



BEAT CF
PATIENT DRIVEN EVIDENCE

Bayesian Evidence Adaptive Treatment of Cystic Fibrosis.

Pulmonary Exacerbations Treatment Platform

Domain Specific Appendix A

Backbone Antibiotics

Protocol V2

15 Nov 2022

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE

The signature below constitutes the approval of this Domain-Specific Appendix to the PEx Treatment Platform Protocol, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable Australian regulations and International Council for Harmonisation (ICH) guidelines.

Signed _____ Date _____

Name:

Role:

DOCUMENT ORIENTATION

This BEAT CF Pulmonary Exacerbations (PEX) Treatment Platform Domain-Specific Appendix A is to be read in conjunction with

- PEx Core Protocol
- PEx Treatment Platform Protocol
- PEx Treatment Platform Protocol appendices:
 - DSA B: Adjunct Antibiotics Domain-Specific Appendix
 - Statistical Appendix

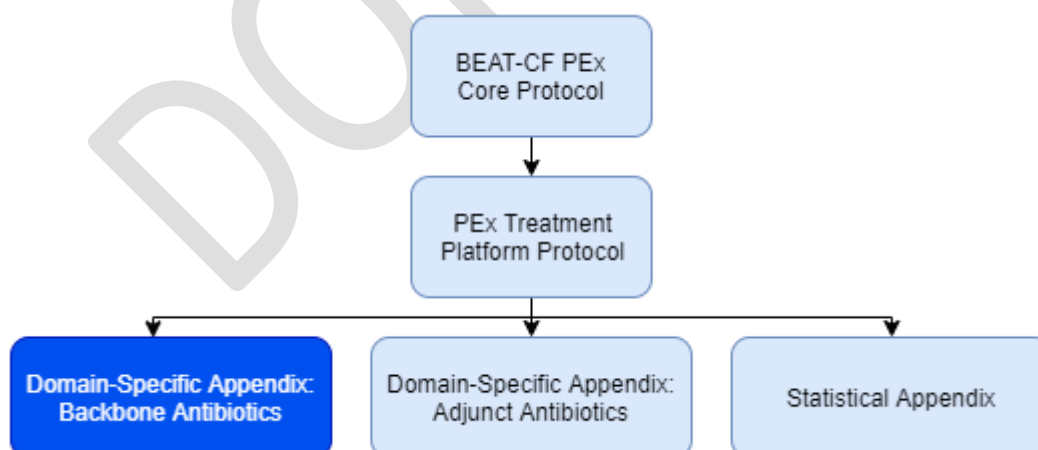


Figure 1: Backbone Antibiotics Domain-Specific Appendix in relation to other BEAT CF documents

	Section	Document Where Information is located		
		PEx Core Protocol	PEx Treatment Platform Protocol	PEx Treatment Platform Domain-specific appendix
1.	Overview	Overall BEAT-CF	Treatment Platform	Domain-specific
2.	Administration	Overall BEAT-CF	Treatment Platform	None
3.	Background/ Rationale	Overall BEAT-CF	Treatment Platform	Domain-specific
4.	Aim	Overall BEAT-CF	None	None
5.	Objectives	Overall BEAT-CF	Treatment Platform	Domain-specific
6.	Design and Methods	PEx Cohort	Treatment Platform	Domain-specific
7.	Study Conduct	PEx Cohort	Treatment Platform	Domain-specific
8.	Data Management	Overall BEAT-CF		None
9.	Protocol Deviations and Serious Breaches	PEx Cohort	Treatment Platform	None
10.	Statistical overview	PEx Cohort	Treatment Platform	None
11.	Quality assurance and monitoring	Overall BEAT-CF	Treatment Platform	None
12.	Ethics and regulatory	Overall BEAT-CF	Treatment Platform	None
13.	Reporting/ Publication	Overall BEAT-CF	Treatment Platform	None

