



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

www.torpedo-cf.org.uk

Version 9.0 date 21/10/2016

Study Sponsor:

University Hospitals Bristol NHS Foundation Trust
Bristol Royal Children's Hospital
Upper Maudlin Street
Bristol
BS2 8BJ

EudraCT number: 2009-012575-10

ISRCTN number: ISRCTN02734162

Funder reference: HTA 07/51/01

Sponsor reference: CH/2007/2661

Co Sponsor:

University of Liverpool
Liverpool



Protocol Approval

Authorised by Chief Investigator:

Signature: _____

Date: _____

Dr Simon Langton Hewer
Consultant Respiratory Paediatrician
Department of Cystic Fibrosis and Paediatric Respiratory Medicine
University Hospitals Bristol NHS Foundation Trust
Bristol Royal Hospital for Children
Upper Maudlin Street
Bristol, BS2 8BJ

Authorised on behalf of the Sponsor:

Signature: _____

Date: _____

Diana Benton
Research and Development Department
University Hospitals Bristol NHS Foundation Trust
Bristol Royal Children's Hospital
Upper Maudlin Street
Bristol, BS2 8BJ

Authorised on behalf of the Co-Sponsor:

Signature: _____

Date: _____

Alex Astor
Research Support Office
University of Liverpool
2nd Floor Block D
Waterhouse Building
3 Brownlow Street
Liverpool, L69 3GL

Authorised on behalf of the Senior Trial Statistician:

Signature: _____

Date: _____

Ashley Jones
Medicines for Children Clinical Trials Unit, Clinical Trials Research Centre
University of Liverpool, Institute of Child Health
Alder Hey Children's NHS Foundation Trust
Liverpool, L12 2AP

General Information

This document describes the TORPEDO-CF trial and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoir or guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. Any amendment to the protocol will be circulated to the registered investigators in the trial. However, centres entering participants for the first time are advised to contact the coordinating centre: Medicines for Children Clinical Trials Unit (MC CTU), Clinical Trials Research Centre, Department of Biostatistics, Liverpool to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the Chief Investigator via the MC CTU.

Statement of Compliance

This study protocol is designed to comply with the Guideline established by the International Conference on Harmonisation (ICH) on the topic Good Clinical Practice (GCP) and published by the European Agency for the Evaluation of Medicinal Products as "Note for Guidance on Good Clinical Practice" (CPMP/ICH/135/95) (Approval 17 July 1996).

This study will be 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), Edinburgh (2000), Seoul (2008) and Fortaleza (2013)* amendments, ICH Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, MC CTU Standard Operating Procedures, EU Directive 2001/20/EC and GCP directives (2005/28/EC), transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments. Data will be collected and retained in accordance with the Data Protection Act 1998.

As per the MC CTU Standard Operating Procedures, no waivers from the TORPEDO-CF protocol will be granted.

* With regards to clause 34 of the 2013 Fortaleza amendment, post-trial access to trial treatments has not been arranged as the treatment regimens applied in the TORPEDO protocol are for a time limited period and post-trial access is not necessary. However, the trial treatments are licenced and already routinely available at sites as part of routine clinical care, and should it be considered necessary to reinstate eradication therapy outwith the trial protocol, the decision on future treatment of patients will be made locally by the treating physician.

Relationship Statements

University Hospitals Bristol NHS Foundation Trust are the Sponsoring organisation and will delegate some Sponsor responsibilities to the MC CTU, University of Liverpool and the Chief Investigator; they will be legally responsible for the UK arm of the trial. The MC CTU based in Liverpool will have overall management responsibility for the trial from a CTU perspective, and will be responsible for co-ordination of all centres.

University of Liverpool are Co-Sponsor, they will collaborate with the MC CTU and will act as sole sponsor for non-UK centres i.e. they are legally responsible for the non-UK arm of the trial.

Medicines for Children Clinical Trials Unit (MC CTU), Clinical Trials Research Centre, Department of Biostatistics:

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including medicines for paediatrics, neuroscience, pharmacogenetics, ophthalmology, infection and obstetrics and gynaecology (<http://www.ctrc.org.uk/>). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

Contact Details: Institutions

Sponsor:	Co Sponsor:	Funder:
University Hospitals Bristol NHS Foundation Trust, Trust Headquarters Marlborough Street Bristol BS1 3NU	University of Liverpool Research Support Office 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL	NETSCC, HTA Alpha House, University of Southampton Science Park, Southampton SO16 7NS Tel: +44 (0)23 8059 5586 Fax: +44 (0)23 8059 5639 Email: hta@hta.ac.uk
Management and Monitoring:	Genotyping Facility:	
Medicines for Children Clinical Trials Unit (Director: Professor Paula Williamson) Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool L12 2AP Tel: +44 (0)151 282 4724 Fax: +44 (0)151 282 4721 Email: helpdesk@mcrnctu.org.uk	Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (AMRHA) Public Health England Microbiology Services 61 Colindale Avenue London NW9 5HT Tel: +44 (0)20 8327 7724 Email: AMRHA1@phe.gov.uk	

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Co-Sponsor:	Chief Investigator (CI):
<p>Diana Benton Head of R&I Research and Development Department University Hospitals Bristol NHS Foundation Trust Level 3 Education Centre Upper Maudlin Street Bristol BS2 8AE Tel: +44 (0)117 343 0233/0266 Fax: +44 (0)117 342 0239 Email: Diana.Benton@uhbristol.nhs.uk</p>	<p>Alex Astor Head of Research Support Office – Faculty of Health and Life Sciences Research Support Office University of Liverpool 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: +44 (0)151 794 8739 Email: sponsor@liv.ac.uk</p>	<p>Dr Simon Langton Hewer Consultant Respiratory Paediatrician Department of Cystic Fibrosis and Paediatric Respiratory Medicine University Hospitals Bristol NHS Foundation Trust Bristol Royal Hospital for Children Upper Maudlin Street Bristol BS2 8BJ Tel: +44 (0)117 342 8258 Fax: +44 (0)117 342 8494 Email: simon.langtonhewer@bris.ac.uk</p>
<p>Medical Expert who will Advise on Protocol Related Clinical Queries and evaluate SAE reports (In the absence of CI):</p>	<p>Statistics team:</p>	
<p>Professor Alan Smyth Professor of Child Health Department of Child Health E Floor East Block Queens Medical Centre Nottingham NG7 2UH Tel: +44 (0)115 823 0612 Email: alan.smyth@nottingham.ac.uk</p>	<p>Professor Deborah Ashby Chair in Medical Statistics and Clinical Trials Divisions of Epidemiology, Public Health & Primary Care VC10 Norfolk Place St Mary's Campus Tel: +44 (0)20 7594 8704 Email: Deborah.ashby@imperial.ac.uk</p>	<p>Mr Ashley Jones Senior Statistician Medicines for Children Clinical Trials Unit Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool L12 2AP Tel: +44 (0)151 282 4524 Fax: +44 (0)151 282 4721 Email: apjones@liv.ac.uk</p>
<p>Trial Statistician:</p>	<p>Health Economist:</p>	<p>Head of Trial Management:</p>
<p>Miss Michaela Blundell Medicines for Children Clinical Trials Unit Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool L12 2AP Tel: +44 (0)151 282 4723 Fax: +44 (0)151 282 4721 Email: michaela.blundell@liv.ac.uk</p>	<p>Dr Li-Chia Chen Faculty of Science University of Nottingham Room C01 Pharmacy School Building University Park Nottingham NG7 2RD Tel: +44 (0)115 846 8596 E-mail: Li- Chia.Chen@nottingham.ac.uk</p>	<p>Ms Helen Hickey Medicines For Children Clinical Trials Unit Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool L12 2AP Tel: +44 (0)151 282 4723 Fax: +44 (0)151 282 4721 Email: hickeyh@liverpool.ac.uk</p>

Contact Details: Individuals

Trial Manager:	Senior Data Manager:	Pseudomonas species genotyping:
<p>Ms Hannah Short Medicines for Children Clinical Trials Unit Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation TrustLiverpool L12 2AP Tel: +44 (0)151 282 4714 Fax: +44 (0)151 282 4721 Email: torpedo.trial@liv.ac.uk</p>	<p>Miss Joanne Eatock Medicines for Children Clinical Trials Unit Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation TrustLiverpool L12 2AP Tel: +44 (0)151 252 47144714 Fax: +44 (0)151 282 4721 Email: torpedo.trial@liv.ac.uk</p>	<p>Dr Dervla Kenna Senior Scientist Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (AMRHA) Public Health England Microbiology Services 61 Colindale Avenue London NW9 5HT Tel: +44 (0)20 8327 7224 Fax: +44 (0)20 8327 7449 Email: Dervla.Kenna@hpa.org.uk</p>

Table of Contents

1	Background Information	15
1.1	Introduction	15
1.2	Rationale.....	16
1.3	Objectives.....	16
1.4	Potential Risks and Benefits	16
1.4.1	Potential Risks	17
1.4.2	Known Potential Benefits.....	17
2	Selection of Centres/Clinicians	18
2.1	Centre/Clinician Inclusion Criteria	18
2.2	Centre/Clinician Exclusion Criteria.....	18
3	Trial design.....	19
3.1	Primary Endpoint	19
3.2	Secondary Endpoint(s).....	19
4	Study Population	20
4.1	Inclusion Criteria.....	20
4.2	Exclusion Criteria.....	20
4.3	Participant Transfer and Withdrawal	20
4.3.1	Participant Transfers	21
4.3.2	Withdrawal from Trial Intervention	21
4.3.3	Withdrawal from Trial Completely.....	21
5	Enrolment and Randomisation	22
5.1	Recruitment Strategy /Baseline.....	22
5.2	Randomisation	22
6	Trial Treatments	23
6.1	Introduction.....	23
6.2	Formulation, Packaging, Labelling, Storage and Stability	24
6.3	Arm A Administration	24
6.3.1	Ceftazidime	24
6.3.2	Tobramycin	24
6.3.3	Dispensing / Administration of Arm A Study Treatments.....	25
6.3.4	Precautions required*	25
6.4	Arm B Administration	25
6.4.1	Ciprofloxacin	25
6.4.2	Dispensing / Administration of Arm B Study Treatments.....	26
6.4.3	Precautions required*	26
6.5	Non Investigational Medicinal Product Administration.....	26
6.6	Data on Concomitant Medication.....	27
6.7	Accountability Procedures for Study Treatment/s.....	27
6.8	Assessment of Compliance with Study Treatments.....	27
6.9	Dose Modifications	28
6.10	Co-enrolment Guidelines.....	28
7	Assessments and Procedures.....	29
7.1	Trial Schedule.....	29
7.1.1	Recruitment Strategy.....	29

7.1.2	Diagnosis of <i>P. aeruginosa</i>	29
7.1.3	Baseline assessment (T0 months)	29
7.1.4	Randomisation (T0 months)	30
7.1.5	Treatment Allocation (T0 months)	30
7.1.6	Study visits (follow-up).....	31
7.1.7	Scheduled study visit (T+3 months).....	31
7.1.8	Scheduled study visit (T+6 to T+15 / T+24 months).....	31
7.1.9	Unscheduled assessments.....	31
7.1.10	Assessments for participants who are withdrawn from trial treatment.....	31
7.2	Procedures for assessing Efficacy	33
7.2.1	Spirometry.....	33
7.2.2	Quality of Life	33
7.3	Procedures for Assessing Safety	33
7.4	Other Assessments	33
7.4.1	Quality of Life	33
7.4.2	Health Status.....	34
7.4.3	Health Economics (UK sites only)	34
7.4.4	Genotyping of <i>P. aeruginosa</i>	36
7.5	Loss to Follow-up	38
7.6	Trial Closure	38
8	Statistical Considerations	39
8.1	Introduction	39
8.2	Method of Randomisation	39
8.3	Outcome Measures	39
8.4	Sample Size	40
8.5	Interim Monitoring and Analyses	40
8.6	Analysis Plan.....	41
9	Pharmacovigilance	42
9.1	Terms and Definitions.....	42
9.2	Notes on Serious Adverse Reactions	43
9.2.1	Events to be reported on a SAR report form include.....	43
9.2.2	Events to be reported on a SAR report form do not include.....	43
9.3	Notes Severity / Grading of Adverse Events	43
9.4	Relationship to Trial Treatment.....	43
9.5	Expectedness.....	44
9.6	Reporting Procedures.....	44
9.6.1	Non serious ARs/AEs.....	45
9.6.2	Serious ARs/ SUSARs	45
9.7	Reporting of Pregnancy.....	45
9.8	Reporting of Death	46
9.9	Follow-up After Adverse Events	46
9.10	Responsibilities – Investigator	46
9.11	Responsibilities – MC CTU.....	48
9.12	Safety reports	48
10	Ethical Considerations	50
10.1	Ethical Considerations	50
10.2	Ethical Approval.....	50
10.3	Informed Consent Process.....	51
10.3.1	General	51

10.3.2	Assent in minors.....	52
10.4	Transition from paediatric to adult in relation to consent.....	52
10.5	Study Discontinuation	52
11	Regulatory Approval.....	53
12	Trial Monitoring.....	54
12.1	Risk Assessment	54
12.2	Source Documents	54
12.3	Data Capture Methods	55
12.3.1	Case Report Forms	55
12.3.2	Participant completed questionnaires / diaries.....	56
12.4	Data Monitoring at MC CTU.....	56
12.4.1	Confidentiality.....	56
12.4.2	Direct access to data.....	57
12.4.3	Quality Assurance and quality control of data.....	57
12.5	Records Retention	57
13	Indemnity.....	59
14	Financial Arrangements	60
15	Trial Committees.....	61
16	Publication.....	62
17	Protocol Amendments.....	63
17.1	Version 1 (21/08/2009).....	63
17.2	Version 2 (15/02/2010).....	63
17.3	Version 3 (01/09/2010).....	73
17.4	Version 4 (13/12/2011).....	74
17.5	Version 5 (11/01/2012).....	75
17.6	Version 6 (17/10/2013).....	76
17.7	Version 7 (12/08/2014).....	77
17.8	Version 8 (23/12/2015).....	77
18	References.....	80

Deleted:

Glossary

List of Abbreviations	
AE	Adverse Event
AR	Adverse Reaction
BD	<i>bis die</i> -twice per day
CEACS	Cost effectiveness acceptability curves
CACE	Comparing Adults' and Children's Experiences of Randomised Controlled Trials
CI	Chief Investigator
CF	Cystic Fibrosis
CFQ	Cystic Fibrosis Questionnaire
CFTR	Cystic fibrosis transmembrane conductance regulator
CRF	Case Report Form
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
DM	Data Manager
EQ-5D	50 item Health Questionnaire
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
FEF25-75	Forced Mid-expiratory Flow Rate
GP	General Practitioner
PHE	Public Health England
ICER	Incremental Cost Effectiveness Ratios
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
IV	Intravenous
kg	Kilo Gram
L	Litre
MC CTU	Medicines for Children Clinical Trials Unit
MMOL	millimoles
ML	Millilitre
REC	Research Ethics Committee
mg	Milli Gram
NIHR CRN	National Institute for Health Research Clinical Research Network
OD	Once Daily
PI	Principal Investigator
PSS	Personal Social Services
NIMP	Non Investigational Medicinal Product
MRSA	Methicillin Resistant <i>Staphylococcus aureus</i>
R&D	Research & Development
RN	Research Nurse
QALY	Quality-Adjusted Life-Year
QoL	Quality of Life
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristic
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Trial Co-ordinator
TDS	Three Times Daily
TM	Trial Management
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
VNTR	Multiple-Locus Variable-Number Tandem-Repeat

Protocol Summary

Title of Study:	Trial of <u>O</u> ptimal Therapy for <u>P</u> seudomonas <u>E</u> radication in <u>C</u> ystic <u>F</u> ibrosis
Phase:	IV
Name of Active Substances:	Ceftazidime, Tobramycin, Ciprofloxacin, Colistin
Study Design:	Multi-centre parallel group, randomised controlled trial comparing fourteen days of intravenous therapy to three months (12 weeks)* of oral therapy
Target Population:	All cystic fibrosis patients who have isolated <i>P. aeruginosa</i> and fulfil the inclusion criteria
Number of Study Centres and Distribution:	CF centres throughout the UK and Internationally
Study Period:	15months/24months
Main Objective(s):	This trial will assess whether fourteen days intravenous ceftazidime with tobramycin is superior to three months (12 weeks)* oral ciprofloxacin. Both treatment regimes will be in conjunction with three months (12 weeks)* nebulised colistin *One month is defined as 28 days
Number of Participants to be Enrolled:	286 are to be randomised in total,
Criteria for Inclusion:	<ol style="list-style-type: none"> 1. Diagnosis of cystic fibrosis (CF) 2. Children over the age of 28 days, older children and adult CF participants are all eligible with no upper age limitation 3. Competent adults should provide fully informed written consent to participate in the trial 4. Minors should have proxy consent by the parent or legal guardian and should provide assent where applicable to participate in the trial 5. The participant should have isolated <i>P. aeruginosa</i> and should be either: <ol style="list-style-type: none"> a. <i>P. aeruginosa</i>-naïve (i.e. has never previously isolated <i>P. aeruginosa</i>) or b. <i>P. aeruginosa</i>-free (i.e. any cough or sputum samples within the previous year (365 days) should be <i>P. aeruginosa</i> free.) 6. The participant should be able to commence treatment no later than 21 days from the date of a <i>P. aeruginosa</i> positive microbiology report
Criteria for Exclusion:	<ol style="list-style-type: none"> 1. Antibiotic resistance of the current <i>P. aeruginosa</i> sample to any of: ciprofloxacin, ceftazidime, tobramycin or colistin reported by local microbiology laboratory 2. Known participant hypersensitivity to either ciprofloxacin, ceftazidime, tobramycin or colistin

3. Other known contraindications to any of ciprofloxacin, ceftazidime, tobramycin or colistin including previous aminoglycoside hearing or renal damage
4. Participant receiving *P. aeruginosa* suppressing treatment, in particular nebulised colistin or tobramycin, or oral ciprofloxacin for the previous 9 calendar months. Please 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*
5. Treatment with other anti-pseudomonal nebuliser
6. Pregnant and nursing mothers (women of child bearing age will be counselled on the risks of becoming pregnant during the trial and will be offered a pregnancy test)
7. Previous randomisation in TORPEDO-CF study
8. Previous participation in another related intervention trial within four weeks of taking part in TORPEDO-CF

Please note: The participant should not be consented unless they are prepared to receive either treatment arm.

