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

Pulmonary Exacerbations

Statistical Appendix

V3, 16 Dec 2021

STATISTICAL COMMITTEE ENDORSEMENT

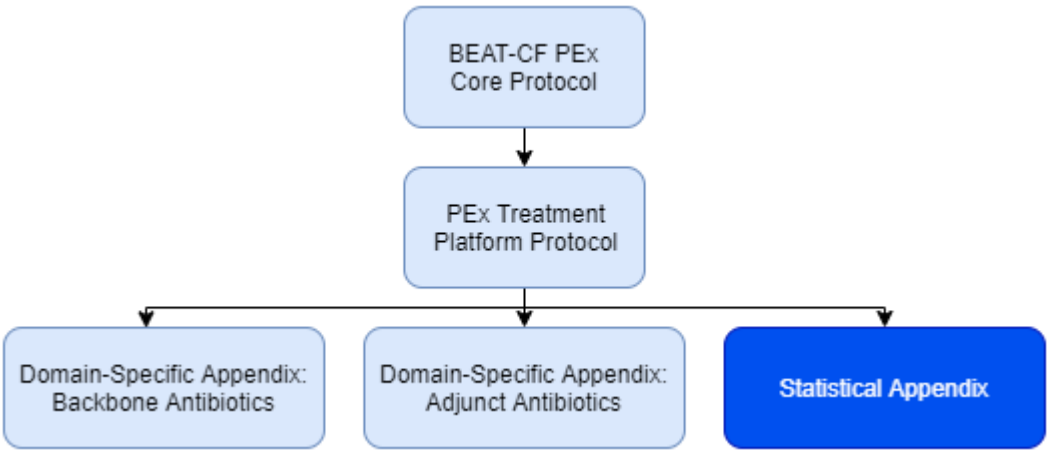
The signature below constitutes the approval of this Statistical Appendix on behalf of the BEAT CF Statistical Committee, and provides the necessary assurances that the analyses will be conducted according to all stipulations of the protocol, and according to local legal and regulatory requirements and applicable Australian regulations and International Council for Harmonisation (ICH) guidelines.

Signed **Date**

Name:

Title:

DOCUMENT ORIENTATION



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2.2 Domain Specific Appendices & Version Histories

For an overview of the Domain-Specific Appendices, refer to DSA A: Backbone Antibiotics, and DSA B: Adjunct Antibiotics

2.3 PEx Statistical Appendix Overview

This Statistical Appendix describes the statistical methods for comparing the effectiveness of Interventions, and decision criteria for making adaptations, and for reporting final analyses by Stratum for the BEAT CF PEx Treatment Platform. It draws on information in the BEAT CF PEx Core Protocol, the BEAT CF PEx Treatment Platform Protocol and associated Domain-Specific Appendices to define the project Objectives within an estimand framework, including target populations, endpoints, statistical methods and models, and population level estimators. It provides a technical bridge between the PEx Treatment Platform Protocol and its Domain Specific Appendices and the Statistical Implementation Guide.

The version of the Statistical Appendix is indicated in this document's header and it is designed to support the starting PEx Treatment Platform structure (shown below) and the addition of new Interventions and Domains, as outlined in the PEx Treatment Platform protocol and associated Domain-Specific appendices.

For ease of reference, the following is transcribed from the PEx Treatment Platform Protocol:

"Individual treatments for a PERIT are nominated 'Interventions', where an Intervention is a prescription for a therapy which is intended to improve the outcome of a patient. An Intervention may be a prescribed medicine (which may be further defined by route of administration, dose, and duration), or a prescribed non-medicinal therapy, for example chest physiotherapy (which may be further defined by the exact technique, frequency and duration). Interventions are grouped into Domains, which are sets of Interventions which are mutually exclusive, i.e. they cannot be co-administered by their nature (e.g. alternative dosages of the same medicine), or co-administration is unacceptable because of expected sub-additive effects (for example medicines of the same class or target of action) or because of unacceptable toxicities (for example medicines which cause high risk of nephrotoxicity if used in concurrently). The treatment of a PERIT is generally multi-modal, and generally comprises prescription of a Regimen, where a Regimen is a specific combination of Interventions across multiple Domains."

"Eligible participants are grouped into Strata, where Strata are predefined, mutually exclusive category of participant based on factors which are defined at baseline for each PERIT. It is anticipated, a priori, that treatment effects may be heterogenous across Strata and so the effects of Interventions and Regimens are reported separately for each. For an individual participant, the baseline factors which define each Stratum may change over time, and so an individual may belong to more than one Stratum over time. "

"For each PERIT, a participant will be Assigned to be prescribed one (and only one) Intervention in each of the Domains for which they are eligible. The Responsible Clinician will first nominate a Selected Intervention in each of the Domains. The participant will then be randomised 1:4 to either be Assigned to the Selected Regimen ('Clinician's Choice'), or to a Randomly Assigned Intervention (Random Intervention) in each Domain. Randomly Assigned Interventions in each Domain will be Assigned using Response Adaptive Randomisation (RAR) as described in the Statistical Appendix."

Stratum	**Domain A** Backbone Antibiotics		**Domain B** Adjunct Antibiotics	
[1] ppFEV$_1$≥70 & PsA negative	Random Assignment to Piperacillin plus tazobactam or Ceftazadime or Cefepime or Ceftriaxone*	Clinician's Choice of Piperacillin plus tazobactam or Ceftazadime or Cefepime or Ceftriaxone*	Random Assignment to IV Tobramycin or Inhaled Tobramycin or no Tobramycin	Clinician's Choice of IV Tobramycin or Inhaled Tobramycin or no Tobramycin
[2] ppFEV$_1$≥70 & PsA positive				
[3] ppFEV$_1$<70 & PsA negative				
[4] ppFEV$_1$<70 & PsA positive				

* Ceftriaxone in Domain A is only available for Stratum [1] participants.
# If participant is randomised to Clinician's Choice then this will apply to all Domains.
Note that domains and interventions may be added or dropped during the life of the platform. This design is given only as an illustration of the trial's structure at the start of recruitment.

2.4 Statistical Appendix Version History

The Statistical Appendix v1.0 supports the following versions of the PEx Core Protocol, PEx Treatment Platform and Domain-Specific Appendices:

PEx Core Protocol:	Version 6.0
PEx Treatment Protocol:	Version 1.0
DSA A: Backbone Antibiotics:	Version 1.0
DSA B: Adjunct Antibiotics:	Version 1 .0

3. INTRODUCTION

The overall aim of BEAT CF is to improve outcomes for people with CF by optimising their management. Its objective is to evaluate the comparative effectiveness of clinical interventions on the change in ppFEV1 from baseline to approximately one week after commencement of intensive therapy for a pulmonary exacerbation requiring intensive therapy (PERIT), and efficiently implementing this evidence into routine care. BEAT CF aims to accurately and efficiently collect treatment and outcome data for this purpose. The PEx Treatment Platform is designed to be adaptive and has the capacity to accommodate additional pharmacological and non-pharmacological interventions either within existing Domains or as part of entirely new Domains, allowing the standard of care to evolve over time. The PEx Treatment Platform is designed with an overarching Bayesian primary model, as specified here and augmented, as necessary, in the Statistical Implementation Guide as the

Platform evolves., Posterior distributions for estimating model parameters are used to evaluate pre-specified decision criteria, which will drive adaptations and reporting of results summaries.

