Bayesian **E**vidence **A**daptive **T**reatment of **C**ystic **F**ibrosis.

Pulmonary Exacerbations Treatment Platform

Domain Specific Appendix B

Adjunct 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 B is to be read in conjunction with

- PEx Core Protocol
- PEx Treatment Platform Protocol
- PEx Treatment Platform appendices:
  - DSA A: Backbone Antibiotics Domain-Specific Appendix
  - Statistical Appendix

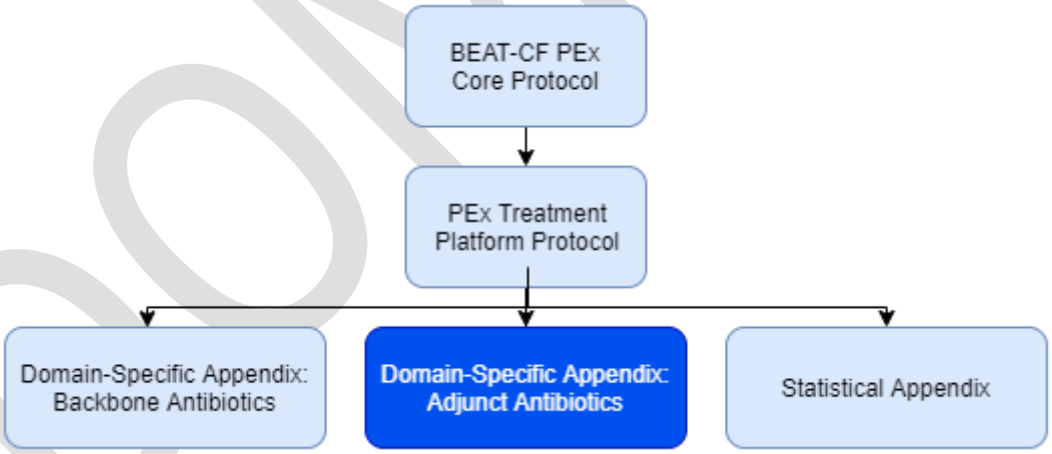

Figure 1: Adjunct Antibiotics Domain-Specific Appendix in relation to other BEAT CF documents

	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

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1.0 OVERVIEW

1.1 Key Details

Protocol	BEAT CF Domain Specific Appendix B: Adjunct 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: Adjunct 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 standard of care Adjunct Antibiotics currently in use, and no adjunct antibiotic therapy, 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	1. Enrolment in the BEAT CF PEx Treatment Platform 2. Informed consent
DOMAIN-SPECIFIC EXCLUSION CRITERIA	1. Revealed Intervention Assignment in the Domain in the preceding 28 days. 2. More than 2 doses in the preceding 28 days of any IV aminoglycoside, IV polymixin (including colistin), or IV fluoroquinolone. 3. Planned to receive any IV aminoglycoside, IV or inhaled polymixin (including colistin), or IV or oral fluoroquinolone in the next 14 days (apart from their Assigned Intervention).
INTERVENTION-SPECIFIC EXCLUSION CRITERIA	4. Known or suspected significant drug hypersensitivity to tobramycin or other aminoglycosides 5. Intervention is deemed unacceptable, e.g. because of failed PERIT treatment response to that Intervention in the preceding 12 months 6. For IV Tobramycin only: Recognised contraindication including known renal, auditory or vestibular impairment which precludes its use.

RANDOMISATION	PEx Treatment Platform participants will be randomised (1:4) to either their Clinician's Choice of Intervention in the Adjunct 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).
BLINDING	Participants and outcome assessors will not be blinded to Intervention Assignment in the Adjunct Antibiotics Domain.
ANALYSIS	Refer to the PEx Treatment Platform Protocol and Statistical Appendix
DATA MANAGEMENT	Refer to the PEx Core Protocol

1.3 Abbreviations & Definitions

Refer to the PEx Core Protocol: Attachment 1 Abbreviations and Definitions

1.4 Purpose and scope of this document

The BEAT CF Pulmonary Exacerbation (PEx) Treatment Platform Domain-Specific Appendix B (DSA B): Adjunct 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 Adjunct Antibiotics Domain. Unless stated elsewhere, this DSA applies to all Interventions delivered as part of the Adjunct 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 Adjunct Antibiotics Domain, including methods of Domain enrolment, any Domain-specific consent issues, and any Domain-specific data collection
- 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 (e.g. other Domain-Specific and Statistical Appendices).

1.5 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 BEAT CF PEx Core Protocol.