Duration of Treatment: Participants who start allocated treatment before 1st January 2016 will have a total maximum study duration of 24 months (96 weeks). Participants who start allocated treatment on 1st January 2016 or later will have a total maximum study duration of 15 months (60 weeks). Total study duration is calculated from start of allocated treatment. Participants will be seen every three months (12 weeks) as a minimum during the course of the trial. Treatment will last for three months (12 weeks) from the date allocated treatment is started, for guidance on scheduling of visits see table 1 below.

Table 1: Guidance on Scheduling of Visits

Scheduled Study Visit	Time after Treatment Start	Study Visit Window
3 months	12 weeks	At least 48 hours after treatment cessation and no more than 2 weeks
6 months	24 weeks	+/- one week
9 months	36 weeks	+/- one week
12 months	48 weeks	+/- one week
15 months	60 weeks	- one week or + two weeks
18 months*	72 weeks	+/- one week
21 months*	84 weeks	+/- one week
24 months*	96 weeks	+/- one week

*Only applicable to participants who start allocated treatment before 1st January 2016

Primary Outcome: Successful eradication of *P. aeruginosa* infection three months (12 weeks) after allocated treatment has started, remaining infection free through to 15 months (60 weeks) after the start of allocated treatment

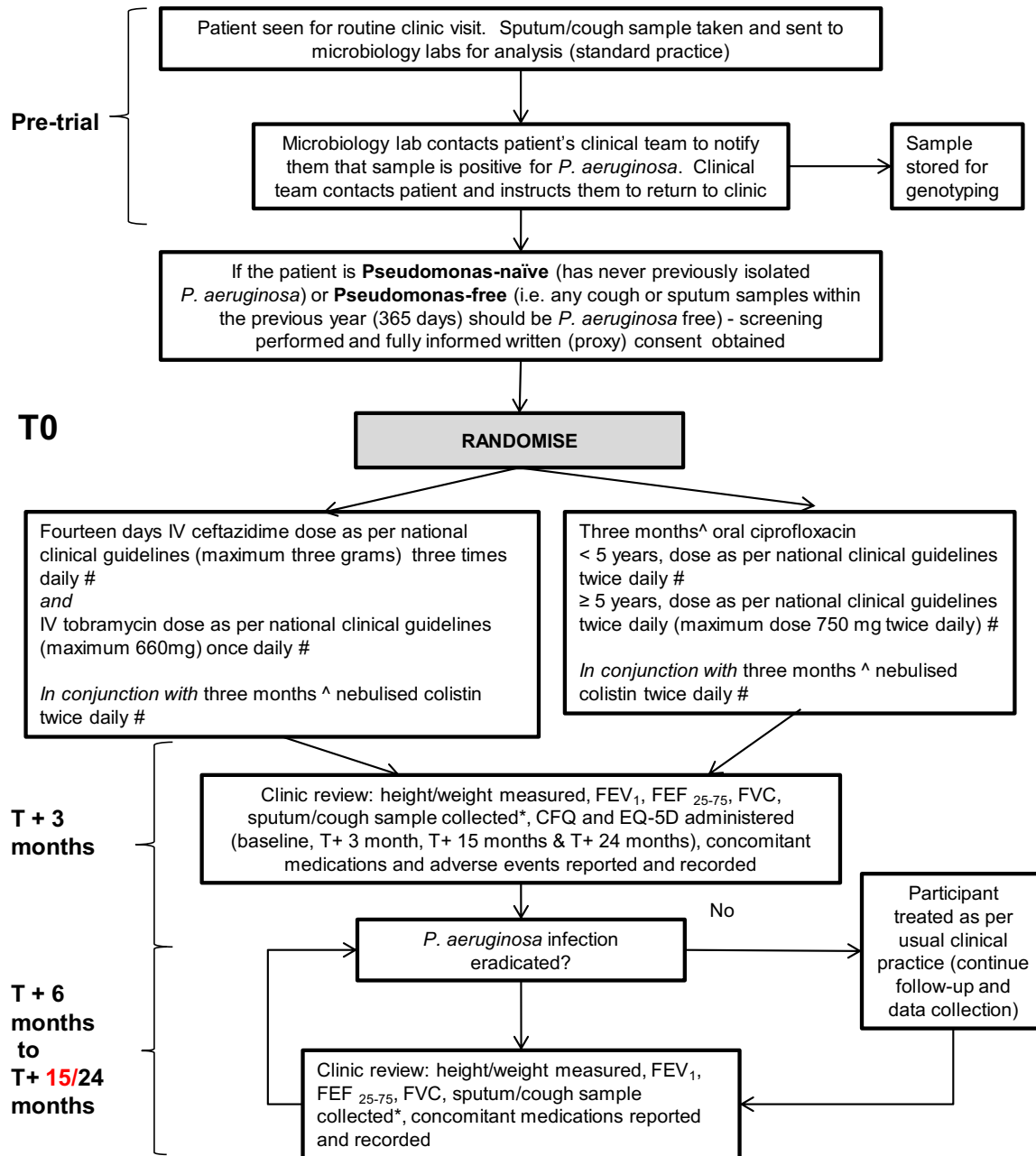
Secondary Outcomes:

1. Time to reoccurrence of original *P. aeruginosa* infection
2. Re-infection with a different genotype of *P. aeruginosa*
3. Lung function - FEV₁, FVC, FEF₂₅₋₇₅
4. O₂ saturation
5. Growth and nutritional status – height, weight and body mass index

6. Number of pulmonary exacerbations
7. Admission to hospital
8. Number of days spent as inpatient in hospital over the three-month period after allocated treatment has finished and between three months and 15 months after allocated treatment has finished (other than 14 days spent on initial IV treatment)
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)

**Definition of Pulmonary exacerbation listed in section 3.2*

Figure 1: Protocol Summary



* sample stored for genotyping

^ three months is defined as 12 weeks

sites that are unable to comply with the trial dosing regime n can use their current dosing regimen as long as the total daily dose administered is within national clinical guidelines

1 BACKGROUND INFORMATION

1.1 Introduction

Cystic fibrosis (CF) is the most common life-limiting recessively inherited condition in Caucasian populations. It is a multisystem disorder where 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* (*P. aeruginosa*) is a common infection in the lungs of patients with cystic fibrosis. The age specific prevalence of *P. aeruginosa* in pre-school children is 9%, rising to 32% for 10 to 15 year olds¹. 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 mortality². Long term infection is associated with poor outcomes including more rapid decline in lung function such as the amount of air expired in one second of forced expiration (FEV₁)^{3,4}. New isolation of *P. aeruginosa* is treated with antibiotics in an attempt to eradicate the infection and to delay acquisition of chronic infection⁵. 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, intravenous and nebulised antibiotics⁶⁻¹⁰.

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, there have been few studies that have compared efficacy and cost effectiveness of these treatments.

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

Intravenous aminoglycosides are commonly used and require further blood tests for monitoring of plasma levels and can be associated with kidney and inner ear damage¹¹. No study has yet been conducted to investigate the therapeutic advantage of one strategy over another.

In 2005 the NHS National Institute for Health Research (NIHR) commissioned the Medicines for Children Research Network to perform a study 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 (Personal Communication Prof RL Smyth and Prof PR Williamson) having surveyed UK clinical practice, surveyed opinions of CF patients and families and assessed the number of potentially eligible patients for such a trial. The result of this feasibility study was to show that generally clinicians treat first or new growth of *P. aeruginosa* in accordance with UK CF Trust guidelines and 95% reported that they would consider IV treatment of first isolation of *P. aeruginosa*. 71% of clinician and 43% of consumer respondents would consider entry for themselves/their patients' into a randomised controlled trial comparing oral with intravenous antibiotics. The conclusion stated "The 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 a response to addressing this clinical equipoise and has been commissioned by the NIHR.

1.2 Rationale

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 the inhaled antibiotics such as colistin, tobramycin^{9,12,13} oral quinolones such as ciprofloxacin^{6,10} and intravenous antibiotics usually consisting of 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 trials¹⁴ which concluded “There is an urgent need for well-designed and well-executed trials, which are specifically designed to examine the hypothesis: that 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. This requires randomised controlled trials enrolling adequate numbers of participants to ensure the trial has sufficient power. Eradication treatment is part of routine clinical practice in many CF centres and clinical trials comparing alternative eradication regimens may be preferable for pragmatic reasons. Consideration should be given to appropriate outcome measures particularly spirometric lung function, nutritional¹¹ status, socio-economic outcomes including quality of life and duration of follow up. Long-term follow-up trials with careful clinical and bacteriological surveillance are required.”

The UK CF Trust has published guidance for antibiotic treatment for CF, including treatment for eradication of newly acquired *P.aeruginosa*¹¹. 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. This report has recommended that appropriate treatment in this situation will include oral ciprofloxacin for duration of treatment up to three months or intravenous treatment such as a beta-lactam (e.g. ceftazidime or meropenem) or an anti-pseudomonal penicillin in combination with intravenous tobramycin¹¹. Intravenous antibiotics are usually administered for 10-14 days in CF though there have been no randomised controlled trials of shorter duration of treatment.

The rationale for choosing fourteen days of intravenous treatment and for choosing three months for oral treatment is that both of these are standard practice for many UK CF centres identified in the HTA feasibility study and both are standard recommendations within the published UK guideline and believed to represent current best practice.

1.3 Objectives

This study will test the question of establishing superiority of fourteen days intravenous therapy to three months of oral therapy. Both treatment arms will also include three months of nebulised colistin. The primary outcome measure will be successful 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.

Lists of outcome measures are presented in section 3.

1.4 Potential Risks and Benefits

The medications used in this study are subject to Marketing Authorisations and are to be prescribed in accordance with their licensed indications.

The management of any symptoms or exacerbations will be in accordance with usual clinical practice and either the local Principal Investigator (PI) or delegated research staff, will be available throughout the study to discuss specific issues with individuals concerned. Any concerns, which cannot be satisfied at a local level, will be forwarded to the Chief Investigator via the TORPEDO-CF Trial Coordinator based at the Medicines for Children Clinical Trials Unit (MC CTU). Any participant can withdraw from the study at any time with no detriment to their future care. All ethical aspects of the study will be discussed when informed written consent is obtained. Appropriate information leaflets have been developed and are discussed at the screening consultation. Potential participants and their families will be provided with a copy of the information sheets and their signed consent/assent forms.

1.4.1 Potential Risks

Chronic pulmonary infection with *P. aeruginosa* in CF is associated with a more rapid decline in lung function and an increase in mortality^{14,15}. Infection with *P. aeruginosa* may be eradicated in its early stages. Later the organism forms a biofilm on damaged respiratory epithelium and eradication becomes impossible. There is a likely window of opportunity that exists to eradicate this early, non-mucoid *P. aeruginosa* before it has formed a biofilm, known as a mucoid *P. aeruginosa* and associated with a greater degree of CF lung disease progression⁴. Eradication treatment for *P. aeruginosa* has therefore emerged as a high priority for patients, parents and the multidisciplinary CF team.

However, there is no good evidence to determine whether oral or intravenous strategies are more effective^{14,15}. Intravenous treatment is associated with the risk of renal¹⁶ and inner ear damage¹⁷ from tobramycin and drug allergy with ceftazidime. The risks of oral treatment are less, though ciprofloxacin causes photosensitivity and participants randomised to this treatment will be advised to avoid direct sun exposure during their time taking ciprofloxacin. Either strategy could be associated with the emergence of antibiotic resistant *P. aeruginosa* or other resistant organisms.

There are risks from all antibiotics of development of allergic reactions, other underlying infections such as methicillin resistant *Staphylococcus aureus* (MRSA) and fungal infection, and development of antibiotic resistance. These potential effects will be monitored as an integral part of this study.

1.4.2 Known Potential Benefits

All of the medications have been shown to be efficacious for patients suffering from CF. The ultimate aim of the trial is not only to eliminate *P. aeruginosa* infection from the lungs of CF patients but also to show whether intravenous treatment is significantly superior to oral therapy.

This study will measure clinical as well as non-clinical outcomes and will allow comparison of treatments arms in terms of clinical treatment effect and of cost-effectiveness.

2 SELECTION OF CENTRES/CLINICIANS

Each participating centre (and Investigator) has been identified on the basis of:

- Having at least one lead clinician with a specific interest in, and responsibility for supervision and management of patients with CF
- Showing enthusiasm to participate in the study
- Ensuring that sufficient time, staff and adequate facilities are available for the trial
- Providing information to all supporting staff members involved with the trial or with other elements of patient management
- Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibility of the study including adhering to GCP and other regulatory documentation

2.1 Centre/Clinician Inclusion Criteria

- Ethical and competent authority (regulatory) approval as appropriate
- Any other required centre specific approval such as R&D approval for UK centres
- Any other required approvals for non-UK centres
- Signed non-commercial agreement between centre and sponsor / co-sponsor
- Completion and return of 'Signature and Delegation Log' to MC CTU
- Curriculum Vitae (CV) including a record of International Conference for Harmonisation (ICH) of GCP training or equivalent – Principal Investigator (PI)
- CV including a record of ICH GCP training or equivalent – Other personnel as appropriate to their role on the delegation log
- Fulfilling MC CTU regulatory green light process

2.2 Centre/Clinician Exclusion Criteria

- Not meeting the inclusion criteria listed above

3 TRIAL DESIGN

3.1 Primary Endpoint

Successful 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.

3.2 Secondary Endpoint(s)

- Time to reoccurrence of original *P. aeruginosa* infection
- Re-infection with a different genotype of *P. aeruginosa*
- Lung function - FEV₁, FVC, FEF₂₅₋₇₅,
- O₂ saturation
- Growth and nutritional status – height, weight and body mass index
- Number of pulmonary exacerbations*
- Admission to hospital
- 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)
- Quality of life (CFQ)
- Utility (EQ-5D)
- Adverse events
- Other sputum/cough Microbiology (Methicillin resistant *Staphylococcus aureus* (MRSA), *Burkholderia cepacia* complex, Aspergillus, Candida Infection)
- Cost per patient (from NHS perspective)
- Incremental cost effectiveness ratio (cost per successfully treated patient, cost per QALY)
- Carer burden (absenteeism from education or work)
- Participant burden (absenteeism from education or work)

*Pulmonary exacerbations will be defined using guidelines by Rosenfeld¹⁸

4 STUDY POPULATION

4.1 Inclusion Criteria

All CF patients (adults and children) from participating centres who meet the following criteria will be considered eligible to take part in the study.

1. Diagnosis of cystic fibrosis
2. Children over the age of 28 days, older children and adult CF participants are all eligible with no upper age limitation.
3. Competent adults should provide fully informed written consent to participate in the trial
4. Minors should have proxy consent by the parent or legal guardian and should provide assent where applicable to participate in the trial
5. The participant should have isolated *P. aeruginosa* and should be either:
 - a. *P. aeruginosa* -naïve (i.e. has never previously isolated *P. aeruginosa*) or
 - b. *P. aeruginosa* -free (i.e. any cough or sputum samples within the previous year (365 days) should be *P. aeruginosa* free)
6. The participant should be able to commence treatment no later than 21 days from the date of a *P. aeruginosa* positive microbiology report

4.2 Exclusion Criteria

1. Antibiotic resistance of the current *P. aeruginosa* sample to any of: ciprofloxacin, ceftazidime, tobramycin or colistin reported by local microbiology laboratory lab
2. Known participant hypersensitivity to either ciprofloxacin, ceftazidime, tobramycin or colistin
3. Other known contraindications to any of ciprofloxacin, ceftazidime, tobramycin or colistin, including previous aminoglycoside hearing or renal damage
4. Participant receiving *P. aeruginosa* suppressing treatment, in particular nebulised colistin or tobramycin, or oral ciprofloxacin for the previous nine calendar months. Please 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*
5. Treatment with other anti-pseudomonal nebuliser
6. Pregnant and nursing mothers (women of child bearing age will be counselled on the risks of becoming pregnant during the trial and will be offered a pregnancy test)
7. Previous randomisation in TORPEDO-CF study
8. Previous participation in another related intervention trial within four weeks of taking part in TORPEDO-CF

4.3 Participant Transfer and Withdrawal

In consenting to the trial, participants are consented to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the participant (or parent/legal representative) should be asked to allow continuation of scheduled evaluations, and complete an end-of-study evaluation. Withdrawn participants should also be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the participant's condition becomes stable.

4.3.1 Participant Transfers

For participants moving from the area, or transferring from paediatric CF centres to adult CF centres every effort should be made for the participant to be followed-up at another participating trial centre and for the participants new trial centre to take over responsibility for the participant. Where this is not possible, if the participant is still happy for their data to be collected, the recruiting centre should make every effort to obtain data collected as part of routine care from the centre that is now responsible for the participants care. Participant transfer should not take place until the MC CTU have confirmed that the transfer centre has received local approvals and has received the green light for recruitment onto the TORPEDO-CF study (see section 2: Selection of Centres/Clinicians). Once the MC CTU has confirmed the transfer centres participation in the TORPEDO-CF study a copy of the participants CRFs should be provided to the new centre. The participant (or parent/legal representative) will have to sign a new consent form at the new site, and until this occurs, the participant remains the responsibility of the original centre. The MC CTU should be notified in writing of participant transfers.

4.3.2 Withdrawal from Trial Intervention

Participants may be withdrawn from treatment for any of the following reasons:

- a. Participant (or, where applicable, Parent/ legal representative,) withdraws consent
- b. Unacceptable toxicity
- c. Intercurrent illness preventing further treatment
- d. Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion

If a participant is withdrawn from treatment the appropriate Treatment CRF and the End of Treatment CRF should be completed.

Centres should explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the participant explicitly also withdraws consent for follow-up (see section 4.3.3).

4.3.3 Withdrawal from Trial Completely

Participants are free to withdraw consent at any time without providing a reason. Participants who wish to withdraw completely from the trial will have anonymised data collected up to the point of that withdrawal of consent included in analyses unless the participant explicitly states that this is not their wish. A Withdrawal CRF, the appropriate scheduled Follow-up or Unscheduled Visit CRF, and the appropriate Questionnaire should be completed and returned to the MC CTU. The participant will not contribute further data to the study.