Specification of the methods for summarising and analysing the accumulating data is described in this document, however additional technical details will be provided in the Statistical Implementation Guide as necessary. We note that while the Statistical Implementation Guide may supplement what is specified here, any substantive modifications, for example of the Primary Endpoint definition or the primary analysis model will be reflected in a formal amendment of the Statistical Appendix and/or PEx Treatment Platform Protocol. Additionally, the Statistical Implementation Guide may include further detail on the communication plan for disclosing results during the ongoing platform trial.

4. TRIAL STRUCTURE

4.1 Summary of the overall design of the PEx Treatment Platform

For a detailed description, refer to the PEx Treatment Platform Protocol

The BEAT CF PEx Treatment Platform is an investigator initiated, randomised, embedded, multi-arm/ multi-factorial, adaptive platform (REMAP), conducted across multiple CF Centres in Australia. Its objective is to determine the optimal Regimens, i.e. combinations of Interventions across multiple treatment Domains for distinct Strata of patients, for the management of pulmonary exacerbations of CF. It is adaptive in nature, with frequent Scheduled Analyses to update treatment allocation probabilities, evaluate Decision Thresholds, and make conclusions about comparative effectiveness.

4.2 Domains and Interventions

For a detailed description of the Domains and Interventions within each Domain, refer to the relevant Domain-Specific Appendix

A Domain defines a set of mutually exclusive Interventions, typically sharing a common mechanism of action or clinical context of use (e.g. Backbone antibiotics, Adjunct antibiotics). Both the number of Domains and the number and identity of individual Interventions within each of these Domains may vary in one or more Strata across the life of the PEx Treatment Platform, as new Interventions of interest arise.

In this documentation, Domains are referred to by capitalized alpha-letter for convenience (i.e. A=Backbone antibiotic, B=Adjunct antibiotic) and the set of domains is given by $\mathcal{D} = \{A, B, \dots\}$. A domain $D \in \mathcal{D}$ consists

of interventions $D = \{d_1, d_2, \ldots, d_{K_d}\}$, where d_k denotes intervention k within domain D, and K_d is the total number of interventions within domain D. The subscript is sometimes omitted from d_k when only one intervention is being discussed and the meaning is clear. The starting Domains included in the PEx Treatment Platform are:

- A: Backbone Antibiotics Domain
- B: Adjunct Antibiotics Domain

4.3 Strata

Participants are grouped into Strata for each PERIT, defined by the status of specific stratification variables at the time of each randomisation; $S = \{s_1, s_2, \ldots s_J\}$, where each S denotes a categorical classification (e.g. binary) for each of the J variables. Mutually exclusive Strata denoted as $G = \{g_1, g_2, \ldots g_M\}$ are defined based on distinct combinations of the stratification variables. It is anticipated that the direction of Intervention/Regimen treatment effects will be consistent within these Strata, but may be heterogeneous across the Strata. Therefore, treatment effects will be estimated separately for each Stratum unless stated otherwise in the DSAs. The design is flexible to accommodate new (mutually exclusive) Strata. At commencement of the PEx Platform Trial, the stratification variables s_1 and s_2 will consist of:

1. Higher baseline lung function ($ppFEV_1 \geq 70$) versus Lower baseline lung function ($ppFEV_1 < 70$), based on the highest $ppFEV_1$ measured within the 12 months preceding the commencement of therapy for a PERIT;
2. Known Pseudomonas aeruginosa colonisation (PsA+) versus no known *Pseudomonas aeruginosa* colonisation (PsA-), in the 24 months preceding the commencement of therapy for a PERIT.

Initially, four distinct and mutually exclusive Strata are based on the four combinations of these two stratification variables, e.g. $g_1 = \{s_1 = 1, s_2 = 1\}$ denotes a Stratum with higher lung function and no known Pseudomonas colonisation, and $g_2 = \{s_1 = 1, s_2 = 0\}$ denotes a Stratum with higher lung function and known Pseudomonas colonisation. Lung function classification is based on multiple spirometries in the 12-months prior to baseline, in which the highest calibrated spirometry in that period will be used. Individual participants can contribute multiple PERITs for the same Stratum and/or contribute to different Strata over time, should their baseline lung function and/or recent *Pseudomonas* colonisation status fluctuate between successive PERITs.

4.4 Regimens

For each eligible PERIT, participants will be Assigned to a single Intervention within each Domain. The unique combination of Interventions across the Domains will be referred to as a Regimen, denoted by r. The set of

available Regimens within a Stratum g is denoted $\mathcal{R}_g \ r$. For example, the initial two-Domain design allows for up to four Intervention options in the Backbone Antibiotics Domain (A) to be combined with any of three Intervention options in the Adjunct Antibiotic Domain (B), so in the absence of treatment contraindications or other ineligibilities there are 12 possible Regimens (i.e. 4x3=12) in Stratum 1 (high lung function & no known *Pseudomonas aeruginosa* colonisation) and 9 potential regimens (i.e. 3x3 =9) in Strata 2-4.

4.5 Randomisation

For each eligible PERIT, the randomisation can be conceptualised as a two-step process. In the first step, eligible PERITs are randomized to either "Clinician's Choice" or to "Random Assignment". If randomized to Clinician's Choice, PERITs are assigned the Regimen corresponding to the Clinician's Selection recorded immediately prior to randomisation. If randomized to "Random Assignment", a second randomization step assigns eligible PERITs to one of the eligible Regimens at random (see Section 5.4).

Participants may contribute to the study at multiple PERITs. Randomization is performed independently for each eligible PERIT, so participants may be Assigned multiple (and potentially different) Regimens over time. Participants will not be assigned to Interventions for which they have one or more of the contraindications or ineligibilities documented in the PEx Treatment Platform Protocol or the DSAs, or for which Interventions are not open to Assignment at their Site (for example due to non-availability).

Due to potential delays before commencement of intensive therapy, it will be necessary to generate and "Provisionally Assign", but delay the "Reveal" of the Assigned Interventions for each Domain until immediately before the participant is able to commence treatment. The PERIT will not be considered to be Assigned to an Intervention until that Assignment has been Revealed.

4.5.1 Response Adaptive Randomisation

The PEx Treatment Platform will begin with equal allocation to the Regimens available within each Stratum until a pre-specified number of randomizations occur within the Stratum (e.g. 120 randomized PERITs). Subsequently, response adaptive randomization (RAR) will be activated at the Regimen level within each Stratum per the pre-specified algorithm. RAR will be performed proportionally to the probability that each Regimen is Best within that Stratum, weighted by the sample size of each regimen. Allocation probabilities to each Regimen within a Stratum will be permitted to vary across the life cycle of the platform. Additional details are provided in section 8.8.

4.5.2 Clinician choice and preference

The clinician's Selected Regimen for each PERIT will be chosen from among the available Regimens defined above and will be recorded immediately prior to randomisation. Assignment to Clinician Choice vs Random Assignment will be based on a fixed ratio as specified in the PEx Treatment Platform Protocol (1:4). If a PERIT is randomized to Clinician's Choice then the PERIT will be assigned to the clinician's Selected Regimen for the current PERIT. The clinician and participant will remain blinded to whether they were randomised to Clinician Choice or Random Assignment. Even if they know that the PERIT's Assigned Regimen aligns with the Selected Regimen, they will not know whether this occurred because the participant was randomised to Clinician's Choice, or whether they were Assigned to receive a Randomly Assigned Regimen, which happened to align with the clinician's Selected Regimen by chance.

