A multi-centre, randomised, multi-arm, adaptive platform trial in people with or without cystic fibrosis Finding the Optimal Regimen for *Mycobacterium abscessus* Treatment (FOR*Ma*T)

MASTER PROTOCOL

Protocol Version	Version 4.1
Protocol Date	20 February 2024
Protocol Number	FOR*Ma*T001
Funding	1- Medical Research Future Fund, Australian Government Department of Health 2- Cystic Fibrosis Foundation 3- Anonymous Donor 4- Thoracic Society of Australia and New Zealand 5- The University of Queensland 6- Children's Hospital Foundation
Australian and New Zealand Clinical Trials Registry Number	ACTRN12618001831279
ClinicalTrials.gov Identifier	NCT04310930
EudraCT Number	2020-000050-10
EU-CT Number	2023-506575-99-00-EU CT
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ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
AFB	Acid-Fast Bacilli
ATS	American Thoracic Society
BAL	Bronchoalveolar Lavage
BAR	Bayesian Adaptive Randomisation
BCM	Biased Coin Minimisation
CAG	Consumer Advisory Group
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DISC	Drug and Intervention Selection Committee
DNA	Deoxyribonucleic Acid
eCRF	electronic Case Report Form
eISF	electronic Investigator Site File
eTMF	electronic Trial Master File
FDA	Food and Drug Administration
FOR*Ma*T	Finding the Optimal Regimen for *Mycobacterium abscessus* Treatment
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLI	Global Lung Initiative

HRCT	High-Resolution Computed Tomography
HREC	Human Research Ethics Committee
IA	Inhaled Amikacin
ICH-GCP	International Council for Harmonisation Good Clinical Practice Guidelines
ICMJE	International Committee of Medical Journal Editors
iDSMB	Independent Data Safety Monitoring Board
IEC	Independent Ethics Committee
IRB	Independent Review Board
ISO	International Organization for Standardization
IV	Intravenous
IVA	Intravenous Amikacin
LAI	Liposomal Amikacin for Inhalation
LLN	Lower Limit of Normal
MABS	*Mycobacterium abscessus*
MABS-PD	MABS Pulmonary Disease
MBS	Medicare Benefits Scheme
MCRI	Murdoch Children's Research Institute
MoOP	Manual of Operating Procedures
MRL	Mycobacterial Reference Laboratory
NTM	Non-Tuberculous Mycobacteria
PBS	Pharmaceutical Benefits Scheme
PI	Principal Investigator
PICF	Participant Information and Consent Form
PK	Pharmacokinetics
QA	Quality Assurance
QoL	Quality of Life

R-Con	Randomisation – Consolidation
RCT	Randomised Control Trial
REDCap	Research Electronic Data Capture
REMAP-CAP	Randomised, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
R-PI/IC	Randomisation – Prolonged Intensive or Immediate Consolidation
rRNA	ribosomal ribonucleic acid
R-SI	Randomisation – Short Intensive
SAEs	Serious Adverse Events
SAHMRI	South Australian Health and Medical Research Institute
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SSI	Significant Safety Issues
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TDM	Therapeutic Drug Monitoring
TMC	Trial Management Committee
TPF	Time Point Final
TPST	Time Point Start Treatment
TSC	Trial Steering Committee
ULN	Upper Limit of Normal
USMs	Urgent Safety Matters
UQ	University of Queensland
WGS	Whole Genome Sequencing
6MWD	Six-minute walk distance
6MWT	Six-minute walk test

PRINCIPAL INVESTIGATORS STATEMENT

I confirm that I have read the FOR*Ma*T Master Protocol **Version 4.1, dated 20th February 2024.** As the Principal Investigator, I understand it, and I agree to adhere to the study conduct requirements and agree to conduct this protocol in accordance with International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), the Declaration of Helsinki, the United States (US) Food and Drug Administration (FDA), and local regulations and guidelines. I agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse events. I will accept the monitors', auditors' and regulatory inspectors' oversight of the study. I will promptly submit the protocol to the applicable ethical review board as required.

…….....

Principal Investigator Signature

……..

Principal Investigator Name

……..

Date (dd/mmm/yyyy)

1 INTRODUCTION

1.1 SYNOPSIS

Background: Mycobacteria in the *Mycobacterium abscessus* group (MABS) are a species of non-tuberculous mycobacteria (NTM) found in water and soil habitats that exhibit high levels of intrinsic multi-drug resistance (1). NTM includes more than 160 species that are recognised opportunistic human pathogens, with chronic pulmonary infections the most common clinical presentation. Individuals with underlying inflammatory lung diseases are more susceptible to MABS pulmonary disease (MABS-PD), but MABS also affects patients with no underlying condition. MABS-PD can result in significant morbidity, increased healthcare utilisation, accelerated lung function decline, impaired quality of life (QoL) (2), more challenging lung transplantation (3), and increased mortality (2). Of particular concern is the increasing prevalence of pulmonary infections occurring worldwide in patients with bronchiectasis and cystic fibrosis (CF), with prevalence between 5 to 20% (2, 4, 5). There is real evidence of this in Queensland, Australia (where the infection is notifiable) with the prevalence increasing from 0.85/100,000 in 2001 to 2.35/100,000 in 2016, where now over 100 cases are reported annually, clearly illustrating the emerging threat of this infection. While the increasing prevalence might be reflective of enhanced surveillance and improved microbiological detection (6-8) (9) the reasons for this changing epidemiology are poorly understood (2, 4, 10, 11).

Treatment regimens for MABS are highly variable, not evidence-based and involve complex, expensive, and often poorly tolerated drug combinations for prolonged periods (>12 months). Some individuals will have positive cultures that clear spontaneously, some will initially have positive cultures without obvious MABS-PD but go on to develop disease at a later stage, and some may present with established MABS-PD. MABS-PD can be associated with a rapid decline in health status, and there is evidence that successfully clearing infection is associated with better health outcomes (12, 13). However, toxicity, poor tolerance and the prolonged and complex nature of therapy may increase the reluctance of clinicians to initiate treatment and for patients to accept it. A recent systematic review and meta-analysis revealed that such treatment regimens are often ineffective and may even worsen QoL (14). The costs and treatment burden of NTM infection are high, and highest for MABS-PD, estimated at $AUD12-28,000/month (15) highlighting the need to assess the healthcare costs and cost-effectiveness of therapies to inform health policy around NTM. Pathogen, host, and treatment factors all likely play a role in clinical and microbiological outcomes.

Aims:

1. To build an iterative, standing, platform trial with innovative and adaptive properties to evaluate combinations of therapies for patients with MABS-PD. Initially this will test therapies that are currently used and recommended in published international consensus guidelines and are the basis for the current treatment guidelines for MABS-PD. Once the best combinations have been established the platform described in the Master Protocol will have the capacity to add new treatments and to eliminate therapies because of futility as they either lack efficacy or cause unacceptable toxicity. The data obtained as part of the trial will be used to plan for new waves of the platform trial using novel therapeutic approaches that may be tested against the previously determined optimal approaches, thus leading in an iterative fashion to improving microbiological clearance and health outcomes associated with MABS-PD.

2. To use the opportunities afforded by the clinical trial platform to establish discovery studies to:
    i. Understand the effects of MABS-PD and therapeutic interventions on health-related quality of life and determine the cost effectiveness of proposed therapy combinations;
    ii. To develop strategies for optimising drug dosing using robust pharmacokinetics;
    iii. Understand susceptibility to MABS-PD and develop biomarkers of clinical disease, disease progression and response to therapy;
    iv. Investigate the genomics of human MABS strains and antibiotic resistance genes and impact of therapeutic interventions.
3. To investigate the use of registries to facilitate the long-term monitoring of patient outcomes from MABS-PD and treatment.

Methodology: Entry into the Finding the Optimal Regimen for *Mycobacterium abscessus* Treatment (FOR*Ma*T) trial can occur at two different levels;

1 - participants of any age from their first MABS isolate and not receiving current MABS therapy are eligible to enrol in the Observational Cohort and;

2 - participants of any age meeting the American Thoracic Society (ATS) criteria for the diagnosis of MABS-PD and are untreated for MABS-PD at the time of starting intensive therapy are eligible to enrol in the Intervention Program. Participants initially enrolled into the Observational Cohort who go on to meet the ATS criteria for MABS-PD can transition to the Intervention Program at any time. Intervention Program participants will be randomised to receive MABS-PD therapy combinations and additional outcomes will be assessed.

Participants in both the Observational Cohort and Intervention Programs will contribute the same core data, thus providing the opportunity to examine what happens to both treated and untreated patients with positive cultures longitudinally as well as the transition to MABS-PD.

Primary Outcome

The primary outcome of the Intervention Program is microbiological clearance of MABS with good tolerance of the interventions.

Definition of MABS clearance at final outcome:

Negative MABS cultures from four consecutive sputum samples with one of those sputum specimens collected four weeks after the completion of consolidation therapy, or a MABS negative Bronchoalveolar Lavage (BAL) collected four weeks after completion of consolidation.

Definition of tolerance:

Tolerance is based on the Common Terminology Criteria for Adverse Events (CTCAE version 5.0). Only adverse events that are attributed as either "possibly-", "probably-", or "definitely-" related to study drug will be assessed in the determination of tolerance. "Good" tolerance is defined as no adverse events occurring or only adverse events coded as CTCAE grades 1 and 2. "Poor" tolerance is defined as any adverse events attributed as possibly-, probably-, or definitely-related to study drug coded as CTCAE grades 3, 4, or 5.

The Intervention Program within the FOR*Ma*T platform will adopt an adaptive design with Bayesian Adaptive Randomisation (BAR) when there is randomisation across three or more interventions and may also include interim rules for dropping or adding treatment arms. BAR allows the randomisation probabilities to each of the interventions to be updated during the trial to enable more participants to be randomised to more promising interventions. The probabilities of allocation to each intervention are based on the posterior probability of the intervention being superior to the control (16). The approach used will carry forward the most promising arms that achieve a minimum level of efficacy with acceptable toxicity. If a treatment is carried forward until the end it will be tested against the control/reference group and recommended if the test statistic is above a certain threshold. The Intervention Program will consist of treatment modules specified in Appendix A starting with sequential Phase II trials, including a randomised intensive treatment phase, and a randomised consolidation treatment phase. In the future, interventions reaching a probability threshold of demonstrating success at the end of the Phase II trial will have the potential to seamlessly continue to recruit to a Phase III study to enable the Phase II data to be utilised as part of a Phase III study, thus reducing the resources required to achieve high quality evidence on which to base treatments.

The FOR*Ma*T Master Protocol describes the adaptive platform trial to evaluate microbiological, functional, radiological, and quality of life outcomes of interventions utilised in the treatment of MABS-PD, in combination with the Observational Cohort.