5 ENROLMENT AND RANDOMISATION

5.1 Recruitment Strategy /Baseline

A log of all potential participants should be kept (Screening and Enrolment Log) at each participating centre and returned to the MC CTU on a monthly basis. All potential participants with CF that are considered eligible for the trial, including those who decide not to participate in, or who are found to be unsuitable for the study, will be documented on this log. Potential participants should be screened, consented and commence trial treatment within 21 days from the date of a *P. aeruginosa* positive microbiology report. Full details of the baseline assessments required before randomisation are listed in section 7.

Participants who have given informed consent and have been found to comply with all inclusion and exclusion criteria will be randomised using the web randomisation process as detailed in section 5.2.

5.2 Randomisation

Participants will be randomised using a secure (24-hour) web based randomisation programme controlled centrally by the MC CTU to ensure allocation concealment. Randomisation lists will be generated in a 1:1 ratio using simple block randomisation with random variable block length. Factors within this protocol that are being used to stratify randomisation will not be disclosed to prevent prediction in this open trial.

Participant treatment allocation will be displayed on a secure webpage and an automated email confirmation sent to the authorised randomiser and the PI or Co-investigator (where applicable). It is the responsibility of the PI or delegated research staff to inform the pharmacy department at their centre prior to randomisation to ensure there is enough supply of the study drugs.

In the event of an internet connection failure between the centre and the randomisation system, the centre should contact the MC CTU immediately to try to resolve the problem.

Randomisation: web access <http://www.torpedo-cf.org.uk/forResearchers>

If there are any problems with web randomisation, please contact the MC CTU on:

+44 (0)151 282 4714

Or via email on torpedo.trial@liv.ac.uk

Research staff will be trained to use the web randomisation system during the initiation process. After research staff are trained they will be issued with personal login and password details.

6 TRIAL TREATMENTS

6.1 Introduction

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

Participants recruited into the study will be randomised to one of the following treatment arms:

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

- Ceftazidime 150 milligram (mg)/kilogram (kg)/day, in 3 divided doses (maximum of 3 grams (g) three times daily (tds)). Some centres may use a once daily continuous infusion (where the maximum daily dose would usually be 6g/day) or twice daily regimen for ceftazidime. These centres may continue to use this regimen for the study and should follow their local dosing guidelines.
- Tobramycin 10mg/kg/day once daily (od) (maximum 660mg /day). Some centres may use a twice daily or three times daily regimen for tobramycin. These centres may continue to use their current regimen for the study and should follow their local dosing guidelines. Therapeutic drug monitoring should be used to guide tobramycin dosing as per national guidelines (https://www.cysticfibrosis.org.uk/media/82010/CD_Antibiotic_treatment_for_CF_May_09.pdf) and usual clinic procedures.

**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). (Ciprofloxacin dose will be 20 mg/kg twice daily (maximum 750mg twice daily. This is in line with the BNF for children (<http://bnfc.org/bnfc/>). Some clinicians may prefer to use a lower dose of 15mg/kg twice daily for children under 5 years, as used in national CF guidelines (https://www.cysticfibrosis.org.uk/media/82010/CD_Antibiotic_treatment_for_CF_May_09.pdf).

Both treatment arms will receive 3 months#of nebulised colistin in conjunction to the randomised treatment. Colistin dose will be 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 is administered via an I-neb a lower dose of 1,000,000 units twice daily for all ages should be used.

During the study period it is likely that a small proportion of participants will develop a further *P. aeruginosa* infection. These participants should be treated as per local centre guidelines.

Three months is defined as 12 weeks

6.2 Formulation, Packaging, Labelling, Storage and Stability

TORPEDO-CF is a pragmatic trial that uses market authorised products, as such IMPs and NIMPs should be stored in accordance with local hospital practice. In accordance with SI 2004/1031 market authorised products used in a CTIMP can waive labelling requirements. When a market authorised product is used in a CTIMP and there is no modification to the product or its outer packaging; the annex 13 requirements are exempted and a pharmacy label is sufficient when the product is dispensed against a prescription.

Colistin is classified as a NIMP for the TORPEDO-CF trial. As NIMPs do not fall within the definition of investigational medicinal products, Articles 13 and 14 of Directive 2001/20/EC are not directly applicable. Therefore, normal pharmacy labels should be used.

IMPs in this trial can be dispensed by hospital and community pharmacies as they would be normally in clinical practice, without any specific trial labels. It is the responsibility of the PI to ensure that the GP prescribes the remainder of any trial treatment not dispensed by the hospital pharmacy.

The PI or delegated research staff should inform the pharmacy team of any potential participants to be randomised prior to randomisation and provide the pharmacy department with confirmation of treatment allocation.

6.3 Arm A Administration

Ceftazidime is a semi synthetic bactericidal antibacterial agent of the cephalosporin class. Like other beta lactam drugs, ceftazidime exerts antibacterial activity by binding to and inhibiting the action of certain bacterial cell wall synthetic enzymes (transpeptidases). Inhibition of one or more of these essential penicillin-binding proteins results in the interruption of cell wall biosynthesis at the final stage of peptidoglycan production, resulting in bacterial cell lysis and death

6.3.1 Ceftazidime

Active ingredient	Ceftazidime
Excipients	Refer to SPC
Pack Size(s)	Varies according to manufacturer
Route of Administration	Intravenous
Storage temperature / time	Refer to SPC
Supplier's name	Local supply chain (local pharmacy)

Please refer to the reference (Summary of Product Characteristics) SPC provided as separate documents to this protocol.

6.3.2 Tobramycin

Tobramycin belongs to the aminoglycoside group of antibacterials. It enters the cells via complex active transport mechanism and exerts its activity primarily on the 30S ribosomal subunit, interfering with initial and subsequent steps in protein synthesis. It also acts to induce misreading of the genetic code of the mRNA template, resulting in incorporation of incorrect amino acids.

Tobramycin, is primarily antibacterial against aerobic Gram-negative bacilli. Tobramycin is considered more active than most other aminoglycosides against *P. aeruginosa*.

Active ingredient	Tobramycin
Excipients	Refer to SPC
Pack Size(s)	Clear type I glass vials with elastomeric stoppers in packs of 5 vials 1ml vial contains 40mg tobramycin with 2ml and 6ml containing 80 & 240 mg tobramycin respectively
Route of Administration	Intravenous
Storage temperature / time	Please refer to the SPC
Supplier's name	Local supply chain (local pharmacy)

Please refer to the reference SPC provided as a separate document to this protocol

6.3.3 Dispensing / Administration of Arm A Study Treatments

Ceftazidime & Tobramycin should be reconstituted and used in accordance with the manufacturers SPC. The decision as to whether a participant receives treatment as an inpatient or at home should be made in line with local hospital policy and can be any combination of inpatient or home treatment, whichever is more suitable to the participant.

Homecare companies can be used. Homecare companies that reconstitute intravenous medicines centrally and supply reconstituted injectables directly to patient's home must be a registered pharmacy. In addition, the IMPs shall be dispensed to a subject in accordance with a prescription given by an authorised health care professional and labelled in accordance with the requirements that apply to dispensed relevant medicinal products.

6.3.4 Precautions required*

Ceftazidime

A second cephalosporin should not be used

Tobramycin

A second aminoglycoside should not be used (either in intravenous or nebulised form)

Caution required with:

1. Nephrotoxic and ototoxic drugs.
 - a. Non-steroidal anti-inflammatory drugs e.g ibuprofen.
 - b. Loop diuretics e.g. frusemide.
 - c. Some antifungals e.g. amphotericin
 - d. Some chemotherapeutic agents e.g. cisplatin
2. Anaesthetic agents and neuromuscular blocking agents
3. Anticoagulants e.g. warfarin
4. Immunosuppressives e.g. ciclosporin

**Please refer to the appropriate SPC for additional detailed guidance*

6.4 Arm B Administration

6.4.1 Ciprofloxacin

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

Active ingredient	Ciprofloxacin
Excipients	Please refer to the SPC
Pack Size	Please refer to the SPC
Route of Administration	Oral
Storage temperature / time	Please refer to the SPC
Supplier's name	Local supply chain (local pharmacy)

Please refer to the reference SPC provided as a separate document to this protocol.

6.4.2 Dispensing / Administration of Arm B Study Treatments

Ciprofloxacin should be reconstituted and used in accordance with the manufacturers SPC. Treatment can be dispensed by the hospital and/or community pharmacy in line with normal clinical practice. It is the responsibility of the PI to ensure that the GP prescribes the remainder of any trial treatment not dispensed by the hospital pharmacy.

6.4.3 Precautions required*

Ciprofloxacin

1. Caution required with Antacids (interfere with absorption)
2. Theophylline (ciprofloxacin can increase theophylline levels)
3. Immunosuppressives e.g. methotrexate (ciprofloxacin can increase methotrexate levels)
4. Anti-convulsants e.g. phenytoin (ciprofloxacin can increase or decrease phenytoin levels)
5. Anticoagulants e.g. warfarin

* Please refer to the appropriate SPC for additional detailed guidance.

6.5 Non Investigational Medicinal Product Administration

Colistimethate sodium is a polymyxin antibiotic and is derived from *Bacillus polymyxa* var. *colistinus*. It is a polypeptide and is active against a number of aerobic, gram-negative bacteria. The polymyxin antibiotics are surface active agents and act by binding to and changing the permeability of the bacterial cell membrane causing bacterial cell death. Polymyxins are bactericidal against Gram-negative bacteria with a hydrophobic outer membrane.

For the purposes of the TORPEDO-CF trial colistin is being used in line with normal clinical care, and as such will be used in the trial as a Non Investigational Medicinal Product (NIMP) in accordance EU directive 2001/20/EC Article 13 and 14.

Colistin should be dispensed from normal pharmacy stock, in accordance with local practice.

Active ingredients	Colistin
Excipients	None
Pack Size(s)	The product is supplied in clear type I glass vials sealed with a siliconised chlorobutyl type I rubber stopper. The product is supplied in packs of 30 vials.
Route of Administration	Nebulised

Storage temperature / time	Please refer to the manufacturers SPC
Supplier's name	Local supply chain (local pharmacy)

6.6 Data on Concomitant Medication

The dose and name of all concomitant medications should be documented on the Concomitant Medication CRF. The PI or delegated research member should reassess concomitant medications at each trial visit. Any new medications introduced or any changes to current medications should be documented on the CRF. At each follow-up visit a photocopy of the original Concomitant Medication CRF should be sent to the MC CTU within 7 days. An original copy of the CRF should only be sent to the MC CTU once fully completed.

6.7 Accountability Procedures for Study Treatment/s

There are no formal accountability measures required for the trial. TORPEDO-CF has put the following measures in place to safeguard the safety of trial participants:

- Participant completed treatment diaries to record treatment compliance;
- Collection of unused trial IMP*
- Collection of packaging of used IMP
- Verbal interview conducted by the PI at the 3 month follow-up visit
- Local procedures should be used if a manufacturer issues a recall

**Any un-used medication including outer packaging and packaging of used medication should be returned at the next scheduled follow up visit to assess treatment compliance, this information should be recorded on the Treatment CRF. All returned medication should be destroyed as per local procedure.*

6.8 Assessment of Compliance with Study Treatments

Participants compliance with trial treatment will be monitored using participant completed treatment diaries to record their daily treatment routine. Direct questioning will also be used to record overall compliance with treatment at the 3 months follow up visit.

The majority of trial treatment for Arm A participants will be administered during hospital in-patient visits ensuring accurate monitoring of IMP compliance. Participants who have experience of administering IV antibiotics at home or those who would prefer to have home IV will be allowed to self administer IV antibiotics at the discretion of their local Principle Investigator. In this event participants will be asked to complete a Home IV treatment diary each day to ensure compliance with the study medication. Any un-used medication should be returned at the next scheduled follow up visit to assess treatment compliance, this information should be recorded on the Treatment CRF. All returned medication should be destroyed as per local procedure. The packaging of all used medication should also be returned at the next scheduled follow up visit to allow the treatment prescribed to be calculated and facilitate the assessment of treatment compliance.

6.9 Dose Modifications

The decision to interrupt or discontinue trial therapy is at the discretion of the treating physician. Doses may be interrupted or discontinued at any point during the trial period for reasons such as unacceptable adverse events, intercurrent illness, development of serious disease or any change in the participant's condition that the physician believes warrants a change in medication. Any changes in medication must be documented in the appropriate Treatment CRF along with the justification for those changes. If a participant's treatment stops prematurely, the reason for discontinuation should be recorded on the Treatment CRF.

6.10 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally participants should not be recruited into other trials. Individuals who have participated in a trial testing a medicinal product likely to influence *P. aeruginosa* isolation (such as oral quinolones or intravenous or nebulised beta-lactams or aminoglycosides within 9 months preceding screening) will be ineligible for the TORPEDO-CF trial. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the TORPEDO-CF trial this must first be discussed with the coordinating centre (MC CTU) who will contact the Chief Investigator (Dr Simon Langton Hewer).

7 ASSESSMENTS AND PROCEDURES

7.1 Trial Schedule

7.1.1 Recruitment Strategy

Given the epidemiology of *P. aeruginosa* within the CF community, it is likely that CF patients could be diagnosed with *P. aeruginosa* during their lifetime. Therefore, posters, summary leaflets and copies of the Patient Information Sheet and Consent form (PISC) will be made available to CF centres and should be on public display to increase awareness of the trial amongst the potential trial population. This will allow CF patients to familiarise themselves with the trial prior to diagnosis of *P. aeruginosa* and give greater time for potential participants to consider their future involvement in the study should they be diagnosed with *P. aeruginosa*.

7.1.2 Diagnosis of *P. aeruginosa*

Samples of respiratory secretions (sputum or cough swabs) should be sent for bacterial culture in line with normal hospital visits. Microbiology laboratories should culture bacterial samples on both enriched (e.g. blood agar) and on selective media in accordance with hospital policy. Once a potential participant has been diagnosed with *P. aeruginosa* a check of eligibility should be carried out*. Potential participants and their parent or guardian where applicable should be provided with the PISC and asked to consent to participate in the trial. Informed consent should be obtained prior to any trial related procedures being carried out. Once informed consent and assent, where appropriate, has been provided, participants should be randomised to one of the treatment regimens (please refer to section 5.3 for details of the randomisation process). Treatment must commence within 21 days from the date of a positive *P. aeruginosa* microbiology laboratory report.

UK Sites only:

The microbiology laboratory should be made aware that sputum /cough samples that yield a positive *P. aeruginosa* sample should be kept and the resulting isolate sent to Public Health England (PHE) for genotyping if the patient is subsequently randomised onto the TORPEDO-CF trial. This sample will act as a reference if subsequent re-infection occurs (section 0). In order to highlight to Microbiology Departments that CF patients are being considered for the trial high-visibility labels will be provided to CF centres. These labels should be attached onto the Microbiology Request Slip (section 0).

**All cough or sputum samples within the previous year (365 days) should be P. aeruginosa free to satisfy eligibility.*

For details of genotyping arrangements outside of the UK see supplementary document TORPEDO Genotyping Arrangements Outside of the UK.

7.1.3 Baseline assessment (T0 months)

Baseline assessments should be performed prior to randomisation and administration of *P. aeruginosa* eradication treatment. The following data should be recorded on the baseline CRF:

- Medical history;
- Concomitant medications;
- Physical examination including measuring; height, weight, and vital signs (heart rate, breathing rate and blood pressure);

- Collect sputum / cough swab sample (positive *P. aeruginosa* isolates should be sent to PHE if the original *P. aeruginosa* isolate used for diagnosis has not been retained);
- Females of child-bearing potential will be counselled about the risks of the trial treatments should they become pregnant and will be offered a pregnancy test (refusal of a pregnancy test will not preclude trial entry);
- Spirometry will be carried out to measure participants FEV₁, FVC and FEF₂₅₋₇₅.

In addition to this, the participant should complete the appropriate TORPEDO-CF Questionnaire Booklet which contains the age appropriate Questionnaires (the timetable for when these questionnaire should be administered can be found in Table 3: Trial Assessments. Further information about these questionnaires can be found in section 7.4).

Questionnaires should be administered to the participant before their treatment allocation is revealed.

7.1.4 Randomisation (T0 months)

Once all the baseline assessments listed in section 7.1.3 have been completed the participant should be randomised (refer to section 5.2).

7.1.5 Treatment Allocation (T0 months)

Participants should start to receive eradication treatment no later than 21 days after the date of a positive *P. aeruginosa* microbiology report.

Participants receiving IV treatment should have serum creatinine* measured at the time of starting treatment and should have tobramycin serum concentrations** measured during the course of their treatment.

For participants randomised to IV antibiotics:

** serum creatinine measured at the time of commencing treatment with IV tobramycin or in line with local site practice*

*** monitoring tobramycin levels should follow standard unit practice:*

- *Should include measuring trough concentrations before the second dose and again after 1 week of treatment. Adjustments to dose based on these measurements and further actions (e.g. repeat measurements) should be recorded in the CRF.*
- *May include measuring peak serum concentrations - in which case a record should be made of the serum concentration and any actions taken in response to this.*

Once the participant has been informed of their treatment allocation they should be given the appropriate treatment diary to record their daily treatment compliance and should be provided with a copy of the Health Service Diary (UK sites only) (please refer to table 2 for guidance on which treatment diary should be used). The PI or a delegated member of the Research staff should explain how to complete the diaries before the participant leaves hospital. Participants should be instructed to bring back copies of the treatment diary, Health Service Diary, any unused medication and the packaging of used medication at their next scheduled visit to assess compliance with eradication treatment and to assess their resource use during that time.

Table 2: Guidance on Treatment Diary Administration

Treatment Diary	Administration
Treatment Diary 1	Arm A: To be given to participants who have received IV treatment as an in-patient
Treatment Diary 2	Arm A (Home IV): To be given to participants who have received IV treatment at home
Treatment Diary 3	Arm B: To be given to participants receiving oral antibiotics

7.1.6 Study visits (follow-up)

Scheduled study visits are designed to fit with routine hospital visits where possible. At each visit, data similar to that collected at baseline should be recorded in the Case Report Form Booklet on the appropriate follow-up CRF. The follow-up CRFs should be returned to the MC CTU as soon as they are fully completed. Study visits should take place every three months as a minimum. Care should be taken to ensure that the 3 and 15 month primary endpoint visits are arranged from the date that treatment started irrespective of earlier visit dates (please refer to table 1, page 12 for guidance on scheduling of study visits).