4.5.3 Domain-specific and Intervention-specific ineligibilities

The potential reasons for Domain-specific ineligibilities are listed in the individual DSAs and may include contraindications (allergies, intolerances, adverse events) and non-contraindication ineligibilities (lack of access, site opted out of Domain). If a participant with a PERIT is not eligible for at least two Intervention options within a Domain and/or an entire Domain is unavailable at a site at the time of randomisation, then they will be deemed ineligible for that Domain for that PERIT. At the Responsible Clinician's discretion, Temporary Exclusions to an Intervention may be based on a participant's poor response to a Regimen containing that Intervention (requiring a change in therapy) during a previous PERIT in the 12 months prior to randomisation.

When RAR is used, if a PERIT is ineligible for one or more Interventions within a Domain, the allocation probabilities will be re-normalised across the remaining eligible Interventions, provided the participant with the PERIT is eligible for at least two different Intervention options in each Domain. If an intervention within a Domain is unavailable at randomisation for a site-specific reason (e.g. temporary unavailability of the Intervention), then allocation probabilities will be re-normalised across the remaining available Interventions, as long as there are a minimum of two eligible Interventions within that Domain that are available for that PERIT. Data on Primary and Secondary Endpoints in participants flagged as ineligible for some or all Interventions will still be captured and used in the Primary Analysis according to the Statistical Implementation Guide.

5. ENDPOINTS, ESTIMANDS & INTERCURRENT EVENTS STRATEGY

For the Outcomes and Endpoints refer to the PEx Core Protocol. Any Domain-specific Outcomes or Endpoints are defined in the Domain-Specific Appendices.

The PEx Population of Interest is defined by the inclusion and exclusion criteria described in the BEAT CF PEx Core Protocol and the PEx Treatment Platform, hereafter known as Randomisation-eligible PERITs. The Primary Endpoint, which is defined in the PEx Core Protocol, is the same for Interventions across all Domains and all Strata of participants, unless specified otherwise in the DSA. For each planned analysis, we specify the treatment effect which is the target of estimation in compliance with the ICH GCP estimand framework. Each is specified in terms of the analysis population (eligibility), intervention and comparator, outcome and when it is measured (endpoint and window), the population summary (effect measure), and the approach to intercurrent events (post-randomisation events).

5.1 Treatment Platform Primary Efficacy

Objective/ Target population	Endpoint / Population level summaries	Post-randomisation events strategy
Estimand 1 In each Stratum, the effect of each regimen compared to each other regimen, on the change in $ppFEV_1$, **~7 days** after commencing intensive therapy, including all Randomisation-eligible PERITs.	Endpoint: Absolute change in the $ppFEV_1$ after commencing intensive therapy, compared to Day 0 (continuous). Day 0 $ppFEV_1$ measured closest in time to the first dose of IV therapy, *and not* ≥ 14 days (14*24hr) before, *and not* ≥72 hours afterwards. Window: Day 7 $ppFEV_1$ selected as first measured $ppFEV_1$ ≥7 days (7*24hr) afterwards, *but no later than* 10 days (10*24hr) afterwards. Population summary*: Difference in mean change in $ppFEV_1$ between each regimen and each other regimen within each Stratum.	Treatment policy strategy (intent-to-treat principle)

5.2 Treatment Platform Secondary Efficacy & Safety

Objective / Target population	Endpoint / Population level summaries	Post-randomisation events strategy
Estimand 1b As for Estimand 1b, but excluding PERITs in which < 90% of all prescribed doses of the Assigned Regimen were documented as received, and no treatment crossover occurred.	Endpoint: As for Estimand 1. Window: As for Estimand 1 Population summary*: As for Estimand 1	The de jure estimand (per-protocol principle)
Estimand 2 As for Estimand 1, but excluding PERITs randomized to Clinician's Choice.	Endpoint: As for Estimand 1 Window: As for Estimand 1 Population summary*: As for Estimand 1	Treatment policy strategy (intent-to-treat principle)
Estimand 3 As for Estimand 1, but wider assessment window for primary endpoint.	Endpoint: As for Estimand 1: Window: Day 7 ppFEV1 measured closest in time to 7 days (7*24hr) after the first dose of IV therapy, but ≥ 5 days (5*24hr) afterwards, but < 14 days (14*24hr) afterwards. Population summary*: As for Estimand 1	Treatment policy strategy (intent-to-treat principle)
Estimand 4 As for Estimand 1, but ~**14 days** after commencing intensive therapy.	Endpoint: As for Estimand 1 Window: Day 14 ppFEV1 selected as first measured ppFEV1 ≥ 14 days (14*24hr) afterwards, but < 30 days (30*24hr) afterwards. Population summary*: As for Estimand 1	Treatment policy strategy (intent-to-treat principle)
Estimand 5 As for Estimand 1, but ~**30 days** after commencing intensive therapy.	Endpoint: As for Estimand 1 Window: Day 30 ppFEV1 selected as first measured ppFEV1 ≥ 30 days (30*24hr) afterwards, but < 60 days (60*24hr) afterwards. Population summary*: As for Estimand 1	Treatment policy strategy (intent-to-treat principle)
Estimand 6 As for Estimand 1, but ~**60 days** after commencing intensive therapy.	Endpoint: As for Estimand 1 Window: Day 60 ppFEV1 selected as first measured ppFEV1 ≥ 60 days (60*24hr) afterwards, but < 90 days (90*24hr) afterwards. Population summary*: As for Estimand 1	Treatment policy strategy (intent-to-treat principle)
Estimand 7 As for Estimand 1, but ~**180 days** after commencing intensive therapy.	Endpoint: As for Estimand 1 Window: Day 180 ppFEV1 selected as first measured ppFEV1 ≥ 180 days (180*24hr) afterwards, but < 240 days (240*24hr) afterwards. Population summary*: As for Estimand 1	Treatment policy strategy (intent-to-treat principle)
Estimand 8 In each Stratum, the effect of each regimen compared to each other regimen, on the **relative** change in ppFEV1, ~**7 days** after commencing intensive therapy, including all Randomisation-eligible PERITs.	Endpoint: **Relative** change in the ppFEV1 after commencing intensive therapy compared to Day 0 (continuous) Window: as for Estimand 1 Population summary*: Difference in mean **relative** change in ppFEV1 between each regimen and each other regimen within each Stratum.	Treatment policy strategy (intent-to-treat principle)
Estimand 9 As for Estimand 8, but ~**14 days** after commencing intensive therapy.	Endpoint: As for Estimand 8 Window: as for Estimand 4 Population summary*: As for Estimand 8	Treatment policy strategy (intent-to-treat principle)
Estimand 10 As for Estimand 8, but ~**30 days** after commencing intensive therapy.	Endpoint: As for Estimand 8 Window: as for Estimand 5 Population summary*: As for Estimand 8	Treatment policy strategy (intent-to-treat principle)

