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

Pulmonary Exacerbations Treatment Platform

Protocol V4, 15 Nov 2022

SIGNATURE PAGE

The signature below constitutes the approval of this PEx Treatment Platform Protocol and the attachments on behalf of the BEAT CF Steering Committee, and provides the necessary assurances that this project 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.

Signature of Coordinating Principal Investigator, on behalf of the BEAT CF Steering Committee

Signed	Date
Name:	
Role:	

DOCUMENT ORIENTATION

This BEAT CF Pulmonary Exacerbations (PEx) Treatment Platform Protocol is to be read in conjunction with

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

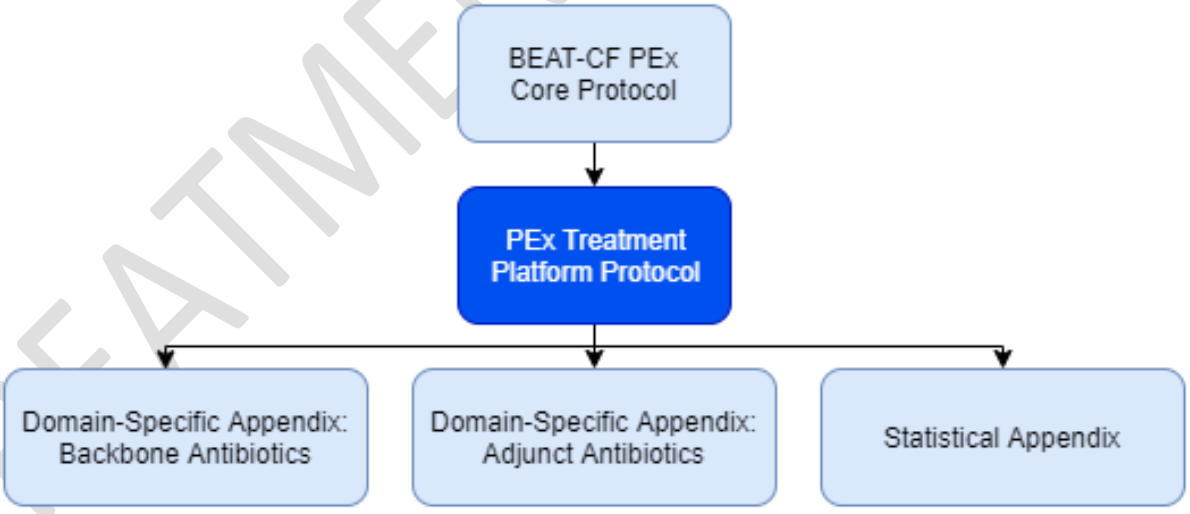

Figure 1: PEx Treatment Platform Protocol in relation to higher and lower-level documents.

	Section	Document Where Information is located		
		PEx Core Protocol	**PEx Treatment Platform Protocol**	**PEx Treatment Platform Domain-Specific Appendices**
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 documents

Contents

1. OVERVIEW

1.1 Key Details

Protocol	BEAT CF PEx Treatment Platform Protocol
Version / Date	Version 4 / 11 Nov 2022
Core Protocol Registration	Refer to the 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
BACKGROUND	With every pulmonary exacerbation of CF, approximately 25% of patients do not return to their baseline lung function measured as the FEV_1. Antibiotics are a cornerstone of treatment, but most antibiotic regimens are only informed by old, underpowered, or poor-quality trials so no consensus exists on the treatment of pulmonary exacerbations (PEx) of CF. Across Australia, CF centres use a range of approaches and antibiotic regimens. Because preservation of lung function is important for extending life and quality of life, there is a need to determine the most effective empirical treatments of exacerbations. In addition to numerous antibiotic options, there are other unanswered questions pertaining to the use of mucolytic agents, anti-inflammatory medication and chest physiotherapy, alone and in combination. The range of regimens used for treating CF exacerbations cannot be feasibly compared using conventional clinical trials (comparing one treatment at a time to another

	treatment or placebo) due to the large number of comparisons that are needed. The BEAT CF PEx Treatment Platform aims to optimise the management of CF pulmonary exacerbations by systematically evaluating the effectiveness of alternative treatment options, and by efficiently implementing these findings in routine care. To this end, members of the BEAT CF PEx Cohort who participate will be Assigned to alternative PEx treatments using response-adaptive randomisation.
PRIMARY OBJECTIVE	The primary objective of BEAT CF, as stated in the BEAT CF PEx Core Protocol is to: "Identify the effectiveness, or comparative effectiveness, of alternative interventions that are currently in routine use, or proposed for future use, in the management of Pulmonary Exacerbations Requiring Intensive Therapy (PERIT) in children and adults with CF, with respect to short-term improvements in lung function." The primary objective of BEAT CF will be achieved through implementation of the PEx Core Protocol together with this PEx Treatment Platform Protocol and its appendices.
PRIMARY ENDPOINT	The primary endpoint of BEAT CF, as stated in the BEAT CF PEx Core Protocol is: "The change in lung function approximately 1 week after commencing Intensive Therapy, measured as the absolute change in ppFEV1 from initiation of intensive therapy (measured closest in time to the first dose on IV therapy, and not ≥ 14 days before, and not ≥72 hours afterwards) to the first measured ppFEV1 ≥7 days (7*24hr) afterwards (but not ≥ 10 days (10*24hr) afterwards)."

STUDY DESIGN	The PEx Treatment Platform is a randomised embedded multi-arm adaptive platform (REMAP) nested within the BEAT-CF PEx Cohort. Those enrolled in the PEx Treatment Platform consent to having one or more aspects of the treatment of their pulmonary exacerbations randomly assigned.
NUMBER OF PARTICIPANTS	Unlimited
INCLUSION CRITERIA	1. Enrolment in the BEAT CF PEx Cohort 2. Informed consent
EXCLUSION CRITERIA	1. Unable to reliably perform spirometry 2. Responsible Clinician deems enrolment is not in the patient's best interest
RANDOMISATION	PEx Treatment Platform participants will be randomised (1:4) to either their Clinician's Choice of Intervention, or to a Randomly Assigned Intervention. For those Assigned to Randomly Assigned Intervention, the probability of Assignment will be determined using response-adaptive randomisation (RAR).
BLINDING	Unless stated elsewhere, participants and outcome assessors will not be blinded to Intervention Assignment.
ANALYSIS	Statistical inference will be based on the analysis of accumulated data using pre-specified Bayesian models at regularly Scheduled Analyses. The Primary Model will be linear regression on the Primary Endpoint and will incorporate model parameters which represent the effect of a prescription of a Revealed Intervention on participants in each Stratum, and any specific interactions with strong a priori plausibility. Secondary models will investigate additional interaction effects as well as heterogeneity of intervention effects across pre-specified subgroups.

	The unit-of-analysis is each PEX Treatment Platform-participant in each randomised PERIT. An individual participant may be included for multiple PERITs, and data for each PERIT will be used. At each Scheduled Analysis and at the Final Analysis, these models will be used to calculate for each Regimen the posterior probabilities that, compared to all other Regimens in that Stratum, that it is Best. These probabilities, estimated from the Primary Model will be used to inform the ratio of Allocation to Regimens where RAR is implemented, and will be used as the basis for implementing adaptations to the PEx Treatment Platform.
DATA MANAGEMENT	The BEAT CF database and data management system will be used as detailed in the PEx Core Protocol. De-identified data will be periodically transferred securely to Berry Consultants for Scheduled Analyses.

1.3 Abbreviations & Definitions

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

1.4 Purpose and scope of this document

The BEAT CF Pulmonary Exacerbation (PEx) Treatment Platform Protocol contains information which builds upon and is supplementary to the PEx Core Protocol, and which is specific to the PEx Treatment Platform. Unless stated elsewhere, the PEx Treatment Platform Protocol applies to all aspects of the PEx Treatment Platform including all its Domains.

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 PEx Treatment Platform Protocol, are in addition to those for the PEx Cohort which are detailed in the PEx Core Protocol. PEx Treatment Platform Domains nested in this PEx Treatment Platform may entail additional eligibility (exclusion) criteria, data collection and secondary outcome measures which will be detailed in their Domain-Specific Appendix. Therefore, the PEx Treatment Platform Protocol needs to be read in conjunction with the

higher-level PEx Core Protocol and the lower-level appendices (e.g. Domain-Specific and Statistical Appendices).

1.5 Overall BEAT CF Structure

Refer to the PEx Core Protocol

2. PEx TREATMENT PLATFORM ADMINISTRATION

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

2.1 Steering Committee

As part of its overall responsibility for BEAT CF, the BEAT CF Steering Committee (SC) takes overall responsibility for design and oversight of the PEx Treatment Platform including all of its Domains. Its membership and scope are covered in its Terms of Reference.