7.1.7 Scheduled study visit (T+3 months)

T+3 month scheduled study visit should be arranged to take place after cessation of eradication treatment. Cough / sputum samples should be taken at least 48 hours after cessation of eradication treatment and should take place no later than fourteen days after treatment cessation. The participant should be instructed to bring back their Treatment Diary, Health Service Diary (if applicable), any un-used medication and the packaging of used medication. Treatment compliance should be recorded on the appropriate Treatment CRF.

7.1.8 Scheduled study visit (T+6 to T+15 / T+24 months)

Planned study visits will take place every three months and should be calculated from the date that treatment started. The visit window is +/- one week for all scheduled study visits from T+6 onwards apart from the 15 month visit which can be - one week or + two weeks. A detailed list of assessments that should be carried out at each study visit can be found in table 3. Participants who start allocated treatment before 1st January 2016 should continue their follow-up up to 24 months. Participants who start allocated treatment on 1st January 2016 or later should continue their follow-up up to 15 months.

7.1.9 Unscheduled assessments

During the course of the trial, some participants may need to attend hospital for unscheduled study visits. In these instances, the PI or delegated member of the research team should complete the Unscheduled Visit CRF. If the unscheduled visit results in a change to the participants medication this should be recorded on the Concomitant Medication CRF. If a cough or sputum sample is taken at the visit details should be recorded on the Microbiology CRF. Recurrence of *P. aeruginosa* infection should be treated promptly with oral or intravenous antibiotics in line with CF Trust Guidelines¹¹.

7.1.10 Assessments for participants who are withdrawn from trial treatment

Participants withdrawn from trial treatment will be asked to continue with trial follow-up and attend for 3-monthly study visits. If a participant does not wish to continue in the study, a

Withdrawal CRF will be completed to capture the date and reason for trial withdrawal as detailed in section 4.3

Table 3: Trial Assessments

Procedures	Recruitment / T0 Baseline	Follow-Up Schedule									
		T + 3 month (clinic) [^]	T + 6 month (clinic)	T + 9 month (clinic)	T + 12 month (clinic)	T + 15 month (clinic)#	T + 18 month (clinic)	T + 21 month (clinic)	T + 24 month (clinic) *	Unscheduled visit	Withdrawal of Consent
Timelines	0 weeks	12 weeks	24 weeks	36 weeks	48 weeks	60 weeks	72 weeks	84 weeks	96 weeks	N/A	N/A
Signed Consent Form	X										
Assessment of Eligibility Criteria	X										
Physical Exam	X	X	X	X	X	X	X	X	X		(X)
Positive culture/sputum for genotyping (UK sites only)	X	X	X	X	X	X	X	X	X	(X)	(X)
FEV ₁ , FVC, FEF ₂₅₋₇₅	X	X	X	X	X	X	X	X	X	(X)	(X)
O ₂ saturation	X	X	X	X	X	X	X	X	X	(X)	(X)
Nutritional status	X	X	X	X	X	X	X	X	X	(X)	(X)
Questionnaire Booklet (containing Quality of Life (CFQ) and EQ-5D) administration	X	X				X			X		(X)
Health Service Diary (UK sites only)	X	X	X	X	X	X					(X)
Review of Medical history	X										
Review of Concomitant meds		Complete for each concomitant medication for the duration of the trial									
Blood Biochemistry	X										
Randomisation: Study Intervention	X										
Assessment of Adverse Events		Complete until 28 days after treatment cessation									

#Participants who start allocated treatment on 1st January 2016 or later should continue their follow-up up to a maximum of 15 months

*Participants who start allocated treatment before 1st January 2016 should continue their follow-up up to a maximum of 24 months.

[^]T+3 month scheduled study visit should be taken at least 48 hours after cessation of eradication treatment and should take place no later than fourteen days after treatment cessation.

Where possible all visits should be scheduled from start of allocated treatment however, no slippage should be allowed for primary endpoint visits (shaded in dark blue).

Participants should be seen for follow-up every three months as a minimum, in line with local site practice

(X) Assessment should be carried out where applicable

7.2 Procedures for assessing Efficacy

Efficacy of trial treatments will be measured throughout the period of the study using both objective and subjective measures.

7.2.1 Spirometry

Spirometry* will be carried out at baseline (T0) and every 3 months throughout the trial (T0 to T+24) and will provide an objective measure of efficacy.

*Spirometry is not routinely carried out in those under 5 years of age

7.2.2 Quality of Life

The Quality of Life (QoL) scores obtained throughout the trial can be used as a subjective measure of efficacy.

7.3 Procedures for Assessing Safety

An assessment of adverse events will be undertaken at each study visit from baseline (T0) until 28 days after treatment cessation. These reviews should be carried out by the PI or delegated research staff. Adverse event reporting is detailed fully in Section 9.

7.4 Other Assessments

Quality of Life and Health Status instruments have been combined into age appropriate questionnaire booklets for ease of administration and should be administered as detailed in Table 4.

Table 4: Guidance for questionnaire booklet administration

Questionnaire Booklet administration	Completed by:
Children under the age of 6	Parent or caregiver
*Children ages 6-13	Parent or caregiver
*Children ages 6-11	Interviewer**
Children ages 12 and 13	Self administered
Adolescents and adults ages 14 and above	Self administered

*For children aged 6-11 both the parent / caregiver self-administered version and the interviewer-administered version should be completed. For children aged 12 and 13 the parent / caregiver and the interviewer administered booklets should be completed.

**Interviewer should be one of the local CF study team

7.4.1 Quality of Life

The CFQ is the only published disease specific measure of health-related QoL for children (aged 6 and over), adolescents, and adults with cystic fibrosis¹⁹. Twelve domains of Health Related QoL 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 symptoms²⁰. Quality of life questionnaires (CFQ) will be completed at baseline, T+3 months, T+15 months and T+24 months (T+24 month scores only collected for trial participants who start allocated treatment before 1st January 2016) after allocated treatment started.

Administration of Questionnaire Booklet:

The questionnaire booklet should be completed at the specified study visits, and should ideally precede any discussion with the PI or delegated other. The PI or delegated other should ensure all questions have been answered and should ensure that the randomisation number and time point at which the questionnaire booklet was administered are recorded on the booklet.

Participants must complete the baseline booklet before treatment allocation has been revealed. If the participant is too unwell to receive the questionnaire booklet or has missed a time point the delegated research staff must inform the MC CTU. Participants who fail to complete their full treatment allocation will still be administered the QoL questionnaire at the same time points in order to avoid bias.

Child Participants: Children should be on their own and in a quiet room where there are no distractions if possible. Parents /carers should be instructed to wait in another room where they can complete the parent and caregivers questionnaire booklet (Children ages 6-13). While the child is completing the questionnaire booklet they should be made to feel comfortable and relaxed but be aware that they need to complete the questionnaire carefully.

Where the questionnaire booklet is interviewer administered (i.e. for children ages 6-11) the questionnaire should be read out exactly as they appear on the form. Questions should not be re-worded or paraphrased for the child, even if they ask for clarification. Two coloured cards will be provided with the questionnaire booklet which list sets of response options appropriate to the different questions. The interviewer should explain both cards to the child, reading each of the response options with the younger child and asking the older ones to read each of the responses aloud to ensure they understand. The child should be reminded that they are only able to choose one option.

7.4.2 Health Status

EQ-5D²⁹ scores will be collected at baseline, T+3 months, T+15 months and T+24 months post treatment (T+24 month scores only collected for trial participants who start allocated treatment before 1st January 2016) . Participants must complete the baseline booklet before treatment allocation has been revealed. The PI or delegated research staff should ensure that the randomisation number and time point at which the questionnaire booklet was administered are recorded.

If the participant is too unwell to receive the questionnaire booklet or has missed a time point the delegated research staff must inform the MC CTU. Participants who fail to complete their full treatment allocation will still be administered the questionnaire booklet at the same time points in order to avoid bias.

7.4.3 Health Economics (UK sites only)

Health economic data will be collected on primary and secondary health care contacts and medications prescribed. Although not the primary focus of the study, it will aim to incorporate patient and societal costs in terms of time lost to school or work by the participant and time lost to work for the parents or guardian. It will include any out of pocket expenses such as personal money spent on medications and aids and appliances. It is important to determine differences in the participant pathway as a result of the different treatment regimes. Health Economic data will be collected from the participant as a Health Service Diary that will be given to the participant to complete prospectively between each scheduled follow up visit (child participants will be asked to complete the diary in conjunction with their parent or guardian). The Health Service Diary

should be returned at the next scheduled study visit and reviewed by the PI/RN in conjunction with the participant and their parent or guardian where applicable.

The Health Service Diary will only be given to participants in UK sites.

7.4.3.1 Resource use and cost estimation

Costs will be estimated for each participant in the trial. [Table 5: Summary of resources use and unit cost parameters to be collected](#), lists the resource use and unit cost data. The costs will be calculated as resource use multiplied by the unit cost of the specific resource. Long term medication such as pancreatic enzymes and vitamins that are not likely to change between treatment arms, will not be collected.

Deleted:
parameter

Table 5: Summary of resources use and unit cost parameters to be collected

Parameters	Source	Unit costs
<i>Index intervention resource use:</i> IV and oral antibiotics; sputum microbiology; blood drug level assays; standard home kits for both intervention procedure and subsequent infections, index length of stay or clinic visit.	In situ data collection (clinical records)	Unit costs, BNF, NHS reference costs, local unit cost source
<i>Follow up secondary care resource use:</i> clinic appointment and category of appointment; CF physician, CF physiotherapist, CF nurse inpatient days and category of admission; home visits, A&E visits.	Health Service Diary	NHS reference costs
<i>Follow up primary care resource use:</i> GP appointment; nurse from GP practice, GP/nurse home visit, GP out-of-hours services.	Health Service Diary	NHS reference costs and PSSRU reference costs
<i>Follow up personal social services:</i> resource use: Social worker; Home care worker.	Health Service Diary	

7.4.3.2 Cost analysis

The analysis will include cost estimates for all participants enrolled in the study. The objective of the statistical analysis will be to test whether there were statistically significant differences in between groups in the costs. If the sample size and degree of skewness means that standard parametric-based approaches are not robust, non-parametric bootstrapping will be used to compare arithmetic means of cost data⁸. Non-parametric statistical tests are considered inappropriate because they do not test differences in arithmetic means⁹. The arithmetic mean is considered to be the most relevant measure for health care policy decisions, which should be

based on information about the distribution of the costs of treating a patient group, as well as the average cost.

7.4.3.3 Economic analysis and generation of ICERs and CEACs

An economic analysis will be carried out from the perspective of the NHS and PSS in terms of the direct costs of providing 2 weeks intravenous therapy with ceftazidime and tobramycin over 3 months of oral ciprofloxacin and impact on the primary outcome measures and QALYs. The effectiveness measure for the calculation of incremental cost effectiveness ratio will be cost per unit of outcome. If the lower cost intervention is also associated with better outcomes than the more costly comparator, this will be treated as efficient. In this scenario, incremental ratios would not be calculated for this intervention, since its use would lead to both net savings and greater benefits. Incremental Cost Effectiveness Ratios (ICER) will be calculated if the higher cost intervention is associated with better outcomes. The incremental ratios will be calculated as:

$$(\text{Cost}_{\text{Arm A}} - \text{Cost}_{\text{Arm B}}) / (\text{Outcome}_{\text{Arm A}} - \text{Outcome}_{\text{Arm B}})$$

Statistical analysis is not appropriate to test the robustness of ICERs. It is not possible to generate 95% confidence intervals around ICERs because the ratio of two distributions does not necessarily have a finite mean, or therefore, a finite variance²¹. Therefore, generation of a bootstrap estimate of the ICER sampling distribution to identify the magnitude of uncertainty around the ICERs is required. Bootstrapping with replacement will be employed, utilising MS Excel®, using a minimum of 1000 iterations to obtain 2.5% and 97.5% percentiles of the ICER distribution.

7.4.3.4 Cost effectiveness acceptability curves and net benefit

A cost effectiveness acceptability curve will be constructed to express the probability that the cost per extra unit of outcome gained from within the trial (y-axis) is cost effective as a function of the decision-makers ceiling cost effectiveness ratio (λ) (x-axis)²². Net benefit will be determined when λ is £30,000.

7.4.3.5 Sensitivity analysis

In addition to the probabilistic economic analysis outlined above, key assumptions in the economic analysis that may be expected to affect the magnitude and direction of ICERs will be tested in one- and two-way sensitivity analysis. These are expected to be: definitions of effectiveness, unit costs and differences in standard care pathways between centres.

7.4.4 Genotyping of *P. aeruginosa*

As part of standard clinical care to screen for *P. aeruginosa* infection in CF patients sputum or cough samples are routinely sent to microbiology laboratories within the site for diagnosis. Once a positive culture has been isolated the microbiology report is sent back to the patients CF team to decide on the appropriate course of treatment.

Genotyping of positive *P. aeruginosa* cultures will enable assessment of whether the participants have re-isolated the same strain of *P. aeruginosa* that originally infected them or whether they have grown a distinct new organism.

7.4.4.1 Genotyping of *P. aeruginosa* - UK sites only

TORPEDO-CF will collect nutrient agar slopes of positive cultures for genotyping of *P. aeruginosa*. This genotyping work is over and above the microbiological analysis which is

carried out as standard practice on all sputum samples taken from CF patients and will be vital when assessing recurrence of *P. aeruginosa* in participants taking part in the TORPEDO-CF trial.

P. aeruginosa isolates will be genotyped using a technique known as Multiple-Locus Variable-Number Tandem-Repeat (VNTR), a Polymerase Chain Reaction (PCR) -based system that differentiates isolates based on variation in the number of repetitive-elements at multiple loci, with each strain being designated a numerical code. VNTR has been successfully used to type numerous bacterial species, including *P. aeruginosa*^{23,24}. Public Health England's (PHE's) in-house method has been successfully trialled alongside pulsed-field gel electrophoresis, the current gold standard for typing *P. aeruginosa* (J. Turton, Personal communication), and is based on differences at nine of the 19 loci from the original publications^{23,24}.

7.4.4.1.1. Procedures for storage and transport of *P. aeruginosa* isolates

Microbiology laboratories within CF centres should be made aware of the TORPEDO-CF trial prior to recruiting participants to draw their attention to the genotyping aspect of the trial. Members of the microbiology laboratory will also be invited to the site initiation meetings to give microbiology staff the chance to raise any specific centre issues / needs that should be addressed prior to the centre opening to recruitment.

Centres will be provided with high visibility labels (screening and follow-up labels) for all CF patients that might be considered eligible for the TORPEDO-CF trial if a positive *P. aeruginosa* sample is isolated. These labels should be used to highlight that a positive *P. aeruginosa* sample should be stored on nutrient agar slopes for a minimum of 28 days to allow for potential participants to be randomised onto the trial. Once randomisation has occurred it is the responsibility of the PI or delegated member of the research team to inform the microbiology laboratory that the appropriate *P. aeruginosa* isolate should be sent to Public Health England for genotyping. The original sample taken for diagnosis of *P. aeruginosa* infection will be used as the reference strain if *P. aeruginosa* re-occurs after eradication.

All subsequent positive *P. aeruginosa* isolates should be stored on nutrient agar slopes and sent to PHE for genotyping to see if the participant has been re-infected with the same strain of *P. aeruginosa* as before, or if different a *P. aeruginosa* genotype has been isolated.

7.4.4.1.2 Consumables provided

Participating CF centres will be provided with high visibility labels, nutrient agar slopes, identification labels and postage paid Royal mail safe boxes that can be used to post the sample to PHE.

Microbiology laboratories can request further stocks directly from the MC CTU or via the PI or delegated research staff at that centre.

7.4.4.1.3 Transport of samples to PHE

Nutrient agar slopes should be labelled with the participant's randomisation number and initials and sent via first class post to PHE (postage paid royal mail safe boxes will be provided pre-labelled with the PHE address).

7.4.4.2 Genotyping of P. aeruginosa - Sites outside of the UK

Due to the potential regulatory difficulties surrounding posting human tissue samples across country borders sites outside the UK will not send P. aeruginosa isolates to PHE in the UK for genotyping.

In countries / sites (outside of the UK) where genotyping of P. aeruginosa isolates is standard practice, the feasibility of transferring genotyping data for recruited patients to PHE will be explored as part of the site set-up process.

If deemed feasible, prior to transfer, the process for transferring genotyping data to PHE and the format / content of the data files themselves will be reviewed and agreed by the local site, PHE and TMG to ensure that the UK Data Protection Act 1998 and any relevant country-specific regulatory provision is followed.

7.5 Loss to Follow-up

If any of the trial participants are lost to follow up contact will initially be attempted through the PI or delegated research staff at each centre. If the lead investigator at the trial centre is not the participants usual clinician responsible for their specialist care then follow up will also be attempted through this latter clinician. Where these attempts are unsuccessful, the participants GP will be asked to contact the patient or the participants' family to provide follow up information to the recruiting centre. This information will be included on the Patient Information Sheet. Wherever possible, information on the reason for loss to follow up will be recorded.

7.6 Trial Closure

The end of the trial will be considered as the date of the final database lock. At the time of database lock, data entry privileges are withdrawn from the trial database.

The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (ISDMC).

8 STATISTICAL CONSIDERATIONS

8.1 Introduction

A separate and full Statistical Analysis Plan (SAP) will be developed prior to the final analysis of the trial. The SAP will be agreed by the TSC before being sent to the IDSMC for comment and approval.

8.2 Method of Randomisation

Participants will be randomised using a secure (24-hour) web based randomisation programme controlled centrally by the MC CTU to ensure allocation concealment. Randomisation lists will be generated in a 1:1 ratio using simple block randomisation with random variable block length. Factors within this protocol that are being used to stratify randomisation will not be disclosed to prevent prediction in this open trial.