1.2 PROTOCOL STRUCTURE

The FOR*Ma*T trial is designed as a standing iterative, platform trial with innovative and adaptive properties. This is reflected in the multi component structure of the FOR*Ma*T Protocol outlined in Figure 1. The framework for the FOR*Ma*T trial is established within the FOR*Ma*T Master Protocol. The Intervention Program(s), the Observational Cohort, Discovery, Registry Linkage studies, Health Economics and General Statistical Principles are described in specific Appendices.

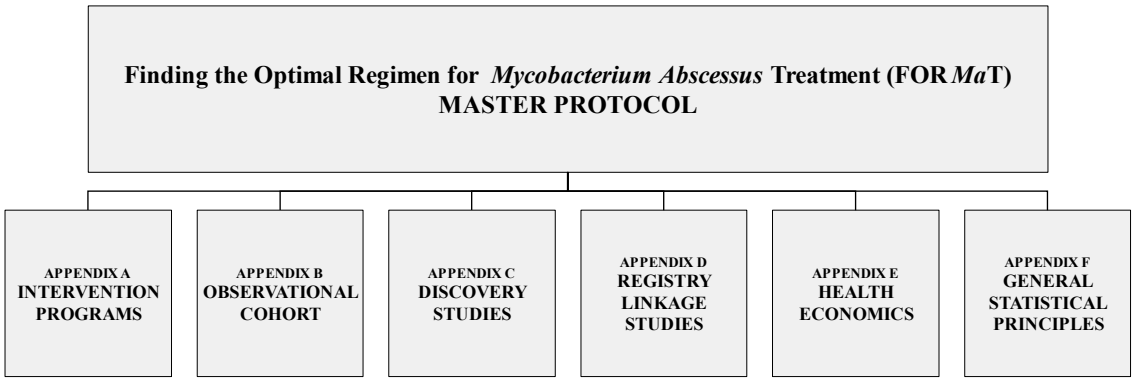

Figure 1 Design of the FOR*Ma*T Master Protocol and Appendices

1.3 FOR*MA*T MASTER PROTOCOL

The FOR*Ma*T Master Protocol outlines the core structure, procedures, and processes of the FOR*Ma*T trial. The information described in the FOR*Ma*T Master Protocol applies to all participants regardless of if they are receiving intervention treatment for MABS-PD or are enrolled in the Observational Cohort, unless otherwise stated.

The Master Protocol has the following structure:

- The background and rationale for determining the optimal treatment regimens for MABS-PD.
- The overarching objectives of the FOR*Ma*T trial (including both the Intervention Program and the Observational Cohort).
- The design of the FOR*Ma*T trial including the two-level approach to assessing eligibility into the trial, the trial endpoints and the general statistical principles to be used in the analysis of the trial.
- The conduct of the FOR*Ma*T trial detailing recruitment methods and consent processes, the core trial timepoints and procedures, safety monitoring processes and data management procedures.
- Details of The FOR*Ma*T trial oversight, ethical and administrative considerations.

1.3.1 FOR*MA*T APPENDICES AND SUPPLEMENTS

The FOR*Ma*T Appendices describe in detail the information specific to the Appendices and the sub-studies and integrated studies nested within them. As such, appendix specific information is not described within the FOR*Ma*T Master Protocol but rather the Master Protocol sets the framework within which the Appendices exist. As the trial progresses, new interventions and methodologies can be added to the FOR*Ma*T trial through the addition of a new appendix. Conversely, as interventions and methodologies are found to be futile the corresponding studies in the appendix can be removed. It is not anticipated that these changes will affect the framework of the Master Protocol. Any changes to appendix specific studies require ethics approval.

The FOR*Ma*T Supplements are additional documents that expand the scope of the relevant appendices. They provide additional detail and information to supplement the specific appendix they are linked to. Changes to supplements do not require ethical approval as they are not a part of the Master Protocol or appendices but are an additional document to elaborate on the specific components contained within an appendix. **FOR*Ma*T Appendices are structured as follows:**

- Each appendix has a theme: for example, Appendix A for Interventions, Appendix B for Observation, Appendix C for Discovery studies, Appendix D for Registry Interactions, Appendix E for Health Economics, and Appendix F for General Statistical Principles.
- Appendix A describes the details for the Intervention Programs of the FOR*Ma*T Trial including intensive and consolidation interventions (Figure 2). For example, Appendix A1 describes the first of such Intervention Programs and if new interventions are added to either the intensive or consolidation phases these would be added in new Appendices A2, A3 etc. Data from previous programs using the same intervention combinations may be incorporated in the analysis of a new program. Thus, data from Appendix A1 could be combined with data from Appendix A2 for example.

- Within some of the Appendices are nested studies that have been designed to investigate specific objective(s).

The components described within each appendix are variable and dependant on the nature of the appendix and the studies nested within it. Overall, FOR*Ma*T Appendices will contain the following components:

- The overall objective specific to that appendix.
- Where relevant, information about the features of the interventions or the study to be investigated.
- Appendix specific eligibility criteria.
- Appendix specific consent requirements.
- Appendix specific procedures and safety measures to be assessed.
- Appendix specific statistical methods and simulations where relevant.

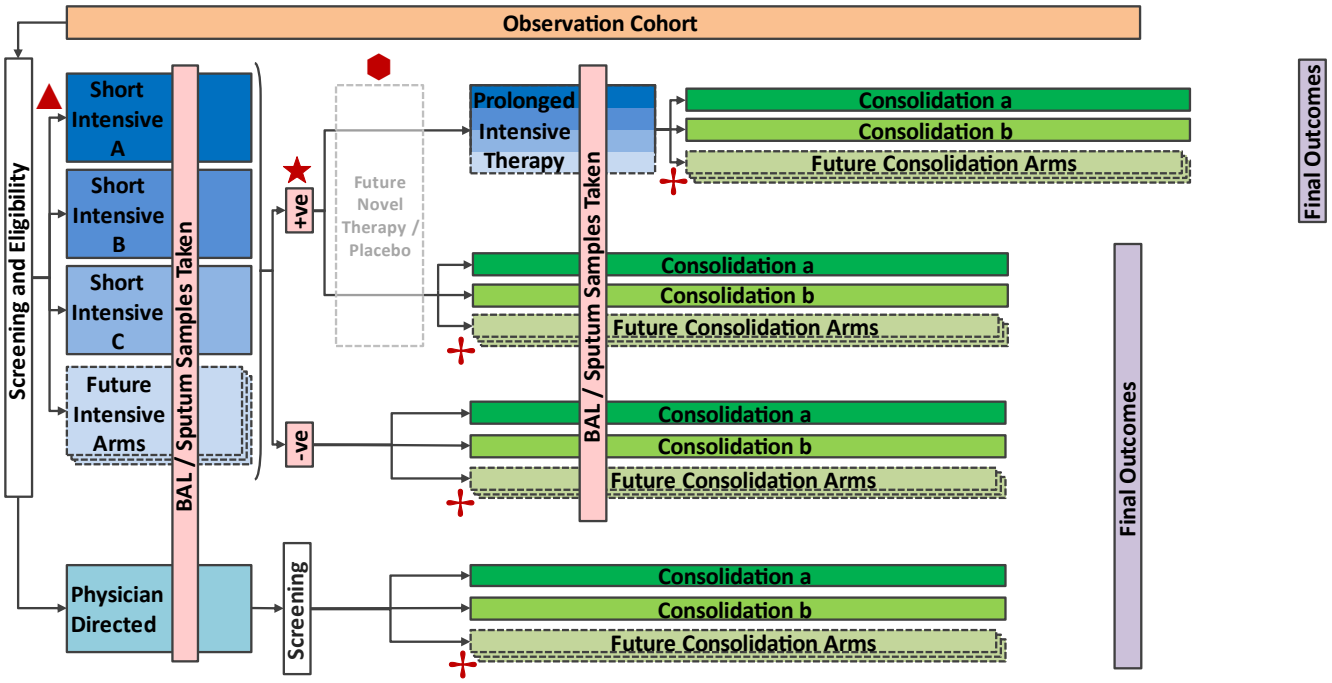

Figure 2 FOR*Ma*T participant flow diagram
Eligibility into the Intervention Program or Observational Cohort is determined at Screening. For the first iteration of the Intervention Program, there will be up to three randomisations between Screening and the Final Outcome Visit. Symbols (▲★⬢✢) indicate possible randomisation points (see the relevant appendix for further information on randomisation).

2 BACKGROUND

2.1 MICROBIOLOGY OF MABS

Of the many pathogenic NTM species, MABS are recognised as causing the most serious pulmonary infections, associated with the greatest problems of antibiotic resistance, toxicity and treatment failure (12, 17). MABS are currently divided into 3 subspecies: *M. abscessus* subspecies *abscessus* (*M. a. abscessus*), subs. *massiliense* (*M. a. massiliense)* and subs. *bolletii* (*M. a. bolletii)*. While there is variation in the prevalence of the subspecies in different populations, *M. a. abscessus* is the most common overall (45-68%), followed *M. a. massiliense* (20-55%) and *M. a. bolletii* (8-25%) (18-20). Progression of MABS-PD due to the different subspecies (21) appears to be similar, although treatment outcomes vary significantly and are partially explained by differential antimicrobial susceptibility to macrolide antibiotics. MABS are intrinsically drug resistant to multiple classes of antibiotics and they can also acquire antibiotic resistance genes to macrolides and aminoglycosides, leading to clearance rates of ≈50% following intensive therapy (19, 22, 23). After apparently successful treatment, relapse or recurrences with new strains occur in 15-33% of patients (19). Nevertheless, macrolides provide the therapeutic backbone of guideline-based MABS treatment (1, 4). Furthermore, they are the only antibiotic class where there is some correlation between *in vitro* susceptibility data and clinical response (14). Macrolide resistance in MABS is either constitutive or inducible (20). The less common, constitutive resistance may be acquired during macrolide therapy and results from mutations in the 23S rRNA gene (*rrl*). Inducible macrolide resistance is related to the MABS ribosomal methyl transferase gene, *erm(41).* Such isolates appear susceptible at day 3 following infection, but resistant by day 14 using prolonged incubation drug susceptibility testing. *M. a. massiliense* has a truncated and dysfunctional *erm(41)* gene, thus making it more susceptible to macrolides, whereas *M. a. abscessus* and *M. a. bolletii* usually, but not invariably, have inducible resistance (20). It is not surprising then that microbiological cure rates of MABS-PD appear partly related to macrolide resistance with clearance rates up to 88% in those with macrolide susceptible isolates, and only 36% in the setting of inducible macrolide resistance (19). Molecular detection of the subspecies, including identifying the *erm(41)* and *rrl* genes is important in understanding treatment response, and potentially targeting novel treatment approaches.