Table 1 Location of information within BEAT CF documentation

Contents

1. OVERVIEW	6
1.1 Key Details	6
1.2 Project Synopsis	6
1.3 Abbreviations & Definitions	8
1.4 Purpose and scope of this document	9
1.5 Overall BEAT CF Structure	9
2. ADMINISTRATION	10
3. BACKGROUND/ RATIONALE	10
4. AIMS	10
5. OBJECTIVES	10
6. DESIGN AND METHODS	10
6.1 Domain Design	11
6.2 Description of the Interventions	11
6.2.1 IV Piperacillin with tazobactam	12
6.2.2 IV Cefepime.....	12
6.2.3 IV Ceftazidime	13
6.2.4 IV Ceftriaxone	13
6.3 Inclusion criteria	14
6.4 Exclusion criteria	14
6.4.1 Domain exclusion criteria	14
6.4.2 Intervention-specific exclusion criteria.....	15
6.5 Study Estimands	15
6.6 Co-enrolment with other studies	15
6.7 End of the Domain	15
7. STUDY CONDUCT	16
7.1 BEAT CF PEx participant flow	16
7.2 Identification of potential Domain participants	16
7.3 Informed consent	16
7.4 Timing of Intervention	16
7.5 Standard of care	17
7.6 Discontinuation of participation	17
7.7 Concomitant care and interventions	17

7.8	Laboratory procedures	17
7.9	Patient Reported Outcomes	17
7.10	Domain Data Collection.....	18
7.11	Domain participation randomisation	18
7.12	Blinding	19
7.13	Trial Periods.....	20
8.	DATA MANAGEMENT	20
9.	PROTOCOL DEVIATIONS AND SERIOUS BREACHES.....	20
10.	STATISTICAL METHODS.....	20
10.1	Domain Decision Thresholds	20
10.2	Interactions with Interventions in Other Domains.....	21
10.3	Nesting of Interventions.....	21
11.	QUALITY ASSURANCE AND MONITORING	21
11.1	Overview	21
11.2	Safety Monitoring and Reporting	21
11.3	Domain and Intervention-specific Adverse Events of Special Interest	21
12.	ETHICS AND REGULATORY	21
12.1	Backbone Antibiotics Domain-specific benefits and risks.....	22
13.	REPORTING/ PUBLICATION.....	22
14.	REFERENCES.....	22

1. OVERVIEW

1.1 Key Details

Protocol	BEAT CF Domain Specific Appendix A: Backbone Antibiotics
Version / Date	Version 2 / 15 Nov 2022
Domain-Specific Appendix Registration	ACTRN12622000950763
Core Protocol Registration	Refer to the BEAT CF PEx Core Protocol
Coordinating Principal Investigator	
Sponsor	
Collaborators	
Coordinating Centre	
Funding Sources	

1.2 Project Synopsis

TITLE	BEAT CF (Bayesian Evidence Adaptive Treatment of Cystic Fibrosis): Pulmonary Exacerbations Treatment Platform - Backbone Antibiotics Domain
BACKGROUND	Refer to the PEx Core Protocol
PRIMARY OBJECTIVE	Refer to the PEx Core Protocol
DOMAIN-SPECIFIC OBJECTIVE	To determine the comparative effectiveness of prescribing alternative first-line Backbone Antibiotics used as standard care in the management of PERIT in children and adults with CF, with respect to their short-term improvement in lung function

PRIMARY ENDPOINT	Refer to the PEx Core Protocol
STUDY DESIGN	Refer to the PEx Treatment Platform Protocol
STUDY DURATION	Perpetual
NUMBER OF PARTICIPANTS	Unlimited
INCLUSION CRITERIA	<ol style="list-style-type: none"> 1. Enrolment in the BEAT CF PEx Treatment Platform 2. Informed consent
DOMAIN-SPECIFIC EXCLUSION CRITERIA	<ol style="list-style-type: none"> 1. Revealed Intervention Assignment in the Backbone Antibiotics Domain in the preceding 28 days. 2. More than 2 doses in the preceding 28 days of any broad spectrum intravenous antibiotic therapy, including any anti-pseudomonal penicillin, third or fourth generation cephalosporin, carbapenem, monobactam, tigecycline, or IV fluoroquinolone. 3. Planned to receive any specific broad spectrum intravenous antibiotic therapy in the next 14 days (apart from their Assigned Intervention), including any anti-pseudomonal penicillin, third or fourth generation cephalosporin, carbapenem, monobactam, tigecycline, IV or oral fluoroquinolone.
INTERVENTION-SPECIFIC EXCLUSION CRITERIA	<ol style="list-style-type: none"> 1. They have a known or suspected significant drug hypersensitivity to that antibiotic 2. They have another recognised contraindication to that antibiotic 3. The Intervention is deemed unacceptable by the Responsible Clinician e.g. because of failed PERIT treatment response to that antibiotic (requiring a