Estimand 11 As for Estimand 8, but ~**60 days** after commencing intensive therapy.	Endpoint: As for Estimand 8 Window: as for Estimand 6 Population summary*: As for Estimand 8	Treatment policy strategy (intent-to-treat principle)
Estimand 12 As for Estimand 8, but ~**180 days** after commencing intensive therapy.	Endpoint: As for Estimand 8 Window: as for Estimand 7 Population summary*: As for Estimand 8	Treatment policy strategy (intent-to-treat principle)
Estimand 13 In each Stratum, the effect of each regimen compared to each other regimen, on the **probability of ppFEV1 returning to ≥90%** of baseline $ppFEV_1$, ~**7 days** after commencing intensive therapy, including all Randomisation-eligible PERITs.	Endpoint: Return of $ppFEV_1$ to ≥90% of baseline $ppFEV_1$ (binary). Baseline $ppFEV_1$ taken to be the highest $ppFEV_1$ measured <365 days prior to first dose of IV therapy. Window: as for Estimand 1 Population summary*: Log odds ratio of return of $ppFEV_1$ to ≥90% of baseline between each regimen and each other regimen within each Stratum.	Treatment policy strategy (intent-to-treat principle)
Estimand 14 As for Estimand 13, but ~**14 days** after commencing intensive therapy.	Endpoint: As for Estimand 13 Window: as for Estimand 4 Population summary*: As for Estimand 13	Treatment policy strategy (intent-to-treat principle)
Estimand 15 As for Estimand 13, but ~**30 days** after commencing intensive therapy.	Endpoint: As for Estimand 13 Window: as for Estimand 5 Population summary*: As for Estimand 13	Treatment policy strategy (intent-to-treat principle)
Estimand 16 As for Estimand 13, but ~**60 days** after commencing intensive therapy.	Endpoint: As for Estimand 13 Window: as for Estimand 6 Population summary*: As for Estimand 13	Treatment policy strategy (intent-to-treat principle)
Estimand 17 As for Estimand 13, but ~**180 days** after commencing intensive therapy.	Endpoint: As for Estimand 13 Window: as for Estimand 7 Population summary*: As for Estimand 13	Treatment policy strategy (intent-to-treat principle)
Estimand 18 In each Stratum, the effect of each regimen compared to each other regimen on the **CRISS**, ~**7 days** after commencing intensive therapy, including all Randomisation-eligible PERITs.	Endpoint: Chronic Respiratory Infections Symptom Score (CRISS) (ordinal) Window: as for Estimand 1 Population summary*: Difference in mean CRISS between each regimen and each other regimen within each Stratum.	Treatment policy strategy (intent-to-treat principle)
Estimand 19 As for Estimand 18, but ~**14 days** after commencing intensive therapy.	Endpoint: As for Estimand 18 Window: as for Estimand 4 Population summary*: As for Estimand 18	Treatment policy strategy (intent-to-treat principle)
Estimand 20 As for Estimand 18, but ~**30 days** after commencing intensive therapys.	Endpoint: As for Estimand 18 Window: as for Estimand 5 Population summary*: As for Estimand 18	Treatment policy strategy (intent-to-treat principle)
Estimand 21 As for Estimand 18, but ~**60 days** after commencing intensive therapy.	Endpoint: As for Estimand 18 Window: as for Estimand 6 Population summary*: As for Estimand 18	Treatment policy strategy (intent-to-treat principle)
Estimand 22 As for Estimand 18, but ~**180 days** after commencing intensive therapy.	Endpoint: As for Estimand 18 Window: as for Estimand 7 Population summary*: As for Estimand 18	Treatment policy strategy (intent-to-treat principle)
Estimand 23 In each Stratum, the effect of each regimen compared to each other regimen, on the **time between PERITs**, including all Randomisation-eligible PERITs.	Endpoint: Length of time between consecutive PERITs (in days), from Day 0 for $PERIT_{t1}$ to Day 0 for $PERIT_{t2}$ (time to event) Population summary*: Difference in median time between consecutive PERITs between each regimen and each other regimen within each Stratum.	Treatment policy strategy (intent-to-treat principle) An individual will be right censored on the first of: *The date of data cut for the Scheduled Analysis

		*The date of Withdrawal from the Treatment Platform for any reason
Estimand 24 In each Stratum, the effect of each regimen compared to each other regimen, on **early cessation** of the Assigned Regimen, **<7 days** after commencing intensive therapy, including all Randomisation-eligible PERITs.	Endpoint: Cessation of the Assigned Regimen after the first dose of intensive therapy for any reason (binary) Window: Up to 7 days (7*24hr) after the first dose of intensive therapy Population summary*: Log odds ratio of cessation of Assigned Intervention between each regimen and each other regimen within each Stratum.	Treatment policy strategy (intent-to-treat principle)
Estimand 25 As for Estimand 24, but <**14 days** after commencing intensive therapy.	Endpoint: As for Estimand 24 Window: Up to 14 days (14*24hr) after the first dose of intensive therapy Population summary*: As for Estimand 24	Treatment policy strategy (intent-to-treat principle)
Estimand 26 In each Stratum, the effect of each regimen compared to each other regimen, on the probability of developing **C. difficile** diarrhoea, <**90 days** after commencing intensive therapy, including all Randomisation-eligible PERITs.	Endpoint: Development of laboratory-confirmed C. difficile diarrhoea after the first dose of intensive therapy. This means a stool submitted to a clinical laboratory has tested positive for C. difficile toxin or toxin gene (binary). Window: Up to 90 days (90*24hr) after the first dose of intensive therapy Population summary*: Log odds ratio of development of C. difficile diarrhoea between each Regimen and each other Regimen, within each Stratum.	Treatment policy strategy (intent-to-treat principle)
Estimand 27 In each Stratum, the effect of each regimen compared to each other regimen, on the probability of developing a new gram negative resistant bacteria, <**90 days** after commencing intensive therapy, including all Randomisation-eligible PERITs.	Endpoint: Development of laboratory-confirmed gram negative resistant bacteria after the first dose of intensive therapy. The gram-negative bacteria must demonstrate by gene test, or in vitro, resistance to any aminoglycoside, anti-pseudomonal penicillin, cephalosporin, carbapenem, tigecycline or monobactam class antibiotic not previously documented for any airway isolate in that participant since enrolment in BEAT CF, or I the 24 months prior (binary). Window: Up to 90 days (90*24hr) after the first dose of intensive therapy Population summary*: Log odds ratio of development of gram negative resistant bacteria between each Regimen and each other Regimen, within each Stratum.	Treatment policy strategy (intent-to-treat principle)

5.3 Post-randomisation events

A post-randomisation event is one that occurs after the Reveal of the Assigned Regimen and prior to observation of an Endpoint (primary or secondary). Post-randomisation events may include: premature discontinuation of an Assigned Intervention due to intolerance, adverse events or perceived poor response, inability to ascertain an Endpoint, treatment switching, or the introduction of rescue or symptomatic treatments. Details of post-randomisation events likely to be encountered during the conduct of the PEx Treatment Platform, including strategies for statistically managing each type of event, will be detailed in the Statistical Implementation Guide. However, the general strategies for each Objective and Estimand are defined in Sections 6.1 and 6.2 above.

6. STATISTICAL MODELLING

6.1 Notation

Notation for Domains & Interventions, Strata and Regimens are given in sections 4.2, 4.3 and 4.4, respectively.

6.2 Primary analysis

A Bayesian linear model will be used for the primary analysis. This model is used to estimate the mean change in ppFEV_1 from Day 0 (primary endpoint) for each regimen in each Stratum. These estimates can then be used to compare response to treatment for different Regimens or Interventions in each Stratum.