2.2 EPIDEMIOLOGY

NTM can cause both asymptomatic and symptomatic infections in humans (1). Pathogenic strains of MABS have been isolated from potable water, and MABS infections are more prevalent in coastal areas and regions with humid tropical climates (12, 24, 25). While most infections are thought to be acquired from environment aerosols (26), in patients with CF there is evidence supporting the emergence of worldwide dominant clones (of increased virulence) that may be capable of patient-to-patient transmission (18).

2.2.1 HIGH-RISK PATIENT POPULATIONS

CF is an autosomal recessive condition caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene. Mortality and morbidity of CF patients are predominantly related to chronic suppurative lung disease (27). CF

is a risk factor for MABS-PD (and NTM more broadly) and even carrier status of disease-causing mutation in *CFTR* (24) may also increase risk. Other structural lung diseases, bronchiectasis, chronic obstructive pulmonary disease, previous mycobacterial disease (including Tuberculosis (TB) and NTM), severe gastro-oesophageal reflux and immunosuppression (where dissemination can occur) (11) also increase risk of infection. The age range of CF and non-CF affected patients with MABS-PD overlap, with non-CF patients generally being older than those with CF (>55 vs <30 years) (24).

2.3 CLINICAL PRESENTATION AND DIAGNOSTIC CHALLENGES

Due to their ubiquitous nature, the clinical significance of positive MABS cultures in respiratory specimens can be challenging. It may appear transiently in sputum cultures, persistently colonise the lower airways or progress to MABS-PD. The radiological and clinical features of underlying chronic respiratory disorders overlap considerably with changes attributable to MABS-PD making diagnosis and treatment decisions difficult and care is required to follow the ATS criteria in making the diagnosis of MABS-PD. Inclusion into the intervention program(s) will require meeting all the ATS criteria including both microbiological and clinical criteria.

2.4 TREATMENT REGIMENS GUIDELINES AND CHALLENGES

MABS treatment outcomes differ according to the etiologic organism. Recurrence rates for infection are high, despite successful treatment completion (28) but these approaches have not been evaluated in any trials. Differing treatment outcomes present multiple therapeutic challenges in the treatment of MABS. In recognition of these challenges, the ATS and the United States CF Foundation/European CF Society have published guidelines on NTM pulmonary disease (1, 4). In agreement with the latest Cochrane Review (29), they note there are no drug regimens of proven or predictable efficacy for treating MABS. Therefore, the guidelines are based on expert opinion only and in practice the treatments vary considerably (30). Suggested regimens include an intensive phase of 4-12 weeks (based on microbiological response) of intravenous (IV) antibiotics (usually amikacin, cefoxitin or imipenem + tigecycline) plus an oral macrolide. This is followed by consolidation therapy that includes oral drugs (usually a macrolide, plus others based on antibiograms, tolerability and experience) and an inhaled IV formulation of amikacin for 3 to >12 months. Dosing by individual pharmacokinetic (PK) data and therapeutic drug monitoring (TDM) may lead to optimal drug levels at infection sites and better treatment outcomes, although measuring levels within the lower airways frequently and non-invasively is challenging. Few PK studies involving antibiotics for NTM have been performed and few assays are currently available. Inhaled antibiotics have the potential advantages of achieving higher airway concentrations, while reducing the risk of systemic toxicity.

2.5 HEALTH RELATED QUALITY OF LIFE

A recent systematic review and meta-analysis revealed that MABS treatments are often ineffective and may even worsen QoL (14). The review strongly recommended that "clinical, functional and QoL parameters should be given more emphasis in the evaluation of treatment outcomes" and that "better applications of current antibiotics are

urgently needed" (14, 30). In addition, the costs and the treatment burden of NTM infection are high, and highest for MABS-PD; estimated at $AUD12-28,000/month (15), highlighting the need to assess the healthcare costs and cost-effectiveness of therapies to inform health policy around NTM. Pathogen, host and treatment factors are all likely to play a role in clinical and microbiological outcomes. Consequently, there is an urgent need for evidence to support treatment decision-making for patients with MABS lung infection.

2.6 THE PATIENT VOICE

In October 2015, the Food and Drug Administration (FDA) held a public meeting on NTM infection with patients and carers with the key theme to emerge (31) being the need for better, less toxic treatment with lower therapeutic burden. Participants also prioritised "validating and using tools to measure QoL and developing disease specific activity and severity assessment tools" (32). In January 2017, The James Lind Alliance released their top 10 research priorities for people with CF developed by CF patients, their families, and healthcare providers. The third top priority was "What is the best treatment for NTM, including when to start and what medication?" (33). Patients and healthcare providers are asking for evidence to guide the best approaches to manage this challenging infection.

A consumer representative is a member of the FOR*Ma*T Trial Steering Committee and will be involved in the ongoing oversight of the trial. In addition, the FOR*Ma*T consumer advisory group will enable a range of consumers to participate in the review of the protocol, trial development plans and consumer materials. The consumer group will be able to provide their views and advice which will then be taken on board by the investigators and trial management team.

2.7 GENERATING EVIDENCE USING A RANDOMISED PLATFORM TRIAL DESIGN

Platform trials using Bayesian statistical models, provide the opportunity to efficiently investigate multiple treatments for difficult-to-treat infections (e.g. multi-drug resistant TB (34)) requiring complex drug regimens in a heterogeneous population and can provide an iterative resource facilitating the translation of findings to improve clinical outcomes (35-37). New adaptive trial approaches are now recognised and accepted by regulatory authorities, including the FDA. Such trials are now being used in infectious diseases (38) and TB (34), complex chronic diseases (36) and rare oncology conditions (39). MABS-PD is a serious but relatively rare problem which can benefit from such methodology. FOR*Ma*T provides a common platform that will enable a broad enrolment of patients who both do and do not have cystic fibrosis and across all ages that enables generalisability but also maintains the ability to examine the heterogeneity of treatment responses across specific subgroups, while also enabling a comparison with non-treated patients through an Observational Cohort who are followed up simultaneously. The ability to examine novel therapeutic approaches using a common platform, along with the option to seamlessly move from phase II to phase III if warranted, also reduces the resources and the time required to deliver evidence-based treatments to patients who need it compared with conducting a series of independent trials.

2.8 SUMMARY

There is no evidence currently to guide therapy for MABS-PD, a complex and increasing health problem. The FOR*Ma*T trial seeks to provide answers to key questions by healthcare providers and patients on the timing and nature of treatments for the growing number of people infected with MABS, as well as the potential to model the progression of this condition in both treated and untreated patients. Furthermore, the trial will provide a platform for improving health outcomes for MABS patients and build a solid foundation for future testing of new therapeutics in the treatment of MABS.

3 OBJECTIVES

3.1 PRIMARY OBJECTIVE

To determine the optimal therapy for the treatment of patients with MABS-PD.

3.2 SECONDARY OBJECTIVES

1. To investigate the optimal approaches to antibiotic dosing and therapeutic drug monitoring.
2. To investigate the health-related quality of life and cost effectiveness of proposed therapy combinations.
3. To examine changes in clinical markers such as chest imaging and lung function to predict the onset of MABS-PD and response to therapies.
4. To develop biomarkers to predict the onset of MABS-PD and response to therapies.
5. To understand susceptibility to infection with MABS associated with the development of MABS-PD and host immune responses to infection and with treatment.
6. To characterise the genomics of human MABS strains and antibiotic resistance genes in patients in the observation and intervention studies.

4 TRIAL DESIGN

4.1 ELIGIBILITY CRITERIA

Eligibility criteria for the FOR*Ma*T trial can be applied at two levels:

1. Eligibility into the Intervention Program, or;
2. Eligibility into the Observational Cohort.

Potential participants can only be enrolled in either the Intervention Program or the Observational Cohort at any one time. Provided the eligibility criteria are met, potential participants may either:

1. Enrol directly into the Intervention Program, or;
2. Enrol into the Observational Cohort and transition into the Intervention Program once they satisfy the inclusion criteria for this program which can occur at any time during the trial (see Figure 3).

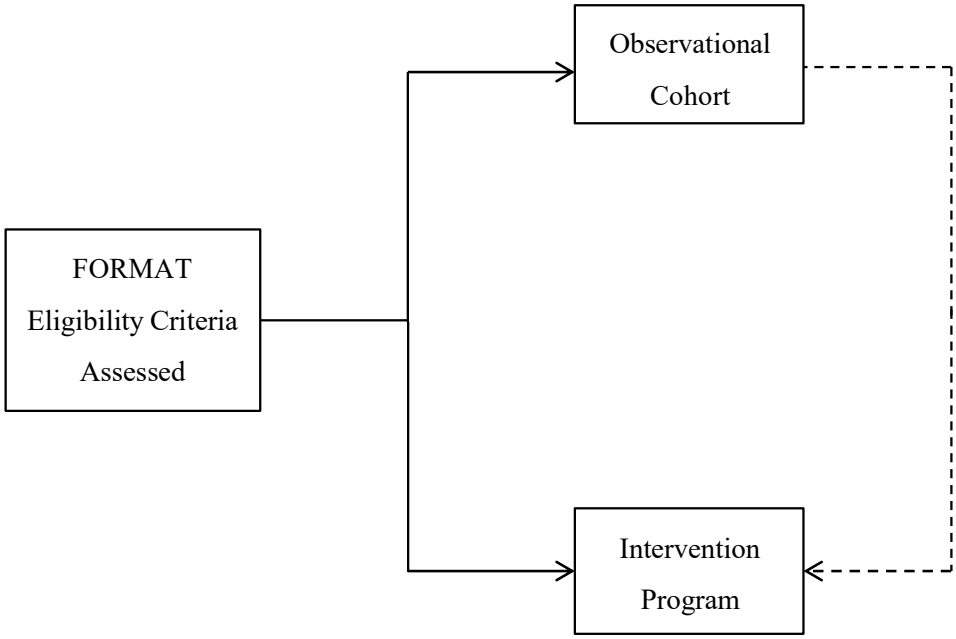

Figure 3 Participant enrolment into the FOR*Ma*T trial.
Eligibility into the FOR*Ma*T trial will be assessed at screening. Observational Cohort participants who go on to meet the Intervention Program eligibility criteria can transition from the Observational Cohort to the Intervention Program.

4.2 INTERVENTION PROGRAM ELIGIBILITY (APPENDIX A)

Potential participants are eligible for the Intervention Program (Appendix A) if the criteria below are met. Eligible participants with mixed NTM infections (slow growers + MABS) or with recurrence of MABS infection following completion of previous treatment will be eligible if they meet the inclusion and exclusion criteria listed below. For eligible participants with mixed NTM infections additional therapy combinations are available as detailed in the relevant appendices.