2.2 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be constituted comprising experts in clinical medicine, biostatistics and clinical trials who are independent of the investigators.

The DSMB will review the progress of the PEx Treatment Platform and monitor adherence to the protocol and analysis plan, participant enrolment, outcomes, complications, accuracy and completeness of data capture and other issues related to PEx Treatment Platform-participant safety and project integrity. The DSMB will also monitor the assumptions underlying the power simulations for the PEx Treatment Platform and alert the Steering Committee to substantial departures as the data accumulate.

The DSMB will make periodic recommendations to the Steering Committee as to whether the PEx Treatment Platform, any of its Domains, or any of the Interventions within those Domains, should continue or be Terminated.

In addition to considering recommendations by the Analytic Team (refer section 2.5 below) with regard to pre-determined Decision Thresholds, the DSMB will also consider participant safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment effects or feasibility of meeting the PEx Treatment Platform Objectives.

Conversely, the DSMB may advise the Steering Committee that assignment to an Intervention should continue after a Decision Threshold is met to allow evaluation of important subgroup effects or secondary endpoints, if and only if the expected benefit of doing so outweighs any risk to participants.

The DSMB will operate under the rules of a Charter approved by the Steering Committee and agreed to by the DSMB members.

2.3 PEx Treatment Platform Statistical Committee

A Statistical Committee will be formed comprising several members with expertise and experience in designing and analysing Bayesian trials. The primary role of the Statistical Committee will be to advise the Steering Committee on all aspects of design and analysis of the PEx Treatment Platform, including development of the plan for analysis. Members of the Statistical Committee will remain blinded to both participant data and analyses throughout the project. Specific responsibilities of the Statistical Committee are:

1. Review the PEx Core Protocol, PEx Treatment Platform Protocol, the Domain-Specific Appendices, and any other relevant appendices, including any amendments
2. Review Estimands to ensure the planned analysis aligns with the PEx Treatment Platform Objectives, and that potential sources of bias attributable to post-randomisation events are minimised
3. Undertake and review PEx Treatment Platform simulations, including scenarios and operating characteristics, both in the initial PEx Treatment Platform design stage and whenever new Interventions or Domains are added as the PEx Treatment Platform evolves
4. Develop the PEx Treatment Platform Statistical Appendix
5. Develop the Statistical Implementation Guide, including updates as necessary, and co-author arising reports and publications
6. Review data specifications, in terms of content, structure and coding, and provide feedback on the BEAT CF Database and data dictionary to the Steering Committee and external database provider

2.4 PEx Treatment Platform Analytic Team

An Analytic Team will be formed comprising several biostatisticians with a sound understanding of the PEx Treatment Platform analysis plan, and with experience in analysing Bayesian trials. The primary role of the Analytic Team will be to monitor the PEx Treatment Platform data quality, perform unblinded scheduled analyses, evaluate the Decision Thresholds for PEx Treatment Platform adaptations, summarise the safety data and produce regular closed (unblinded) reports for the DSMB.

Prior to becoming unblinded to the PEx Treatment Platform data, members of the Analytic Team may serve on the Statistical Committee. Once individuals in the Analytic Team have viewed participant data (eg. at the first scheduled analysis), they will have no further role on the Statistical Committee, or the

development of any parts of the PEx Treatment Platform Protocol, the PEx Treatment Platform Statistical Appendix or Domain Specific Appendices; their communication with the BEAT CF Steering Committee and the Statistical Committee will be minimized to prevent inadvertent unblinding of the members of these committees. These procedures will be specified in the Analytic Team Terms of Reference.

Specific responsibilities of the Analytic Team:

1. Perform and report the Scheduled Analyses and Final Results
2. Calculate the statistical quantities and evaluate them against the pre-specified Decision Thresholds at each Scheduled Analysis
3. Provide blinded summaries to the Steering Committee of the progress of the PEx Treatment Platform
4. Provide unblinded summaries of PEx Treatment Platform progress, safety and efficacy to the DSMB, including communicating to the DSMB whether a Decision Threshold has been met and whether the PEx Treatment Platform should continue to enrol participants into each Intervention, Domain, Stratum, or the PEx Treatment Platform overall, without violating the integrity of the PEx Treatment Platform.
5. Provide updated Intervention allocation probabilities after each Scheduled Analysis (as appropriate) to personnel managing the randomisation process

3. BACKGROUND/ RATIONALE

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

3.1 Rationale for the BEAT CF PEx Treatment Platform

There is no single standard of care for managing CF pulmonary exacerbations. Standard care comprises a range of interventions and varies across and within CF treatment centres and may evolve over the course of the PEx Treatment Platform.

At the time of initiation of the PEx Treatment Platform Protocol, management of pulmonary exacerbations generally involves the use of one or more intravenous (IV) antibiotic therapies. The duration of IV antibiotic therapy is typically 14 days, and generally ranges from 10 days to 21 days. A recent RCT[i] found evidence that 10 days was non-inferior to 14 days of IV antibiotics therapy in those

with a rapid treatment response, and found no evidence that 21 days was superior to 14 days of IV antibiotics therapy in those without a rapid treatment response.

Most Australian clinicians manage pulmonary exacerbations with an antipseudomonal beta-lactam or carbapenem, combined with a non-beta lactam antibiotic - most typically the aminoglycoside IV tobramycin. Some, but not all, clinicians reserve the use of IV aminoglycoside for patients known to be colonised with *Pseudomonas aeruginosa*. Some, but not all, clinicians use the results of microbiology and *in vitro* susceptibilities to guide antibiotic selection. Many centres provide additional antibiotic cover targeted to specific pathogens, but only if identified on sputum microbiology, e.g. for *Stenotrophomonas maltophilia* or *Staphylococcus aureus.*

CF clinicians prescribe physiotherapy for airway clearance as a core part of the management of CF pulmonary exacerbations, though there is variation in the nature and frequency of this therapy. Some, but not all, CF clinicians all prescribe muco-active or anti-inflammatory therapies. As for the use of antibiotics, there is no evidence to support any of these modes of treatment as a single best standard of care.

The primary objectives, outcomes and endpoints for the PEx Cohort were informed by a systematic review of the literature and involvement of key clinical and consumer stakeholders. The Primary Objectives, Outcomes, and Endpoints therefore align with those set out PEx Core Protocol and are described in detail in that document.

The Primary Endpoint also aligns with the endpoint used in the recent STOP studies. The STOP Study Investigators used change in FEV_1 as a proportion (percentage) of that predicted based on sex, age and height ($ppFEV_1$), from the time of commencement of therapy (or admission) as the most appropriate measure of improved lung function. In that prospective study of North American adults with CF, the mean absolute change in $ppFEV_1$ was 8.4 after 7 days of therapy, with a standard deviation of 11.3[vii].

4. AIMS

The overall Aim, per the PEx Core Protocol is to:

"Optimise the management of CF pulmonary exacerbations by systematically evaluating the effectiveness of alternative interventions and management options, and by efficiently implementing any conclusions into routine care."

5. OBJECTIVES

The Primary Objective, per the PEx Core Protocol is to.

"Identify the effectiveness, or comparative effectiveness, of alternative interventions that are currently in routine use, or proposed for future use, in the management of Pulmonary Exacerbations Requiring Intensive Therapy (PERIT) in children and adults with CF, with respect to short-term improvements in lung function."

The secondary objective, per the PEx Core Protocol is to:

"Identify the effectiveness, or comparative effectiveness, of alternative interventions that are currently in routine use, or proposed for future use, in the management of acute pulmonary exacerbations in children and adults with CF, with respect to:

- Long-term improvements in lung function
- Short and long-term improvements in symptoms and quality of life and life expectancy
- Short and long-term healthcare utilisation, including recurrent intensive treatment for respiratory exacerbations
- The toxicity and comparative toxicity of alternative interventions
- The comparative cost-effectiveness of alternative interventions

The impact of alternative interventions on the generation or selection of antibiotic resistant bacteria, and the impact of this on lung function and quality of life."

6 DESIGN AND METHODS

6.1 BEAT CF and the BEAT CF PEx Cohort

For details regarding overall design of BEAT CF and the BEAT CF PEx Cohort, refer to the PEx Core Protocol.