In this section, we describe the primary analysis model. Examples are provided using the starting Domains, Interventions and Strata. The main effects of the model are given by:

$$\mathbb{E}(Y_i) = \beta_0 + \sum_{s \in S} [s]_i + \sum_{D \in \mathcal{D}} [D]_i + [eD]_i + \cdots$$

where $\mathbb{E}(Y_i)$ denotes the expected absolute change in ppFEV$_1$ from Day 0 to Day 7 for PERIT i, and β_0 is a model intercept. The notation $[\quad]_i$ indicates the parameters associated with the quantity within the brackets. For example, if PERIT i is randomized to IV Tobramycin within the Adjunct Antibiotic Domain (B) then $[B]_i = \beta_{\text{IV Tobramycin}}$. The notation eD indicates eligibility for randomization to Domain D. The terms s indicate the parameters associated with the stratification variable (e.g. PsA+/- and lung function status). If all randomized PERITs are eligible for a particular Domain, the eligibility coefficient will be omitted from the model and may be re-introduced later as necessary. Interactions will also be included for some of the main effects:

$$\mathbb{E}(Y_i) = \beta_0 + \cdots + \sum_{s \in S} \sum_{D \in \mathcal{D}} [D \cdot s]_i + \sum_{D' \in \mathcal{D} \setminus D} [D \cdot D']_i + \cdots$$

The interpretation of $[\ \ ]_i$ is similar for the interactions. The notation $\mathcal{D}\backslash D$ indicates the set of Domains excluding D. If PERIT i is randomized to Cefepime within the Backbone Antibiotics Domain (A) and is in the subgroup with stratification variable PsA+ then $[A \cdot s_2]_i = \beta_{\text{Cefepime},PsA+}$. Interactions will not be included between the stratification variables. Certain combinations of Interventions and/or stratification variables are excluded by the protocol, such as the administration of Ceftriaxone (in Domain A) is only permitted in the Stratum with High lung function and PsA-. Interactions for these combinations will be omitted from the model. Additional pre-randomisation covariates (eligibility, Selected Intervention (i.e. elicited treatment preferences pre-randomisation), and randomization to Clinicians' Choice) and their interactions will also be included in the model.

$$\mathbb{E}(Y_i) = \beta_0 + \cdots + [CC]_i + [Age]_i + \sum_{s\in S}\sum_{D\in\mathcal{D}} [pD]_i + [pD \cdot s]_i + \sum_{D'\in\mathcal{D}\backslash D} [pD \cdot pD']_i + \cdots$$

The notation pD represents the pre-randomisation Selected Intervention for domains D. The parameters $[CC]_i$ indicates whether PERIT i has been randomized to receive Clinician's Choice. The parameters $[X]_i$ indicate additional baseline covariates (site, age, sex, concurrent prescription of any non-Assigned antibiotics, steroids and CFTR modulator therapy) for PERIT i.

In addition, the primary analysis model includes random effects for individual participants, allowing multiple randomizations to occur across multiple PERITs for a single participant; as well as parameters corresponding to time, denoted as $\eta(t)$, that adjust for temporal trends over the course of the PEx Treatment Platform.

$$\mathbb{E}(Y_i) = \beta_0 + \cdots + \alpha_{h(i)} + \eta(t)$$

The random intercept $\alpha_{h(i)} \sim N(0, \tau)$ denotes the offset for participant h corresponding to PERIT i. The parameters for time are based on the time of randomization for each exacerbation, and are smoothed across time using a Bayesian second order normal dynamic linear model, as specified in the Statistical Implementation Guide. For the Primary Analysis, each measurement is assumed to have Gaussian measurement error with variance, σ^2, conditional on the mean model structure.

In summary, the Bayesian primary analysis model has the following mean structure:

$$\mathbb{E}(Y_i) = \beta_0 + \sum_{s\in S}[s]_i + \sum_{D\in\mathcal{D}}[D]_i + [eD]_i + \sum_{s\in S}\sum_{D\in\mathcal{D}}[D \cdot s]_i + \sum_{D'\in\mathcal{D}\backslash D}[D \cdot D']_i + [CC]_i + [X]_i +$$
$$+ \sum_{D\in\mathcal{D}}[pD]_i + \sum_{s\in S}\sum_{D\in\mathcal{D}}[pD \cdot s]_i + \sum_{D'\in\mathcal{D}\backslash D}[pD \cdot pD']_i + \alpha_{h(i)} + \eta(t)$$

6.2.1 Estimate of the treatment response by Regimen & Stratum

The average treatment response for each Regimen will be estimated using the average value of each covariate in the Randomisation-eligible population, with the time coefficient based on the most recent randomized PERIT. Letting $r \in \mathcal{R}_g$ indicate a particular Regimen for Stratum $g$and the average treatment response for Regimen r in Stratum g is denoted by $\mu_{r,g}$.the relative benefit of Regimen r versus Regimen r' within Stratum g is given by the difference $\Delta_{r-r',g} = \mu_{r,g} - \mu_{r\prime,g}$. The probability that Regimen r is the Best within a particular Stratum is:

$$\pi_{r,g} = \Pr\left(\mu_{r,g} \geq \max_{r\prime \neq r} \mu_{r',g} \;\middle|\; Study\ Data \right).$$

6.2.2 Estimate of the treatment response by Domain & Stratum

The average treatment response for each Intervention within each Domain will be estimated in the same manner as the Regimens, using the observed allocation to Interventions in other Domains and average value of each covariate in the Randomisation-eligible population, with the time coefficient based on the most recent randomized PERIT. This is done by holding all variables constant except for the Intervention within a given Domain. Letting d indicate a particular Intervention in Domain $D \in \mathcal{D}$ and g a particular Stratum, and let $\theta_{d,g}$ denote the corresponding average treatment response, then the comparative effectiveness of Interventions d vs. d' within Domain $D \in \mathcal{D}$ for Stratum g is given by the difference $\Gamma_{d-d',g} = \theta_{d,g} - \theta_{d\prime,g}$. The probability that Intervention d is the Best within a particular Domain and Stratum is:

$$\rho_{d,g} = \Pr\left(\theta_{d,g} \geq \max_{d\prime \in D \setminus d} \theta_{d',g} \;\middle|\; Study\ Data \right)$$

6.2.3 Orthonormal transformation

The Primary Analysis uses a fully parameterized model, rather than a reference-based approach. For example, in the full parameterization, there is a coefficient associated with each Domain A main effect: $\beta_{PipTaz}, \beta_{Cefepime}, \beta_{Ceftazadime}$ and $\beta_{Ceftriaxone}$ rather than the usual approach of omitting a category (the reference) and interpreting the remaining coefficients as relative to that category. The advantage of the fully parameterized approach is that it ensures that each Regimen/Stratum combination is equal *a priori*, a key criterion in a comparative effectiveness study. To address the issues caused by this over-parameterization, the orthonormal transformation described in Rouder et al. (2012) will be used to ensure that the model is identifiable. The model will be fit in a constrained space where the design matrix is full rank and then transformed back to the fully parameterized space for inference.

6.2.4 Prior specification

The coefficients in the model will be assigned uninformative, independent $\mathcal{N}(0,\ \sigma^2/16)$ priors. The prior for the variance term σ^2 is an uninformative $\mathcal{IG}(1, 1)$.

6.2.5 Posterior inference

The Primary Analysis uses a conjugate prior and samples from the posterior distribution, whichcan be drawn independently (see Bannerjee for additional details). Quantities such as posterior means, 95% credible intervals, and the probability that a Regimen/Intervention is the best within a Stratum will be computed using averages of these samples.

For any Regimen in a Stratum g indexed by $r \in \mathcal{R}_g$, an empirical estimate of the multivariable integral corresponding to the probability that r has a greater treatment effect than all others is as follows:

$$\pi_{r,g} \approx \frac{1}{B}\sum_{l=1}^{B} I(\hat{\mu}_{l,r,g} \geq \max_{r' \neq r} \hat{\mu}_{l,r',g})$$

where $\hat{\mu}_{l,r,g}$ denotes the lth posterior draw from Regimen r or r'as applicable, I represents an indicator function that evaluates to 1 when the contained identity is true and zero otherwise and B denotes the number of MCMC samples.