The Domain-specific Objective of the Adjunct Antibiotics Domain is to determine the comparative effectiveness of alternative standard of care Adjunct Antibiotics currently in use, and no adjunct antibiotic therapy, 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 Adjunct Antibiotics (including no Adjunct Antibiotic) 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 Adjunct Antibiotics Domain will be nested in the PEx Treatment Platform.

Eligible participants in the Adjunct 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 Adjunct Antibiotic Domain, the Intervention is a Prescription for the Assigned antibiotic (or no Adjunct Antibiotic) at the commencement of intensive therapy made by the Responsible Clinician or their authorised delegate.

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 Adjunct Antibiotic Domain:

1. IV Tobramycin
2. Inhaled Tobramycin
3. No adjunct antibiotic

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

Formulation	Be any formulation of that antibiotic which is registered on the Australian Register of Therapeutic Goods
Delivery	See below
Start time	Adjunct antibiotics will be commenced as soon as practicable, preferably within 6 hours of Reveal of the Assignment. Because of incompatibilities between tobramycin and penicillin/ cephalosporin class antibiotics, for those assigned to IV tobramycin as Adjunct Antibiotic therapy, either Backbone or Adjunct Antibiotic may be given first, but it is recommended that the IV cannula is flushed between doses.
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 **Frequency** **Mode of administration**	Be guided by section 6.2, but will ultimately be at the discretion of the Responsible Clinician in accordance with local guidelines and policies.

In general, it is expected that changes in Adjunct 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 Tobramycin

Tobramycin is an aminoglycoside antibiotic that inhibits bacterial protein synthesis by irreversibly binding to the 30S ribosomal subunit, resulting in cell membrane damage. Tobramycin is active against a broad range of gram negative bacteria, including *Pseudomonas aeruginosa*.

6.2.2 IV Tobramycin

- Regular renal function testing should be performed and IV tobramycin must be used with caution in patients with renal impairment and the dose reduced. Risk factors for nephrotoxicity include length of treatment, high plasma concentrations, dehydration and treatment with other nephrotoxic medications. Regular monitoring for vestibular and ototoxicity is recommended, and care should also be taken in patients with a previous vestibular or auditory toxicity due to an aminoglycoside.
- **Therapeutic drug monitoring** (TDM) with dose adjustment as required is recommended for all patients receiving IV tobramycin, but approaches to TDM vary and should adhere to local policies. Trough concentrations are generally recommended to be below the level of detection of a sensitive assay. An area under the curve (AUC) of 70-100mg/L/hr has been recommended in CF patients.
- Administration should adhere to local CF Centre/ hospital guidelines, and policies. As a guide:

Administration	IV injection over several minutes, OR An IV infusion over up to 1 hour. It may also be given by IM injection.
Dose Adjustment	The dose needs to be adjusted for age and renal function. Follow hospital guidelines for appropriate dosing
Contra-indications and Precautions	Tobramycin is generally contraindicated in patients with a history of high risk allergy to tobramycin and other aminoglycosides. Individuals with the A155G gene mutation are strongly predisposed to ototoxicity and should not receive aminoglycosides. IV tobramycin should be used with caution in patients with patients with neuromuscular disease e.g. myasthenia gravis as the risk of muscle weakness and respiratory depression is increased. Some formulations contain sodium metabisulfite which may cause allergic reactions in susceptible people.

6.2.3 Inhaled Tobramycin

Systemic absorption of tobramycin administered by inhalation is low so it can usually be safely administered in renal impairment without dose adjustment, but care should still be taken. Assessment of renal function monitoring is recommended prior to initiation of inhaled tobramycin treatment and infrequently thereafter, although more frequent monitoring is

recommended for patients with renal impairment or taking other nephrotoxic medications.

- Administration should adhere to local CF Centre/ hospital guidelines, and policies. As a guide:

Administration	Several formulations are used for inhalational therapy. Generally ampoules for nebulisation are used in preference to capsules for inhalation for PERIT. 500mg/5mL vial - (Tobra-Day); 300mg/5mL ampoule Tobramycin solution for inhalation (various brands), and 28mg capsules for inhalation (Tobi® Podhaler) which is PBS-subsidised for children ≥6years old only.
Dose Adjustment	Not applicable
Contra-indications and Precautions	Inhaled tobramycin is contraindicated in patients with a known hypersensitivity to any aminoglycoside or any components of the formulation. In patients with a history of severe haemoptysis, there may be a risk of further haemorrhage. Acute bronchospasm can occur in the 15 minutes after inhalation, so the first dose of inhaled tobramycin is recommended to be given under clinical supervision in those who have not previously been shown to tolerate inhaled tobramycin. Mild bronchospasm may sometimes be managed with co-administration of bronchodilator therapy.