Members of the BEAT CF PEx Cohort are people with CF who consent to having information regarding the management of their pulmonary exacerbations and their outcomes systematically captured over time, for describing variation in their management and outcomes, and for understanding which background and treatment factors are associated with better or worse outcomes. Formation of the PEx Cohort was intended to enable the nesting of substudies to address more specific research questions related to the management of pulmonary exacerbations, including this PEx Treatment Platform. In the absence of any Cohort-nested substudies, the PEx Cohort is an observational cohort. The establishment of the PEx Cohort is set out in the PEx Core Protocol.

6.2 PEx Treatment Platform

We provide here a high-level description of the Treatment Platform for orientation purposes only.

The PEx Treatment Platform is an investigator-initiated, multi-centre, open-label, randomised controlled Bayesian adaptive PEx Treatment Platform nested within the BEAT CF PEx Cohort. The PEx Treatment Platform is designed using REMAP principles, i.e. it is randomized, embedded in routine healthcare, multi-arm and multi-factorial, adaptive, and pragmatic. The design is based on and extends the existing REMAP designs for community-acquired pneumonia (REMAP-CAP)[ii], COVID-19 (REMAP-COVID[iii] and ASCOT-ADAPT[iv]) and *Staphylococcus aureus* bacteraemia (SNAP)[v], by also incorporating clinician treatment preferences in the Assignment of Interventions[vi].

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 a 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.

After approximately every 200 enrolments (~12 weeks), accumulated outcome data from the PEx Treatment Platform captured in the BEAT CF Database will undergo regular Scheduled Analysis. The analysis is outlined in the Statistical Appendix. It will be carried out by the unblinded Analytic Team in accordance with procedures outlined in their Terms of Reference. At each Scheduled Analysis, the Analytic Team will assess the comparative effectiveness of each Regimen, and of each Intervention in each Domain, in relation to the Primary Estimand.

At each Scheduled Analysis:
The Analytic Team will calculate,

1. for each Regimen, for each Stratum, the probability it is 'Best', or a part of a set of 'Best Equivalent Regimens, meaning that Regimen (or set of Equivalent Regimens) results in the greatest expected increase in the Primary Endpoint, and
2. for each Intervention, the Probability it is a 'Critical Intervention', meaning the probability it is in the Best Regimen.

These probabilities will be assessed against pre-specified Decision Thresholds for making Platform Conclusions regarding Efficacy and Futility. Specifically, if a Regimen (or set of Regimens) achieves a sufficiently high probability of being Best (or Best Equivalent) for a Stratum, further Assignment of Regimens in that Stratum will be stopped, and a Platform Conclusion of Superiority will be made. Similarly, if an individual Regimen achieves sufficiently low probability of being a Critical Intervention for a Stratum, further Assignment to Regimens containing that Intervention will be stopped, and a Platform Conclusion of Futility will be made.

The Analytic Team will implement any updates to the ratio of Random Allocation of each Regimen as described in the Statistical Appendix. They will make recommendations to the DSMB regarding any Platform Conclusions based on any Decision Thresholds having been met. If accepted, the DSMB will recommend to the BEAT CF Steering Committee that one or more Interventions in a Stratum is Terminated, meaning that they are eliminated from further Assignment (but with the Domain remaining open), or that the Domain should be Closed. Closure of a Domain or all Domains (i.e. the PEx Treatment platform), will result in a Final Analysis of the affected Domains including all secondary analyses specified in the Statistical Appendix. Subject to the advice of the independent DSMB, Platform Conclusions will generally give rise to a Public Disclosure. If a Platform Conclusion results in the Closure of a Domain, the Public Disclosure will relate to the Final Analysis of the affected Domains.

Evolution of the BEAT CF PEx Treatment Platform (including the addition of interventions for random assignment) will occur through the addition or modification of appendices to the PEx Treatment Platform Protocol. The intended evolution of the Treatment Platform can be demonstrated in Figure 1.

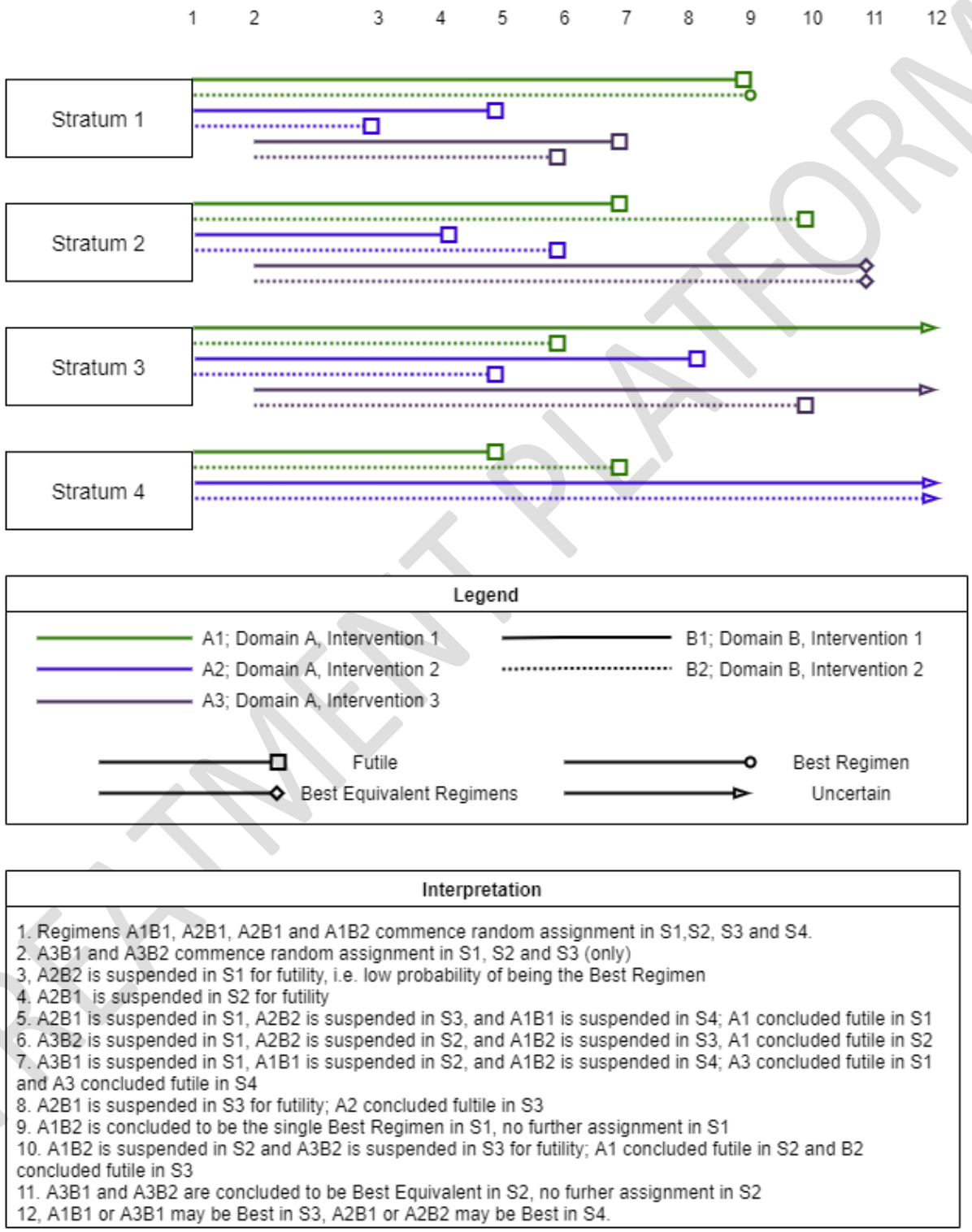

Figure 1. BEAT CF Treatment Platform Evolution

This figure represents a hypothetical example of how BEAT CF PEx Treatment Platform could evolve. The number of interventions are for example only.

6.3 PEx Treatment Platform Population

For a description of the PEx Cohort, refer to the PEx Core Protocol.

Enrolment will be restricted to PEx Cohort participants (i.e. at sites implementing the PEx Core Protocol), who can reliably perform spirometry.

As the PEx Treatment Platform only assigns first line therapies, the following CF patients fall outside the target population:

1. those for whom first line therapies are inappropriate because of multi-drug hypersensitivities,
2. those requiring broad spectrum therapy targeted for a specific airway pathogen,
3. those who are refractory to first line therapies
4. those who are failing intensive therapy for a pulmonary exacerbation.

