.2 Analysis

The number of patients with hospital stays and their median, interquartile range and minimum and maximum total length of stay will be calculated for each treatment arm and each time-period. A Mann-Whitney test will be used to detect differences between treatment groups for each time-period of interest.

Two sensitivity analyses will be carried out: in each case where linear interpolation is needed (1) assume that all time spent hospitalised refers to the most probable time-period (so in the example assume that all 5 days recorded at 3.5 month visit occurred in the treatment phase; (2) assume that all time spent hospitalised refers to the least probable time-period (so in the example assume that all 5 days recorded at 3.5 month visit occurred during follow-up.

17.4.2.9 Quality of life (CFQ)

The Cystic Fibrosis Questionnaire - Revised (CFQ-R) is a disease specific measure of health related quality of life (QoL) for children (aged 6 and over), adolescents and adults with cystic fibrosis. It covers nine quality of life domains, and three symptom scales.

The participant is asked to indicate their response to each question by ticking the most appropriate statement. Questions responses all have 4 possible responses. These are coded 1 to 4 from left to right or top to bottom.

There are three versions of the questionnaire:

- **CFQ-R Teen/Adult Version** (aged 14 and over) - this is a self-administered questionnaire and consists of 50 questions. Participants are asked to complete the questionnaire alone in a quiet room.
- **CFQ-R Child version** (children aged 6-13 years) – this questionnaire consists of 35 questions. For participants aged 12 and 13 years, it is a self-administered questionnaire and they are asked to complete the questionnaire alone in a quiet room. For participants aged 6 to 11 years, it is an interviewer-administered questionnaire whereby the research nurse reads out the questions to the participant and asks them to hold up coloured cards as their response to the questions.
- **CFQ-R Parent Version** (children aged 6-13 years) – this is a self-administered proxy questionnaire to be completed by the parent or caregiver and consists of 44 questions.

See Table 3 below for details of which domains and symptom scales are measured in each questionnaire and how many questions relate to each.

NB There is no CFQ-R questionnaire available for children aged <6 years, therefore patients of this age are excluded from this analysis.

17.4.2.9.1 Derivation

The CFQ-R data are collected within the questionnaire booklet CRFs: Adolescents & Adults; Children aged 12 or 13; Children aged 6-11; and Parent/care-giver.

There are four time-points for data collection: baseline, T_3, T_{15} and (if applicable) T_{24}. For each time-point, a total of 23 domain response variables will be calculated using the scoring system developed for the CFQ [12]. 8 of these are derived by combining data from the two self-completed questionnaires; 4 of these relate only to teens/adults (health perceptions, role functioning, vitality and weight); 11 are derived from the parent/carer questionnaire.

A handful of questions' scores are reversed at the derivation stage: these are indicated in the scoring system guidelines. All response variables are derived by finding the mean score of question responses within a domain, subtracting 1, and then multiplying by 3/100 to obtain a standardised 0-100 scale.

A categorical time-point variable will be created with values 0,1,2,3 or 4 denoting whether the response is measured at baseline, T_3, T_{15} or T_{24} resp.

Missing data: the guidelines suggest that where less than half of questions have been answered within a domain, then the score for the domain will be treated as missing.

Table 3: Number of questions asked, corresponding to each domain/scale within each questionnaire

	Self-report		
Domain/Scale	**Teen/Adult (>13)**	**Child (6-13)**	**Parent/Carer**
Physical functioning	8	6	8
Role/school functioning	4	-	4
Vitality	4	-	5
Emotional functioning	5	8	5
Social functioning	6	7	-
Body Image	3	3	3
Eating problems	3	3	2
Treatment Burden	3	3	3
Health perceptions	3	-	3
Weight	1	-	1
Respiratory symptoms	7	4	7
Digestive symptoms	3	1	3
Total number of questions	50	35	44

17.4.2.9.2 Analysis

For each of the 23 domains:

A mixed-effects model for repeated measures will be fitted, with an unstructured covariance matrix. The baseline measurement of the domain will be fitted as a covariate along with

treatment group, time-point as a categorical variable and an interaction term (treatment group*time). The following will be reported: mean (SD) for each treatment group; mean (95% CI) difference between treatment groups at T_{15} (derived from the model); and a p-value of the treatment effect. A plot of mean (SE) for each time-point, by treatment group will be presented.

17.4.2.10 Utility (EQ-5D)

17.4.2.10.1 Derivation

The derivation of this outcome will be described in the health economics analysis plan.

17.4.2.10.2 Analysis

The analysis of this outcome will be described in the health economics analysis plan.

17.4.2.11 Adverse events

See Section 20 below.

17.4.2.12 Other sputum/cough Microbiology (Methicillin resistant *Staphylococcus aureus* (MRSA), *Burkholderia cepacia* complex, Aspergillus, Candida Infection)

17.4.2.12.1 Derivation

All microorganisms detected at each visit are recorded in the CRF: *Microbiology*. MRSA, *Burkholderia cepacia* complex (BC) and Candida are listed in the CRF explicitly and are identified by the variables MBOC3C='Yes', MBOC4C='Yes' and MBOC2C='Yes' respectively. All other detected organisms (other than *P.aeruginosa*) are recorded in the variable MBOCT. The date of detection of a microorganism is recorded by the variable MBDSTD.