4.2.1 INTERVENTION PROGRAM INCLUSION CRITERIA

1. Positive MABS-PD diagnosis meeting all three American Thoracic Society clinical, radiological and microbiological diagnostic criteria for MABS-PD. Defined as:
    a. ***Clinical:*** Pulmonary symptoms and exclusion of other diagnoses.
    b. ***Radiological:*** Nodular or cavitary opacities on chest radiograph or a chest high-resolution computed tomography (HRCT) scan showing multifocal bronchiectasis with multiple small nodules.
    c. ***Microbiological:*** MABS positive culture results from at least two separate expectorated sputum samples.

    or

    Positive culture results from at least one bronchial wash or lavage.

    or

Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid-fast bacilli (AFB)) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washes that are culture positive for NTM.

Screening samples must be collected within the timeframes stated in the relevant appendix.

2. Male or female participants of any age.
3. Participant has not received treatment for MABS-PD in the 12 months preceding assessment of eligibility or as specified in the relevant appendix (this includes drugs prescribed for the treatment of other mycobacteria and/or other indications that may have activity against MABS, as specified in the FOR*Ma*T Prohibited Drug List Standard Operating Procedure (SOP)).
4. Informed consent signed by participant or parent/legal guardian if participant is under 18 years of age.
5. Ability to comply with study visits, therapies and study procedures as judged by the site investigator.

4.2.2 INTERVENTION PROGRAM EXCLUSION CRITERIA

- Participants receiving current treatment for MABS (this includes drugs prescribed for the treatment of other mycobacteria and/or other indications that may have activity against MABS, as specified in the FOR*Ma*T Prohibited Drug List SOP), except for participants taking azithromycin as part of routine treatment for CF or chronic infection-related pulmonary disease, or as specified in the relevant appendix.
- Participants who have a QTc interval of >500 milliseconds (QT interval corrected based on Fridericia method).
- Participants who are pregnant or planning to continue breast feeding.
- Known hypersensitivity to any of the therapies for which no alternative option(s) have been provided.

4.3 OBSERVATIONAL COHORT (APPENDIX B)

4.3.1 OBSERVATIONAL COHORT INCLUSION CRITERIA

To be eligible to participate in the Observational Cohort the following criteria must be met:

1. Male and female participants of any age with at least one positive respiratory culture for MABS.
2. Informed consent signed by participant or parent/legal guardian if participant is under 18 years of age.
3. Ability to comply with study visits and study procedures as judged by the site investigator.

4.3.2 OBSERVATIONAL COHORT EXCLUSION CRITERIA

Potential participants will be ineligible to participate in the Observational Cohort if any of the following criterion are met:

- Receiving active treatment for MABS within the previous 12 months (this includes drugs prescribed for the treatment of other mycobacteria and/or other indications that may have activity against MABS, as specified in the FOR*Ma*T Prohibited Drug List SOP, except for participants taking azithromycin as part of routine treatment for CF or chronic infection-related pulmonary disease).

4.4 ADDITIONAL ELIGIBILITY CRITERIA

Mixed NTM infections

Participants who have cultured slow growing NTM of the same species two or more times in the 24 months prior to screening, with one of those cultures within the 6 months prior to screening, will be considered to have mixed NTM infection at the time of screening. The participants must meet all other inclusion criteria and no exclusion criteria to be eligible for participation. Ethambutol may be used in addition to trial therapies to cover mixed NTM infections considered to require treatment by their clinician.

Appendix specific sub-studies and integrated studies

Appendix specific sub-studies and integrated studies may have additional eligibility criteria which are described in each of the relevant appendices.

4.5 TRIAL SETTING AND PARTICIPATING REGIONS

The trial will be conducted in multiple regions and trial sites. There is no limit to the number of countries or participating sites. A list of participating countries and sites are available on the FOR*Ma*T trial website (www.formattrial.com) and the clinical trial registries and will be updated as required.

Race and Ethnicity

Race and ethnicity will be collected as part of the demographic information for each participant. This information may be used to determine whether there are any potentially clinically significant racial and/or ethnic differences in the effects of any trial interventions.

4.6 TRIAL ENDPOINTS

The primary outcome for the FOR*Ma*T Trial (Appendix A Intervention Program) is MABS clearance from respiratory samples with treatment tolerance. MABS clearance is defined as negative MABS cultures from four consecutive sputum samples with one of those sputum specimens collected four weeks after the completion of consolidation therapy or a MABS negative Bronchoalveolar Lavage (BAL) collected four weeks after completion of consolidation therapy.

The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be applied for the coding of all adverse events (AEs) and serious adverse events (SAEs) that occur during the FOR*Ma*T trial that are categorised as "possibly-", "probably-," or "definitely-" related to study medications and/or interactions between study medications

and concomitant medications. "Good" tolerance will be defined as no adverse events occurring or only adverse events coded CTCAE grades 1 or 2. "Poor" tolerance will be defined as any adverse events coded as CTCAE grades 3, 4, or 5.

The primary outcome of the FOR*Ma*T Trial will be assessed as per the relevant appendices.

5 TRIAL CONDUCT

5.1 SITE INITIATION

The FOR*Ma*T Trial is a multicentre, international clinical trial and the initiation of the FOR*Ma*T Master Protocol (including the Appendices) will be staggered across trial sites. This staggered approach will allow the FOR*Ma*T Trial Management Team to closely examine the effectiveness of the FOR*Ma*T Trial Master Protocol. Any changes required to improve the trial processes can be shared and implemented in other trial sites prior to site initiation. The FOR*Ma*T Trial will open in Australia, and as feasible expand to other countries including centres in Europe, the United Kingdom, the Asia Pacific Region, Canada and North and South America. Site activation and initiation will be performed in accordance with the FOR*Ma*T Site Initiation and Activation SOP.

5.2 TRIAL DURATION

The FOR*Ma*T Master Protocol describes a standing platform trial with an innovative design tailored to the clinical setting that will enable new therapies to be tested as they become available. As such, there is no specific limit to the duration of the FOR*Ma*T trial while there is clinical need for the trial except for logistic issues which include trial funding. A detailed outline of the trial timeline for participants is described in the relevant appendix.

5.3 RECRUITMENT OF POTENTIAL PARTICIPANTS

Potential participants will be identified at study sites by the treating physician. Once identified, potential participants or their parent/guardian will be approached by the FOR*Ma*T Trial site-specific research team or treating physician to discuss the FOR*Ma*T trial and provided with the FOR*Ma*T Participant or Parent/Guardian Information and Consent Forms (PICFs). The FOR*Ma*T Trial site-specific research team members will allow participants and/or their parent/guardian adequate time to read the PICFs and an opportunity to ask any trial related questions and to have these questions answered to the satisfaction of the potential participant or their parent/guardian.

5.4 INFORMED CONSENT

5.4.1 CONSENT TO THE FOR*MA*T MASTER PROTOCOL

In accordance with the International Council for Harmonisation Good Clinical Practice Guidelines (ICH-GCP) and/or the Declaration of Helsinki, consent to the FOR*Ma*T Master Protocol will be obtained by the FOR*Ma*T trial site-specific research team prior to any study related procedures being performed or study data being collected. All

participants, regardless of whether they are enrolled in the Observational or Intervention Program are required to consent to the FOR*Ma*T Master Protocol. If the participant is under 18 years of age or unable to provide consent (due to severe cognitive impairment, an intellectual disability, or a mental illness, including patients with dementia) then informed consent will be obtained from the participant's parent/legal guardian in accordance with FDA guidance (40). Where it is expected that the subject population will not understand English, the written participant information and consent forms will be translated into the anticipated specific language that will be understood in accordance with FDA guidance (40). Participants who are enrolled and are under 18 years of age who turn 18 during the study period will require re-consent on the adult consent form. Telephone consent, re-consent, and re-consent via email will be acceptable (using the informed consent checklist outlined in the FOR*Ma*T Trial Site Manual of Operating Procedures (MoOP)) when face-to-face consent is not possible.

The FOR*Ma*T Master Protocol consent form is required to be signed and dated by the individual providing consent or the participant's parent/guardian where appropriate. A copy of the signed consent form will be given to the participant or their parent/guardian for their records with the original signed consent form(s) stored at the site in the participant's medical record and a copy of the signed consent form(s) stored in the participant's study file. Any Independent Review Board (IRB) / Independent Ethics Committee (IEC) / Human Research Ethics Committee (HREC) approved changes to the trial Master Protocol that affect the participant's rights and/or safety will require the participant's reconsent.

5.4.2 CONSENT TO SPECIFIC APPENDIX INTERVENTION PROGRAM(S), OBSERVATION, DISCOVERY SUB-STUDIES AND INTEGRATED STUDIES

If a participant meets the eligibility criteria for the FOR*Ma*T Appendices and/or specific sub-studies and integrated studies, additional appendix specific consent will be required in accordance with the procedures detailed above in section 5.4.1. Appendix specific consent requirements are detailed in the appendices. If additional sub-studies and/or integrated studies are added or removed from an appendix, or any changes are made to the appendix specific sub-studies and/or integrated studies, IRB/IEC/HREC approval for these changes will be sought. Reconsent will be required for additional trial specific procedures and changes that affect the participant's rights and/or safety.

5.5 CORE TRIAL PROCEDURES

Table 1 lists the special considerations that are applicable to Table 2 Core Trial Procedures and Schedule. Scheduling of core trial procedures (including collection time points) are detailed in Table 2 and in the Schedule of Assessment Tables in the relevant appendix.

Table 1 Special Considerations for Core Trial Procedures and Schedule

Symbol	Definition
A	Trial phases relate to various stages of treatment, participant cohorts and/or FOR*Ma*T substudies as outlined in the relevant appendices.
B	Start of trial phase, Interim and End of trial phase visits are required for FOR*Ma*T participants as per the Schedule of Assessments in the relevant appendices.
C	Participant reconsent is required with IRB/ IEC/HREC approved changes to the protocol that affect participants' rights and/or safety and/or if a child turns 18 years old during the trial and must reconsent as an adult participant.
D	MABS-PD status reviewed in accordance with the ATS criteria as per the Schedule of Assessments in the relevant appendices.
E	Respiratory Samples are required to be collected for FOR*Ma*T participants as per the Schedule of Assessments in the relevant appendices.
F	Participants unable to produce a sputum sample (expectorated or induced) to be marked as unproductive on the CRF.
G	If participants are unable to provide the minimum requested sputum samples as per the Schedule of Assessments in the relevant appendices, then a BAL sample is to be collected.
H	Adult participants require height to be recorded once only during the study (ideally at the Screening Visit).
I	Adult participants do not require weight to be measured at every visit.
J	Chest CT Scan at early withdrawal visit will only be requested if clinically indicated.
K	Safety/Toxicology Monitoring assessments are to be performed as per the Schedule of Assessments in the relevant appendices.
L	Specific Health Related Quality of Life questionnaires are required to be completed by FOR*Ma*T participants as per the Schedule of Assessments in the relevant appendices.
M	Six-minute walk test to be performed in participants ≥ 18 years of age only.