	<p>change in antibiotic treatment) in the preceding 12 months</p> <p>4. For Ceftriaxone only: In Stratum 2, 3 or 4.</p>
RANDOMISATION	<p>PEX Treatment Platform participants will be randomised (1:4) to either their Clinician's Choice of Intervention in the Backbone Antibiotics Domain, or to a Randomly Assigned Intervention. For those Assigned to Randomly Assigned Intervention, the probability of Assignment will be determined by response-adaptive randomisation (RAR).</p>
BLINDING	<p>Participants and outcome assessors will not be blinded to Intervention Assignment in the Backbone Antibiotics Domain.</p>
ANALYSIS	<p>Refer to the PEX Treatment Platform Protocol and Statistical Appendix</p>
DATA MANAGEMENT	<p>Refer to the PEX Core Protocol</p>

1.3 Abbreviations & Definitions

Refer to the PEX Core Protocol: Attachment 1

1.4 Purpose and scope of this document

The BEAT CF Pulmonary Exacerbation (PEX) Treatment Platform Domain-Specific Appendix A (DSA A): Backbone Antibiotics, contains information which builds upon and is supplementary to the PEX Core Protocol and the PEX Treatment Platform Protocol, and which is specific to the Backbone Antibiotics Domain. Unless stated elsewhere, this DSA applies to all Interventions delivered as part of the Backbone Antibiotics Domain. It is anticipated that the DSA will require modification over time, for example as Interventions are Terminated or new Interventions included.

It contains the following information:

- Any Domain-specific design issues, including any additional eligibility (exclusion) criteria for participation beyond those for the PEX Cohort (which are detailed in the PEX Core Protocol) and for all Domains of the PEX Treatment Platform (which are detailed in the PEX Treatment Platform Protocol).
- Any Study procedures which are specific to the Backbone Antibiotics Domain, including methods of Domain enrolment, any Domain-specific consent issues, and Domain-specific data collection information.
- Any Domain-specific procedures for randomisation and Intervention Assignment, and any additional procedures to control bias beyond those generic to the PEX Cohort and PEX Treatment Platform.
- Any Domain-specific or Intervention-specific procedures related to participant safety and monitoring.
- Any Domain-specific criteria for Termination of this Domain or Interventions in this Domain.

Note that the documentation for BEAT CF is modular and hierarchical. Lower levels of the hierarchy build upon, and provide detail and specificity to, the higher levels. The eligibility criteria, data collection, and secondary outcomes described in this DSA, are in addition to those for the PEX Cohort which are detailed in the PEX Core Protocol, and those which cover all Domains of the PEX Treatment Platform which are detailed in the PEX Treatment Platform Protocol. Therefore, this DSA needs to be read in conjunction with those higher-level documents, and any other appendices to the PEX Treatment Platform Protocol (e.g. other Domain-Specific and Statistical Appendices).

1.5 Overall BEAT CF Structure

Refer to the PEX Core Protocol

2. ADMINISTRATION

Detailed information about the overall BEAT CF Administration Structure is contained in the PEx Core Protocol, and the PEx Treatment Platform Protocol.

3. BACKGROUND/ RATIONALE

For detailed background information on CF pulmonary exacerbations and their management, refer to the PEx Core Protocol and PEx Treatment Platform Protocol.

4. AIMS

For the overall Aim of BEAT CF, refer to the PEx Core Protocol.

5. OBJECTIVES

For the Primary Objective and Secondary Objectives of BEAT CF, refer to the PEx Core Protocol.

The Domain-specific Objective of the Backbone Antibiotics Domain is to determine the comparative effectiveness of prescribing alternative first-line Backbone Antibiotics used as standard care in the management of PERIT in children and adults with CF, with respect to their short-term improvement in lung function.