For the time-period: 1st 15 months post randomisation, the following four outcome variables will be derived:

(1) MRSA = 1 if there is at least one instances where MBOC3C='Yes' and date of detection < 15 months post randomisation;

= 0 otherwise

(2) BC = 1 if there is at least one instances where MBOC4C='Yes' and date of detection < 15 months post randomisation;

= 0 otherwise

(3) Candida = 1 if there is at least one instances where MBOC2C='Yes' and date of detection < 15 months post randomisation;

= 0 otherwise

(4) Asp = 1 if there is at least one instances where MBOCT contains 'Aspergillus' and date of detection < 15 months post randomisation;

= 0 otherwise

17.4.2.12.2 Analysis

For each microorganism, the number and percentage with at least one positive result will be presented split by treatment arm, and a relative risk and 95% confidence interval calculated. Chi-squared tests (or if necessary Fisher's exact test) will be used to test for differences between treatment groups.

Secondly, for each microorganism: the number and percentage with at least one positive result during the treatment phase; and by 15 months will be presented split by treatment-arm. Of those that were followed up to T_{24}, and for each microorganism, the number and percentage with at least one positive result by T_{24} will be presented split by treatment-arm.

Chi-squared tests will be used to test for differences between treatment groups.

Other organisms detected will be listed as a frequency table split by treatment arm. Frequencies presented will be the number of children with at least one positive culture of the organism during the study.

17.4.2.13 Cost per patient (from NHS perspective)

17.4.2.13.1 Derivation

The derivation of this outcome will be described in the health economics analysis plan.

17.4.2.13.2 Analysis

The analysis of this outcome will be described in the health economics analysis plan.

17.4.2.14 Incremental cost effectiveness ratio (cost per successfully treated patient, cost per QALY)

17.4.2.14.1 Derivation

The derivation of this outcome will be described in the health economics analysis plan.

17.4.2.14.2 Analysis

The analysis of this outcome will be described in the health economics analysis plan.

17.4.2.15 Carer burden (absenteeism from education or work)

17.4.2.15.1 Derivation

Carer burden is the self-reported measure of absenteeism from education or work because of caring responsibilities. It is measured at each follow-up visit – scheduled and unscheduled.
Absenteeism from work is given as a binary outcome by FUPTOWVC and as a length of time by FUPTOWVI (weeks) and FUPTODVI (days) for scheduled visits. The respective variables for unscheduled visits are UVPTOWVC, UVPTOWVI (weeks) and UVPTODVI (days).
Absenteeism from education is given as a binary outcome by FUPTOEVC and as a length of time by FUPTOEWI (weeks) and FUPTOEDI (days) for scheduled visits. The respective variables for unscheduled visits are UVPTOEVC, UVPTOEWI (weeks) and UVPTOEDI (days).

If the scheduled visit at T_{15} does take place, we can derive:
A binary variable X measuring carer absenteeism from education/work during the first 15 months (from baseline to T_{15}) will be derived as follows:

X=1 if a participant had at least one day off work or missed at least one day of education during any follow-up visit (scheduled or unscheduled) taking place on or before the scheduled visit at T_{15} (FUPTOWVC='Yes' or FUPTOEVC='Yes' or UVPTOWVC ='Yes' or UVPTOEVC ='Yes')

X=0 otherwise

A length of time variable Y measuring carer days of absenteeism from education/work during the study (from baseline to T_{15}) will be derived as follows:

Y = (FUPTOWVI + UVPTOWVI + FUPTOEWI + UVPTOEWI) x 7

+ (FUPTODVI + UVPTODVI + FUPTOEDI + UVPTOEDI) added up for all visits taking place after the scheduled visit on or before the scheduled visit at T_{15}

If the scheduled visit at T_{15} does not take place, there is ambiguity as to whether carer burden reported at the next visit after T_{15} relates to pre or post T_{15} or both. The same methodology as given in 17.4.7.2.1 and 17.4.7.3.1 will be used to estimate whether the carer burden was likely to be pre T_{15} or after, and to interpolate an estimated number of days spent absent that can be attributed pre T_{15}.

17.4.2.15.2 Analysis

This outcome will be presented in two ways. Firstly, whether carers have been absent from education or work or not during the first 15 months post randomisation, will be analysed using a relative risk, presented with a 95% confidence interval and a chi squared test. Secondly, the number of days spent absent from work or education will be presented as a median with 95% confidence interval for each treatment arm, together with the interquartile range, min and max. A Mann Whitney test will be used to detect differences in the distributions of carer burden between the two treatment groups.

17.4.2.16 Participant burden (absenteeism from education or work)

17.4.2.16.1 Derivation

This is the same as for carer burden (see 17.4.2.15.1 above), but with the absenteeism binary variable derived from variables FUTOEVC, FUTOWVC, UVTOEVC and UVTOWVC; and length of time away from education and work derived from the variables FUTOEWVI, FUTOEDVI, FUTOWWVI, FUTOWDVI, UVTOEWVI, UVTOEDVI, UVTOWWVI, and UVTOWDVI.