8.3 Outcome Measures

Primary

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

Secondary

- Time to reoccurrence of original *P. aeruginosa* infection
- Re-infection with a different genotype of *P. aeruginosa*
- Lung function - FEV₁, FVC, FEF₂₅₋₇₅
- O₂ saturation
- Growth and nutritional status – height, weight and body mass index
- Number of pulmonary exacerbations*
- Admission to hospital
- 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 allocated treatment has finished (other than 14 days spent on initial IV treatment)
- Quality of life (CFQ)
- Utility (EQ-5D)
- Adverse events
- Other sputum/cough Microbiology (Methicillin resistant *Staphylococcus aureus* (MRSA), *Burkholderia cepacia* complex, Aspergillus, Candida Infection)
- Cost per patient (from NHS perspective)
- Incremental cost effectiveness ratio (cost per successfully treated patient, cost per QALY)
- Carer burden (absenteeism from education or work)
- Participant burden (absenteeism from education or work)

*Definition of pulmonary exacerbations listed in section 3.2

8.4 Sample Size

The sample size calculation is based on the primary outcome of initial eradication following start of allocated treatment and continued eradication until 15 months after the start of allocated treatment. Data on eradication three months post start of treatment and 12 months following end of treatment was obtained from an audit conducted on all current CF participants at Alder Hey Children's Hospital (Provided by Louisa Heaf and Kate Davenport), dating back to 1995, treated according to a standard UK CF Trust Protocol. Data on 48 children were collected with 77% (37/48) having eradicated the infection three months following treatment and 58% (28/48) continuing to remain infection free at twelve 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 a difference between the control group (oral ciprofloxacin) and the treatment group (IV) of 20% (a difference between 55% and 75%), 128 participants are required in each group. A 20% difference between the two treatment regimes would be of clinical importance, since the more intensive IV treatment would need to be justified by such a substantial benefit. Based on the experience of the TOPIC²⁵ trial in which five participants out of the 244 (2%) who were randomised did not provide primary outcome data for the intention to treat analysis, we expect that the number of participants who will not provide data for the primary outcome during the TORPEDO-CF trial will be quite small. We would expect less than 10% not to provide primary outcome data in total; this will include reasons such as intolerance or withdrawal of consent. In estimating that 10% will potentially not provide primary outcome data, we feel that this may be overestimated but it is important that we are prepared for all eventualities to ensure that the trial is adequately powered in terms of the primary outcome. We will endeavour to follow-up all randomised participants, regardless of treatment tolerance.

Based on the results on the feasibility study conducted for the HTA²⁰, it was found that the median rate per annum for the number of first or new growths of *P. aeruginosa* in adults was 3% (range 1% to 8%) and in children was 10% (range 2.5% to 23%). Applying these estimates to the UK CF population (based on figures from 22 adult centres, 28 paediatric centres and 2 centres with combined populations) would enable a possible 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 number of eligible participants as presented in this report would be approximately 54 adults and 209 children per annum. Over half of these centres have thus far shown an interest in participating in the trial and hence we would expect to see approximately half the numbers from the entire potential population and therefore we would require 33 months for recruitment.

8.5 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. These analyses will be performed by the MC CTU trial statistician. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further participants or further follow-up. A decision to discontinue recruitment, in all participants or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is

made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. All closed results (results split by treatment) will be confidential to the IDSMC members and will not be for review by the trial management group (except the statistical team preparing the IDSMC report). The IDSMC members will make formal recommendations to the trial working group and TSC (TSC, see section 15) regarding the continuation of recruitment of participants into the study and will comply with a trial-specific IDSMC charter according to ICH GCP guidelines. The IDSMC will be asked to consider patient safety, particularly any Sudden Unexpected Serious Adverse Reactions (SUSARs) leading to death, alongside treatment efficacy when making their recommendation regarding continuation, amendment or discontinuation of the trial.

A report shell will be discussed with the IDSMC at its first meeting before recruitment starts and circulated prior to the first report being produced. Sign off of the report shell will be formally documented.

8.6 Analysis Plan

All analyses will be pre-specified in detail in the statistical analysis plan and agreed by both the TSC and the IDSMC.

The primary analysis will use the principle of intention to treat based on all the randomised participants, as far as is practically possible. If consent for treatment is withdrawn, but the participant is happy to remain in the study for follow-up, then they will be followed up until completion. However, if they decide to withdraw consent completely then the reasons for withdrawal of consent will be collected (if possible) and reported for both groups.

For a participant to have a 'success' on the primary outcome, they will need to have had their initial *P. aeruginosa* infection eradicated following treatment at three months and remain infection free until 15 months following start of allocated treatment. *P. aeruginosa* eradication will be reported in terms of the relative risk of success and its 95% confidence interval. For the secondary outcomes, continuous data will be reported as a difference in means and binary data will be reported in terms of the relative risk each with 95% confidence intervals. Time to re-occurrence of *P. aeruginosa* infection will be summarised by Kaplan-Meier curves for each treatment group and compared overall using logrank tests and survival regression methods. Missing data will be monitored and strategies developed to minimise its occurrence. Missing data will be handled by considering the robustness of the complete case analysis to sensitivity analyses using various imputation assumptions. However, these will be informed by data collected on the reasons for missing data.

9 PHARMACOVIGILANCE

9.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event (AE)

Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)

An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics for that product.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR)

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death;
- is life-threatening* (subject at immediate risk of death);
- requires in-patient hospitalisation or prolongation of existing hospitalisation**;
- results in persistent or significant disability or incapacity, or;
- consists of a congenital anomaly or birth defect;
- Other important medical events***

**'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

***Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.*

****Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition*

Suspected Serious Adverse Reaction (SSAR)

An adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out in the summary of product characteristics for that product.

“Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics for that product.

9.2 Notes on Serious Adverse Reactions

9.2.1 Events to be reported on a SAR report form include

Include the following only if they are possibly, probably or almost certainly related to the trial treatment:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event)
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

9.2.2 Events to be reported on a SAR report form do not include

- Any AE that has been assessed and judged by the investigator to be not serious
- Any SAE whose causal relationship to the trial treatment is assessed and judged by the investigator to be unrelated or unlikely to be related to the trial treatment
- Medical or surgical procedures- the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition
- Any occurrence of an AE resulting in admission where admission is due to social reasons rather than a clinical need

9.3 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.

Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities

Moderate: interferes with routine activities

Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 9.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

9.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 6.

If any doubt about the causality exists, the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the relevant regulatory authority will be informed of both points of view.

Table 6: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

For the purpose of pharmacovigilance reporting in TORPEDO-CF, an AE whose causal relationship to the randomised study drug/s assessed by the investigator as “possible”, “probable”, or “almost certainly” is classed as an Adverse Reaction (AR) and is reportable for TORPEDO-CF (see section 9.7).

9.5 Expectedness

Expectedness should be assessed for all serious adverse reactions; refer to the relevant SPC for a list of expected adverse reactions for each study treatment.

All events judged by the investigator to be possibly, probably, or almost certainly related to the IMP and graded as serious will be assessed for expectedness by the Chief Investigator (or designated other specified in the protocol). If latter judged as **unexpected** (i.e. not listed in the relevant SPC) it should be reported as a SUSAR.

9.6 Reporting Procedures

The reporting timeframe starts when the participant commences their allocated treatment (i.e. once the participant receives their first dose of medication) and continues for 28 calendar days after cessation of allocated trial treatment (IMP & NIMP).

All adverse events should be recorded on the adverse event CRF and submitted to the MC CTU as per routine schedule.

Serious Adverse Events should **only** be reported on a Serious Adverse Reaction (SAR) report form where the causal relationship to the trial treatment has been assessed and judged by the investigator to be possibly, probably or almost certainly related to the trial treatment and the event has occurred within the reporting timeframe.

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the MC CTU in the first instance. Please refer to [Figure 2: Reporting Procedures](#), to determine reporting requirements.

Deleted: Figu

9.6.1 Non serious ARs/AEs

All such events, whether expected or not, should be recorded on an Adverse Event Form, which should be transmitted to the MC CTU within seven days of the form being updated.

9.6.2 Serious ARs/ SUSARs

SARs and SUSARs to any of the trial treatments should be reported within 24 hours of the local site becoming aware of the event. All reported SARs will be assessed for expectedness by the Chief Investigator (or designated other specified in the protocol) and if judged as unexpected will be reported by the coordinating centre as SUSARs (see section 9.4).

The SAR form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should assign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

All SUSARs occurring during the study will be notified to the relevant regulatory authorities and Research Ethics Committees (RECs) for all participating sites according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs, SAEs or SARs as required to their Research and Development Office.

SARs and SUSARs must be reported by faxing a completed SAR report form within 24 hours of becoming aware of the event to the MC CTU
Fax: +44 (0)151 282 4721

9.7 Reporting of Pregnancy

Any pregnancy which occurs up to 28 calendar days after cessation of allocated trial treatment should be reported to the MC CTU using a pregnancy CRF within 24 hours of the site becoming aware of its occurrence. All reported pregnancies need to be followed up until after the outcome using the pregnancy CRF. If a reported pregnancy has been assessed and judged by the investigator to be possibly, probably or almost certainly related to any of the trial treatments it must also be reported on the SAR report form.

The investigator should contact the participant to discuss the risks of continuing with the pregnancy and the possible effect to the foetus. Appropriate Obstetric care should be arranged.

Pregnancies must be reported by faxing a completed pregnancy CRF within 24 hours of the PI becoming aware of the event to the MC CTU
Fax: +44 (0)151 282 4721

9.8 Reporting of Death

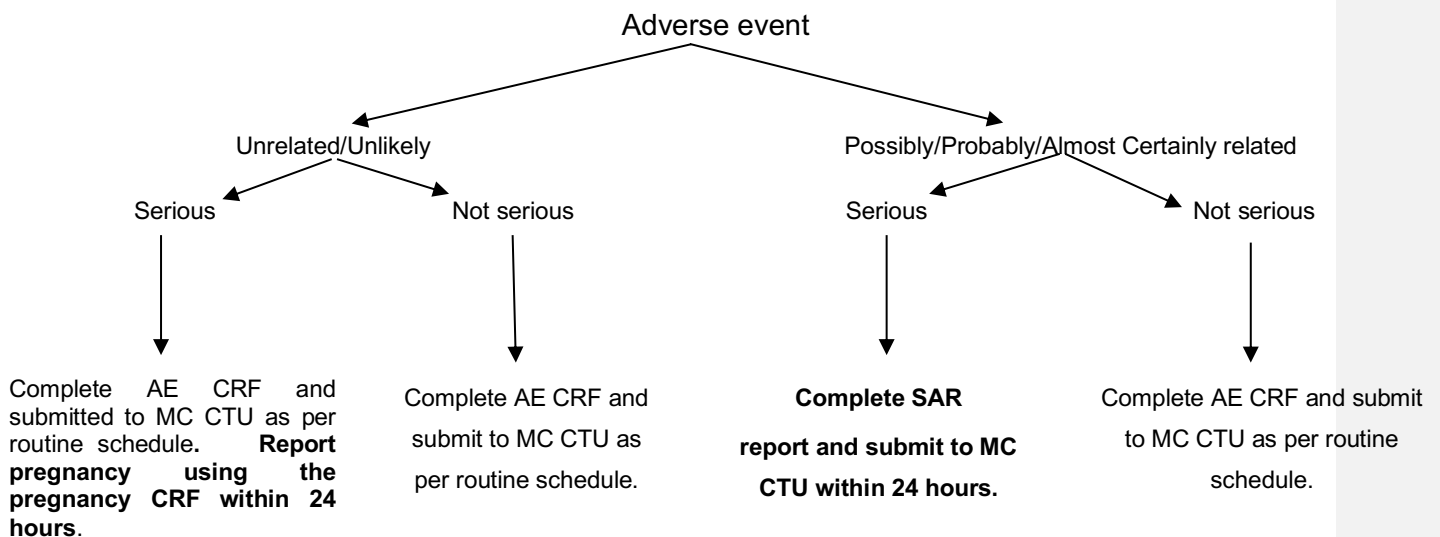
Any deaths which occur during the study should be reported to the MC CTU using a death CRF within 7 days of the site becoming aware of its occurrence. If a patient's death occurs up to 28 calendar days after cessation of allocated trial treatment and it has been assessed and judged by the investigator to be possibly, probably or almost certainly related to any of the trial treatments it must also be reported on the SAR report form.

9.9 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the participant to be stable.

When reporting SARs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

Figure 2: Reporting Procedures



9.10 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the reporting timeframe of the study, regardless of their relationship to study product.

All AEs that has been assessed and judged by the investigator to be not serious should be reported on an AE form and returned to MC CTU as per routine schedule.

All SAEs that have been assessed and judged by the investigator to be unrelated or unlikely to be related should be reported on an AE form and returned to MC CTU as per routine schedule unless it is a pregnancy (see section 9.7 for reporting procedures).

All SARs and SUSARs must be reported immediately by the investigator to the MC CTU on an SAR report form.

Minimum information required for reporting:

- Study identifier
- Study centre
- Participant randomisation number
- A description of the event
- Date of onset
- Current status
- Study drug(s)
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment
- SAR outcome

- i. All AEs should be assessed for seriousness and causality by a designated investigator, a physician named on the delegation log as responsible for reporting SAEs and making trial related medical decisions. If the AE is assessed and judged by the investigator to be a SAR or SUSAR a SAR report form should be completed by a designated investigator. In the absence of the designated investigator, the form should be completed and signed by a delegated member of the site trial team. In the event that an appropriate delegated investigator is not available to complete the assessments, the MC CTU should be contacted as soon as possible.

Prior to submission of the completed SAR report form to the MC CTU, the trial co-ordinator should be notified of the occurrence of the SAR/SUSAR via telephone on:

Telephone number: +44 (0)151 282 4714 (Office Hours)

. Send the SAR form form as soon as possible by fax (within 24 hours or next working day) to the MC CTU:

Fax number: +44 (0)151 282 4721

- ii. The responsible investigator must **notify** their R&D department of the event (as per standard local procedure).
- iii. In the case of a SAR or SUSAR the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
- iv. Follow-up information is noted on another SAR report form by ticking the box marked 'follow-up' and faxing to the MC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
- v. The participant **must** be identified by trial number, date of birth and initials only. The participant's name **should not** be used on any correspondence.

9.11 Responsibilities – MC CTU

The MC CTU is undertaking duties delegated by the trial sponsor, University Hospitals Bristol NHS Foundation Trust and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities and, if required, the research ethics committees as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the MC CTU is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the MC CTU first becoming aware of the reaction.
- A list of all SARs must be reported in line with national requirements (see supplementary document TORPEDO Pharmacovigilance Reporting Guidance).

It is recommended that the following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
 - a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
 - b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
 - c. A major safety finding from a newly completed animal study (such as carcinogenicity).
 - d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the MC CTU will liaise with the Chief Investigator (or delegated other specified in the protocol) who will evaluate all SARs and SUSARs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs expedited as appropriate. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

Participant safety incidents that take place in the course of research should be reported in accordance with local reporting procedures by each participating institution (e.g. in the UK they may be reported to the National Patient Safety Agency (NPSA)).

9.12 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of SAE reporting rates across sites. The coordinating centre will send Developmental Safety Update Reports containing a list of all SARs to regulatory authorities and RECs as applicable. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the coordinating centre to carry out site visits if there is suspicion of unreported ARs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines.

Copies of the safety reports will be sent to the Principal Investigator at all institutions participating in the trial.

10 ETHICAL CONSIDERATIONS

10.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

We consider the specific ethical issues relating to participation in this trial to be:

Informed consent in a paediatric population: The parent or legal representative of the child will have an interview with the investigator, or a delegated member of the investigating team, during which opportunity will be given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. They will be provided with written information and contact details of the study nurse, from whom further information about the trial may be obtained, and will be made aware of their right to withdraw the child from the trial at any time without the child or family being subject to any detriment in the child's treatment. Children will receive information, according to their capacity of understanding, about the trial and its risks and benefits and their assent will be obtained, where appropriate.

Use of IV instead of oral antibiotic treatment: Participants allocated to IV treatment will be inconvenienced, as they will be treated as an inpatient rather than an outpatient. This could lead to time off school and/or work for participants and their families. The treatment is also more invasive than simply taking oral medication. However, IV antibiotic treatment is used as standard for some participants so those randomised to this intervention in the trial may have been treated in the same way if they had not been participating in the study. The risks and inconveniences of both possible trial treatments will be fully explained to the participant (and their family, where appropriate) during the informed consent discussion and will be outlined in the patient information sheet and consent form (PISC).

Use of Ciprofloxacin in children under five years of age: In clinical practice ciprofloxacin is commonly used for the eradication of *P. aeruginosa* in children below 5 years of age and including children below one year of age. The UK CF Trust 2009 Guideline recommends ciprofloxacin 15mg/kg twice daily for up to three months duration in children aged 1 month to 5 years with first *P. aeruginosa* isolation¹¹. The inclusion of these younger children within this study is justifiable as these are the children with potentially more to gain through delayed acquisition of persistent infection especially with the more resistant biofilm-producing (mucoid) *P. aeruginosa*. The result of this study will not be generalisable to this age group if these children are excluded from study. Children prescribed medication off license will be closely monitored whilst on treatment and any adverse events will be recorded and reported.

Collection of samples: The sample collection for the genotyping study will be part of the main consent process as the time to recurrence of *P. aeruginosa* infection is the primary outcome of this trial. The consent obtained will be related to sample collection for genotyping of *P. aeruginosa* isolates only. The samples collected will not be used for any other studies and participant identifiers will not be disclosed to any laboratory staff, only the hospital and MC CTU will have access to this information.

10.2 Ethical Approval

The trial protocol has received the favourable opinion of the London Research Ethics Committee (MREC) but must undergo independent review at the R&D offices at participating

sites. The local R&D office should be sent the appropriate SSI form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to MC CTU before the site is initiated and participants recruited.

Consent and or proxy consent from the patient or legally acceptable representative should be obtained prior to participation in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Age and stage-of development specific Patient Information and Consent Forms (PISC) should also be implemented and participant assent obtained where appropriate. The right of the participant or their legal representative to refuse consent for themselves or a minor to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant or their legal representative remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing the further treatment.