In keeping with this Objective, this DSA may be amended to enable Termination of any Backbone Antibiotics that prove to have low probability of being Optimal, or to include new Interventions that may become part of the standard of care.

6. DESIGN AND METHODS

For an overview of the design of the PEx Treatment Platform, refer to the PEx Treatment Platform Protocol.

6.1 Domain Design

The Backbone Antibiotics Domain will be nested in the PEx Treatment Platform.

Eligible participants in the Backbone Antibiotics Domain will be Assigned to one (and only one) Intervention in this Domain. The participant will be randomised (1:4) to either be Assigned to the Responsible Clinician's Selected Intervention for this Domain ("Clinician's Choice") or to a Randomly Assigned Intervention (Random Intervention). Randomly Assigned Interventions in this Domain will be Assigned using RAR as described in the Statistical Appendix.

At each Scheduled Analysis, the unblinded Analytic Team will assess the comparative effectiveness of each Intervention in this Domain in relation to the Primary Estimand. They will calculate for each Intervention, for each Stratum, the Probability it is in the Best Regimen, and the Probability it is in the Optimal Regimen.

6.2 Description of the Interventions

In the Backbone Antibiotic Domain, the Intervention is a Prescription for the Assigned antibiotic at the commencement of intensive therapy made by the Responsible Clinician or their authorised delegate. In the Backbone Antibiotic Domain, all options are active (there are no treatment options).

At the commencement of the Domain, Domain participants will be Assigned to receive a prescription for one of the following open-label Interventions in the Backbone Antibiotic Domain:

1. IV Piperacillin + tazobactam
2. IV Cefepime
3. IV Ceftazadime
4. IV Ceftriaxone

In each case, the prescription for the Assigned Backbone Antibiotic will, at a minimum, specify:

Formulation	Be any formulation of that antibiotic which is registered on the Australian Register of Therapeutic Goods
Delivery	Be prescribed to be delivered intravenously
Start time	To commence as soon as practicable, and preferably within 6 hours of Reveal of the Random Assignment
Duration	Have a planned duration of at least 7 days, but need not specify the exact duration of treatment
Modifications	Allow for modifications at the discretion of the Responsible Clinician (or their

	delegate) based on toxicities or therapeutic drug monitoring, including stopping therapy for intolerable side effects or otherwise where continuation is considered to carry an unacceptable risk to the participant.
Dose	Be guided by section 6.2, but will ultimately be at the discretion of the Responsible Clinician in accordance with local guidelines and policies.
Frequency	
Mode of administration	

In general, it is expected that changes in Backbone Antibiotics for perceived poor clinical response will only occur after 7 days of completed therapy, and after the Day 7 spirometry has been performed.

6.2.1 IV Piperacillin with tazobactam

- Piperacillin is a penicillin antibiotic which interferes with cell wall peptidoglycan synthesis by binding to penicillin-binding proteins resulting in cell lysis.
- Tazobactam is a beta-lactamase inhibitor with limited antibacterial activity. It extends the spectrum of activity of piperacillin to cover many beta-lactamase producing organisms in addition to many strains of *Pseudomonas aeruginosa*.
- Administration should adhere to local CF Centre/ hospital guidelines, and policies. As a guide:

Administration	IV infusion over 30 minutes or longer, or by continuous infusion over 24 hours.
Dose Adjustment	May be required in cases of impaired renal function (creatinine clearance of < 40mL/min)
Contra-indications and Precautions	Piperacillin with tazobactam is generally contraindicated in patients with a history of high-risk allergy to penicillins and in patients with a history of jaundice or hepatotoxicity from piperacillin with tazobactam.

6.2.2 IV Cefepime

- Is a bactericidal, broad spectrum 4th generation cephalosporin antibiotic.
- Interferes with bacterial cell wall peptidoglycan synthesis by binding to penicillin-binding proteins resulting in cell lysis.
- Is active against most enteric Gram-negative bacilli, including many strains of *Pseudomonas aeruginosa*.
- Administration should adhere to local CF Centre/ hospital guidelines, and policies. As a guide:

Administration	IV push over several minutes, OR IV infusion over up to 30 minutes, OR continuous IV infusion over 24 minutes. It may also be given by IM injection.
Dose Adjustment	May be required in cases of impaired renal function (creatinine clearance < 50mL/min).
Contra-indications and Precautions	Cefepime is generally contraindicated in patients with a history of high risk allergy to cephalosporins or penicillins. It should be used with caution in patients with seizure disorders or renal impairment due to increased risk of neurotoxicity; patients with renal impairment may also have an increased risk of neutropenia

6.2.3 IV Ceftazidime

- Is a broad-spectrum, third generation cephalosporin antibiotic.
- Interferes with bacterial cell wall peptidoglycan synthesis by binding to penicillin-binding proteins resulting in cell lysis.
- Is inactivated by extended spectrum beta-lactamases (ESBL) and by cephalosporinase enzymes.
- Is active against most enteric Gram-negative bacilli, including many strains of *Pseudomonas aeruginosa*.
- Administration should adhere to local CF Centre/ hospital guidelines, and policies. As a guide:

Administration	IV bolus over several minutes, or as an infusion over up to 30 minutes. Doses <1000mg may also be given by IM injection.
Dose Adjustment	May be required in cases of impaired renal function (with creatinine clearance < 50mL/min).
Contra-indications and Precautions	Ceftazidime is generally contraindicated in patients with a history of high risk allergy to cephalosporins or penicillins.

6.2.4 IV Ceftriaxone

- Is a bactericidal broad-spectrum third generation cephalosporin antibiotic.
- Interferes with bacterial cell wall peptidoglycan synthesis by binding to penicillin-binding proteins resulting in cell lysis.

- Is active against most community-associated enteric Gram negative rods, beta-haemolytic *Streptococci* and *Streptococcus pneumoniae*.
- Has dose dependent anti-staphylococcal activity and significant activity against gram negative organisms, but not against *Pseudomonas aeruginosa*.
- Administration should adhere to local CF Centre/ hospital guidelines, and policies. As a guide:

Administration	IV infusion over 30 minutes, or by push over 5-15 minutes. It may also be given by IM injection
Dose Adjustment	May be required in cases of significant renal impairment (creatinine clearance of <10mL/minute).
Contra-indications and Precautions	Ceftriaxone is generally contraindicated in patients with a history of high risk allergy to cephalosporins or penicillins. Ceftriaxone and calcium containing solutions may be administered sequentially (or concurrently if using separate lines), if the lines are flushed well with a compatible fluid between infusions.

6.3 Inclusion criteria

For each PERIT, a participant will be eligible for randomisation in the Backbone Antibiotic Domain if:

1. They are enrolled in the PEx Treatment Platform.
2. Their Site is participating in the Backbone Antibiotic Domain.
3. They are eligible for at least two Interventions in the Backbone Antibiotic Domain available at that Site.
4. Their informed consent to participate in the Backbone Antibiotics Domain has been documented, and is confirmed before randomisation.

6.4 Exclusion criteria

6.4.1 Domain exclusion criteria

A participant will be excluded from the Backbone Antibiotics Domain if:

5. They have already had a Revealed Intervention Assignment in the Backbone Antibiotics Domain in the preceding 28 days.
6. They have already received more than 2 doses in the preceding 28 days of any broad spectrum intravenous antibiotic therapy, including any anti-pseudomonal penicillin, third or fourth generation cephalosporin, carbapenem, monobactam, tigecycline, or IV or oral fluoroquinolone.

7. They are planned to receive any specific broad spectrum intravenous antibiotic therapy in the next 14 days (apart from their Assigned Intervention), including any anti-pseudomonal penicillin, third or fourth generation cephalosporin, carbapenem, monobactam, tigecycline, IV or oral fluoroquinolone.

6.4.2 Intervention-specific exclusion criteria

A participant will be excluded from Assignment to a specific Intervention in the Backbone Antibiotics Domain if:

1. They have a known or suspected significant drug hypersensitivity to that antibiotic
2. They have another recognised contraindication to that antibiotic
3. The Intervention is deemed unacceptable by the Responsible Clinician e.g., because of failed PERIT treatment response to that antibiotic (requiring a change in antibiotic treatment) in the preceding 12 months

Additional Intervention-specific exclusion criteria, include:

Intervention	Exclusion Criteria
Ceftriaxone	Participant in Stratum 2-4 at the time of randomisation.