6.2.6 Sensitivity analysis of the Primary Estimand

Inferences for an estimand need to be robust to the limitations in the data and deviations from the assumptions used in the statistical model. Upon reaching a Platform Conclusion, and upon certain other Decision Thresholds being met, sensitivity analyses are planned for the Primary Estimand to investigate the effect of the choice of Bayesian linear model priors on the population level parameter estimate. Priors will be explored that promote or inhibit information sharing (borrowing) across Strata and detailed in the Statistical Implementation Guide. This includes a frequentist linear model with an identical mean structure as the Bayesian primary analysis model, but lacking Bayesian prior distributions.

The effect of treatment adherence on the Primary Estimand will be quantified in Estimand 1b (the *de jure* estimand, comparable to a per protocol analysis). Estimand 1b is secondary and will exclude from the analysis participants who, before ascertainment of the Primary Endpoint at approximately 7 days after the Reveal of the Assigned Regimen, discontinue one or more of their Assigned Interventions, switch treatment, or have other modifications that result in the participant not remaining on the Assigned Regimen through to ascertainment of the Primary Endpoint.

6.3 Secondary analyses

A key secondary analysis, Estimand 2, will be refitting the primary analysis model but omitting PERITs randomized to Clinician's Choice, and removing corresponding parameters in the model. This will allow us to assess the sensitivity of our primary analysis model for the adequacy of covariate adjustment to treatment effects for differences in pre-randomisation treatment preference across the Assigned Interventions. It will also enable a comparison of the average treatment effects of participants who receive Randomly Assigned therapy (via the response-adaptive randomisation algorithm), with those who receive Clinician's Choice.

Secondary analyses of the other estimands will be performed using the same Bayesian linear model as the primary analysis. A generalized linear model will be used when appropriate. The following modifications will be used for each type of data:

- **Continuous:** no modifications (Estimands 1-12)
- **Binary:** a binomial density with a logit-link function (Estimands 13-17, 24-27)
- **Time-to-event**: a Weibull density with a log-link function (Estimand 23)
- **Ordinal endpoint:** a multinomial density with a cumulative logit link (aka proportional odds model) (Estimands 18-22).

6.4 Stratum and Subgroup-specific treatment effects

At each Scheduled Analysis, treatment effects will be estimated and reported by Stratum. In the Final Analysis for an Intervention or Regimen (i.e. following a Platform Conclusion regarding the Efficacy or Futility of an Intervention or Regimen), and where numbers permit, we will further assess the heterogeneity in treatment effects for that Intervention or Regimen across patient subgroups defined by:

- Sex
- Detection of the following pathogens on respiratory specimens from 28 days before, to 7 days after, commencement of intensive therapy: methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), Stenotrophomonas species, *Burkholderia cepacia*, Aspergillus species
- Concomitant therapy (at the time of commencement of intensive therapy) with: CFTR-modulating therapy, azithromycin, flucloxacillin/ dicloxacillin/ cephalothin/ cefazolin, trimethoprim with sulfamethoxazole

Heterogeneity in treatment effects by subgroup will be modelled through interaction terms between the main effects for treatment and subgroup factor.

7. STATISTICAL QUANTITIES

7.1 Key Analyses

The quantities described in this section are used to make decisions about the comparative effectiveness of the Regimens and the Interventions within each Domain.

7.1.1 Best Regimen

At each Scheduled Analysis, a Regimen $r \in \mathcal{R}$ will be considered Best for a Stratum $g \in G$ if $\pi_{r,g} \geq T_{sup}$, where T_{sup} is a superiority threshold. The default threshold for T_{sup} will be 0.8.

7.1.2 Critical Intervention

At each Scheduled Analysis, we will calculate the probability that each Intervention d is within the Best Regimen for each Stratum $g \in G$. This quantity is denoted $\Pr(\text{inBest}|Data)_{d,g}$. If this probability exceeds T_{inBest} the Intervention d will be considered critical to the treatment of PERITs of participants within Stratum g. The default threshold for T_{inBest} will be 0.8.

7.1.3 Best Equivalent Regimens

At each Scheduled Analysis, for each Stratum, we identify the minimum number of Regimens required to provide a cumulative Bayesian probability best of at least T_{BestK}. For example, if $T_{BestK} = 0.80$, and there are three Regimens with $\pi_{r,g} = 0.3, 0.27, 0.25$ (respectively), then the sum of these three quantities exceeds the $T_{BestK} = 0.80$ threshold. Let Q_g be the set of these Regimens.

We then conduct pairwise comparisons for each of candidate Regimen in Q_g relative to the Best Regimen within that Stratum. The probability of equivalence for Regimen $r \in Q_g$ to the Best regimen r' is:

$$\Pr\left(\left|\Delta_{r-r',g}\right| < NI_m | Data\right)$$

where NI_m denotes the non-inferiority margin (e.g. $NI_m = 2.0$). If the probability of equivalence is at least T_{equiv} for each $r \in Q_g$ then we conclude that we have identified the Best Equivalent Regimens within Stratum g. The default threshold for declaring two Regimens to be equivalent T_{equiv} will be 0.70. The default non-inferiority margin NI_m will be 2.0, but may be varied to account for differences in toxicity/ burden of a given Regimen, as will be pre-specified in the Statistical Implementation Guide.

8. BAYESIAN SCHEDULED ANALYSES AND ADAPTATIONS

For the process for reporting and Public Disclosure of Platform Conclusions please refer to the PEx Treatment Platform Protocol, Section 13.

The PEx Treatment Platform will involve regular Scheduled Analyses, assessing pre-planned Decision Thresholds (outlined in section 7 and specified in the Statistical Implementation Guide), based on the accruing data, to use accumulating evidence to inform the Assignment of participants to Regimens, and to minimise the time until Public Disclosure of any Platform Conclusions. The pre-planned adaptations are:

- adding new Interventions in an existing Domain or adding new Domains subject to available resources (Section 8.5),
- stopping Assignment to Regimens once a single Best Regimen is identified in a Stratum or in all Strata (Section 8.6),
- stopping Assignment to an Intervention for futility in a Stratum or in all Strata (Section 8.7), and

- response adaptive randomization (Section 8.8)

Similarly, Interventions may be Suspended or Terminated based on external trial results or other prevailing conditions, under the guidance of the independent DSMB and the BEAT CF Steering Committee. The primary analysis model described in section 7.1 has been designed to accommodate these adaptations.

8.1 Data Sources

All participants contributing data from randomised PERITs will become a part of the accruing data and comprise the analysis population for the Primary Estimand (Section 6.1). All participants defined for the analysis of the Primary Estimand will remain in that population for as long as the platform is running. Data will be extracted from the BEAT CF Database immediately prior to each Scheduled Analysis and provided to the unblinded Analytic Team.

8.2 Estimand for adaptations

Estimand 1 (Section 6.1) will be used for all adaptations, unless specified otherwise in the Statistical Implementation Guide.

8.3 Model for adaptations

The primary statistical model (Section 6.2) will be used to estimate posterior probability distributions for model parameters for all Decision Thresholds, that may result in adaptations, unless specified otherwise in the DSA.