6.4 PEx Treatment Platform Eligibility criteria

6.4.1 INCLUSION CRITERIA

To be enrolled in the PEx Treatment Platform, a person must:

1. Be enrolled in the BEAT CF PEx Cohort (for Cohort eligibility criteria, refer to the PEx Core Protocol)
2. Documented informed consent to participate in one or more PEx Treatment Platform Domains

6.4.2 EXCLUSION CRITERIA

A person will be excluded from the PEx Treatment Platform if any of the following apply:

1. The person is unable to reliably perform spirometry (for example due to young age),
2. The person's Responsible Clinician deems enrolment in the PEx Treatment Platform is not in their best interest

Note that additional eligibility criteria, typically exclusion criteria, may apply to specific Domains or to specific Interventions within each Domain. For these specific exclusions, refer to the relevant Domains-Specific Appendices.

6.5 Study Outcomes, Endpoints, Estimands

Per the PEx Core Protocol, the Primary Estimand, Outcome and Endpoint are:

"The Primary Estimand for each PERIT in the PEx Platform Cohort, including the nested PEx Treatment Platform and all of its Domains is:

Study Population: People with CF with a PERIT who are able to perform spirometry, who are suitable for first line therapy, and for whom there is reasonable equipoise about the most appropriate starting Regimen.

Primary Outcome and Endpoint: The change in lung function approximately 1 week after commencing Intensive Therapy, measured as the absolute change in ppFEV1 from initiation of intensive therapy (measured closest in time to the first dose on IV therapy, and not ≥ 14 days before, and not ≥72 hours afterwards) to the first measured ppFEV1 ≥7 days (7*24hr) afterwards (but not ≥ 10 days (10*24hr) afterwards).

Primary Effect measure: The absolute difference in the mean of the primary Endpoint between those in the Intervention versus the Comparator group, adjusting for any differences in baseline factors between Intervention and Comparator arms that might otherwise confound or reduce the certainty of the treatment effect

Intervention: Prescription of each Intervention within a Domain.

Comparator: Prescription of each other Intervention within a Domain.

Post-randomisation events: Participants will be included in the primary analysis irrespective of whether and how the Intervention or Comparator is received, any non-adherence, any subsequent change in therapy, or loss to follow-up, (i.e. the effect attributable to the prescription, or the treatment policy or de facto estimand)."

Secondary Outcomes and Endpoints

Per the PEx Core Protocol, the Secondary Outcomes and Endpoints are:

"For each PERIT, we will also report the following outcomes measured as the following endpoints:

1. The change in lung function up to 6 months after commencement of intensive therapy, *measured* as the absolute change in the ppFEV1 from initiation of intensive therapy until approximately 14 days, 30 days, 60 days, and 180 days after commencement of intensive therapy.
2. The change in lung function up to 6 months after commencement of intensive therapy, *measured* as the proportional change (expressed as a percentage) in the ppFEV1 from initiation of intensive therapy until 7 days, 14 days, 30 days, 60 days, and 180 days after commencement of intensive therapy, Return of measured lung function to close to its baseline (pre-exacerbation) best function, up to 6 months after commencement of intensive therapy, measured as a binary

outcome of whether the ppFEV1 has returned to ≥ 90% of the ppFEV1 at baseline, at approximately 7 days, 14 days, 30 days, 60 days, and 180 days after commencement of intensive therapy, where the baseline ppFEV1 is the highest recorded ppFEV1 in the 180 days (or 365 days if no ppFEV1 <180 days) preceding the commencement of intensive therapy.

3. The change in CF-related symptoms up to 4 weeks after commencement of intensive therapy, *measured* as the absolute change in the CRISS score approximately 7 days, 14 days and 30 days after commencement of intensive therapy.

4. The time to the next PERIT, *measured* as the time (in days) from commencement of intensive therapy to the next commencement of intensive therapy, after a period of no intensive therapy of > 7 days.

5. Adverse reactions resulting in treatment cessation, *measured* as any early termination of planned therapy before 7 days (7*24hr) and before 14 days (14*24hr) after commencement of intensive therapy, owing to one or more adverse events presumed by the Responsible Clinician to be attributable to the prescribed therapy.

6. Treatment failure resulting treatment cessation, *measured* as any early termination of planned therapy before 7 days (7*24hr) and before 14 days (14*24hr) after commencement of intensive therapy, owing to inadequate improvement in symptoms or lung function, presumed by the Responsible Clinician to be attributable to a poor response to the prescribed therapy.

Note that additional outcomes (including safety outcomes) may apply to substudies or specific Domains. For these outcomes, refer to the PEx Treatment Platform Protocol and relevant Domain-Specific Appendices.

For all participants, we will also report:

1. The CFQR approximately every 12 weeks for all participants ≥ 6 years old

2. Any new detection of any strain of gram-negative bacteria with *in vitro* resistance to any aminoglycoside, fluoroquinolone, antipseudomonal penicillin (including beta-lactam/beta-lactamase inhibitor combination), antipseudomonal cephalosporin, or carbapenem not previously detected since enrolment in the PEx Cohort or in the 2 years prior.

3. Any new onset of *Clostridium difficile* associated diarrhoea not previously detected since enrolment in the PEx Cohort or in the 2 years prior."

6.6 Co-enrolment with other studies

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

6.7 Cooperation between BEAT CF and other studies with overlapping populations or interventions

For guidance on cooperation with other studies, please refer to the PEx Core Protocol.

6.8 End of the PEx Treatment Platform

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

It is anticipated that the PEx Treatment Platform will continue to enrol participants and evaluate Interventions until one of the following occurs:

- Funding or other necessary support for the PEx Treatment Platform and/or the PEx Cohort is no longer available
- Pulmonary exacerbations are no longer deemed to be an important health problem for people with CF
- The effectiveness of all relevant Interventions for pulmonary exacerbations in people with CF are known

The DSMB may, at any time, recommend to the Steering Committee that the PEx Treatment Platform should be Closed if they believe that it is not in the interest of participants, including if the cost or burden of continuation outweighs and potential benefit. Should the whole PEx Treatment Platform be Closed, its end is the date of the last scheduled follow up for any participant. . A Final Analysis of the PEx Treatment Platform, inclusive of all relevant data captured in the PEx Treatment Platform, will be conducted as soon as practicable after Closure.