10.3 Informed Consent Process

10.3.1 General

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all participants participating in MC CTU coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

All Patient Information Sheets and Consent (PISC) forms used in the TORPEDO-CF trial will be made available in the native language of countries participating in the trial (with the exception of Wales where the majority language will be used), see supplementary document TORPEDO Trial Procedure for Translating Documents.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to participants by staff with experience in obtaining informed consent. Where appropriate, age-and-stage-of-development appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient (parent/legal representative in the case of minors) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient (parent/legal representative in the case of minors). This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. All participants will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the study with their surrogates and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided.

Both the person taking consent and the participant (parent or legal representative in the case of minors) must then personally sign and date the consent form. A copy of the informed

consent document will be given to the participant and their legally acceptable representative for their records. The original copy will be filed in the participant's notes and a further copy of the signed consent form will be given to the participant. One final copy of the consent form should be faxed or posted to the MC CTU. Where country specific regulations prohibit the transfer of the consent form, the consent form will not be sent to the MC CTU, instead a consent form checklist will be completed by the site and faxed in its place. The regulations will be clarified on a site by site basis at study initiation. Consent forms and / or consent form checklists where appropriate will be checked for completeness by designated staff members on the delegation log at the MC CTU.

10.3.2 Assent in minors

If capable, and under appropriate circumstances, minors should be approached to provide assent by a member of the research team with experience with minors. Age-and-state-of-development IEC-approved Patient information Sheet and Assent forms, describing (in simplified terms) the details of the trial treatment, trial procedures and risks should be used. The minor should personally write their name and date the assent form, which is then signed by the parent/legal representative and the researcher.

Assent forms do not substitute for the consent form signed by the participant's legally acceptable representative. Assent should be taken where appropriate and documented in the patient notes, however the absence of assent does not exclude the participant provided consent has been obtained from the parent/legal representative.

10.4 Transition from paediatric to adult in relation to consent

For the purposes of the trial, a minor is defined as under 16 years. Should a trial participant turn 16 during the course of the trial they will need to be re-consented as an adult. If during the course of the trial the participant moves from a paediatric CF centre to an adult CF centre that is taking part in the study, they will need to be re-consented by the new centre (see section 4.3.1 for details on participant transfers).

10.5 Study Discontinuation

In the event that the study is discontinued, participants will be treated according to usual standard clinical care. Participants who withdraw early from trial treatment but continue to allow follow-up as part of normal clinic visits will still have data collected as part of the trial. If participants withdraw from the trial completely all data collected up until the time of withdrawal will be anonymised and included in the study analysis.

11 REGULATORY APPROVAL

This trial has been registered on EudraCT and Clinical Trial Authorisation (CTA) will be sought individually from the National Competent Authority in each country taking part in the study.

The EudraCT reference is 2009-012575-10.

12 TRIAL MONITORING

“The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring, before, during and after the trial; however central monitoring in conjunction with procedures such as investigators’ training and meetings and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.” (ICH GCP 5.18.3)

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. Details of the monitoring to be carried out for the TORPEDO-CF trial are included in the TORPEDO-CF Trial Monitoring Plan.

12.1 Risk Assessment

A risk assessment is performed for each trial coordinated by the MC CTU to determine the level and type of monitoring required for specific hazards. The type of trial monitoring should be specific to the individual trial and can take the form of on-site visits or central monitoring. In accordance with the CTRC SOP TM005 this trial has undergone a risk assessment, completed in partnership between:

- Representatives of the Trial Sponsor;
- Chief Investigator;
- Trial Coordinator and supervising Senior Trial Manager;
- Trial Statistician and Supervising Statistician;
- MC CTU Director.

In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment is expressed as a percentage, assigned according to the following categories:

- Score $\leq 33\%$ = Low risk
- Score ≥ 34 to $\leq 67\%$ = Moderate risk
- Score ≥ 68 to $\leq 100\%$ = High risk

The outcome of the TORPEDO-CF trial risk assessment was a score of **19.46%**. Therefore, it has been judged to be a **low risk** clinical trial. This level of risk has determined the approach to trial monitoring described in this section.

12.2 Source Documents

Source data: *All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*

Source documents: *Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*

In order to resolve possible discrepancies between information appearing in the CRF and any other participant related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. The following data recorded in the CRF should be consistent and verifiable with source data in source documents *other* than the CRF (e.g. medical record, laboratory reports and nurses' notes). The following parameters that will be documented in the CRF are not source data:

- Relevant medical history and diagnosis (medical notes are source documents)
- Laboratory / Microbiology (medical notes are the source documents)
- Data for evaluation of eligibility criteria (medical notes are source documents)
- Physical examinations and assessments (medical notes are source documents).
- Concomitant medications (including changes) and diagnoses (medical notes are source documents)
- Dispensing of trial medication (pharmacy records are source documents)
- Adverse events (medical notes are source documents)

Therefore, for data where no prior record exists and which is recorded directly in the CRF, the CRF e.g. CFQ Questionnaires, EQ-5D Questionnaires, Treatment Diary and Health Service Diary will be considered the **source document**, unless otherwise indicated by the investigator. All such exemptions should be identified prior to the clinical phase of the trial. In addition to the above, date(s) of conducting informed consent (plus assent where appropriate and if taken) process including date of provision of patient information, screening number, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically, i.e. when treatment is allocated to the patient).

12.3 Data Capture Methods

Trial data will be captured using paper CRFs. The original CRF should be sent to the MC CTU and a copy representing the site copy that should be retained at site.

12.3.1 Case Report Forms

The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. **DO NOT ERASE OR WHITE OUT ERRORS.** For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Once each section of the CRF has been fully completed and signed off a copy should be taken to be kept in the CRF folder. The originals should then be sent to the MC CTU within 7 days. If data queries are raised after the originals have been sent to the MC CTU, these queries should be responded to via the data query form, with the copies left unaltered.

In the case of the following sections of the CRF which are updated on an ongoing basis, photocopies should be forwarded to the MC CTU as and when changes have been made;

- Adverse event
- Concomitant medications
- Microbiology
- Medical History

The originals should only be sent to the MC CTU when fully completed.

12.3.2 Participant completed questionnaires / diaries

Participants complete the following questionnaires at specified time points throughout the trial:

- Quality of Life
- Health Questionnaire (EQ-5D)
- Treatment Diary
- Health Service Diary

The participant initials and randomisation number should be clearly labelled on all documents. The 'centre use only' section on the front cover of the questionnaire and diaries should also be completed. This records the dates given/completed and the type of visit (if applicable). Diaries and questionnaires should be returned to the MC CTU alongside the relevant CRF pages where possible (e.g. 3 month Health Service Diary forwarded with the 3 month follow-up CRF pages).

12.4 Data Monitoring at MC CTU

Data stored at MC CTU will be checked for missing or unusual values (range checks) and checked for consistency. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the MC CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation of authority log). Sites will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to MC CTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at the MC CTU to ensure reliability and validity of the trial data, which will be detailed in the trial monitoring plan.

Participant completed questionnaires such as Treatment Diaries, Health Service Diaries and Questionnaire booklets are considered source data as they are completed by the participant and or their Parent /Caregiver. Data queries will be raised where the CRF indicates that a questionnaire or diary has been completed but has not yet been received by the MC CTU. The reason for Participant non-compliance in completing diaries or questionnaires should be recorded in the appropriate section of the CRF.

12.4.1 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Case report forms, diaries, questionnaires and microbiology samples will be labelled with the participant's initials and unique trial screening and/or randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The MC CTU will be undertaking activities requiring the transfer of identifiable data:

Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent/assent forms being supplied to the MC CTU by recruiting centres, which requires that name data will be transferred to the MC CTU.

This transfer of identifiable data is disclosed in the PISC. The MC CTU will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

12.4.2 Direct access to data

In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Because this affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

12.4.3 Quality Assurance and quality control of data

This trial has undergone a risk assessment, the outcome of which indicates it to be a low risk trial. As such, site visits will be conducted and source data verification performed if indicated to be required as a result of central statistical monitoring processes.

To this end:

- The Trial Co-ordinator will verify appropriate approvals are in place prior to initiation of a site and that relevant personnel have attended trial specific training
- The Trial Co-ordinator will check safety reporting rates between centres
- The Trial Co-ordinator is to monitor screening, recruitment and drop-out rates between centres
- The Trial Co-ordinator will oversee data entry consistency checks and follow-up of data queries.

12.5 Records Retention

(ICH GCP 4.9.5) "Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no ending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained".

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File, until the MC CTU informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The MC CTU undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

13 INDEMNITY

The TORPEDO-CF trial is sponsored by University Hospitals Bristol NHS Foundation Trust, co-sponsored by University of Liverpool (for sites outside of the UK) and co-ordinated by the MC CTU in the University of Liverpool.

Sponsor: UK only

The University Hospitals Bristol NHS Foundation Trust cover for negligent harm is in place through the Clinical Negligence Scheme for Trusts. For NHS sponsored research HSG(96)48 reference no.2 refers 'If there is any negligent harm during the study when the NHS body owes a duty of care to their person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim'.

For the purposes of the study clinical negligence is defined as:

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

Co-Sponsor: Non-UK Sites

University of Liverpool cover for negligent harm.

Equivalent cover to that provided by the Clinical Negligence Scheme for UK Trusts should be confirmed to be in place for non-UK sites during site suitability assessment and this cover must be summarised in the sponsor-site contract.

14 FINANCIAL ARRANGEMENTS

This study is funded by the Health Technology Assessment Programme (HTA) of the Department of Health. Contractual agreements will be in place between the sponsor and collaborating sites in the UK that will incorporate financial arrangements.

Non-UK sites will not be financed by the HTA; the sponsor is responsible for determining that sufficient funding is in place to support set-up, co-ordination and monitoring (if necessary) prior to site opening. Financial arrangements will be described in contracts.

15 TRIAL COMMITTEES

For details of trial committees, membership and responsibilities see separate document entitled 'Trial Committees'.

16 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (<http://www.icmje.org/>) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial. The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

17 PROTOCOL AMENDMENTS

17.1 Version 1 (21/08/2009)

Original version approved by MHRA & MREC.

17.2 Version 2 (15/02/2010)

Amendment and clarification (V.10 (21/08/2009) to V2.0 (15/02/2010))

Page Number	Amendment Comment
Throughout	Updated version and date; correction of typographical errors
5	Addition of Miss Michaela Blundell to contacts table
11	CACE added to list of abbreviations
11	Removal of IB and LREC from list of abbreviations
11	list of abbreviations updated
13	Phase: text "III" replaced with "IV" to reflect MHRA classification
13	Study design: text 'ten' replaced with "fourteen" to reflect clinical practice
13	Centres & distribution: text "upto 45" replaced with 'CF'
13	Main objectives: text "ten" replaced with "fourteen" to reflect clinical practice
Throughout	Inclusion 1: text "(clinical feature + Cl- > 60 mmol/L + 2 CFTR mutations)" inserted
Throughout	Inclusion 3: text "or" replaced with "and"
Throughout	Inclusion 5b: text "has not isolated P. aeruginosa from cough, sputum or bronchoalveolar lavage" 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" Inclusion 6: Text "three weeks after the clinical team has been informed that P. aeruginosa has been isolated replaced with "21 days"
Throughout	Exclusion 1: text "or" deleted, text "or colistin" inserted
Throughout	Exclusion 2: text "or" deleted, text "or colistin" inserted
Throughout	Exclusion 3: text "or" deleted, text "or colistin" inserted
Throughout	Exclusion 4: text "The", "should not be" deleted
Throughout	Exclusion 5: text "that may become available" deleted
Throughout	Exclusion 7: "Previous participation in another intervention trial within four weeks of taking part in TORPEDO-CF" inserted
Throughout	Secondary outcome 1: text "original" inserted

Throughout	Secondary outcome 1: text “time to new P. aeruginosa infection” replaced with “re-infection with a different genotype of P. aeruginosa”
Throughout	Text “Re-infection with a different strain of P. aeruginosa” deleted
Throughout	Secondary outcome 15: text “school” replaced with “education”
14	Secondary outcome 16: text “Participant burden (absenteeism from education or work)” inserted
17	Section 1.1: Change to duration of treatment to reflect clinical practice ‘ten’ replaced with ‘fourteen’
18	Section 1.2: Change to duration of treatment to reflect clinical practice “ten” replaced with “fourteen”
18	Section 1.3: Change to duration of treatment to reflect clinical practice “ten” replaced with “fourteen”
18-1	Section 1.4: text “with exception of ciprofloxacin, which is being used in this study off licence (SPC: states maximum treatment duration of fourteen days). However, use of ciprofloxacin for eradication of P. aeruginosa infection for periods of upto three months is already a established standard practice” deleted
19	Section 1.4 text “designated” replaced with “delegated”
19	Section 1.4.1 text “of development of”, “of”, “all” deleted
20	Section 2.1: text “positive SSA &” deleted
20	Section 2.1: text “signed non-commercial agreement between centre & sponsor” inserted
20	Section 2.1: text “signed contract between site and sponsor’ deleted
23	Section 4.3.1: text “their” deleted
23	Section 4.3.3: text “unless the patient explicitly states that this is not their wish. A Premature Discontinuation CRF, the appropriate scheduled follow-up or Unscheduled Visit CRF and the appropriate CFQ and EQ-5D should be completed and returned to the MCRN CTU”
23	Section 4.3.3: text “and the MCRN CTU should be informed in writing by the responsible physician and a Premature Discontinuation withdrawal CRF should be completed” deleted
24	Section 5.1: text “Screening” replaced with “Recruitment Strategy / Baseline”
24	Section 5.1: text “will” replaced with “should”
	Section 5.1: text “and returned to the MCRN CTU on a monthly basis” inserted
24	Section 5.1: text “of receipt confirmation of their diagnosis of P. aeruginosa positive microbiology report” replaced with “from the date of a P. aeruginosa positive microbiology report. Full details of the baseline assessment required before randomisation are listed in section 7”
	Section 5.1: text “The following assessment should be performed during screening: Confirmation of cystic fibrosis diagnosis Confirmation of P. aeruginosa infection Fulfilment of inclusion / exclusion criteria Obtain written informed consent Potential participants who fulfil the screening requirements will be eligible for randomisation” deleted
24	Section 5.1: text “ Participants who have given informed consent and have been found to comply with all inclusion and exclusion criteria will be randomised using the web randomisation process detailed in section 5.3” inserted
24	Text: “ Enrolment /Baseline The following baseline assessment should be performed: Verification that the eligibility criteria for randomisation are fulfilled Completed physical examination performed Assessment of medical history

	A check of concomitant medications prescribed / administered Participants who have given informed consent and have been found to comply with all inclusion and exclusion criteria will be randomised using the web randomisation process detailed in section 5.3" inserted" deleted
24	Section 5.2: text "Randomisation will be stratified by centre." deleted
24	Section 5.2: text "and the PI or Co-Investigator (where applicable)" inserted
25	Section 5.2: text "If this is not possible at the time (for example out of hours) then each centre will be provided with pressure sealed emergency randomisation envelopes. These envelopes will only be accessed should a temporary problem be experienced with the web based randomisation system." deleted
25	Section 5.2: text " Or via email on helpdesk@mcrnctu.org.uk " inserted
26	Section 6.1: text "maximum 660 mg/day" inserted
26	Section 6.2.1.1: text " Finished product (Brand) name Ceftazidime / Fortum / Kefadim" deleted
26	Section 6.2.1.1: text " s" and "(as pentahydrate)" deleted
26	Section 6.2.1.1: text "Please refer to the appropriate SPC" deleted
26	Section 6.2.1.1: text "Manufacturer's name Wockhardt, GlaxoSmith Kline, Flynn Pharma" deleted
27	Section 6.2.1.1: text "Unopened: Do not store above 25°C. Keep the vials in the outer carton" and "for shelf life" deleted
27	Section 6.2.1.1: text " Please refer to the product insert for Ceftazidime" deleted
27	Section 6.2.1.2: text "Finished product (Brand) name Tobramycin" deleted
27	Section 6.2.1.2: text "Manufacturer's name Hospira UK Limited" deleted
27	Section 6.2.1.2: text " Manufacturers" and " 24 hours at 24°C in the presence of light" deleted
27	Section 6.2.1.2: text "24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions" deleted
27	Section 6.2.1.2: text "Please also refer to the product insert of tobramycin" deleted
27	Section 6.2.1.2: text "also" deleted
28	Section 6.2.1.3: text " Ceftazidime should be reconstituted and used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions" deleted
28	Section 6.2.1.3: text "Tobramycin may be administered by withdrawing the appropriate dose directly from the vial. Tobramycin injection may be given by intravenous infusion or by direct intravenous injection. When given by infusion, tobramycin injections may be diluted to volumes of 50-100ml for adult doses. The diluted solution should be infused over a period of 20-60 minutes avoiding admixture with any other drug" deleted
28	Section 6.2.1.4 text "The investigator is fully responsible for the Investigational Products at the site. Dispensing of medication may be delegated to, e.g. a hospital pharmacy as locally applicable" inserted
28	Section 6.2.1.4 text "(as a minimum batch number, expiry date and dispensing date must be documented)" inserted
28	Section 6.2.1.4 text "Pharmacy will use TORPEDO-CF dispensing labels, including information such as participant name or initials, pharmacy address, telephone number and date of dispensing. The pharmacy must complete, sign and date the dispensing log. A second member of the pharmacy team must countersign the log to document

	dispensing. The pharmacy department will be responsible for the management and recording of destruction of all returned trial medication according to local hospital procedures." deleted
28	Section 6.2.1.4 text "Investigational Products must be stored in a safe and secure place (only accessible to authorized personnel), and proper dispensing arrangements must be made." deleted
28	Section 6.2.1.5 text "Arm A" and "Adult CF" deleted
28	Section 6.2.1.5 text "or those who would prefer to have home IV" inserted
28	Section 6.2.1.5 text "home IV" inserted
28	Section 6.2.1.5 text "to the" replaced with " at the next scheduled follow up visit"
28	Section 6.2.1.5 text "CF designated research staff who will record" replaced with "to assess" and "this information should be recorded on the treatment CRF"
28	Section 6.2.1.5 text "All returned medication should be destroyed as per local procedure" inserted
29	Section 6.2.1.6: text "e.g." replaced with "e.g."
29	Section 6.2.1.7: text "Medication" inserted
29	Section 6.2.1.7: text "This will be reassessed at each trial visit by the PI or delegated person. Any new medication introduced or any changes to current medications should be documented" deleted
29	Section 6.2.1.7: text "The PI or delegated research member should reassess concomitant medications at each trial visit. Any new medications introduced or any changes to current medication should be documented on the CRF. At each follow-up visit a photocopy of the original Concomitant Medication CRF should be sent to the MCRN CTU within 7 days. An original copy of the CRF should only be sent to the MCRN CTU on completion of the follow-up" inserted
29	Section 6.2.2.1: text "Finished product (Brand) name Ciproxin" and "s" and "manufacturers" deleted
30	Section 6.2.2.1: text "Manufacturer's name Bayer plc" deleted
30	Section 6.2.2.1: text "Please refer to the product insert for Ciprofloxacin" and "also" deleted
30	Section 6.2.2.2: text "Ciprofloxacin tablets and suspension can be taken independent of mealtimes. If taken on an empty stomach the active substance is absorbed more rapidly. Ciprofloxacin should not be taken with dairy products or mineral fortified fruit juice." deleted
30	Section 6.2.2.3: text "Following randomisation the following accountability procedures at pharmacy will apply." deleted
30	Section 6.2.2.3: text "The investigator is fully responsible for the Investigational Products at the site. Dispensing of medication may be delegated to, e.g. a hospital pharmacy as locally applicable" inserted
30	Section 6.2.2.3 text "(as a minimum batch number, expiry date and dispensing date must be documented)" inserted
30	Section 6.2.2.3 text "Pharmacy will use TORPEDO-CF dispensing labels, including information such as participant name or initials, pharmacy address, telephone number and date of dispensing. The pharmacy must complete, sign and date the dispensing log. A second member of the pharmacy team must countersign the log to document dispensing. The pharmacy department will be responsible for the management and recording of destruction of all returned trial medication according to local hospital procedures." deleted
30	Section 6.2.2.3 text "Investigational Products must be stored in a safe and secure place (only accessible to authorized personnel), and proper dispensing arrangements must be made." deleted
30	Section 6.2.2.4 text "Arm B" inserted