6.5 Study Estimands

For the Primary Estimand (i.e. the specific target of statistical inference), refer to the PEx Core Protocol and the Statistical Appendix.

6.6 Co-enrolment with other studies

For overall guidance on co-enrolment with other studies, please refer to the PEx Core Protocol and the PEx Treatment Platform Protocol.

Participants in the FORMaT trial may not be randomised in the Backbone Antibiotic Domain.

6.7 End of the Domain

For considerations regarding the end of the PEx Cohort, refer to the PEx Core Protocol.
 For considerations regarding the end of the PEx Treatment Platform, refer to the PEx Treatment Platform Protocol.

The Backbone Antibiotics Domain, like the Treatment Platform, is designed to be perpetual; multiple Backbone Antibiotics may be evaluated concurrently or sequentially over time. Adaptive methods with pre-specified Decision Thresholds for terminating Assignment to any Interventions will be outlined within the Statistical Appendix and detailed in the Statistical Implementation Guide.

It is anticipated that the Backbone Antibiotics Domain will continue to enrol participants and evaluate Interventions until one of the following occurs:

1. Funding or other necessary support for the Domain, the PEx Treatment Platform and/or the PEx Cohort is no longer available
2. PEx are no longer deemed to be an important health problem for people with CF
3. The comparative effectiveness of all relevant Backbone Antibiotics for treating PEx in people with CF are known

Should the Domain be Closed, its end is the date of the last scheduled follow up for any Domain-participant.

7. STUDY CONDUCT

7.1 BEAT CF PEx participant flow

For a description of the overall flow of participation in the PEx Cohort and the PEx Treatment Platform, refer to the PEx Core Protocol and the PEx Treatment Platform Protocol.

7.2 Identification of potential Domain participants

For a description of how potential participants for all Domains of the PEx Treatment Platform are identified, refer to the PEx Core Protocol and the PEx Treatment Platform Protocol.

7.3 Informed consent

For an overall description of the approach to obtaining and documenting consent for BEAT CF, refer to the PEx Core Protocol.

For guidance on obtaining consent to the PEx Treatment Platform, refer to the PEx Treatment Platform Protocol.

7.4 Timing of Intervention

The prescription for Backbone antibiotics will be made and therapy commenced as soon as practicable after Reveal of the Intervention Assignment, and preferably within 6 hours. Because of incompatibilities between tobramycin and penicillin/ cephalosporin class antibiotics, for those assigned to IV tobramycin as Adjunct Antibiotic therapy, either antibiotic may be given first, but it is recommended that the IV cannula is flushed between doses.

7.5 Standard of care

There is no single standard of care for the prescription of Backbone antibiotics among children and adults with CF and PERIT¹.

Piperacillin plus tazobactam is most commonly prescribed, but broad spectrum antipseudomonal cephalosporins ceftazadime and cefepime are also sometime preferred. At some centres ceftriaxone is often preferred in those without known Pseudomonas colonisation and with preserved lung function. Ceftriaxone has the convenience of single daily dosing, and because it is thought it might preserve broader spectrum therapy for later use. At other centres, antipseudomonal antibiotics are routinely prescribed in all patients requiring intensive treatment for pulmonary exacerbations, even where airway carriage of Pseudomonas has not been documented, because of the insensitivity of airway microbiology for excluding Pseudomonas infection.

7.6 Discontinuation of participation

For criteria and procedures for participant withdrawal from the PEx Cohort and/or the PEx Treatment Platform, refer to the PEx Core Protocol and the PEx Treatment Platform Protocol.

7.7 Concomitant care and interventions

For a description of the Safety Monitoring and Reporting Refer to the PEx Treatment Platform Protocol.

7.8 Laboratory procedures

Refer to the PEx Core Protocol, and the PEx Treatment Platform Protocol.

There are no Domain-Specific or Intervention-specific laboratory procedures mandated for participants in the Backbone Antibiotics Domain. All laboratory testing will be at the discretion of the Responsible Clinician and in accordance with hospital guidelines and protocols.

7.9 Patient Reported Outcomes

Refer to the PEx Core Protocol.