7 STUDY CONDUCT

7.1 PEx Participant Flow

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

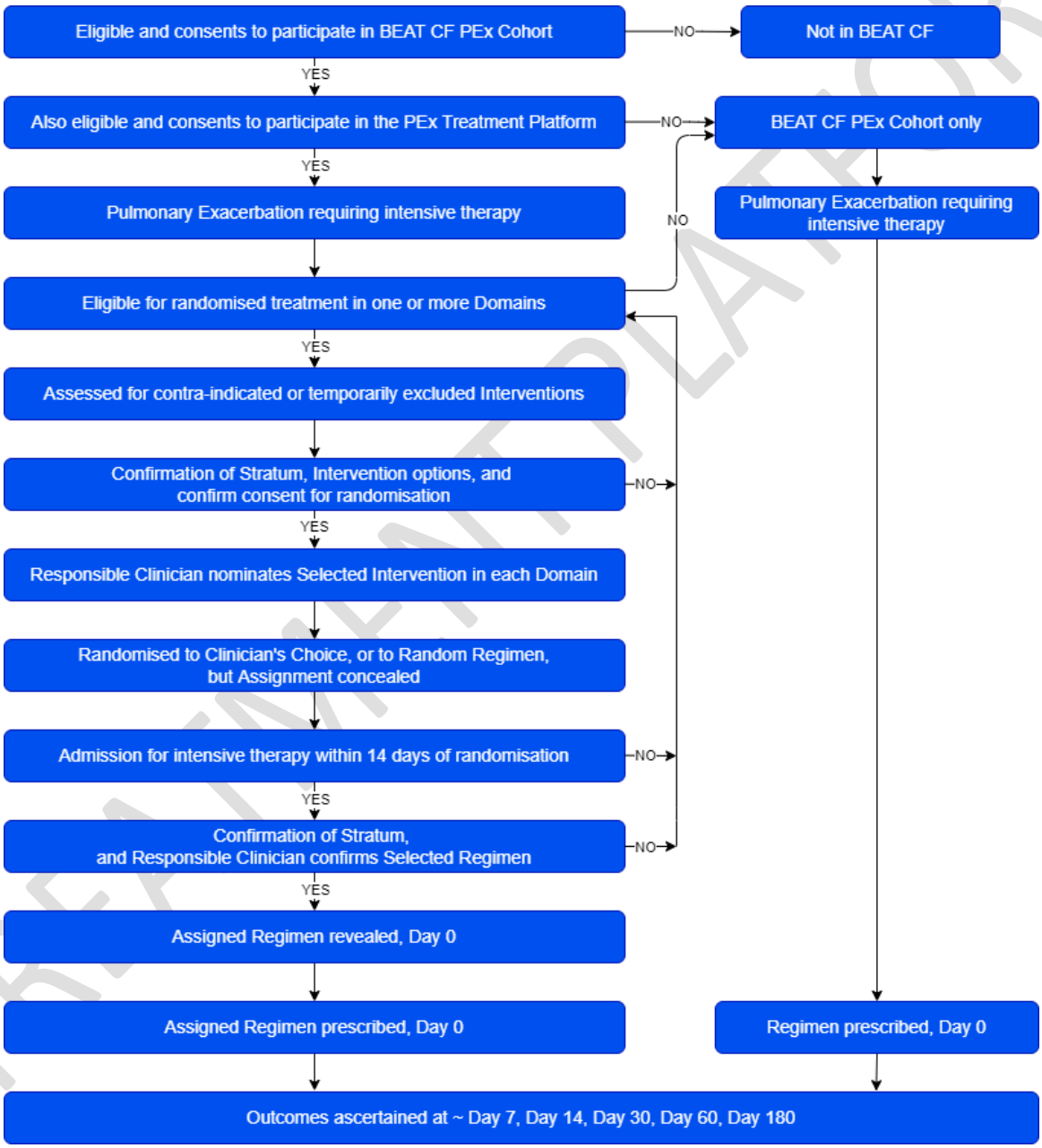

Figure 2 BEAT CF PEx Treatment Platform Participant Flow

7.2 Identification of potential PEx Treatment Platform participants

For a description of the approach to identifying participants for BEAT CF, refer to the PEx Core Protocol.

Participants in the PEx Cohort who are managed at CF Centres participating in the PEx Treatment Platform, will be screened against the PEx Treatment Platform eligibility criteria outlined in this PEx Treatment Platform Protocol. The Site PI (or their delegate) will do this using information in the BEAT CF Database, and potentially additional information ascertained from the medical record or from the patient's Responsible Clinician. Potential PEx Treatment Platform participants will also be screened for any Domain-specific or Intervention-specific exclusion criteria as described in each Domain-Specific Appendix for the Domains the site is participating in.

For each PEx Cohort participant who is screened for eligibility for enrolment in the PEx Treatment Platform, the following information will be entered into a screening log by a member of the study team at the time of assessment: BEAT CF study identifier of the participant, date the eligibility was assessed, and outcome of the eligibility assessment (eligible of not eligible).

If the patient is eligible, the site PI (or their delegate) will document this in the medical records. Patients who are eligible will be approached for an informed consent discussion about participation in the PEx Treatment Platform. PEx Cohort participants who are ineligible for the PEx Treatment Platform, including those who decline to participate, will remain in the PEx Cohort.

7.3 Informed Consent for the PEx Treatment Platform

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

Informed consent to participate in the PEx Treatment Platform will be discussed and documented at the domain level. Documented informed consent will be obtained from the participant (or legally responsible caregiver) for participation in the PEx Treatment Platform prior to any PEx Treatment Platform or Domain-specific procedures. The consent procedure will only be performed by personnel who have been delegated this responsibility by the Site PI, following local processes and in accordance with GCP.

At the first PEx Treatment Platform/ Domain consent discussion, the participant (or legally responsible caregiver) will be provided with HREC-approved information sheet outlining the PEx Treatment Platform. This information document will detail no less than:

- the exact nature of the PEx Treatment Platform and how it relates to the PEx Cohort;
- what is involved for the participant;
- the implications and constraints of the protocol;
- any risks involved in taking part in the PEx Treatment Platform.

The participant will also receive an information sheet and consent form for the Domains open to enrolment at that time.

7.4 Eligibility Assessment and Confirmation of Consent for each PERIT

At subsequent pulmonary exacerbations requiring intensive therapy (PERITs), a participant who has consented to participate in one or more Domains will be assessed for their eligibility to receive randomised treatment, i.e. they are "Randomisation-eligible" in one or more of those Domains. Any additional eligibility (exclusion) criteria will be specified in the respective DSAs. If eligible, participants will be invited to confirm their consent to be randomised. Confirmation of consent will be done after their Intervention-specific eligibilities have been assessed (including any Temporary exclusions), and after the participant and Responsible Clinician have been advised of all the Interventions they could be Assigned to in that Domain. Randomisation will only occur once this consent to randomisation has been confirmed and documented by the Site PI (or their delegate).

For each PEx Treatment Platform participant who is screened for eligibility for randomisation at the time of a PERIT, the following information will be entered into a screening log by a member of the study team at the time of assessment: BEAT CF study identifier of the participant, date the eligibility was assessed, and outcome of the eligibility assessment (eligible of not eligible).

A participant may freely opt-out of randomisation in one or more Domains. They may opt-out of consent after randomisation to a Provisionally Assigned Intervention in the Domain so long as it occurs before the Reveal of the Assigned Intervention; in which case they will not be considered a withdrawal from the Domain. After Reveal of the Assigned Intervention they may withdraw consent to participate in the Domain, but they will be treated as Assigned to the Intervention for the Primary Analysis, regardless of adherence to the Assigned Intervention.

7.5 Documentation of Consent

Electronic and/or paper copy versions of the HREC-approved Participant Information Sheet and Informed Consent will be presented to the participant (or legally responsible caregiver).

It will be clearly stated that the individual does not have to participate in the PEx Treatment Platform and is free to withdraw at any time for any reason without prejudice to future care, and with no

obligation to explain the reason for withdrawal. A participant may withdraw from the PEx Treatment Platform without also withdrawing from the PEx Cohort, or may withdraw from the PEx Cohort altogether (please refer to the Core Protocol.)

The participant (or legally responsible caregiver) will be allowed as much time as required to consider the information and the opportunity to question the study team or independent parties before deciding whether they will participate. Informed consent will then be documented by means of written or electronic signature which will be dated and counter-signed by the person who presented the information and obtained the consent.

At the time of a PERIT, for each PEx Treatment Platform participant who is Randomisation-eligible and who confirms their consent to be randomised in one or more Domains, this confirmation will be noted in the CTMS and documented in the participant's medical record.

7.6 Discontinuation from participation

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

7.6.1 Discontinuation from the PEx Treatment Platform or one of its Domains

A participant may be discontinued from participation in the PEx Treatment Platform or from a specific Domain only, without discontinuing participation from the PEx Cohort. The criteria for discontinuation include:

1. The participant (or their Legal Representative) requests withdrawal from ongoing participation.
2. The participant's Responsible Clinician considers continued participation is not in their best interest.

Participants will not automatically be discontinued due to adverse events; in this case the study Intervention may be ceased, but participation should continue and they will be analysed according to their Assigned Intervention. The decision to withdraw a participant should be discussed with the Site Principal Investigator. Any specific criteria for Domain discontinuation will be specified in the relevant DSA.

In the case of discontinuation, the reason(s) for withdrawal will be documented. Consent to the use of any PEx Treatment Platform-specific study data, including all data collected until the time of discontinuation and data to inform the Primary Estimand, will be requested specifically from participants (or their legally responsible caregiver) who request discontinuation. Following discontinuation, participants will receive usual care per their Responsible Clinician.

If the participant discontinues from the PEx Cohort entirely (see PEx Core Protocol) and also withdraws consent for disclosure of future information, no further evaluations will be performed, and no additional data will be collected. The BEAT CF Steering Committee may retain and continue to use any data or samples collected before such withdrawal of consent.

Participants withdrawn from receiving a study Intervention will continue to be followed to avoid missing data and their outcome data will be used in the relevant analyses. If a patient is enrolled and later found to be ineligible, the study Intervention may be ceased at the discretion of the Responsible Clinician, but data will continue to be collected and used in relevant analyses.

7.7 Concomitant care and interventions

For participants in the PEx Treatment Platform, additional (concurrent) Interventions beyond those Assigned to them by the PEx Treatment Platform will be allowed at the discretion of the Responsible Clinician, except where they constitute a PEx Treatment Platform-specific, Domain-specific, or Intervention-specific exclusion criterion; the latter exclusions will be detailed in their relevant DSA. Concurrent therapies will be captured in the BEAT-CF Database.

7.8 Laboratory procedures

For information regarding the collection of laboratory specimens for the PEx Cohort, refer to the PEx Core Protocol.

For the PEx Treatment Platform, there will be no additional laboratory testing performed outside of routine care. Any Domain-Specific or Intervention-specific laboratory procedures (e.g. to monitor for specific toxicities) will be specified in the relevant DSA.

7.9 Patient Reported Outcomes

For information regarding the capture of patient-reported outcomes for the PEx Cohort, refer to the PEx Core Protocol.