6.3 Inclusion criteria

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

1. They are enrolled in the PEx Treatment Platform.
2. Their Site is participating in the Adjunct Antibiotic Domain.
3. They are eligible for at least two Interventions options in the Adjunct Antibiotic Domain available at that site (including no Adjunct Antibiotic).
4. Their informed consent to participate in the Adjunct 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 Adjunct Antibiotics Domain if:

1. They have already had a Revealed Intervention Assignment in the Adjunct Antibiotics Domain in the preceding 28 days.
2. They have already received more than 2 doses in the preceding 28 days of any IV aminoglycoside, IV polymixin (including colistin), or IV fluoroquinolone.
3. They are planned to receive any IV aminoglycoside, IV or inhaled polymixin (including colistin), or IV or oral fluoroquinolone in the next 14 days (apart from their Assigned Intervention).

6.4.2 Intervention-specific exclusion criteria

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

1. They have a known or suspected significant drug hypersensitivity to tobramycin or other aminoglycosides
2. The Intervention is deemed unacceptable by the Responsible Clinician e.g. because of failed PERIT treatment response to that Intervention (including no Adjunct Antibiotic) requiring a change in antibiotic treatment, in the preceding 12 months

Additional Intervention-specific exclusion criteria, include:

Intervention	**Exclusion Criteria**
Intravenous Tobramycin	Recognised contraindication to IV tobramycin, including known renal, auditory or vestibular impairment which, in the opinion of the Responsible Clinician, precludes its use.

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 Adjunct 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 Adjunct Antibiotics Domain, like the PEx Treatment Platform, is designed to be perpetual; multiple Adjunct 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 Adjunct 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 Adjunct Antibiotic options for treating PEx in people with CF are known.

Should the Domain be Closed, the end date 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 Adjunct 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 Adjunct antibiotics among children and adults with CF and PERIT[i].

Most CF clinicians prescribe IV tobramycin as an Adjunct antibiotic among children and adults with PERIT where the patient is known to be colonised with *Pseudomonas aeruginosa*, although adding aminoglycosides to Backbone antibiotics adds to the treatment burden (it requires therapeutic drug monitoring) and the risk of toxicity and a benefit has not been shown. In patients who are not known to be colonised with *Pseudomonas aeruginosa*, practice is variable with many clinicians withholding IV tobramycin, especially in patients with preserved lung function.

Inhaled tobramycin is thought to avoid the systemic toxicities of IV tobramycin, and is widely used in CF, although it is less frequently used for managing pulmonary exacerbations. Inhaled tobramycin would be preferred to IV tobramycin if it could be shown to have similar effectiveness. Inhaled tobramycin is burdensome to administer and carries a theoretic risk of environmental contamination and inadvertent nosocomial and occupational exposure to antibiotic, so no tobramycin would be preferred to inhaled tobramycin if it could be shown to have similar effectiveness.

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.

Laboratory monitoring for haematologic, renal, and liver toxicities are recommended for patients treated with IV tobramycin, but will be at the discretion of the Responsible Clinician in accordance with local guidelines. It is expected that therapeutic drug monitoring will be performed for all participants assigned to IV tobramycin, but the timing and adjustments of dosing will be at the discretion of the Responsible Clinician in accordance with local guidelines.

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 Adjunct Antibiotics Domain.

7.11 Domain participant 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 Adjunct Antibiotics Domain, a fixed (1:1:1) 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 Adjunct 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 Adjunct 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 Adjunct Antibiotic

Once randomisation has occurred, the Provisionally Assigned Adjunct 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 Adjunct 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 Adjunct Antibiotic will occur simultaneously with the Reveal of the Assigned Backbone Antibiotic.

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

7.11.3 Revoking a Provisionally Assigned Adjunct Antibiotic

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

Randomisation to a Provisionally Assigned Adjunct Antibiotic will be Revoked, and a participant may be re-randomised (if still eligible and after confirming the appropriate Stratum, eligibilities, and Clinician Selected Adjunct 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 Adjunct Antibiotic will be Revoked, and the participant not re-randomised, if, since randomisation:

They have already received two or more doses of any IV aminoglycoside, IV or inhaled polymixin (including colistin), 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 Adjunct Antibiotic in the analysis.

7.12 Blinding

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

All Adjunct 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 Adjunct Antibiotic (if any) 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 Treatment Platform 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. 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 Adjunct 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 Adjunct Antibiotics may differ by the prescribed Backbone 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 Adjunct 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 Adjunct 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 Adjunct Antibiotics Domain-specific benefits and risks

The Interventions evaluated in the Adjunct Antibiotics Domain reflect the range of first line Adjunct 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 additional 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