Table 2 Core Trial Procedures and Schedule

Assessments	Screening Visit	Start of Trial Phase [A]	Interim Visit(s)	End of Trial Phase [A]	Final Outcome	Early Withdrawal Visit
Clinic Visit	✓	✓[B]	✓[B]	✓[B]	✓	✓
Informed Consent [C]	✓					
Review Eligibility	✓					
MABS-PD Status	✓		✓[D]		✓[D]	✓[D]
Randomisation		✓				
Medication Review	✓	✓	✓	✓	✓	✓
Respiratory Sample	✓		✓[E/F/G]	✓[E/F/G]	✓[E/F/G]	✓[E/F]
Height [H] and Weight [I]	✓	✓	✓	✓	✓	✓
Spirometry	✓		✓	✓	✓	✓
Chest Computed Tomography	✓				✓	✓[J]
Physical Examination	✓	✓	✓	✓	✓	✓
Safety/Toxicology Monitoring [K]	✓	✓	✓	✓	✓	✓
Health Related Quality of Life Questionnaires [L]	✓		✓	✓	✓	✓
Costs Questionnaire	✓		✓	✓	✓	✓
Six-minute walk test [M]	✓		✓		✓	✓

5.5.1 RESPIRATORY SAMPLES FOR MICROBIOLOGY ASSESSMENT

Respiratory samples are to be collected for participants enrolled in either the Observational Cohort or the Intervention Program. The respiratory samples will be collected as per the relevant appendix.

Collection of respiratory sample(s) for the identification of MABS at screening may not be required if recent sample(s) have been provided by the participant, (within the specified time frames prior to screening stated in the relevant appendix) have been stored and are available as per the local laboratory guidelines (standard of care) to identify and diagnose MABS. If the screening sample has been stored, then the sample will be analysed retrospectively once consent to participate in the FOR*Ma*T trial is given.

All respiratory samples collected for MABS identification are to be sent to local pathology as per local guidelines.

Acceptable methods for collecting a respiratory sample for the microbiological assessment of MABS include:

5.5.1.1 Expectorated Sputum

Participants able to expectorate sputum are required to provide a 1ml expectorated sputum sample in a specimen jar or separate specimen jars if multiple samples are obtained. Specimen jar(s) are to be labelled and sputum samples processed in accordance with site specific pathology requirements for the detection of MABS.

5.5.1.2 Induced Sputum

Sputum induction is indicated for participants incapable of expectorating sputum. Prior to sputum induction a bronchodilator can be administered to minimise bronchospasm. Sputum induction should be conducted as per local guidelines.

5.5.1.3 Bronchoalveolar Lavage (BAL)

A BAL is indicated if an expectorated or induced sputum sample is unobtainable. Where possible, a six-lobe lavage should be collected. If six-lobe lavage is not feasible, a minimum two-lobe lavage from the area most affected on chest CT scan should be collected. All BAL samples are to be processed in accordance with site specific procedures.

5.5.1.4 Lung/Airway Biopsy

Lung/airway biopsy is only acceptable for the initial MABS diagnosis, but not as a routine method for MABS microbiological assessment throughout the trial.

Please note, cough swabs are not an acceptable respiratory sampling technique for the FORMaT Trial.

5.5.2 WHOLE GENOME SEQUENCING

All MABS-positive isolates cultured from the respiratory samples collected in the FOR*Ma*T Trial will be stored and deoxyribonucleic acid (DNA) extracted according to FOR*Ma*T DNA Extraction SOP. The extracted DNA from all samples will undergo whole genome sequencing (WGS) according to the FOR*Ma*T WGS SOP and/or local laboratory standard procedures). The genetic data generated from the WGS of MABS DNA will be stored by the approved collaborator in a mycobacterial genomic library.

5.5.3 CHEST COMPUTED TOMOGRAPHY

Chest CT will be performed at screening and at final outcome. If at screening a recent chest CT scan has already been performed (within 6 months of screening), as part of the standard of care diagnosis of MABS an additional chest CT will not be required. Any additional chest CT scans performed for clinical purposes at other time points while the participant is enrolled in the FOR*Ma*T Trial will also be collected as an outcome measure. Once consent is provided for the FOR*Ma*T trial these images will be accessed from the participant's medical records and included in trial analysis.

The site and scanner specific protocols for chest CTs as well as the evaluation of trial CTs are described in the relevant appendix. The site and scanner specific protocols are recommended to be used to perform the core trial chest CT scans where feasible at sites that are certified and trained to use the site and scanner specific protocols.

5.5.4 SPIROMETRY

Spirometry will be measured in all participants from three years of age in accordance with the American Thoracic Society and European Respiratory Society standards (41) and according to the appendix specific schedule of assessments where possible. The multi-ethnic global lung initiative (GLI) reference values for all spirometry indices will be applied to participants 3-95 years of age (42).

5.5.5 PHYSICAL EXAMINATION AND VITAL SIGNS

A physical examination of all body systems and vital signs will be completed in accordance with appendix specific schedule of assessments (where possible) and with assessment of any adverse event(s). A physical examination is to be completed by a site investigator or delegate. The physical examination includes a review of the following systems: head/neck/thyroid, eyes/ears/nose/throat, respiratory, cardiovascular, lymph nodes, abdomen, skin, musculoskeletal and neurological systems. Breast, anorectal, and genital examinations will be performed only when medically indicated. After screening, any new clinically significant abnormal findings in physical examinations will be reported as adverse events (AEs), see section 5.8.

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate and respiration rate will be assessed following a 5-minute rest in the seated or supine position.

5.5.6 SIX MINUTE WALK TEST

There are several modalities available for the objective evaluation of functional exercise capacity. The 6-minute walk test (6MWT) is a clinical exercise test that is tolerated by those with chronic respiratory disease and is reflective of activities of daily living. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (6-minute walk distance (6MWD)). The strongest indication for the 6MWT is to measure response to medical interventions in patients with moderate to severe heart or lung disease. Most 6MWTs will be performed before and after an intervention to determine whether the patient has experienced a clinically significant improvement. The change in 6MWD is expressed as an absolute value.

The 6MWT is to be conducted in adult participants only and performed according to the protocol in the ATS Statement: Guidelines for the Six-Minute Walk Test and/or local standard clinical practice guidelines (43). The ATS guideline includes absolute contraindications, relative contraindications and precautions to completing the test.

5.5.7 MEDICATION REVIEW

Current medication use including both prescription, over-the counter medication, herbal remedies and preparations will be recorded from time of consent until final outcome visit as per the schedule of assessments in the relevant appendix. Trade drug names, start and stop dates, dose, route, and indications for use should be recorded in the relevant Case Report Form (CRF).

5.6 QUALITY ASSURANCE (QA)

The FOR*Ma*T trial will be conducted in accordance with the current approved Master Protocol and Appendices. To improve Master Protocol adherence as well as ensure complete data entry, the following QA procedures will be implemented:

1. A FOR*Ma*T trial start-up meeting for research coordinators and site investigators prior to the submission of ethical approval and any other required approvals.
2. A Site Initiation Visit (SIV) once the FOR*Ma*T site has obtained ethics and any other required approvals, but prior to participant recruitment.
3. A CRF Completion Guide detailing all the data to be collected in the CRFs/electronic CRFs (eCRFs).
4. Regular and timely validation of entered data, queries and corrections by the FOR*Ma*T Trial Management Team.
5. Trial monitoring (onsite, remote, central, and/or local) as described in Section 7.7 Monitoring and according to the FOR*Ma*T Monitoring SOP and Monitoring Plan.

5.6.1 MICROBIOLOGY AND DNA EXTRACTION QA

Microbiology is of key importance and samples are processed in each of the participating countries in the local mycobacterial reference laboratories (MRLs). The FOR*Ma*T trial management team will work collaboratively with each MRL to ensure standard approaches for sample processing are followed where feasible.

5.7 NOTES ON SPECIFIC TRIAL VISITS

The timepoint definitions outlined below are overarching concepts that are applicable to each of the intervention studies described within the relevant appendices.

5.7.1 SCREENING

Screening is a window of time between the Date of Consent and the date of first randomisation in which a participant's eligibility into the trial is assessed and screening assessment data is collected according to the schedule of assessments in the relevant Appendices.

5.7.2 TIME POINT START TREATMENT (TPST)

Participants in the Intervention program(s) will commence on the treatment arm allocated by randomisation. Time Point Start Treatment (TPST) is defined as the date the participant undergoes the randomisation allocating a treatment arm. Each separate randomisation will have its own TPST as defined in the relevant appendix.

5.7.3 TIME POINT FINAL (TPF)

Participants will be reviewed at the end of each trial phase (Time Point Final (TPF)) and assessments will be performed as per the appendix specific schedule of assessments. Each treatment phase that follows a randomisation will have its own separate TPF as defined in the relevant appendix.

5.7.4 EARLY WITHDRAWAL VISIT

Participants who are withdrawn or who withdraw from the trial will be asked to attend an Early Withdrawal Visit. Where practical, all efforts should be made for the participants to complete the early withdrawal trial procedures detailed in the appendix specific schedule of assessments. Where possible, if there are any ongoing AEs these should be followed and monitored in accordance with the FOR*Ma*T Master Protocol irrespective of withdrawal from study.

5.7.5 UNSCHEDULED VISIT

Study visits that are conducted in addition to those listed in the appendix specific assessment schedule are known as Unscheduled Visits. If the Investigator deems that a participant should attend the study site to follow up an AE, repeat laboratory testing or any other study-related reason, then this visit should be documented in the FOR*Ma*T Research Electronic Data Capture (REDCap) database via the Unscheduled Visit CRF.

5.8 SAFETY MONITORING

Occurrence of AEs due to the underlying MABS infection and treatments used are well recognised and expected during the FOR*Ma*T trial. As such, AE monitoring procedures outlined in the relevant appendices will be implemented for participants enrolled in the Intervention Program or Observational Cohort. Toxicology monitoring procedures will be implemented for Intervention Program participants.

5.8.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward medical occurrence in a clinical investigation of a participant enrolled in FOR*Ma*T who may or may not be treated with an investigational product.

The Investigator will probe, via discussion with the participant, for the occurrence of AEs during each participant visit and record the information in the participant's medical record or source documents. AEs will be recorded in the AE or SAE eCRF. AEs will be described by duration (start and stop dates), severity, outcome, treatment, and relationship to study medication (where relevant), or if unrelated, the cause.

AEs will be collected from the time of informed consent until the final study visit.

All AEs will be reviewed by the FOR*Ma*T trial Pharmacovigilance Team and coded in accordance with the CTCAE version 5. For any AE that is unable to be categorised in accordance with the CTCAE, the independent data safety monitoring board (iDSMB) will be required to review and categorise the AE.