7.10 PEx Treatment Platform Data Collection

For information regarding the routine capture of data for members of 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 PEx Cohort members who participate in the PEx Treatment Platform, the following timeframes will be targeted for the timing of data collection for spirometry and patient-reported outcomes.

Timepoint	**Spirometry** should be performed using a calibrated device	**CRISS** for those participants 12 years old and over, completed electronically	**Time window**
Day 0	√	√	As soon as possible, and preferably: within 12 hours of commencement of intensive therapy, **AND** Not more than: 14 days (14*24 hours) prior, and 72 hours afterwards
Day 7	√	√	As soon as possible, and preferably: within 24 hours after reaching 7 complete days (7*24 hours) after the Reveal of the Assigned Intervention, **AND** No later than: 14 complete days (14*24 hours) afterwards
Day 14	√	√	As soon as possible, and preferably: within 72 hours after reaching 14 complete days (14*24 hours) after the Reveal of the Assigned Intervention, **AND** No later than: 30 complete days (30*24 hours) afterwards
Day 30	√	√	As soon as possible, and preferably: within 7 days (7*24 hours) after reaching 30 complete days (30*24 hours) after the Reveal of the Assigned Intervention, **AND** No later than: 60 complete days (60*24 hours) afterwards
Day 60	√		As soon as possible, and preferably: within 14 days (14*24 hours) after reaching 60 complete days (60*24 hours) after the Reveal of the Assigned Intervention, **AND** No later than: 90 complete days (90*24 hours) afterwards

Timepoint	Spirometry should be performed using a calibrated device	CRISS for those participants 12 years old and over, completed electronically	Time window
Day 180	√		As soon as possible, and preferably: within 30 days (30*24 hours) after reaching 180 complete days (180*24 hours) after the Reveal of the Assigned Intervention, **AND** No later than: 60 complete days (60*24 hours) afterwards

Table 2 PERIT timing of data collection for spirometry and patient-reported outcomes

7.11 PEx Treatment Platform Participant Randomisation

PEx Treatment Platform participants will be invited to randomisation to Interventions in each Domain they are eligible for, for each PERIT.

A participant will not be randomised until their consent has been confirmed, and the minimum data required for randomisation has been documented, specifically relating to their Stratum, and to any contra-indications to any Interventions., Participants will be randomised 1:4 to either be Provisionally Assigned the Selected Regimen (“‘Clinician’s Choice”) or to be Provisionally Assigned a Randomly Assigned Regimen, for each Domain they are eligible for, and participating in. Prior to the Assignment being Revealed, it will be considered ‘Provisionally Assigned’.

Assignment to a Randomly Assigned Regimen will occur using response-adaptive randomisation (RAR). In RAR, the ratio of allocation to each Regimen varies over time in response to the accumulating data, such that the probability of Assignment to a Regimen is proportional to the posterior probability that, at the most recent Scheduled Analysis, it is the Best Regimen. When RAR is implemented, the initial allocation ratios will be equal across Regimens.

The statistical procedures underlying RAR will be outlined in the Statistical Appendix.

7.11.1 Timing of Randomisation and Timing of Reveal of Assignment

When the Responsible Clinician has assessed that the participant has a PERIT, and that commencement of intensive therapy is indicated within the next 14 days, administrative preparation for randomisation must begin. To randomise the participant, the Site PI (or their delegate) will update the BEAT CF Database with any outstanding PEx Cohort data and enter the details required for randomisation and Provisional Assignment of the Regimen to occur (refer to section 7.13.1).

After randomisation, the participant will have a Provisionally Assigned Regimen. For the purpose of the analysis, the participant will not be considered to be Assigned to an Intervention until that assignment has been Revealed (as described in the relevant DSA). A Provisionally Assigned Intervention which has not been Revealed may be Revoked, for example in response to a change in Stratum due to new airway microbiology results. If the participant is still eligible, they may then be re-randomised to a new Provisionally Assigned Regimen.

7.12 Description of the Intervention

In the PEx Treatment Platform, for the purpose of analysis (i.e., the target of inference by the Primary Estimand) each Intervention is a Prescription for a specific Regimen, where a Prescription is a clinical order made by a Responsible Clinician authorised to make such as an order (or their suitably qualified delegate). A Prescription may be for a pharmacological therapy, but may similarly relate to physiotherapy and other non-pharmacologic therapies. The Prescription will generally specify a dose, duration or intensity of therapy, and may explicitly allow for modification based on response to therapy or side effects.

In the PEx Treatment Platform, the time window for the treatment effect of primary interest is the first week of intensive therapy, and so the Intervention is described in that timeframe, although it is expected that PEx treatment courses will usually be for longer.

For the purpose of the Primary Estimand, the treatment effect of primary interest is the overall effect attributable to a Prescription for a Regimen (the *de facto* estimand of the 'intent-to-treat' effect), and secondarily the treatment effect attributable actually *taking* the Regimen as prescribed (the *de jure* estimand of the 'per protocol' effect).

7.13 Checking drug charts

On the day of planned commencement of intensive therapy (or next business day), the Site PI (or their delegate) will check the medication chart to confirm the Assigned Regimen has been prescribed, and will liaise with the Responsible Clinician (or their delegate) to ensure this is done as soon as practicable. At least twice per week in the first week of intensive therapy, and at least once weekly thereafter, the Site PI (or their delegate) will check the medication chart and medical record to assess participant adherence to the prescribed therapy, and ascertain any cessation or switch in therapy, and any adverse events. In the event of a Serious Adverse Reaction (SAR) requiring intervention, the drug chart will continue to be checked until any intervention for the SAR is discontinued and/or the SAR has resolved.

7.14 Blinding

To the maximum extent possible, the BEAT CF Steering Committee, all Collaborators, the Statistical Committee, and the broader public will remain blinded to any aggregate PEx Treatment Platform data (masked or unmasked), and to any unmasked PEx Treatment Platform data, until any Public Disclosures of Platform Conclusions are made. This includes any aggregate information that might inadvertently reveal the status of the PEx Treatment Platform, including the allocation ratios to alternative Interventions or Regimens if RAR is implemented.

The Analytics Team and the DSMB will have completely unblinded access to all PEx Cohort and Treatment Platform data at all times, including to the ratio of allocation to alternative Regimens. Access to data, including Closed Study Reports, will be limited to members of the Analytic Team and the DSMB, and will be password protected. Once unblinded to aggregate data, a person will be considered unblinded thereafter for the duration of the Treatment Platform. A log will be maintained of who has access to unblinded and/or unmasked data throughout the PEx Treatment Platform.

Unless stated otherwise (in the relevant DSA), all Interventions Assigned in the PEx Treatment Platform are administered open-label and therefore once Revealed, will be known to the participants, the Responsible Clinician, the Site PI and their delegate, and site study and clinical staff. Any participant-level blinding to the Assignment of specific Interventions at the Site will be described in the relevant DSA.

Role	Individual pre-randomisation data	Individual Provisional Assignment	Individual Revealed Assignment	Individual Endpoints	Other individual post-randomisation data	Aggregated Provisional Assignment	Aggregated Revealed Assignment	Aggregated pre-randomisation data	Aggregated Endpoints	Other Aggregated post-randomisation data	Aggregated safety data; pooled across arms	Aggregated enrolment data; pooled across arms	Public Disclosures of Platform Conclusions
DSMB	U	U	U	U	U	U	U	U	U	U	U	U	U
Analytic Team	U	U	U	U	U	U	U	U	U	U	U	U	U
Steering Committee	B	B	B	B	B	B	B	B	B	B	M	M	U
Collaborators	B	B	B	B	B	B	B	B	B	B	M	M	U
Statistical Committee	B	B	B	B	B	B	B	B	B	B	M	M	U
Site PI	U	B	U	U	U	B	B	B	B	B	M	M	U
Site study staff	U	B	U	U	U	B	B	B	B	B	M	M	U
Responsible clinician	U	B	U	U	U	B	B	B	B	B	B	B	U
Site clinical staff	U	B	U	U	U	B	B	B	B	B	B	B	U
Participant	U	B	U	U	U	B	B	B	B	B	B	B	U
Public	B	B	B	B	B	B	B	B	B	B	B	B	U

Table 3: Level of blinding/ masking to different types of information by role.

Key: B = Fully blinded to the information; M = Masked to the identity of Assigned Interventions; U = Unblinded access to the information.