8.4 Frequency and timing of Scheduled Analyses

The first analysis will be performed 10 days after 200 PERITs have been randomised and only those who have reached 10 days after randomisation will be included in the analysis. At each analysis, the primary model (Section 7.1) will be used to assess Decision Thresholds based on the probability a Regimen, in a Stratum, is Best or is a Best Equivalent Regimen (Section 8.1). Adaptations such as Suspending or Terminating Interventions in a Stratum for futility and RAR (section 8.2) may also be performed if eligible. Subsequent analyses will be performed as soon as practicable after every 200 new randomisations, (approximately every 12 weeks).

8.5 Introducing a new Intervention into a Domain

If a new Intervention is added while a Domain is still active (i.e. allocations are still being made to at least two Interventions in the Domain), then the second randomization (i.e. Random Assignment) will be fixed for the new intervention in order to guarantee an initial sample size. If there are K_d interventions in a domain after the new intervention is started, then a fixed allocation of $1/K_d$ will be used to allocate PERITs to the new intervention. The remaining $1-(1/K_d)$ probability will be allocated to the other interventions either equally

or using RAR depending on the number of interventions and observed sample size. The fixed allocation will last until at least 10 PERITs are assigned to each Regimen containing the new Intervention in each active Stratum, unless specified otherwise in the Statistical Implementation Guide. At that point this restriction will be removed and adaptive randomization to all Regimens may be performed if specified in the DSA, otherwise equal allocations will be performed to all Domain Interventions.

8.6 Platform Conclusions regarding Efficacy (inc. non-inferiority or superiority)

At each analysis, performed by the unblinded Analytic Team, the results can trigger adaptive decision rules for efficacy, including non-inferiority and superiority, and may indicate a Public Disclosure of the results and/or removal of Interventions within Domains. In either case, the Analytic Team will prepare an unblinded report for the DSMB who will make recommendations to the BEAT CF Steering Committee. If a Regimen $r \in \mathcal{R}$ is identified as Best, or part of a Best Equivalent Regimen, for a Stratum $g \in G$ if $\pi_{r,g} \geq T_{sup}$, the Analytic Team will recommend to the DSMB that the Decision Threshold for a Platform Conclusion for Efficacy has been reached. If the DSMB confirm this on review of the unblinded Report, all future Randomly Assigned participants in that Stratum will be assigned to the Best Regimen, or one of the Best Equivalent Regimens. Reaching a Platform Conclusion for Efficacy for a Regimen in a Stratum would generally give rise to full Public Disclosure by the Steering Committee, however the DSMB has the discretion to recommend against making a full Public Disclosure if they consider this could impact on the on-going integrity of the platform.

8.7 Platform Conclusions regarding Futility

At each analysis, performed by the Analytic Team, the results can trigger adaptive decision rules for futility, and may give rise to a Public Disclosure of the results and/or Suspension or Termination of Interventions within one or more Strata. In either case, the Analytic Team will prepare an unblinded (Closed) report for the DSMB who will make recommendations to the BEAT CF Steering Committee on whether a Platform Conclusion has been reached and whether to issue a Public Disclosure. At any Scheduled Analysis, if an Intervention d in Domain D is subject to RAR, and $\Pr(\text{inBest}|Data)_{d,g} < T_{fut}$ for *any* Stratum $g \in G$, the Analytic Team will recommend to the DSMB that the Decision Threshold for a Platform Conclusion has been reached. If the DSMB confirm this on review of the Closed Report, no future Randomly Assigned participants in that Stratum will be assigned to Regimens containing that Intervention. The default Decision Threshold for futility, T_{fut} will be 0.025. Reaching a Platform Conclusion for Futility for an Intervention in a Stratum would generally give rise to full Public Disclosure by the Steering Committee, however the DSMB has the discretion to recommend against making a full Public Disclosure if they consider this could impact on the on-going integrity of the platform.

8.8 Response-adaptive randomisation

For participants Assigned to a Randomly Assigned Regimen, an equal allocation to each Regimen will be used until the first Scheduled Analysis (200 PERITs). After any subsequent Scheduled Analysis, once the number of

Assignments in a Stratum has reached at least 120, After this, response adaptive randomization (RAR) will be used to update the allocation probabilities for each Regimen in each Stratum as a function of the Probability it is Best, i.e. $\pi_{r,g}$. The allocation probabilities for the next cohort of participants is given by $q_{r,g}$, which is a function of Probability Best, $\pi_{r,g}$, the estimated variance of the average treatment response for the Regimen in the Stratum, $V(\mu_{r,g})$, and the number of participants previously assigned to that Regimen, $n_{r,g}$.

$$q_{r,g} \propto \sqrt{\frac{\pi_{r,g} * V(\mu_{r,g})}{n_{r,g}+1}}$$

Unless stated otherwise in the Statistical Implementation Guide, RAR will be activated in a Stratum after at least 120 PERITs have been randomized in that Stratum.

8.9 Deviation from Pre-specified Analyses

The BEAT CF Analytic Team will monitor the primary and secondary model behaviour, including numerical stability and scientific appropriateness. Simpler models may need to be constructed and evaluated determining any root cause issues, data issues, or inappropriate model fit. If any numeric instabilities can be fixed using alternative appropriate statistical methods, these will be performed by the Analytic Team and the adjustments recorded and communicated to the DSMB. If the model is deemed to provide an inappropriate fit then the Analytic Team will inform the DSMB of appropriate adjustments, which will be reported to the Steering Committee in a way that does not risk unblinding them to the results.

9. PLATFORM SIMULATION

Virtual trial simulations are used to evaluate the operating characteristics of the BEAT CF PEx Platform and to calibrate the operating characteristics, with a focus on how quickly Best Regimens can be identified and therefore Publicly Disclosed (power), the proportion of participants receive an Best Regimen versus those who are not, and the risk of falsely concluding that a Regimen which is no better, or worse than, the Best Regimen is Best (type 1 error). This includes the (i) parameterisation of the primary model; (ii) number and timing of interim analyses; and (iii) decision quantities and thresholds. Simulations include virtual example 'trials' and summaries over thousands of simulated trials under a wide range of parameter assumptions. Under some assumptions of up to four alternative Backbone antibiotics, with a single Backbone antibiotic with a truly greater benefit on the Primary Endpoint of 4.0 compared to other Backbone antibiotics across all Domains and in all combinations with Adjunct Antibiotics, an equal distribution of PERITs across the Strata, and no difference in treatment effects among those randomized to Clinican's choice, the simulations demonstrate that after approximately 1600 PERITs, that Backbone Antibiotic is correctly judged to be superior (part of an Best regimen), at least 80% of the time. This probability is lower in scenarios in which the Backbone antibiotic treatment benefit is not consistent across the Strata or across the combinations with alternative Adjunct

Antibiotics. Similar power is evident for the Adjunctive Antibiotic Domain. For context, the minimum clinically important difference (MCID) for ppFEV1 has previously assessed to be 3.5. Given the large number of dimensions corresponding to simulation parameters (treatment effect, Domains, Strata, Clinician's choice distributions), and complexity of the design, full details of the simulations are provided in the Statistical Implementation Guide and Simulation Appendix, which will be published on the BEAT CF website.
The brief summary below is based on the status of the trial simulations on September 1, 2021.