5.8.2 ATTRIBUTION OF ADVERSE EVENTS IN THE FOR*MA*T TRIAL

The relationship, or attribution, of an AE to the trial therapies will be determined by the Investigator. The relationship of the AE to the investigational product should be coded according to the following definitions:

Unrelated: The adverse event is clearly not related to the investigational product.

Unlikely: The adverse event is doubtfully related to the investigational product.

Possibly: The adverse event may be related to the investigational product.

Probably: The adverse event is likely related to the investigational product.

Definitely: The adverse event is clearly related to the investigational product.

5.8.3 DEFINITION OF SERIOUS ADVERSE EVENTS

SAEs will be defined as any untoward medical occurrence that:

1. Results in death.
2. Is considered life threatening (i.e., in the view of the Investigator the adverse experience places the participant at immediate risk of death from the reaction, as it occurred; it **does not** include a reaction that, had it occurred in a more severe form, might have caused death).

3. Requires hospital admission or prolongation of an existing hospitalisation.
4. Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions).
5. Is a congenital anomaly/birth defect.
6. Is an important medical event (i.e., when based upon appropriate medical judgment, the adverse experience may jeopardise the participant and may require medical or surgical intervention to prevent one of the above listed outcomes).

5.8.4 REPORTING OF SAFETY EVENTS

Study sites will document all SAEs that occur after informed consent is obtained until the final study visit in an SAE Report (whether or not related to study treatment). All SAEs will be reported to the FOR*Ma*T Trial Management Team within 24 hours of becoming aware of the event. Exclusions to the expedited SAE reporting include:

1. Infective exacerbation of an underlying lung condition requiring hospitalisation or home intravenous antibiotic treatment does not require expedited reporting to the FOR*Ma*T Trial Management Team;
2. Any planned and/or elective hospital admissions does not require expedited reporting;
3. Any planned and/or elective medical procedures does not require expedited reporting.

The site will complete and submit an initial SAE report form via the FOR*Ma*T trial database. Any follow up information about the SAE is to be reported on an SAE follow up report form and submitted in the FOR*Ma*T trial database as soon as relevant information is available.

All SAEs will be reviewed by the FOR*Ma*T trial Pharmacovigilance Team and coded in accordance with the CTCAE version 5. For any SAE that is unable to be categorised in accordance with the CTCAE, the iDSMB will be required to review and categorise the SAE.

Suspected unexpected serious adverse reactions (SUSARs) will be reported on the SAE form via the FOR*Ma*T Trial database. Urgent safety measures (USMs) and significant safety issues (SSIs) will be reported via email to the FOR*Ma*T Trial Management Team and submitted in the FOR*Ma*T trial database (if the USM or SSI is also an SAE). USMs, SSIs, and SUSARs are to be reported by the FOR*Ma*T Trial Management Team and/or the local site investigator to the relevant regulatory bodies within their required timeframes.

The FOR*Ma*T Trial Management Team, as the Sponsor delegate, will notify the Sponsor of all SUSARs, USMs and SSIs as required and submit an Annual Safety Report to the Sponsor. Site investigators are required to report all AEs that are related to study intervention(s) and/or interaction with study intervention(s) within 2 weeks of becoming aware of the event. All other AEs and laboratory abnormalities that are not related to study intervention(s) or interactions with study intervention(s) are to be reported to the FOR*Ma*T Trial Management by the end of specified TPF outlined in the relevant appendix.

Refer to FOR*Ma*T Safety Monitoring and Reporting SOP for detailed procedure(s) for safety reporting.

5.8.5 CODING OF ADVERSE EVENTS FOR ANALYSIS

CTCAE, version 5.0 will be applied for the database coding of all AEs including SAEs but only those categorised as at least "possibly", "probably", or "definitely" related to study medications and/or interactions between study medications and concomitant medications will be used to assess tolerance. Coding for analysis will be completed by the FOR*Ma*T Pharmacovigilance Team. Refer to section 4.6 for the definition of tolerance. Coding and grading is performed in accordance with the FOR*Ma*T Coding and Grading Work Instruction.

If an AE is unable to be coded and/or graded by the pharmacovigilance team or if coding/grading cannot be agreed upon, the iDSMB will be consulted to assess and code and/or grade the AE.

5.8.6 TOXICOLOGY THRESHOLDS

Toxicology monitoring will use the thresholds that match the grading from CTCAE, Version 5.0 as described in Table 3 and toxicity monitoring procedures for trial interventions will be as specified in the relevant intervention appendix. New interventions will require a separate toxicity monitoring plan including any requirements for central laboratory testing of samples.

5.9 PARTICIPANT WITHDRAWAL AND DISCONTINUATION OF TREATMENT

5.9.1 WITHDRAWAL OF CONSENT

All participants are free to withdraw from the study at any time, with or without a specified reason and without prejudice. Where possible, the participant or the participant's parent/legal guardian is required to sign the withdrawal of consent form, formally documenting the withdrawal process including the reason for withdrawal if they choose to provide this information. In the event of a participant withdrawing from the trial, an early withdrawal visit should be completed within the specified window of time from withdrawal if the participant is agreeable. If for any reason the participant is unable to complete the early withdrawal visit this should be noted on the Study Completion eCRF.

5.9.2 DISCONTINUATION OF TREATMENT

Participants enrolled in the Intervention Program can discontinue treatment at any time during the trial if:

- The participant is no longer able to comply with the FOR*Ma*T Master Protocol and relevant appendix, including completing required study assessments for safety requirements.
- The site investigator believes that treatment is no longer in the participant's best interests (due to safety or tolerance concerns).
- The participant no longer wants to continue treatment.

Participants discontinuing treatment prematurely but who do not withdraw consent or assent will be encouraged to continue with the trial according to the specific appendix intervention study and schedule of assessments in accordance with the relevant appendices with the final outcome respiratory sampling assessments to be prioritised.

Table 3: Safety critical monitoring thresholds

Investigations					
	Grade				
CTCAE Term	**1**	**2**	**3**	**4**	**5**
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal, ***or;*** 1.5 – 3.0 x baseline if baseline was abnormal.	>3.0 - 5.0 x ULN if baseline was normal, ***or;*** >3.0 - 5.0 x baseline if baseline was abnormal.	>5.0 - 20.0 x ULN if baseline was normal, ***or;*** >5.0 - 20.0 x baseline if baseline was abnormal.	>20.0 x ULN if baseline was normal, ***or;*** >20.0 x baseline if baseline was abnormal.	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Anaemia	Haemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN – 6.2 mmol/L; <LLN – 100 g/L.	Hgb <10.0 – 8.0 g/ dL; <6.2 – 4.9 mmol/L; <100 - 80 g/L.	Hgb <8.0 g/ dL; <4.9 mmol/L; < 80 g/L; transfusion indicated.	Life-threatening consequences; urgent intervention indicated.	Death
Definition: A disorder characterized by a reduction in the amount of haemoglobin in 100 ml of blood. Signs and symptoms of anaemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal, ***or;*** 1.5 – 3.0 x baseline if baseline was abnormal.	>3.0 - 5.0 x ULN if baseline was normal, ***or;*** >3.0 – 5.0 x baseline if baseline was abnormal.	>5.0 - 20.0 x ULN if baseline was normal, ***or;*** >5.0 – 20.0 x baseline if baseline was abnormal.	>20.0 x ULN if baseline was normal, ***or;*** >20.0 x baseline if baseline was abnormal.	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in the blood specimen.					
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal, ***or;*** >1.0 – 1.5 x baseline if baseline was abnormal.	>1.5 - 3.0 x ULN if baseline was normal, ***or;*** >1.5 – 3.0 x baseline if baseline was abnormal.	>3.0 – 10.0 x ULN if baseline was normal, ***or;*** >3.0 – 10.0 x baseline if baseline was abnormal.	>10.0 x ULN if baseline was normal, ***or;*** >10.0 x baseline if baseline was abnormal.	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					
Electrocardiogram QT corrected interval prolonged	Average QTc 450 - 480 ms	Average QTc 481 - 500 ms	Average QTc >= 501 ms; >60 ms change from baseline.	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia.	-
Definition: A disorder characterised by Electrocardiogram T wave amplitude changes.					

Investigations					
Grade					
CTCAE Term	**1**	**2**	**3**	**4**	**5**
Hearing impaired	**Adults** enrolled on a Monitoring Program (on a 1, 2, 4, 3, 6, and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear; **Adults** not enrolled on a Monitoring Program: Subjective change in hearing in the absence of documented hearing loss; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift >20 dB hearing loss (HL) (i.e., 25 dB HL or greater); sensorineural hearing loss (SNHL) above 4 kHz (i.e., 6 or 8 kHz) in at least one ear.	**Adults** enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear; **Adults** not enrolled on a Monitoring Program: Hearing loss with hearing aid or intervention not indicated; limiting instrumental ADL; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz in at least one ear.	**Adults** enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated; **Adults** not enrolled on a Monitoring Program: Hearing loss with hearing aid or intervention indicated; limiting self care ADL; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 2 to < 4 kHz in at least one ear.	**Adults**: Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); nonservicable hearing. **Pediatric**: Audiologic indication for cochlear implant; > 40 dB HL (i.e., 45 dB HL or more); SNHL at 2 kHz and above.	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures					
Leukocytosis	-	-	>100,000/mm^3	Clinical manifestations of leucostasis; urgent intervention indicated.	-
Definition: A disorder characterised by laboratory results that indicate an increased number of white blood cells in the blood.					
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 – 500/mm^3; <0.8 - 0.5 x 10^9/L	<500 – 200/mm^3; <0.5 - 0.2 x 10^9/L	< 200/mm^3; < 0.2 x 10^9/L	-

Investigations					
Grade					
CTCAE Term	**1**	**2**	**3**	**4**	**5**
Definition: A finding based on laboratory test results that indicate a decrease in the number of lymphocytes in a blood specimen.					
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9/L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9/L	<1000 - 500/mm^3; <1.0 - 0.5 x 10^9/L	<500/mm^3; < 0.5 x 10^9/L	-
Definition: A finding based on laboratory test results that indicate a decrease in the number of neutrophils in a blood specimen.					
Platelet count decreased	<LLN - 75,000/ mm^3; <LLN - 75.0 x 10^9/L	<75,000 - 50,000/ mm^3; <75.0 - 50.0 x 10^9/L	<50,000 - 25,000/ mm^3; <50.0 - 25.0 x 10^9/L	<25,000/ mm^3; <25.0 x 10^9/L	-
Definition: A finding based on laboratory test results that indicate a decrease in the levels of pancreatic enzymes in a biological specimen.					
Tinnitus	Mild symptoms; intervention not indicated.	Moderate symptoms; limiting instrumental ADL.	Severe symptoms; limiting self care ADL.	-	-
Definition: A disorder characterised by noise in the ears, such as ringing, buzzing, roaring or clicking.					
Vertigo	Mild symptoms.	Moderate symptoms; limited instrumental ADL.	Severe symptoms; limiting self care ADL.	-	-
Definition: A disorder characterised by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).					
Vestibular Disorder	-	Symptomatic; limiting instrumental ADL.	Severe symptoms; limiting self care ADL.	-	-
Definition: A disorder characterised by dizziness, imbalance, nausea and vision problems.					
White blood cell decreased	<LLN - 3000/ mm^3; <LLN – 3.0 x 10^9/L	<3000 - 2000/ mm^3; <3.0 – 2.0 x 10^9/L	<2000 - 1000/ mm^3; <2.0 – 1.0 x 10^9/L	<1000/ mm^3; <1.0 x 10^9/L	-
Definition: A finding based on laboratory test results that indicate a decrease in the number of white blood cells in a blood specimen.					