7.15 PEx Treatment Platform Periods

7.15.1 Assessment for Intensive therapy and Randomisation

Screening activity, to evaluate eligibility for randomisation in one or more Domains, will generally be undertaken while the participant is an outpatient, before commencement of intensive therapy. It is possible that enrolment in the PEx Cohort and the PEx Treatment Platform (as described in section

7.2.2) may occur on the same day as the eligibility is assessed for randomisation, but usually this will have occurred in advance.

The sequential activities undertaken at this time are:

1. Re-confirmation with the Responsible Clinician that the participant has a PERIT, and that commencement of intensive therapy is planned to occur within 14 days.
2. Confirmation of eligibility for the PEx Treatment Platform
3. Confirmation of eligibility for randomisation in each Domain
4. Confirmation of any Interventions excluded due to contra-indications or temporary exclusions including recent failed therapy (detailed in the DSA),
5. Confirmation of consent to be randomised
6. Nomination by the Responsible Clinician of a Selected Intervention in each eligible Domain for that participant for that PERIT.
7. Update of the BEAT CF Database with any outstanding PEx Cohort data
8. Confirmation of the current Stratum (defined in the PEx Core Protocol) based on up-to-date spirometry and sputum microbiology results.
9. Documentation of the minimum data required prior to randomisation
10. Randomisation to a Provisionally Assigned Regimen.
11. An entry in the participant's medical record, according to applicable local site practices, to alert clinical staff that the participant has been randomised.

7.15.2 Day 0: Commencement of Intensive Therapy for PEx

The timing of commencement of intensive therapy (the commencement of the first dose of IV antibiotic) will be at the discretion of the participant's Responsible Clinician (or their suitably qualified delegate), and subject to the availability of resources at the Site. It is anticipated that commencement of intensive therapy will occur as soon as practicable, and no later than 14 days after randomisation to a Provisionally Assigned Regimen has occurred.

The sequential activities to be undertaken at this time are:

1. Entry and update of PEx Cohort data in the BEAT CF Database per BEAT CF PEx Core Protocol section 7.8, PEx Cohort Data Collection
2. Confirmation of the Stratum and the Responsible Clinician's Selected Regimen
3. Reveal of the Assigned Regimen per section 7.11.1
4. Prescription and commencement of Assigned Interventions, and any permitted concurrent therapies, per the Responsible Clinician (or their delegate).

If a Provisionally Assigned Regimen has not been Revealed by 14 days after randomisation, it will be automatically Revoked. The participant may be re-assessed and re-randomised to a new Provisionally Assigned Regimen if still eligible.

The Provisionally Assigned Regimen may also be Revoked before it has been Revealed, at the discretion of the Responsible Clinician, for example if the Stratum or Selected Intervention has changed after randomisation and before commencement of Intensive Therapy.

7.15.3 Daily follow up

For every day of hospitalised care, information will be collected in the BEAT CF Database to describe:

1. The location of care
2. Interventions received (both Assigned and concurrent),
3. Any cessation or change of a prescribed Intervention,
4. Any Adverse Reactions to Assigned Interventions or to concurrent antibiotics resulting in cessation of therapy,
5. Any new sputum microbiology and spirometry data, and signs and symptoms per section 7.8 of the Core Protocol.
6. Certain Adverse Events will be captured and reported as per Section 11.1.3 of this PEx Treatment Platform Protocol.

8 DATA MANAGEMENT

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

8.1 PEx Treatment Platform Source Data

Source documents, where data are first recorded and from which BEAT CF Database data are obtained, will include hospital medical records, laboratory results, spirometry results, medication charts, any relevant imaging, and medical correspondence. A further data source will be through direct conversation with the participant or via ePRO, their parent (or legally responsible caregiver), or Responsible Clinician and treating medical team.

8.2 PEx Treatment Platform Data Management

For each PEx Cohort participant screened for inclusion in the PEx Treatment Platform, a record of the screening will be recorded in the BEAT CF database. For each participant enrolled in the PEx Treatment Platform, eCRFs will be completed, including for those lost to follow-up or those who withdraw from

the PEx Treatment Platform. The Site PI will be responsible for the accuracy, completeness, and timeliness of the data entered in the eCRFs and all required reports.

The BEAT CF Database contains validation ranges for each variable to minimise data entry errors, and an audit trail to maintain a record of all entries and any changes made; reasons for change; time and date of entry; and username of person who made the change. Data queries will be raised by the BEAT CF Project Manager, the Data Manager or study monitor on an on-going basis. Priority will be given to ensuring timely completion and accuracy of those fields required for the analysis of the Primary Estimand used in each Scheduled Analysis. Queries will be resolved prior to database lock for the Final Analysis.

A study monitor will assess the accuracy of data collection by verification of the eCRFs against the source documentation for adherence to the protocol, including by checking the eCRF's against the participant's medical record and other source documentation.

9. PROTOCOL DEVIATIONS AND SERIOUS BREACHES

For a description of the processes for documenting and reporting protocol deviations or serious breaches of GCP, refer to the PEx Core Protocol.

10. STATISTICAL METHODS

10.1 PEx Treatment Platform Analytic Approach, Unit-of-Analysis and Intervention Interactions

Statistical inference will be based on the analysis of accumulated PEx Treatment Platform data using pre-specified Bayesian models at regularly Scheduled Analyses. The models will incorporate design features by accounting for potential variation in the Endpoint by patient Stratum, Site, Age and Date of enrolment. Domain eligibility and other baseline factors which plausibly account for variation in the Endpoint.

The Primary Model will be linear regression on the Primary Endpoint and will incorporate model parameters which represent the effect of a prescription of a Revealed Intervention from within each Domain on participants in each Stratum, and any specific interactions with strong *a priori* plausibility. Secondary models will investigate additional interaction effects as well as heterogeneity of intervention effects across pre-specified subgroups.

The unit-of-analysis is each PEx Treatment Platform-participant in each randomised PERIT. An individual participant may be included for multiple PERITs, and data for each PERIT will be used.

At each Scheduled Analysis and at the Final Analysis, these models will be used to calculate for each Regimen the posterior probabilities that, compared to all other Regimens in that Stratum, that it is Best, as outlined in the Statistical Appendix. These probabilities, estimated from the Primary Model will:

1. be used to inform the ratio of Allocation to Regimens where RAR is implemented, and

2. be used as the basis for making Platform Conclusions by applying pre-specified Decision Thresholds, and for implementing PEx Treatment Platform Adaptations such as Termination of less effective Regimens.

The Decision Thresholds will be selected by examining simulations under various scenarios. Details of the statistical models and Decision Thresholds are presented in the Statistical Appendix.

10.2 Decision Thresholds

For a formal description of the Decision Thresholds, please refer to the Statistical Appendix.

The Decision Thresholds will be selected by examining simulations under various scenarios. These simulations will be conducted prior to commencement and may be updated to accommodate the Termination of any Interventions, or the introduction of any new Interventions or Domains over time. Any update required to the Decision Thresholds will be made and specified prior to each Scheduled Analysis.

In keeping with the Primary Objective of BEAT CF, the primary consideration in the design is the benefit to participants, which is assessed by the ability of the PEx Treatment Platform to use accumulating evidence to Assign participants to any Regimens that are Best (or Best Equivalent), rather than to Regimens that are not Best. To assess, this we will conduct at least 1,000 simulations for each of a range of plausible scenarios, including scenarios in which one Regimen is moderately worse than all other Regimens, and assess across simulations the average proportion of participants Assigned to any Regimens that are, in truth, Best versus not Best. A further consideration is the probability of making an erroneous Platform Conclusion that a Regimen is Best in a Stratum, when in truth it is not. To minimise this risk, the Decision Thresholds will be calibrated to ensure that the risk of false Platform Conclusions of Superiority and Futility are acceptable based on long-term (frequency-based) platform operating characteristics. To do this, the frequency of correct and false Conclusions among at least 1,000 simulations will be estimated, for each of a range of plausible scenarios, including the scenario

in which each Regimen is, in truth, equally effective. While the PEx Treatment Platform is designed to be perpetual, the simulations will be based on 1600 randomisations. This corresponds to ~24 months of randomisation, based on an anticipated enrolment of 800 participants in the BEAT CF PEx Cohort, each having on average one PERIT per year. We will also assess the probability of reaching a Platform Conclusion for Superiority under a range of plausible scenarios, including where treatment effects for Interventions are differential across Regimens or across Strata.