30	Section 6.2.2.4 text “will” replaced with “should”, text “used and” deleted
30	Section 6.2.2.4 text “next study” replaced with “scheduled follow up”
30	Section 6.2.2.4 text “in the participants replaced with “on the Treatment”
30	Section 6.2.2.4 text “(Participant Treatment Diary 3: Arm B)” inserted
30	Section 6.2.2.4 text “Once the compliance checks have been completed and recorded, all returned medication will be delivered to pharmacy for destruction via their local procedures. All destroyed medication should be recorded on the trial specific destruction form” deleted and replaced with “All returned medication should be destroyed as per local procedure”
31	Section 6.2.2.6: text “Concomitant Medication” inserted
31	Section 6.2.2.6: text “Concomitant medications should be reassessed at each trial visit by the PI or designated research staff” replaced with “The PI or delegated person should reassess concomitant medications at each trial visit”
31	Section 6.2.2.6: text “At each scheduled (or unscheduled) visit a photocopy of the original Concomitant Medication CRF should be sent to the MCRN CTU within 7 days. An original copy of the CRF should only be sent to the MCRN CTU on completion of follow-up” inserted
31	Section 6.2.3: text “Finished product (Brand) name Promixin” deleted
32	Section 6.2.3: text “Manufacturer’s name Profile Pharma Limited” deleted
32	Section 6.2.3: text “Unopened: 2 years” replaced with “Please refer to the manufacturers SPC”
32	Section 6.2.3: text “Please also refer to the product insert for colistin. Please also refer to the current SPC provided as a separate document to this protocol”. deleted
32	Section 6.2.3.1: text “Following randomisation the following accountability procedures at pharmacy will apply.” deleted
32	Section 6.2.3.1: text “The investigator is fully responsible for the Investigational Products at the site. Dispensing of medication may be delegated to, e.g. a hospital pharmacy as locally applicable” inserted
32	Section 6.2.3.1: text “(as a minimum batch number, expiry date and dispensing date must be documented)” inserted
32	Section 6.2.3.1: text “Pharmacy will use TORPEDO-CF dispensing labels, including information such as participant name or initials, pharmacy address, telephone number and date of dispensing. The pharmacy must complete, sign and date the dispensing log. A second member of the pharmacy team must countersign the log to document dispensing. The pharmacy department will be responsible for the management and recording of destruction of all returned trial medication according to local hospital procedures.” deleted
32	Section 6.2.3.2 text “used and” deleted
32	Section 6.2.3.2 text “scheduled” inserted
32	Section 6.2.3.2 text “Treatment” inserted
32	Section 6.2.3.2 text “All returned medication should be destroyed as per local procedure” inserted
33	Section 6.2.3.2 text “All returned medication should be delivered to pharmacy for destruction via their local procedures. All destroyed trial medication should be recorded on the trial specific destruction form.” deleted
33	Section 6.5 text “As NIMPs do not fall within the definition of investigational medicinal products, Articles 13 and 14 of Directive 2001/20/EC are not directly applicable. Therefore, normal pharmacy labels should be used.” Inserted

33	Section 6.6: text "If a participant's treatment stops prematurely, the reason for discontinuation should be recorded on the Treatment CRF." inserted
34	Section 7.1.1: text "Participants" replaced with "patient"
34	Section 7.1.1: text "possible" deleted
34	Section 7.1.2 "Samples of respiratory secretions (sputum or cough swabs) should be sent for bacterial culture in line with normal hospital visits. Microbiology laboratories should culture bacterial samples both on enriched (e.g. blood agar) and on selective media in accordance with hospital policy" inserted
34	Section 7.1.2 "within" replaced with "no later than"
34	Section 7.1.2 text "of receipt of" replaced with "from the date of"
34	Section 7.1.2 text "and the resulting isolate" inserted
34	Section 7.1.2 text "if the patient is subsequently randomised onto the TORPEDO-CF trial" inserted
34	Section 7.1.2 text "In order highlight to Microbiology departments that CF patients are being considered for the trial high-visibility labels will be provided to CF centres. These labels should be attached onto the microbiology request slip (section 7.4.3). *A minimum number of four consecutive cough or sputum samples should be P. aeruginosa free within a 12 month period to satisfy eligibility." inserted
35	Section 7.1.3: text "randomisation and administration of P.aeruginosa eradication treatment. The following Data should be recorded on the baseline CRF: Medical history Concomitant medications Physical examination including measuring; height, weight, and vital signs (heart rate, breathing rate and blood pressure) Collect sputum / cough swab sample (positive P. aeruginosa isolates should be sent to the HPA if the original P. aeruginosa isolate used for diagnosis has not been retained) Females of child-bearing potential will be counselled about the risks of the trial treatments should they become pregnant and will be offered a pregnancy test (refusal of a pregnancy test will not preclude trial entry) Spirometry will be carried out to measure participants FEV1, FVC and FEF25-75 In addition to this, the participant should complete a health status assessment using the appropriate EQ-5D questionnaire and the appropriate Cystic Fibrosis Questionnaire (the timetable for when these questionnaire should be administered can be found in Table2: Trial Assessments. Further information about these questionnaires can be found in section 7.4" inserted
35	Section 7.1.3: text "randomisation and administration of P.aeruginosa eradication treatment. The following Data should be recorded on the baseline CRF:

	<p>Section 7.1.3: text “is permissible for baseline assessments to be performed at the same time as the screening assessments. However, they should only occur after informed consent has been provided. The following assessments must be carried out:</p> <p>Medical history Concomitant medications Physical examination including measuring; height, weight, and vital signs (temperature, heart rate, breathing rate and blood pressure) Collect sputum / cough swab sample (this will be sent to the HPA if the original P. aeruginosa sample used for diagnosis has not been retained) Serum creatinine* Monitoring tobramycin serum concentrations** Females of child-bearing potential will be counselled about the risks of the trial treatments should they become pregnant and will be offered a pregnancy test (refusal of a pregnancy test will not preclude trial entry) Spirometry will be carried out to measure participants FEV1, FVC and FEF25-75 CFQ + EQ-5D questionnaire booklets should be administered at baseline, prior to randomisation and to revealing treatment allocation to the participant (the timetable for when these questionnaires should be administered can be found in Table 3: Trial Assessments. Further information about these questionnaires can be found in section 7.4).</p> <p>For participants randomised to IV antibiotics: * serum creatinine should be measured prior to commencing treatment with IV tobramycin * monitoring tobramycin levels should follow standard unit practice: Should include measuring trough concentrations before the second dose and again after 1 week of treatment. Adjustments to dose based on these measurements and further actions (e.g. repeat measurements) should be recorded in the CRF. May include measuring peak serum concentrations - in which case a record should be made of the serum concentration and any actions taken in response to this.” deleted</p>
	<p>Section 7.1.4: text “and Treatment Allocation” deleted</p>
	<p>Section 7.1.4: text “Once the participant has been informed of their treatment allocation they should be given a treatment diary to record their daily treatment compliance and explained how to complete it. Participants should be instructed to bring back all unused medication at their next clinic visit along with their complete treatment diary.” deleted</p>
36	<p>Section 7.1.5: text “Treatment Allocation (T0 months)</p> <p>Participants should start to receive eradication treatment no later than 21 days after the date of positive a P. aeruginosa microbiology report.</p> <p>Participants receiving IV treatment should have serum creatinine* measured at the time of starting treatment and should have tobramycin serum concentrations** measured during the course of their treatment.</p> <p>For participants randomised to IV antibiotics: * serum creatinine measured at the time of commencing treatment with IV tobramycin ** monitoring tobramycin levels should follow standard unit practice: Should include measuring trough concentrations before the second dose and again after 1 week of treatment. Adjustments to dose based on these measurements and further actions (e.g. repeat measurements) should be recorded in the CRF. May include measuring peak serum concentrations - in which case a record should be made of the serum concentration and any actions taken in response to this. Once the participant has been informed of their treatment allocation they should be given the appropriate treatment diary to record their daily treatment compliance and should be provided with a copy of the Health Service Diary (please refer to table 1 for guidance on which treatment diary should be used). The PI or a delegated member of the Research staff should explain how to complete the diaries before the participant leaves hospital. Participants should be instructed to bring back copies of the treatment diary, Health Service diary & any unused medication at their next scheduled visit to assess compliance</p>

Deleted

	with eradication treatment and to assess their resource use during that time.” Inserted along with Table 1
37	Section 7.1.6: text “Scheduled study visits (follow-up) Scheduled study visits are designed to fit with routine hospital visits. At each visit, data similar to that collected at baseline should be recorded in the Case Report Form Booklet on the appropriate follow-up CRF. The follow-up CRFs should be returned to the MCRN CTU no later than seven days after each visit. Scheduled study visits should take place every three months from the date of randomisation (+/- one week). Care should be taken to ensure that the 15 months and 24 month primary endpoint visits are arranged from the date of randomisation irrespective of earlier scheduled visit dates.” Inserted
37	Section 7.1.7: text “planned assessments during study visit (T+3 months to T+15 months)” deleted
37	Section 7.1.7: text “T+3 month scheduled study visit should be arranged to take place after cessation of eradication treatment. Cough / sputum samples should be taken at least 48 hours after cessation of eradication treatment and should take place no later than seven14 days after treatment cessation. The participant should be instructed to bring back their treatment diary, HE diary and any un-used medication. Treatment compliance should be recorded on the appropriate treatment CRF.” inserted
37	Section 7.1.7: text “Planned study visits will take place every 3 months from the date of randomisation. Visits should be scheduled no earlier than one week before or after the timetabled date from randomisation” deleted
37	Section 7.1.8 text “Scheduled study visit (T+6 to T+24 months) Planned study visits will take place every three months from the date of randomisation (+/- one week). A detailed list of assessments that should be carried out at each study visit can be found in table 2.” inserted
37	Text: “ 7.1.6 Planned assessments during study visit (T+15 months to T+24 months)” deleted
37	Text “The assessments listed in section 7.1.5 should be carried out at each study visit (T+18, T+21, T+24).” deleted
37	Section 7.1.9: text “hospital” inserted
37	Section 7.1.9: text “due to recurrence of P. aeruginosa” deleted
37	Section 7.1.9: text “designated staff” replaced with “delegated member of the research team”
37	Section 7.1.9: text “Complete the Unscheduled Visit CRF. If the unscheduled visit results in a change to the participants medication this should be recorded on the Concomitant Medication CRF. Recurrence of P. aeruginosa infection should be treated” inserted
37	Section 7.1.9: text “carry out the same assessments listed in section 7.1.5 where appropriate.” deleted
37	Section 7.1.9: text “promptly with oral or intravenous antibiotics in line with CF Trust Guidelines” inserted
38	Section 7.1.10: text “continue with trial follow-up and” and “ Premature Discontinuation” inserted
38	Table 2: updated to reflect the changes to section 7
38	Text “Study completion should be completed after either 15 months for participants recruited near the end of the recruitment period or between 18 -24 months for participants recruited early in the recruitment phase” replaced with “Participants enrolled during the first nine months should continue their follow-up up to 24 months post randomisation. Participants randomised after the first nine months of the recruitment period should be followed up for 15 months to collect the primary endpoint data.”
39	Section 7.4.1: text “The CFQ has a tool for children aged 6 and over (CFQ-Child) for people aged 14 and over (CFQ-Teen/Adult) and parents” replaced with “The CFQ is the only published disease specific measure of health-related QoL for children (aged 6 and over), adolescents, and adults with cystic fibrosis.”

39	Section 7.4.1: text “The CFQ scores range from 1 to 100 (higher scores indicate better quality of life). The CFQ, scoring information, software program, and manual are available by request from the authors. Dr Quittner has agreed that the CFQ can be used in the TORPEDO study.” deleted
39	Section 7.4.1: text “post randomisation. CFQ questionnaires should be administered as detailed in table3.” inserted
	<p>Section 7.4.1: text “Administration of CFQ: The CFQ should be the first questionnaire completed at the specified study visits, and should ideally precede any discussion with the PI or delegated other. The PI or delegated other should ensure all questions have been answered and should ensure that the randomisation number and time point at which the QoL booklet was administered are recorded on the booklet.</p> <p>Participants must complete the baseline booklet before treatment allocation has been revealed. If the participant is too unwell to receive the QoL booklet or has missed a time point the delegated research staff must inform the MCRN CTU. Participants who fail to complete their full treatment allocation will still be administered the QoL questionnaire at the same time points in order to avoid bias.</p> <p>Child Participants: Children should be on their own and in a quiet room where there are no distractions if possible. Parents /carers should be instructed to wait in another room where they can complete the parent and caregivers CFQ (Children ages 6-13). While the child is completing the CFQ they should be made to feel comfortable and relaxed but be aware that they need to complete the questionnaire carefully.</p> <p>Where the CFQ is interviewer administered (i.e. for children ages 6-11)10 the questionnaire should be read out exactly as they appear on the form. Questions should not be re-worded or paraphrased for the child, even if they ask for clarification. Two coloured cards will be provided with the CFQ which list sets of response options appropriate to the different questions. The interviewer should explain both cards to the child, reading each of the response options with the younger child and asking the older ones to read each of the responses aloud to ensure they understand. The child should be reminded that they are only able to choose one option.” Inserted along with Table 3: Guidance of CFQ administration</p>
40	Section 7.4.1: text “For children aged 6-11 both the parent /caregiver self-administered version and the interviewer-administered version should be completed. CFQ questionnaires should not be completed for children under the age of 6” inserted
	<p>Section 7.4.1: text “Baseline: Participants must complete the baseline booklet before treatment allocation has been revealed. The designated research staff should ensure that the trial number, treatment allocation and time point at which the QoL booklet was administered are recorded on the QoL booklet. The baseline QoL booklet should be sent to the MCRN CTU immediately after randomisation.</p> <p>Follow-up: The designated research staff at site will administer the QoL booklets to the participant at each of the scheduled study visits post randomisation (T+3, T+15 & T24). If the participant is too unwell to receive the QoL booklet or has missed a time point the designated research staff must inform the MCRN CTU.</p> <p>Participants who fail to complete their full treatment allocation will still be administered the QoL questionnaire at the same time points in order to avoid bias.” deleted</p>
40	Section 7.4.2: text “Economics” replaced with “Status”
40	Section 7.4.2: text “the beginning of the study and at” deleted
40	Section 7.4.2: text “post randomisation” inserted
40	Section 7.4.2: text “(where appropriate)” deleted

41	Section 7.4.2: text “should be asked to complete the appropriate EQ-5D questionnaire after the CFQ has been administered (refer to table 4 for guidance)” inserted
41	Section 7.4.2: text “will use the brief questionnaire, EQ-5D to rate their own or their child’s current health in 5 health status dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The correlation between CFQ and EQ-5D will also be investigated. The EQ-5D will be completed at T+3, T+15 & T+24 months post randomisation.” deleted
41	Section 7.4.2: text “Participants must complete the baseline booklet before treatment allocation has been revealed. The PI or delegated research staff should ensure that the randomisation number and time point at which the EQ-5D booklet was administered are recorded. If the participant is too unwell to receive the EQ-5D booklet or has missed a time point the delegated research staff must inform the MCRN CTU. Participants who fail to complete their full treatment allocation will still be administered the EQ-5D questionnaire at the same time points in order to avoid bias” inserted along with Table 4: Guidance of EQ-5D administration
41	Section 7.4.2: text “Baseline: Participants must complete the baseline booklet before treatment allocation has been revealed. The designated research staff should ensure that the trial number, treatment allocation and time point at which the EQ-5D booklet was administered are recorded on EQ-5D the booklet. The baseline EQ-5D booklet should be sent to the MCRN CTU immediately after randomisation. Follow-up: The designated research staff at site will administer the EQ-5D booklets to the participant at each of the scheduled study visits post randomisation (T+3, T+15 & T24). If the participant is too unwell to receive the EQ-5D booklet or has missed a time point the designated research staff must inform the MCRN CTU.” deleted Participants who fail to complete their full treatment allocation will still be administered the EQ-5D questionnaire at the same time points in order to avoid bias.” deleted
41	Section 7.4.3: Text “Health Economics: Health economic data will be collected on primary and secondary health care contacts and medications prescribed. Although not the primary focus of the study, it will aim to incorporate patient and societal costs in terms of time lost to school or work by the participant and time lost to work for the parents or guardian. It will include any out of pocket expenses such as personal money spent on medications and aids and appliances. It is important to determine differences in the participant pathway as a result of the different treatment regimes. Health Economic data will be collected prospectively from the participant as a Health Service diary that will be given to the participant to complete prospectively between each scheduled follow up visit (child participants will be asked to complete the diary in conjunction with their parent or guardian). The Health Service diary should be returned at the next scheduled study visit and reviewed by the PI/RN in conjunction with the participant and their parent or guardian where applicable.” Inserted Section 7.4.3.1 text “Table 2” replaced with “Table 5”
42	Table 5: updated to reflect changes to section 7.4.3.1
42	Section 7.4.3.1: text “The total cost will be the sum of all costs incurred on behalf of the patient, from the perspective of the NHS and persona social services (PSS). Indirect costs. Societal costs will be collected in terms of time missed from school and work for the participant, siblings and parents/carers. Participants and their families will be asked to recall these cost parameters at each three month follow-up. These costs will be reported separately from the direct medical costs.” Deleted
44	Section 7.4.4.1: text “designated research staff” replaced with “delegated member of the research team”
44	Section 7.4.4.1: text “sample” replaced with “isolates”
44	Section 7.4.4.1: text “genotype” inserted
44	Section 7.4.4.2 text “designated” replaced with “delegated”
44	Section 7.4.4.3 text “trial number” replaced with “randomisation number”