Adapted from CTCAE, version 5.0

5.10 DATA MANAGEMENT

5.10.1 DATA COLLECTION, ENTRY AND STORAGE

Trial data will be collected from various sources including, but not limited to, medical records, participant questionnaires, output from lab results, study assessments, correspondence and CT scans. These documents and any documents where data is first recorded for a participant will form the source documents. FOR*Ma*T trial site staff will be trained in the collection of the required data during the site initiation visit and data collection instructions will be stored in the site's electronic Investigator Site File (eISF).

The site investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of all trial data reported. All source documents are to be viewable in a neat, legible manner to ensure accurate interpretation of data. The site investigators will maintain adequate case histories of trial participants, including source documentation.

Sites will enter the data required for the trial directly into an eCRF located in a study specific Research Electronic Data Capture (REDCap) FOR*Ma*T database. Data for the eCRF will be obtained directly from the medical record or source documents.

Due to the adaptive design of the trial all **data is to be entered within 14 days from the specified TPF as defined in the relevant appendix unless otherwise stated (e.g. expedited AE/SAE reporting)** Data cleaning will be performed at regular intervals for the trial to ensure that the data are cleaned and ready for interim analyses.

The REDCap FOR*Ma*T database will be hosted on Murdoch Children's Research Institute (MCRI) infrastructure and is subject to the same security and backup regimen as other systems at the MCRI (e.g. the network file servers). Data is backed up nightly to a local backup server, with a monthly backup taken to tape and stored offsite. All data transmissions between users and the REDCap server are encrypted. Regular data quality checks, such as automatic range checks, will be performed to identify data that appear inconsistent, incomplete, or inaccurate.

Access to REDCap is managed by the system administrator. The permissions granted to each user within each REDCap project is controlled by and is the responsibility of the FOR*Ma*T trial management team. REDCap has functionality that makes adding and removing users and managing user permissions straightforward. REDCap maintains an audit trail of data created/updated/deleted that is accessible to project users that are granted permission to view it.

The SiteDocs Portal is an online tool hosted by TrialDocs Clinical Research Document Management and The University of Queensland (UQ) that is compliant with FDA requirements and General Data Protection Regulation (GDPR) which will securely host and track all key trial documents for the FOR*Ma*T Trial, including the electronic Trial Master File (eTMF). SiteDocs includes features such as version control, document protection, temporary remote monitoring access, alerts, archiving and a full audit trail of data and users.

Trial sites will have individual secure access to their site's eISF via SiteDocs, where protocols, templates, trial documents and correspondence will be hosted. Sites will be able to collaborate with the Sponsor and/or their delegate to upload site-specific clinical trial documents or deidentified participant documents to their eISF, receive notifications of changes and easily access the most up-to-date document versions.

Trial sites will have access to their own separate site-specific Portal for SiteDocs where they can upload and manage identifiable source documents. Sites will be responsible for granting access to their site-specific Portal, including temporary access to external monitors.

5.10.2 DATA STORAGE AND RETENTION

Each site is required to maintain source documents for a minimum of 15 years post completion of the trial. If site specific requirements or relevant legislation dictate data retention for periods longer than 15 years, trial sites will be required to adhere to these requirements.

6 STATISTICAL ANALYSIS PRINCIPLES

This section of the Master Protocol provides an outline and summary of the general statistical methods and principles used for FOR*Ma*T. The detailed statistical methods and sample size simulations relevant to each of the Intervention Programs and discovery studies are outlined in the relevant appendix.

6.1 BAYESIAN ANALYSIS AND BAYESIAN ADAPTIVE RANDOMISATION (BAR)

Interim monitoring for the Intervention Program in the FOR*Ma*T trial will use a Bayesian analysis approach (44). This approach will calculate the (posterior) probability of an intervention being found to be superior to the reference arm during the trial. As new data is generated the probability will be updated. This updating will occur at the time of the meetings of the iDSMB, who will have access to blinded and unblinded data and will ask the Trial Steering Committee (TSC) to ratify the updated blinded probabilities. Initially there are no plans to stop any arms of the study arms due to superiority, but such rules may be established as the trial continues and will be detailed in the relevant appendices. The iDSMB may however make a recommendation to the TSC about stopping current interventions if they show poor promise or futility. Stopping rules will be defined to guide the use of the posterior probabilities.

Adaptive randomisation allows intervention arm allocation ratios to be adapted based on interim analyses undertaken during the trial to favour the intervention arm with the highest posterior probability of success (45). This approach can lead to increased efficiency of the trial and reduce patient exposures to less promising or more toxic therapies compared with non-adaptive randomisation. In the FOR*Ma*T trial, BAR will be used for updating allocation probabilities in randomisations when there are more than two interventions being compared at any one of the randomisation stages. BAR will be implemented after every 60 participants have been randomised so that there is sufficient information available to determine the adaptation. Success of an intervention (and hence the adaptations) will be determined by the primary outcome; microbiological clearance with tolerability (refer to sections 1.1 Synopsis and 4.6 Trial Endpoints for definitions of clearance and tolerance).

6.2 RANDOMISATION

6.2.1 BLINDING OF TREATMENT ALLOCATION

The FOR*Ma*T trial may include placebo controlled double blind randomised interventions in the future, but the initial Intervention Program detailed in Appendix A1 is randomised and open label.

Each stage of the FOR*Ma*T intervention program(s) requires randomisation and is detailed in the relevant appendix. The allocated treatment must start on the same day as the randomisation where feasible, or as soon as possible after the randomisation has been performed. Any delays to starting an allocated treatment after randomisation has occurred must be reported to the FOR*Ma*T Trial Management Team.

6.3 MINIMISATION

To ensure balance between arms in important patient characteristics, randomisation at the different stages of the trial will use minimisation with a random element. Minimisation is a dynamic randomisation approach used in clinical trials to balance allocation to treatment arms with respect to a number of important stratification factors. In minimisation, the first participant is allocated to their treatment arm at random. Subsequent participants are assigned to a treatment arm by first selecting the preferred arm that would best improve the balance of participants across the arms based on the stratification variables of interest in terms of the numerical difference in the sample size in each of the treatment arms across all of the stratification factors (46, 47). The preferred arm is then selected with a probability of 0.7, with rest of the probability split between the alternative arms.

Following updating the randomisation allocations through BAR, minimisation will be conducted using Biased Coin Minimisation (BCM) (48). Under this method, the same methodology as standard minimisation will be used to determine the preferred intervention, but the randomisation probabilities will be altered to reflect the minimisation probabilities and the updated allocation ratios from the BAR as detailed in Han et al (48).

Randomisation will be conducted electronically through the trial database following completion of all the specific required data entry by the study team at each site. Participants will be randomised according to the stratification criteria described below using to the weights specified for each factor:

1. Macrolide resistance*: Yes or no (weight = 50% in randomisations 1 and 2 (Randomisation-Short Intensive (R-SI) and Randomisation-Prolonged Intensive or Immediate Consolidation (R-PI/IC), respectively), 25% in randomisation 3 (Randomisation-Consolidation (R-Con))).

   Any of these measurement methods are acceptable for defining macrolide resistance (in order of preference):

   a. Inducible at 14 days or constitutive at 3 days, and/or;
   b. *Erm*(41) status: Functional or dysfunctional, and/or;
   c. MABS subspecies: *M. a. abscessus* & *M. a. bolletii* combined or *M. a. massiliense*.
2. Age: <12 years, 12-30 years and >30 years of age (weight = 20%).
3. Sex: Male or Female (weight = 7.5%).
4. Location: Asia Pacific as one stratum (includes Australia, New Zealand, Singapore and other Asian Pacific countries), United Kingdom and Republic of Ireland as one stratum, Europe as another stratum (includes

Denmark, France, Netherlands), and Canada and the Americas as one stratum (weight = 7.5%). Parts of the world not listed above can be added into the regions based on closest proximity to the regions longitudinally.

5. Cystic Fibrosis Status: Yes or no (weight = 7.5%).
6. Mixed NTM infections at enrolment: Yes or no (weight =7.5%).
7. MABS positive culture (at initial randomisation to intensive therapy (R-SI) and for R-PI/IC all participants will have a positive culture, so this factor will not be required. However, it will be required for R-Con): Yes or no (weight = 25%).

6.4 ADDING AND STOPPING INTERVENTIONS

New interventions, which may include new therapeutics or new timelines either during the intensive or consolidation phase, may be added as a treatment arm either for the intensive or for the consolidation phase as determined by the trial Drug and Intervention Selection committee (DISC) with approval of the TSC. No new therapies will be added until at least 60 subjects have completed the trial phase associated with the proposed new intervention.

Interventions may be stopped early due to a lack of benefit at interim analyses. Interim analyses will be conducted after every 60 participants have completed the trial phase. The statistical team, acting in confidence, will present the results from such analyses only to the iDSMB who will provide guidance around stopping particular interventions. Pre-defined triggers for stopping an intervention will be specified for both intensive and consolidation interventions separately, and for the combination of intensive and consolidation. If a single intervention, or combination of interventions, has less than a 0.01 posterior probability of being an optimal intervention in that phase then that intervention will be regarded as inferior and should be recommended to be discontinued.

For new interventions in the future, if an intervention has a high posterior probability (to be pre-specified prior to the new intervention being added) of being an optimal therapy this invention will be considered as superior, in which case the iDSMB might recommend that the randomisation stage be stopped for superiority. Stopping rules for superiority will be detailed in the relevant section of the appendices. Following the iDSMB meeting, the recommendations from the iDSMB will be notified to the Trial Management Committee (TMC) and TSC. The TSC will consider the recommendations and make a decision regarding the potential to stop the randomisation stage for superiority. If any interventions are stopped, the TMC will have the responsibility of developing a public disclosure as is practical through presentation of results and publications.