7.10 Domain Data Collection

For information regarding the routine capture of data for the PEx Cohort, including data collected at the time of pulmonary exacerbations, refer to the PEx Core Protocol. Time windows for spirometry data are defined in the PEx Core Protocol. For details on the timeframes targeted for data collection for trial-participants, refer to the PEx Treatment Platform Protocol.

There is no Domain-specific data collection for the Backbone Antibiotics Domain.

7.11 Domain participation randomisation

For information regarding the randomisation of PEx Treatment Platform participants, refer to the PEx Treatment Platform Protocol and the Statistical Appendix.

For Randomly Assigned Interventions in the Backbone Antibiotics Domain, a fixed (1:1:1 in Strata 2-4, or 1:1:1:1 in Stratum 1) allocation to the three starting options before the first Scheduled Analysis. Stratum-specific RAR will be used after the first Scheduled Analysis in which the probability of Assignment to an Intervention is proportional to the probability it is in the Best Regimen at the most recent Scheduled Analysis, with respect to the Primary Estimand.

7.11.1 Timing of Randomisation and Timing of Reveal of the Assigned Backbone Antibiotic

For information regarding the timing of randomisation and the timing of the reveal of the Assignment of PEx Treatment Platform-participants, refer to the PEx Treatment Platform Protocol.

After randomisation, the participant will have a Provisionally Assigned Regimen. For the analysis, the participant will not be considered to be Assigned to an Intervention in the Backbone Antibiotic Domain until that Assignment has been Revealed. A Provisionally Assigned Intervention which has not been Revealed may be Revoked, for example in response to a change in Stratum on the basis of new sputum culture results. If the participant is still eligible, they may then be re-randomised to a new Provisionally Assigned Regimen.

7.11.2 Reveal of Assigned Backbone Antibiotic

Once randomisation has occurred, the Provisionally Assigned Backbone Antibiotic (whether Clinician's Choice or Randomly Assigned) will remain concealed for up to 14 days (14*24 hours) until the Reveal of the Assignment is activated by the Responsible Clinician (or their delegate). The Reveal of the

Assigned Backbone Antibiotic will occur as close as practicable before commencement of intensive therapy.

To Reveal the Assigned Regimen, the Site PI or their delegate will log in to the BEAT CF Database, and confirm their intention to Reveal the Assigned Regimen. For those participating in both the Backbone Antibiotic and Adjunct Antibiotics Domains, the Reveal of the Assigned Backbone Antibiotic will occur simultaneously with the Reveal of the Assigned Adjunct Antibiotic.

Once the Assigned Backbone Antibiotic has been Revealed, the participant will be considered to be Assigned to that Backbone Antibiotic for the Primary Estimand, regardless of adherence to the Assignment.

7.11.3 Revoking a Provisionally Assigned Backbone Antibiotic

Under exceptional circumstances, the randomisation to a Provisionally Assigned Backbone Antibiotic will be Revoked if, and only if, it has not yet been Revealed. Once the randomisation to a Provisionally Assigned Backbone Antibiotic has been Revoked, the Assignment will not be Revealed.

Randomisation to a Provisionally Assigned Backbone Antibiotic will be Revoked, and a participant may be re-randomised (if still eligible and after confirming the appropriate Stratum, eligibilities, and Clinician Selected Backbone Antibiotic), if:

1. 14 days have elapsed since the randomisation without the Assignment being Revealed. or
2. The participant's Stratum has changed since the randomisation occurred on the basis of new spirometry or sputum microbiology results.

Randomisation to a Provisionally Assigned Backbone Antibiotic will be Revoked, and the participant not re-randomised, if, since randomisation:

They have already received two or more doses of a broad-spectrum antibiotic before the Assignment is Revealed, including any anti-pseudomonal penicillin, third or fourth generation penicillin, carbapenem, monobactam, tigecycline, or IV fluoroquinolone; in that case, the patient should receive antibiotic therapy at the discretion of their Responsible Clinician, and they will be treated as not Assigned to any Backbone Antibiotic in the analysis.

7.12 Blinding

For information regarding blinding in the PEx Treatment Platform, refer to the PEx Treatment Platform Protocol.