9.1 Description of Treatment Platform simulator

The PEx Treatment Platform design is described in the BEAT CF PEx Treatment Protocol. The primary estimand and primary model, with prior distributions for model parameters, are described in Sections 5.1 and 6.2 of this appendix. These platform simulations are generated for four Strata and two Domains, with up to 4 and 3 Interventions, respectively (see section 2.1 and 2.2). The platform simulator's decision quantities, decision thresholds and subsequent adaptations are documented in Section 7 and 8 of this appendix. The following assumptions are made for the simulations:

- Complete ascertainment and every participant eligible for both Domains.
- Equal enrolment into Strata 1-4. (Approximation based on ~50% of Australian CF patients having *P aeruginosa* and the median ppFEV1 of 71 for adults and 95 for children (Australian CF Data Registry 2017). Among those having PERITs the median ppFEV1 is expected to be lower. In the recent STOP-2 trial, the mean baseline ppFEV1 (among 919 adults only) was 53 to 60).
- Standard deviation in treatment response is 11.0. (A conservative estimate (~3 times the size of the average treatment effect) based on data from the STOP study https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6581041/).
- Analyses start when 200 PERITs have 'complete' data (i.e., follow up until Day 10) and are then performed each additional 200 PERITs, with complete data.
- Regimen assessed as Best with T_{sup}= 0.8, in the set of Regimens with cumulative probability of being Best T_{BestK}= 0.7.
- An Intervention futile with respect to low probability of being in the Best Regimen with $T_{fut} = 0.025$
- Maximum of 1600 PERITs.
- 1,000 simulated data sets for each simulation scenario (see Section 9.2).
- 1:4 Randomised to Clinician's Choice vs Random Assignment
- Assumed distribution of Clinician's choice based on the following table. (Conservative assumption of unequal distribution based on surveys of Australian CF clinicians https://bmjopenrespres.bmj.com/content/8/1/e000956.)

	Domain A	Domain B

	A1	A2	A3	A4	B1	B2	B3
Stratum1	0.40	0.10	0.10	0.40	0.50	0.10	0.40
Stratum 2	0.60	0.10	0.30	0	0.80	0.10	0.10
Stratum 3	0.60	0.10	0.30	0	0.60	0.20	0.20
Stratum 4	0.60	0.10	0.30	0	0.90	0.05	0.05

9.2 Simulation parameters and scenarios

Three scenarios are highlighted to illustrate possible platform outcomes across the Strata. These include a null scenario, of an equal treatment effect (of 4.0) across all Regimens in each Stratum, and scenarios of consistent moderate absolute increase (8.0 vs 4.0) in the primary endpoint ($ppFEV_1$) of a single Backbone Intervention across all Adjunct combinations and vice versa (scenarios 2 & 3). Platform operating characteristics from simulations for other scenarios will be published in supporting documentation on the BEAT CF website. Decision thresholds were explored, to provide adequate control of false positive platform conclusions (type 1 error), whilst maximising true positive platform conclusions (statistical power).

	Simulated Change in Endpoint		
Simulation Scenario	**Domain A**	**Domain B** B1 / B2 / B3	**Description of scenario**
1	A1 A2 A3 A4	4 / 4 / 4 4 / 4 / 4 4 / 4 / 4 4 / 4 / 4	**Null scenario.** Each Regimen associated with a 4.0 increase
2	A1 A2 A3 A4	4 / 4 / 4 8 / 8 / 8 4 / 4 / 4 4 / 4 / 4	**Moderate** increase for **A2** in all Strata (8.0 vs 4.0)
3	A1 A2 A3 A4	4 / 8 / 4 4 / 8 / 4 4 / 8 / 4 4 / 8 / 4	**Moderate** increase for **B2** in all Strata (8.0 vs 4.0)

9.3 Platform operating characteristics

Platform operating characteristics were calculated based on between 1,000 simulations for each scenario defined in Section 9.2. The average number of participants assigned to each Intervention in each Stratum is presented in Table 1, inclusive of those Assigned to Clinician's Choice. In the null scenario, a somewhat higher proportion of participants are Assigned A4 than A1, A2, or A3 reflecting that the only information for A1 is obtained in Stratum 1. Otherwise, the Assignments are similar across the Interventions in each Domain. In Scenario 2 and 3, approximately half of the first 1600 participants receive A2 (53%) and B2 (49%) respectively,

in line with their greater efficacy in those Scenarios. Note that this occurs even though A2 is the Clinician's Choice for only 10% of PERITs in each Stratum, and B2 is the Clinician's Choice for only 10%, 20% and 5% for Strata 1 and 2, 3, and 4 respectively. In Scenario 2, 681 (=841-160) of the first 1600 PERITs who would have otherwise received an inferior treatment are Assigned to A2. In Scenario 3, 599 (=779-180) of the first 1600 PERITs who would have otherwise received an inferior treatment are Assigned to B2.

The proportion of simulations in which an Intervention is declared to be a Critical Intervention (in the Best Regimen) is presented in Table 2. In Scenario 1, the probability of falsely declaring an Intervention to be Critical is controlled at <2% in each Domain (treatment-wise error), and at <5% when pooled across all Domains. In Scenario 2, A2 is correctly declared to be a Critical Intervention in 60-90% of simulations, being higher where it is one of three Interventions (Strata 2-4), and lower in Stratum 1, where it is one of four Interventions, and where it accounts for only 10% of the clinician's selection. In Scenario 3, B2 is correctly declared to be a Critical Intervention in >85% of simulations.

Table 1: Average Number of Participants Assigned Each Intervention in each scenario

Simulation Scenario	Intervention	Stratum 1	Stratum 2	Stratum 3	Stratum 4	Combined
1	A1	91	142	142	144	519
	A2	84	133	134	132	483
	A3	86	122	126	123	457
	A4	140	0	0	0	140
	B1	131	157	141	163	592
	B2	126	121	130	118	495
	B3	144	119	131	118	512
2	A1	67	98	97	97	359
	A2	**164**	**222**	**227**	**228**	**841**
	A3	57	79	77	74	287
	A4	115	0	0	0	115
	B1	97	157	143	165	562
	B2	90	122	128	116	456
	B3	101	120	130	118	469
3	A1	94	145	144	147	530
	A2	84	133	135	132	484
	A3	85	121	131	120	457
	A4	138	0	0	0	138
	B1	58	114	96	119	387
	B2	**141**	**209**	**218**	**211**	**779**
	B3	64	76	96	69	305

Table 2: Proportion of simulations in each scenario where an Intervention is declared a Critical Intervention

Simulation Scenario	Intervention	Stratum 1	Stratum 2	Stratum 3	Stratum 4	Combined
1	A1	0.000	0.005	0.002	0.002	0.009
	A2	0.001	0.011	0.008	0.006	0.026
	A3	0.001	0.013	0.007	0.015	0.034
	A4	0.021	0.000	0.000	0.000	0.021
	B1	0.002	0.005	0.004	0.002	0.013
	B2	0.005	0.007	0.013	0.014	0.037
	B3	0.010	0.013	0.013	0.014	0.021
2	A1	0.00	0.000	0.000	0.000	0.000
	A2	**0.601**	**0.868**	**0.905**	**0.918**	**0.998**
	A3	0.000	0.000	0.000	0.000	0.000
	A4	0.000	0.000	0.000	0.000	0.000
	B1	0.004	0.009	0.006	0.009	0.025
	B2	0.013	0.025	0.022	0.022	0.070
	B3	0.019	0.014	0.023	0.028	0.069
3	A1	0.000	0.009	0.008	0.014	0.031
	A2	0.006	0.009	0.027	0.026	0.060
	A3	0.007	0.013	0.022	0.028	0.062
	A4	0.021	0.000	0.000	0.000	0.021
	B1	0.000	0.000	0.000	0.000	0.000
	B2	**0.854**	**0.887**	**0.907**	**0.913**	**1.000**
	B3	0.000	0.000	0.000	0.000	0.000