17.4.2.16.2 Analysis

The analysis is exactly the same as described in 17.4.2.15.2 above.

18 Missing Data and Withdrawals

Explicit derivations above give methods for handling missing data and withdrawals regarding derivation of outcomes. Section 14.2 above describes how withdrawals will be reported.

19 Additional Analyses

19.1 Sensitivity analyses of to the primary outcome analysis

19.1.1 Withdrawn patients all classified as success

Derivation and analysis as in Section 17.4.1.1 and Section 17.4.1.2 but all patients who have been followed up past 3 months but not had a sample within the 15 month window will be assumed to have not had *P. Aeruginosa*.

19.1.2 Withdrawn patients all classified as failure

Derivation and analysis as in Section 17.4.1.1 and Section 17.4.1.2 but all patients who have been followed up past 3 months but not had a sample within the 15 month window will be assumed to have had *P. Aeruginosa*.

19.1.3 Results of blind review

Derivation and analysis as in Section 17.4.1.1 and Section 17.4.1.2 but all patients that have been followed up for more than 15 months but not had a sample within the 15 month window will be included. These patients will be classified as success or failure based on the next sample that was taken following the 15 month window.

19.1.4 Investigation of heterogeneity across sites

A logistic regression model adjusted for centre as a random effect will be fitted to investigate heterogeneity across sites.

19.2 Additional analyses of secondary outcomes

19.2.1 Sensitivity analysis: Time to reoccurrence of original *P.aeruginosa* infection

Derivation as in Section 17.4.2.1.1 but T_0 amended to be date of treatment commencement rather than date of randomisation. Analysis as in Section 17.4.2.1.2.

19.2.2 Time to first pulmonary exacerbation

19.2.2.1 Derivation

Derivation of pulmonary exacerbation as outlined in Section 17.4.2.6.1. Patients will be categorised with a censoring indicator variable E:

E = 0: no visits for which $PE_{score} > 2.6$; or
1: there was at least one visit during follow-up for which $PE_{score} > 2.6$.

A time to event (T) in months will be calculated for each patient as $T = T_1 – T_0$, where

T_0 = date of first treatment (CRF: *Treatment CRF*, variable: TATRDTD for patients on IV treatment, OCDTCPSD for patients on oral treatment)

If E=0:

T_1 = date of last available follow-up (CRF: *Follow-up*, variable: FUVISITD)

If E=1:

T_1 = first visit date which indicates E=1 (CRF: *Follow-up*, variable: FUVISITD).

19.2.2.2 Analysis

The time-to-first exacerbation in each treatment arm will be presented using Kaplan-Meier curves. The log-rank test will be used to test for a difference between treatment groups.

19.2.3 At least one exacerbation during a time period

19.2.3.1 Derivation

Derivation of pulmonary exacerbation as outlined in Section 17.4.2.6.1. For time-period T_A to T_B, (T_{AB}) a binary outcome variable X_{AB} will be derived:

X_{AB}=0 if for all visits during T_{AB}, E=0.

X_{AB}=1 if for at least one visit during T_{AB}, E=1.

Time periods of interest are treatment phase (1st 3 months), first year after treatment (3-15 months post randomisation) and the remainder of follow-up (15-24 months post randomisation).

19.2.3.2 Analysis

The number and percentage of participants having had at least one exacerbation during the treatment phase, during the first year after treatment, and during the 2nd year after treatment will be presented. Denominators for percentages will be the number of patients followed up during the time-period within treatment arm, in preference to the number randomised.

20 Safety Evaluations

20.1 Data sets analysed

The safety analysis data set will contain all participants that are randomised and commenced treatment.

Only AEs in line with reporting timelines in the protocol (from commencement of allocated treatment (IMP & NIMP) until 28 days after cessation of allocated treatment) will be presented. Versions 1.0-5.0 of the protocol required all SAEs to be reported as such.

20.2 Presentation of the data

All events will be MedDRA coded. The classifications will be presented in a table. The number of occurrences of each AE (at the preferred term and system organ class levels) and the number (and percentage) of patients experiencing each AE will be presented for each treatment arm and overall. A similar table will be produced for all SAEs reported under all versions of the protocol.

A cross-tabulation of AE severity by 'relationship to study drug' will be presented by treatment group and overall.

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

- SAE number
- Treatment
- Preferred term
- System organ class
- Date of onset
- Serious criteria (reporting of all that apply from 7 possible options) [PI and CI assessment]
- Severity (Mild / Moderate / Severe) [PI assessment]
- Relationship to study drug [PI and CI assessment]

- Expectedness [CI assessment]
- Most likely cause (Disease under study / Other illness / Prior or concomitant treatment / Protocol procedure / Lack of efficacy) [PI assessment]
- Outcome

For the purposes of reporting to EUDRACT, a table including only non-serious AEs will also be presented. This will report the number of occurrences of each AE (at the preferred term and system organ class levels) and the number (and percentage) of patients experiencing each AE, for each treatment arm and overall. No formal statistical testing will be undertaken.

21 References

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