All Backbone Antibiotics will be delivered open-label. It is anticipated that the participant, their Responsible Clinician, the Site PI and site study, and clinical staff will know the Assigned Backbone Antibiotic of specific participants at their Site, after it has been Revealed. Unblinding procedures will not be necessary in the event of a medical emergency.

7.13 Trial Periods

For a description of the Trial Period requirements refer to the PEx Trial Protocol.

8. DATA MANAGEMENT

For a description of the processes for data management, refer to the PEx Core Protocol, and the PEx Treatment Platform Protocol.

9. PROTOCOL DEVIATIONS AND SERIOUS BREACHES

For a description of reporting requirements for Protocol Deviations and Serious Breaches, refer to the PEx Treatment Platform Protocol.

10. STATISTICAL METHODS

For an overview of the statistical approach for the PEx Treatment Platform, refer to the PEx Treatment Platform Protocol and the Statistical Appendix.

10.1 Domain Decision Thresholds

The Decision Thresholds for Platform Conclusions in the Backbone Antibiotics Domain will be outlined in the Statistical Appendix and detailed in the Statistical Implementation Guide.

If a Platform Conclusion in relation to the Primary Estimand is made, the DSMB will generally advise the Steering Committee to Terminate any futile Interventions and make a Public Disclosure. Likewise, if a Platform Conclusion is reached that one Intervention is in the Best or Optimal Regimen across all Strata, the DSMB will generally advise the Steering Committee to Close the Domain and make a Public Disclosure.

However, the DSMB may instead direct the Analytic Team to perform secondary and subgroup analyses; based on the results of these analyses, the DSMB may advise the Steering Committee to

continue enrolment into the Domain if clinically important differences in pre-specified Secondary Endpoints or in important Subgroups have not been demonstrated, and if it is considered that the likelihood and benefit of reaching a Conclusion regarding those Endpoints outweighs any risk to participants.

10.2 Interactions with Interventions in Other Domains

An *a priori* interaction between the Backbone Antibiotics Domain and the Adjunct Antibiotics Domain is considered plausible and will therefore be incorporated into the Primary Model. Specifically, it is anticipated that the comparative effectiveness of Backbone Antibiotics may differ by the prescribed Adjunct Antibiotic, and vice versa, although there is no basis upon which to speculate about the likely direction of any heterogeneity in treatment effect.

10.3 Nesting of Interventions

At the commencement of the Domain, no nesting of Intervention treatment effects will be applied in this Domain as detailed in the Statistical Appendix.

10.4 Minimum Clinically Important Difference between Interventions in a Domain

The MCID change in ppFEV1 for two Interventions in the Backbone Antibiotics Domain is 2.0, as specified in the Statistical Appendix. This will be factored into the criteria for declaring a Regimen to be Optimal, or Equivalent, as outlined in the Statistical Appendix and detailed in the Statistical Implementation Guide.

11. QUALITY ASSURANCE AND MONITORING

11.1 Overview

For a description of the Overview of Quality Assurance and Monitoring Refer to the PEx Core Protocol.

11.2 Safety Monitoring and Reporting

For a description of the Safety Monitoring and Reporting for the PEx Treatment Platform, refer to the PEx Treatment Platform Protocol.

11.3 Domain and Intervention-specific Adverse Events of Special Interest

There are no Adverse Events of Special Interest (AESI) pre-specified for the Backbone Antibiotics Domain.

12. ETHICS AND REGULATORY

For a general overview of the ethical considerations of BEAT CF and the PEx Treatment Platform, refer to the PEx Core Protocol and the PEx Treatment Platform Protocol.

12.1 Backbone Antibiotics Domain-specific benefits and risks

The Interventions evaluated in the Backbone Antibiotics Domain reflect the range of first line Backbone Antibiotics that are widely available and used in CF Centres across Australia, so it is unlikely that participation will improve access to therapies, nor is participation unlikely to expose participants to any greater risk than encountered through usual clinical care.

For this Domain, there should be no additional risks to those outlined in the PEx Core protocol.

13. REPORTING/ PUBLICATION

For the overarching reporting and publication policy for BEAT CF, refer to the PEx Core Protocol, and the PEx Treatment Platform Protocol.

14. REFERENCES

ⁱ Grace Currie, Anna Tai, Tom Snelling, Andre Schultz BMJ Open Res 2021