45	Section 7.5: text “designated” replaced with “delegated”
46	Section 8.2: text “randomisation will be stratified by centre” deleted
55	Section 10.1: text “Use of Ciprofloxacin for three months treatment duration: ciprofloxacin is being used off licence in this study (SPC states treatment duration of two weeks). However, ciprofloxacin is routinely used for more than two weeks duration in clinical practice, and in this trial is being used in accordance with the CF trust guidelines for the eradication of <i>P. aeruginosa</i> in CF patients11.” deleted
61	Section 12.4.3: text “e.g. state what clinical site monitoring (and audit) is planned, if any. This section should indicate the plans for local quality control (QC):” deleted
64	Section 14.3: text “Research Site Agreement” replaced with “non-commercial”
65	Section 15.1: text “Professor Rachel Elliott Health Economist” inserted
	Section 15.1: text “Miss Michaela Blundell Trial Statistician” inserted
	Section 12.1: text “Miss Michaela Blundell Trial Statistician” inserted

17.3 Version 3 (01/09/2010)

Amendment and clarification V2.0 (15/02/2010) to V3.0 (01/09/2010)

Page Number	Amendment Comment
Throughout	Updated version and date; correction of typographical errors
5	Addition of Miss Joanne Eatock, Senior Data Manager
9	Updated the table of contents
11	List of abbreviations updated
Throughout	Clarification text added to Exclusion criteria 4. ‘Please 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 <i>P. aeruginosa</i> ’
Throughout	Primary endpoint text amended from ‘Successful eradication of <i>P. aeruginosa</i> infection at three months post randomisation, remaining infection free through to 15 months post randomisation’ changed to read ‘Successful eradication of <i>P. aeruginosa</i> infection at three months post treatment, remaining infection free through to 15 months post treatment’
Throughout	Secondary endpoint 8 changed from ‘Number 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 IV treatment)’ to ‘Number 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 IV treatment)’
16	Section 1.3 text ‘post randomisation’ changed to ‘post treatment’
21	Section 4.3.3 text ‘Premature Discontinuation’ changed to ‘Withdrawal’
22	Details for the web randomisation system changed
23	Section 6.1 text ‘designed as a’ replaced with ‘a phase IV’

23-30	Formal accountability procedures for the trial along with labelling requirements removed and section updated to detail informal accountability introduced to monitor treatment compliance
31-32	Section
35	Addition of guidance table for administration of Questionnaire Booklets
41	Change to the wording of the CACE study to reflect changes in the ethics approved protocol
43	Section 8.4 text in sample size calculation changed to reflect change in analysis from post randomisation to post treatment
47	Section 9.7 Change in the reporting timelines for AE /SAEs, beginning from the time allocation treatment starts up to 28 days after treatment cessation
56 -57	Section 12.3 Data capture section of protocol updated to give clear instructions on CRF completion and guidance on participant completed questionnaires and diaries
57	Section 12.4 text included on the monitoring that will be carried out on participant completed questionnaires and diaries
58	Section 12.4.3 Quality assurance measures updated
62	Section 15.3 text revised to state that oversight committee meetings should take place at least annually

17.4 Version 4 (13/12/2011)

Amendment and clarification V3.0 (01/09/2010) to V4.0 (13/12/2010)

Page Number	Amendment Comment
Throughout	Updated version and date; correction of typographical errors
5	Replacement of Ms Rachel Breen with Ms Helen Hickey as Head of Trial Management
5	Replacement of Dr Chris Smith with Ms Hannah Short as Trial Manager
7	Removal of Independent Oversight Committees table
9	Updated the table of contents
Throughout	Inclusion criteria 1 changed from 'Diagnosis of cystic fibrosis (CF) (clinical feature + Cl > 60mmol/L and / or 2 CFTR mutations)' to 'Diagnosis of cystic fibrosis (CF)'
14	Trial treatment text (Arm A) changed from 'Fourteen days IV ceftazidime 50mg/kg/dose (maximum three grams) three times daily <i>and</i> IV tobramycin 10 mg/kg/d (maximum 660mg) once daily <i>In conjunction with</i> three months nebulised colistin' to 'Fourteen days IV ceftazidime dose as per national clinical guidelines (maximum three grams) three times daily # <i>and</i> IV tobramycin dose as per national clinical guidelines (maximum 660mg) once daily # <i>In conjunction with</i> three months nebulised colistin twice daily #'

14	<p>Trial treatment text (Arm B) changed from 'Three months oral ciprofloxacin < 5 years, 15 mg/kg twice daily, ≥ 5 years, 20 mg/kg twice daily (maximum dose 750 mg twice daily) <i>In conjunction with three months nebulised colistin</i>' to 'Three 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) # <i>In conjunction with three months nebulised colistin twice daily #</i>'</p>
14	<p>Note added '# sites that are unable to comply with the trial dosing regime can use their current dosing regime as long as the total daily dose administered is within national clinical guidelines'</p>
23	<p>Text changed from '14 days* Intravenous (IV) Ceftazidime 50 milligram (mg)/kilogram (kg)/dose, to a maximum of 3 grams (g) three times daily (tds) and IV tobramycin 10mg/kg/dose once daily (od) (maximum 660mg /day).' to '14 days* intravenous (IV) antibiotics as follows:</p> <ul style="list-style-type: none"> • Ceftazidime 150 milligram (mg)/kilogram (kg)/day, in 3 divided doses (maximum of 3 grams (g) three times daily (tds)). Some centres may use a twice daily regimen for ceftazidime. These centres may continue to use this regimen for the study and should follow their local dosing guidelines. • Tobramycin 10mg/kg/day once daily (od) (maximum 660mg /day). Some centres may use a twice daily or three times daily regimen for tobramycin. These centres may continue to use their current regimen for the study and should follow their local dosing guidelines. <p>Therapeutic drug monitoring should be used to guide tobramycin dosing as per national guidelines (http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/Antibiotic_treatment_for_Cystic_Fibrosis.pdf) and usual clinic procedures.'</p>
23	<p>Section 6.1 text changed from '3 months oral ciprofloxacin twice daily (bd) (Ciprofloxacin dose will be 15 mg/kg/dose twice daily for children aged < 5 years and 20 mg/kg/dose twice daily (maximum 750mg twice daily) for those aged ≥ 5 years).' to '3 months oral ciprofloxacin twice daily (bd). (Ciprofloxacin dose will be 20 mg/kg twice daily (maximum 750mg twice daily. This is in line with the BNF for children (http://bnfc.org/bnfc/). Some clinicians may prefer to use a lower dose of 15mg/kg twice daily for children under 5 years, as used in national CF guidelines (http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/Antibiotic_treatment_for_Cystic_Fibrosis.pdf)).'</p>
32	<p>Section 7.1.10, table 2: trial assessments. 'EQ-5D' removed and text for 'Quality of Life administered (CFQ)' row changed to 'Quality of Life administered (CFQ) and EQ-5D'</p>
58	<p>Section 15 trial committees section removed.</p>

17.5 Version 5 (11/01/2012)

Amendment and clarification V4.0 (13/12/2010) to V5.0 (11/01/2012)

Page Number	Amendment Comment
-------------	-------------------

Throughout	Updated version and date; correction of typographical errors
24	Section 6.3.3 changed from 'Home Care companies can be used to provide Home IVs only if the CTU is provided with a copy of the companies MIAIMP licence as part of the green light process.' to 'Homecare companies can be used. Homecare companies that reconstitute intravenous medicines centrally and supply reconstituted injectables directly to patient's home must be a registered pharmacy. In addition, the IMPs shall be dispensed to a subject in accordance with a prescription given by an authorised health care professional and labelled in accordance with the requirements that apply to dispensed relevant medicinal products.'

17.6 Version 6 (17/10/2013)

Amendment and clarification V5.0 (11/01/2012) to V6.0 (17/10/2013)

Page Number	Amendment Comment
Throughout	Updated version and date; correction of typographical errors
5	Replacement of Mary Perkins with Diana Benton as sponsor contact authorised to sign the protocol and protocol amendments
5	Replacement of Dr Rachel Elliott with Dr Li-Chia Chen as Health economist
9	Updated the table of contents
Throughout	Clarification of the definition of one month
11	Study period changed from 5 years to 6 years and 3 months
Throughout	Inclusion criteria 5 b. changed from ' <i>P. aeruginosa</i> -free (i.e. a minimum of four consecutive cough or sputum samples should be <i>P. aeruginosa</i> free within a 12 month period to satisfy eligibility.)' to ' <i>P. aeruginosa</i> -free (i.e. any cough or sputum samples within the previous year (365 days) should be <i>P. aeruginosa</i> free.)'
12	Exclusion criteria 4 changed from 'previous 9 months' to 'previous 9 calendar months'.
12	'Each participant will be followed up for a minimum of 15 months, but up to 24 months.' Removed.
12	Insertion of table 1; guidance on scheduling of visits
31	'Participants enrolled during the first nine months should continue their follow-up to 24 months after allocated treatment started. Participants randomised after the first nine months of the recruitment period should be followed up for 15 months after allocated treatment started to collect the primary endpoint data.' Replaced with 'Participants should continue their follow-up up to 24 months after allocated treatment started.'
31	15 month visit window changed from '+/- one week' to '- one week or + two weeks'
39	Removal of 7.4.6 Comparing Adults' and Children's Experiences of Randomised Controlled Trials (CACE)
41 - 42	Clarification added 'No formal interim analyses of primary or secondary outcome data will be performed.'

43 - 51	Removing requirement for all SAEs to be reported on an SAE report form. Replaced with: All 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 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 SARs and SUSARs must be reported immediately by the investigator to the MCRN CTU on an SAR report form.
45	Removal of requirement for pregnancy to be reported as an SAE. Pregnancies occurring up to 28 days after treatment cessation to be reported on a pregnancy CRF to the MCRN CTU within 24 hours of awareness of event.
46	All deaths to be reported on a a death CRF within 7 days of awareness of event.
51	Further clarification on safety reporting; concerns / inconsistencies may prompt additional training at sites or possibly site visits.
54	Insertion of section 10.4 'Transition from paediatric to adult in relation to consent. '
57 - 58	Removed reference to non-carbon copy CRFs. Replaced with instructions to post original completed cRFs to MCRN CTU and keep a photocopy at site.

17.7 Version 7 (12/08/2014)

Amendment and clarification V6.0 (17/10/2013) to V7.0 (12/08/2014)

Page Number	Amendment Comment
Throughout	Updated version and date
Throughout	Updated contact details
9 - 10	Updated table of contents
Throughout	Replacement of Medicines for Children Research Network with Medicines for Children
Throughout	Participating sites to include international sites
Throughout	Addition of University of Liverpool as Co-Sponsor; they will act as sole sponsor for international sites
11	Study period changed from 6 years and 3 months to 8 years and 7 months
22	Section 4.3.1 changed requirement for follow-up via GP where the participant moves to a non-participating site. Replaced with: "Where this is not possible, if the participant is still happy for their data to be collected, the recruiting centre should make every effort to obtain data collected as part of routine care from the centre that is now responsible for the participants care."
39	Section 7.6 Added sentence: "At the time of database lock, data entry privileges are withdrawn from the trial database."
61	Section 14 Details of financial arrangements removed, described separately in the contracts.

17.8 Version 8 (23/12/2015)

Amendment and clarification V7.0 (12/08/2014) to V8.0 (23/12/2015)

Page Number	Amendment Comment
Throughout	Updated version and date
9 - 10	Updated table of contents
Throughout	Clarifying follow-up period; patients who start randomised treatment before 1 st January 2016 will continue follow-up for 24 months, patients who start randomised treatment on or after 1 st January 2016 will continue follow-up for 15 months.
27	Text changed from "Ceftazidime 150 milligram (mg)/kilogram (kg)/day, in 3 divided doses (maximum of 3 grams (g) three times daily (tds)). Some centres may use a twice daily regimen for ceftazidime. These centres may continue to use this regimen for the study and should follow their local dosing guidelines." To "Ceftazidime 150 milligram (mg)/kilogram (kg)/day, in 3 divided doses (maximum of 3 grams (g) three times daily (tds)). Some centres may use a once daily continuous infusion (where the maximum daily dose would usually be 6g/day) or twice daily regimen for ceftazidime. These centres may continue to use this regimen for the study and should follow their local dosing guidelines."
42	Clarification of genotyping arrangement outside the UK -
45	Corrected tyrographical error inserting "serious" in section 9.5 to correct text to say "Expectedness should be assessed for all serious adverse reactions"
63	Removed reference to supplementary document describing indemnity arrangements for non-Uk sites. Replaced with "Equivalent cover to that provided by the Clinical Negligence Scheme for UK Trusts should be confirmed to be in place for non-UK sites during site suitability assessment and cover summarised in the sponsor-site contract."

17.9 Version 9 (12/10/16)

Amendment and clarification V8.0 (23/12/2015) to V9.0 (12/10/2016)

Page Number	Amendment Comment
Throughout	Updated version and date
11	Updated number of patients to be enrolled

18 REFERENCES

1. UK Cystic Fibrosis Trust, Annual Data Report. *UK CF Database* (2003).
2. Emerson, J., Rosenfeld, M., McNamara, S., Ramsey, B. & Gibson, R.L. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol* **34**, 91-100 (2002).
3. Konstan, M.W. et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr* **151**, 134-9, 139 e1 (2007).
4. Li, Z. et al. Longitudinal development of mucoid *Pseudomonas aeruginosa* infection and lung disease progression in children with cystic fibrosis. *JAMA* **293**, 581-8 (2005).
5. Lee, T.W. Eradication of early *Pseudomonas* infection in cystic fibrosis. *Chron Respir Dis* **6**, 99-107 (2009).
6. Valerius, N.H., Koch, C. & Hoiby, N. Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by early treatment. *Lancet* **338**, 725-6 (1991).
7. Wiesemann, H.G. et al. Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of *Pseudomonas aeruginosa* colonization in cystic fibrosis. *Pediatr Pulmonol* **25**, 88-92 (1998).
8. McCoy, K.S. et al. Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. *Am J Respir Crit Care Med* **178**, 921-8 (2008).
9. Gibson, R.L. et al. Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. *Am J Respir Crit Care Med* **167**, 841-9 (2003).
10. Taccetti, G., Campana, S., Festini, F., Mascherini, M. & Doring, G. Early eradication therapy against *Pseudomonas aeruginosa* in cystic fibrosis patients. *Eur Respir J* **26**, 458-61 (2005).
11. Antibiotic Treatment of Cystic Fibrosis. *UK Cystic Fibrosis Trust Antibiotic Working Group Guidelines* (2009).
12. Littlewood, J.M., Miller, M.G., Ghoneim, A.T. & Ramsden, C.H. Nebulised colomycin for early *pseudomonas* colonisation in cystic fibrosis. *Lancet* **1**, 865 (1985).
13. Ratjen, F., Doring, G. & Nikolaizik, W.H. Effect of inhaled tobramycin on early *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. *Lancet* **358**, 983-4 (2001).
14. Langton Hewer, S., Smyth, A.R.,. Antibiotic strategies for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis. *Cochrane Database Syst Rev* (2009).
15. Wood, D.M. & Smyth, A.R. Antibiotic strategies for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis. *Cochrane Database Syst Rev*, CD004197 (2006).
16. de Jong, W. et al. Quality of life in patients with cystic fibrosis. *Pediatr Pulmonol* **23**, 95-100 (1997).
17. Suri, R., Metcalfe, C., Wallis, C. & Bush, A. Assessing the usefulness of outcomes measured in a cystic fibrosis treatment trial. *Respir Med* **101**, 254-60 (2007).
18. Rosenfeld, M. et al. Defining a pulmonary exacerbation in cystic fibrosis. *J Pediatr* **139**, 359-65 (2001).
19. Quittner, A.L., Buu, A., Messer, M.A., Modi, A.C. & Watrous, M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest* **128**, 2347-54 (2005).
20. Modi, A.C. & Quittner, A.L. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. *J Pediatr Psychol* **28**, 535-45 (2003).
21. Briggs, A. & Gray, A. The distribution of health care costs and their statistical analysis for economic evaluation. *J Health Serv Res Policy* **3**, 233-45 (1998).
22. van Hout, B.A., Al, M.J., Gordon, G.S. & Rutten, F.F. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ* **3**, 309-19 (1994).

23. Onteniente, L., Brisse, S., Tassios, P.T. & Vergnaud, G. Evaluation of the polymorphisms associated with tandem repeats for *Pseudomonas aeruginosa* strain typing. *J Clin Microbiol* **41**, 4991-7 (2003).
24. Vu-Thien, H. et al. Multiple-locus variable-number tandem-repeat analysis for longitudinal survey of sources of *Pseudomonas aeruginosa* infection in cystic fibrosis patients. *J Clin Microbiol* **45**, 3175-83 (2007).
25. Smyth, A. et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis--the TOPIC study: a randomised controlled trial. *Lancet* **365**, 573-8 (2005).