11. QUALITY ASSURANCE AND MONITORING

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

11.1 Safety Monitoring and Reporting

11.1.1 Safety Definitions for medicinal products

For definitions of adverse events, safety issues, and safety measures, please refer to the PEx Core Protocol: Attachment 1

11.1.2 Assessment of AEs

Each adverse event must be evaluated for:

1. Seriousness	An assessment of whether the AE meets the definition of a SAE.
2. Causality (relatedness):	A clinical assessment of whether there is a reasonable causal relationship between the AE and an Assigned Intervention. The Site PI (or medically qualified delegate) will make a judgement as to whether an AE has a reasonable causal relationship with the Assigned Intervention(s). The degree of certainty with which an AE is attributable to an Intervention or an alternative cause will be determined by how well the event can be understood in terms of: • Temporal relationship with the administration of the Intervention or its cessation • Reactions of a similar nature previously observed in the individual or others following treatment The Site PI or delegate's opinion of the relationship between the

	AE and the Assigned Intervention will be specified as follows: • Likely related • Not likely related
3. Expectedness	For SAEs which are likely related to a PEx Treatment Platform Intervention, whether it is an expected occurrence based on the side effect profile documented in the Reference Safety Information (the relevant Australian Production Information) considering the nature and frequency of the event.

11.1.3 Adverse Events To Be Reported

Reporting of AEs will be restricted to those that are considered to be:

1. Any SAEs, occurring during the period of Intensive Therapy, regardless of their likely causal relationship to an Assigned Intervention, which
    a. result in death
    b. are life-threatening
    c. result in severe disability
2. Any SAEs, occurring at any time for the duration of a person's participation that are likely related to Assigned Interventions (SARs).
3. Any ARs (serious or non-serious) resulting in cessation of the Assigned Intervention.
4. Any Events of Special Interest related to specific Interventions defined in the relevant DSAs.

Participants will experience aberrations in laboratory values, signs and symptoms due to their underlying CF and the impact of standard therapies. These will only be considered ARs or SARs if, in the clinical judgement of the Site PI (or their delegate), they are considered to be likely related to an Assigned Intervention, and not more likely related to the participant's underlying disease or concurrent therapies.

Any SARs should be followed up until the event has resolved or a final outcome has been reached. Any change of condition or other follow-up information for the SAR should be reported as soon as it is available.

The Site will report SAEs by completing an AE eCRF. The minimum amount of information that the Site PI (or their delegate) must complete in the initial report is:

1. title of the event
2. date the event started

3. reason the event is considered a SAE
4. causality relationship to Assigned Intervention

11.1.4 Site responsibilities for reporting AEs

The Site PI (or their delegate) should:

1. Assess all AEs among participants in the PEx Treatment Platform occurring during the period of intensive therapy. Only specific AEs will be collected/recorded for this study. Recording and reporting procedures will be outlined in the Safety SOP.
2. Report to the Sponsor within 24 hours of becoming aware of the event:
    a. all SAEs that need reporting as documented in Section 11.1.3 of the PEx Treatment Platform Protocol.
3. Review all safety communications from the Sponsor including any safety issues identified by the DSMB, and ensure any implications for participants are managed appropriately.
4. Report to their local governance office, within 72 hours of becoming aware of the event:
    a. all SSIs reported to the Site by the Sponsor and
    b. any SUSARs arising from their Site (if required by local governance).

11.1.5 Sponsor Reporting Procedures

The Sponsor will assess and report safety events as specified in the Safety SOP and in accordance with the NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016) and any additional requirements of the approving HREC.

Any SARs assigned by the Site PI (or following central review) as both 'likely related' to an Assigned Intervention and 'unexpected' will be classified as SUSARs and will be subject to expedited reporting to the Therapeutic Goods Administration in accordance with the NHMRC Guidance. SUSARs may also be reported to the medicine license holder/supplier of the investigational product.

The Sponsor will report to Sites as well as the HREC(s) and the TGA:

- any Significant Safety Issues (SSIs)* that meet the definition of an Urgent Safety Measure (USM) within 72 hours of becoming aware of the issue.
- All other SSIs within 15 calendar days or becoming aware of the issue.

The sponsor will action all SSIs in accordance with the NHMRC Guidance.

12. ETHICS AND REGULATORY

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

12.1 PEx Treatment Platform specific benefits

The Interventions evaluated in the PEx Treatment Platform reflect the range of treatments that are widely available and used in CF centres across Australia, so it is unlikely that participation will improve access to therapies. However, the PEx Treatment Platform will implement RAR, meaning that the probability of being Assigned the best performing Regimen (or Regimens) is expected to increase with time. It is therefore intended that, overall, participation should confer a benefit, although this cannot be assured for any particular participant.

13. REPORTING/PUBLICATION

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

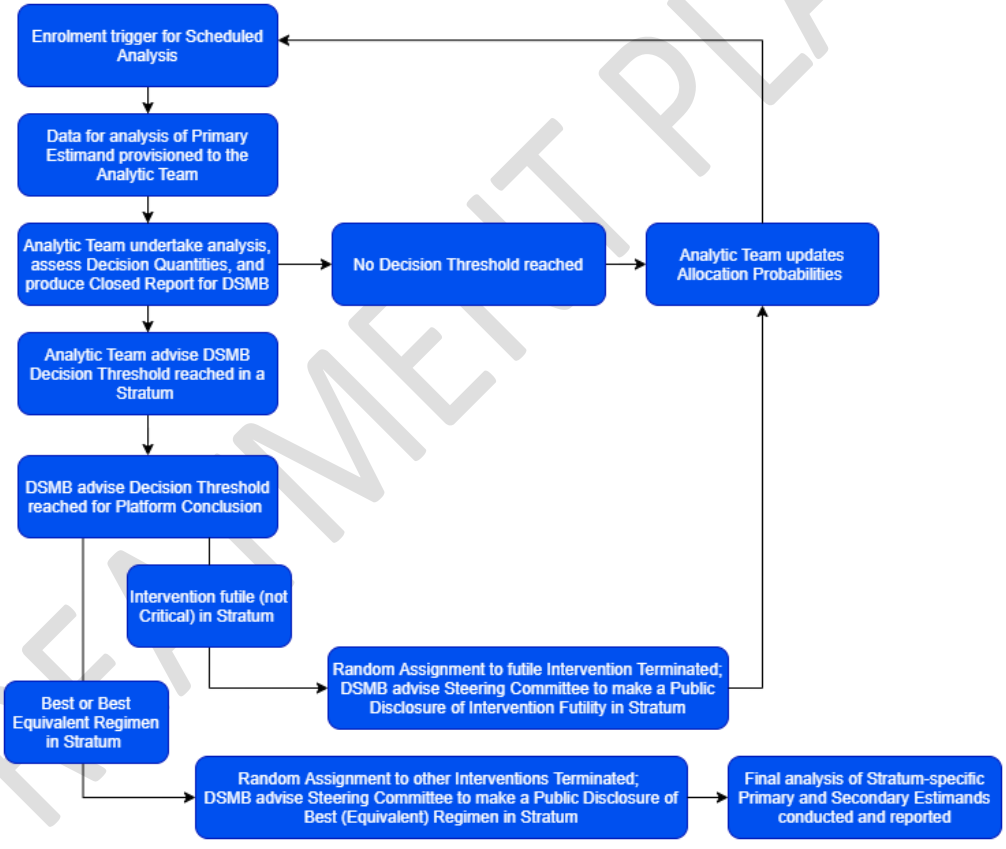

Figure 3 BEAT CF PEx Treatment Platform process for Public Disclosure of Platform Conclusions

Meeting a Platform Conclusion will generally result, at the recommendation of the DSMB, in Termination of an Intervention or Closure of a Domain within one or more Strata. To achieve rapid dissemination of the PEx Treatment Platform results to the broader CF community, the intention will

be to publish as much data as is possible to allow critical review, but without jeopardising the integrity of the on-going Treatment Platform. This would generally include, for example, revealing the identity of any Intervention which is Terminated in a Domain, and the point estimate and the posterior credible interval of the effect size (difference in change in ppFEV1) between the terminated Intervention and the best performing Intervention in that Domain and Stratum, where the identity of the best performing Intervention remains Masked until the Domain is Closed.

14. REFERENCES

[i] https://pubmed.ncbi.nlm.nih.gov/34469706/

[ii] REMAP CAP Core Protocol Version 1. 2016.

[iii] REMAP CAP Pandemic Appendix to the Core Protocol V2.0 18 May 2020

[iv] ASCOT ADAPT Core Protocol 2020

[v] SNAP protocol 2021

[vi] Walter SD, Turner R, Macaskill P, McCaffery KJ, Irwig L. Beyond the treatment effect: Evaluating the effects of patient preferences in randomised trials. Stat Methods Med Res. 2017 Feb;26(1):489-507. doi: 10.1177/0962280214550516. Epub 2016 Jul 11. PMID: 25213116.

[vii]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6581041/