6.5 SEAMLESS PHASE II TO PHASE III

The FOR*Ma*T platform trial provides a resource to enable promising therapies to be more rapidly evaluated and has the potential to facilitate seamless transition from Phase II to a Phase III study. Initially the platform will support a phase II study, but new interventions being evaluated in the future may be considered for the potential to move seamlessly from this Phase II study to a Phase III (49). The principles guiding this move will include planning for the potential of Phase III in the design of the Phase II study and with agreement between the Platform trial team and sponsors of the new therapy around management and access to data. The move to a Phase III trial will be guided by a pre-defined threshold for the probability of a successful intervention during phase III, which would need to be

established in planning the Phase II trial and agreed to by regulatory authorities for pivotal studies. If a seamless transition to Phase III is considered feasible, the TMC along with the trial statistics team will provide the iDSMB and TSC with a Phase III proposal, and if this is approved by the iDSMB and TSC then further recruitment to the target number determined would be undertaken.

6.6 SIMULATIONS AND STATISTICAL POWER

The design (including stopping rules**)** and sample size of each intervention program will be informed by simulations using Monte Carlo methods to give a range of power according to different scenarios and taking into account the probabilities of variable responses to intensive and/or consolidation interventions. Simulations will be updated with the addition of any new interventions. The details of these simulations can be found in the relevant appendix.

6.7 GENERAL ANALYSIS PRINCIPLES

The analyses will be conducted according to the statistical analysis methods described in the relevant appendices, statistical principles appendix and the statistical analysis plan.

7 STUDY OVERSIGHT

7.1 OVERVIEW

The FOR*Ma*T Trial will have several committees established to provide oversight of the FOR*Ma*T Trial.

7.2 TRIAL STEERING COMMITTEE

The TSC is the executive decision-making group and provides overall supervision of the FOR*Ma*T trial. The Terms of Reference (available on request) outlines the roles and responsibilities of the TSC members. Membership to the TSC will consist of independent and non-independent members from a variety of backgrounds including clinical and statistical as well as a member from the general community. The Chair of the TSC will be independent of the FOR*Ma*T Trial.

7.3 INDEPENDENT DATA SAFETY MONITORING BOARD

The iDSMB will review interim analyses, monitor for effectiveness and safety, along with trial conduct. They will meet prior to the commencement of the trial at least annually and at the time of interim analysis after every 60 participants have completed each stage of the trial. The iDSMB will provide advice to the TSC and the Trial Management Committee (TMC). The iDSMB Charter (available on request) outlines the roles and responsibilities of the iDSMB members. Membership to the iDSMB will consist of clinicians and statisticians who are independent of the FOR*Ma*T Trial.

The iDSMB will be responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review and voting procedures prior to initiating any data review. The iDSMB will be responsible for

maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

The iDSMB will review each version of the FOR*Ma*T Master Protocol (including any new or updated appendices). During the trial, the iDSMB will review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, iDSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The iDSMB will also assess the performance of overall study operations and any other relevant issues, as necessary.

Items to be reviewed by the iDSMB may include:

- Interim/cumulative data for evidence of study-related AEs.
- Interim/cumulative data for evidence of efficacy and futility according to pre-established statistical guidelines.
- Data quality, completeness and timeliness.
- Performance of individual centres/countries.
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities.
- Adherence to the protocol.
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol deviations, unmasking, etc.).
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.
- AEs that are unable to be categorised by the FOR*Ma*T Pharmacovigilance Team in accordance with the CTCAE.

The iDSMB will conclude each review with their recommendations to the TSC and the FOR*Ma*T Chief Investigator (CI) as to whether the study should continue without change, be modified, or terminated. Recommendations regarding modification of the design and conduct of the study could include:

- Modifications of the Master Protocol (including appendices) based upon the review of the safety data.
- Suspension or early termination of the study or of one or more study arms because of serious concerns about subjects' safety, inadequate performance or rate of enrolment.
- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines.
- Corrective actions regarding a study centre whose performance appears unsatisfactory or suspicious.

Confidentiality must always be maintained during all phases of iDSMB review and deliberations.

Meeting sessions can be either open or closed at the request of the iDSMB Chair or may involve periods of each. The lead investigators of FOR*Ma*T can attend the open session along with other investigators as requested.

The closed session will only include the iDSMB members who have voting rights and they will formulate recommendations regarding the study to the TSC. The FOR*Ma*T CI may be invited to the closed session to present an update of the trial but will not be present for any other agenda items.

Reports will be provided to iDSMB that include an open report and a closed report. Reports for the iDSMB will be prepared by the Clinical Epidemiology and Biostatistics Unit at MCRI.

Open reports will include information on the study conduct such as accrual data, demographics and baseline characteristics, site performance and protocol compliance and quality control issues along with general toxicity and safety data presented across the study as a whole with no reference to treatment arm.

Closed reports will include the same data as the open reports as well as data on efficacy outcomes at the time of each interim analysis (every 60 patients in randomisation levels with more than two interventions) and will be presented by (masked) treatment arm.

Reports from the iDSMB will provide details of any items that require urgent action as well as any recommendations made by the iDSMB and will be provided to the FOR*Ma*T CI and the TSC and notified to other participating organisations as well as to the IRB/IEC/HRECs involved.

7.4 TRIAL MANAGEMENT COMMITTEE

The Trial Management Committee (TMC) is responsible for reviewing the day-to-day management of the trial and assist the FOR*Ma*T project team with any issues that arise during the study, as well as provide advice to the TSC and iDSMB where relevant. The TMC will include the FOR*Ma*T Trial CI, the Senior Trial Project Managers, appropriate representatives across all the key areas (Statistics, Database, Pharmacovigilance, Drug and Intervention Selection Committee (DISC), and Microbiology), and a representative from each participating country or region. To facilitate and ensure adequate communication across the large number of team members and a wide geographic spread, information from the TMC may be shared on the FOR*Ma*T trial website and SiteDocs. The TMC will report to the TSC. Day-to-day management will be overseen by the FOR*Ma*T CI, the senior trial project managers and the core trial clinical lead physicians. A Terms of Reference (available on request) outlines the roles and responsibilities of the TMC.

7.5 FOR*MA*T PHARMACOVIGILANCE TEAM

All AEs and SAEs will be reviewed by the FOR*Ma*T Pharmacovigilance Team and coded in accordance with the CTCAE, version 5.0. Members of the FOR*Ma*T Pharmacovigilance Team include:

- Senior Clinical Pharmacist (Lead).
- Non-independent senior paediatric physician.
- Non-independent senior adult physician.
- FOR*Ma*T Trial database representative (if required).
- Statistician (If required).

For further detail refer to the Pharmacovigilance Team Terms of Reference (available on request).

7.6 DRUG AND INTERVENTION SELECTION COMMITTEE (DISC)

The DISC includes the DISC chair, FOR*Ma*T CI, FOR*Ma*T Trial Management Team, a representative from each participating country and experts external to the trial. The role of the DISC includes assessment of new intervention or therapies to be considered for inclusion in a new Intervention Program. The DISC will provide a report supported by the Statistical Analysis Team and reviewed by the trial management team, for consideration by the TSC and if approved will lead to a new therapy program being included. For further detail refer to the DISC Terms of Reference (available on request).

7.7 CONSUMER ADVISORY GROUP (CAG)

The purpose of the FOR*Ma*T consumer advisory group (CAG) is to provide a consumer and community perspective to various aspects of the FOR*Ma*T trial. This includes advice on participant facing documents such as consent forms, future research plans including proposals for new treatments to be added to the study, grant applications requesting funding support for the study, and lay summaries of the study and any study results. Members of the CAG may also be invited to join various trial committee meetings to provide their perspective.

7.8 MONITORING

The Sponsor and its delegates will have overall responsibility for monitoring. An SIV will occur prior to sites commencing the recruitment of trial participants. The purpose of the SIV is to train site investigators and local study coordinators with regards to the Master Protocol, the Appendices, data entry, management of trial documentation, and safety monitoring and reporting. The site will be activated once the SIV has been presented and all the essential documentation from the local site has been collected according to FOR*Ma*T Site Initiation and Activation SOP. Monitoring visits will ensure that the study is being conducted according to good clinical practice (GCP), the Master Protocol and relevant appendices, that study participants' safety, rights and well-being are being protected and that data entry is accurate and verifiable from source documentation. These will be conducted via central, remote, local or on-site monitoring. Visits may be conducted either face-to-face or through on-site electronic facilities, at intervals specified in the FOR*Ma*T Trial Monitoring SOP and Trial Monitoring Plan. The FOR*Ma*T trial will accommodate any requests to be audited by ethical, regulatory and/or other relevant authorities.

8 ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

The trial will be conducted according to the Declaration of Helsinki, the International Conference on Harmonization - Good Clinical Practice E6 (ICH-GCP) and with the laws and regulations of the country in which the research is conducted, whichever represents the greater protection of the individual.

8.1 RESEARCH ETHICS APPROVAL AND SITE-SPECIFIC GOVERNANCE

Prior to trial initiation the FOR*Ma*T Master Protocol, appendices, information sheets and consent forms, trial questionnaires and any other patient facing material will be reviewed and approved by the relevant IRB/IEC/HREC

for each participating country and/or site. Approved delegates will keep the IRB/IEC/HREC informed as to the progress of the trial and comply with annual reporting requirements.

The IRB/IEC/HREC must approve any revisions to FOR*Ma*T trial documents and be informed of any serious and/or unexpected AEs occurring during the trial as required and of any new information that may adversely affect the safety of the participants or the conduct of the trial. Reporting requirements are to be adhered to in accordance with local IRB/IEC/HREC and additional site-specific requirements.

8.1.1 FOR*MA*T MASTER PROTOCOL AND TRIAL DOCUMENT AMENDMENTS

Any amendments to the approved IRB/IEC/HREC FOR*Ma*T trial documents may not be initiated without prior written IRB/IEC/HREC approval except when necessary to eliminate immediate hazards to the participants. Amendments will be submitted in writing to relevant IRB/IEC/HRECs and written approval will be obtained before the updated version is implemented.

8.1.2 PROTOCOL DEVIATIONS

A protocol deviation occurs when there is any deviation from the study procedures or treatment plans as specified in the IRB/IEB/HREC approved protocol. Examples of protocol deviations may include non-compliance with GCP, study visits outside of set windows and missing assessments outlined in the protocol. Participants enrolled in the intervention cohort where protocol deviations have occurred involving modifications to the study drug regimen are able to continue to be enrolled and assessed for the remainder of the study.

Protocol deviations may be minor or major. Minor protocol deviations do not carry significant ethical or administrative consequences. Major protocol deviations are those that affect participant's rights, safety or wellbeing and/or accuracy and reliability of the study data. An example of a minor protocol deviation is visit non-compliance (i.e. study visit and assessments are conducted outside of the required timeframe, or a procedure is missed) and there are no participant safety concerns.

Examples of major protocol deviations include:

a. Randomisation of an ineligible participant.
b. Visit non-compliance (e.g., study visit and assessments are conducted outside of the required timeframe, or visit or assessment is missed) and there are participant safety concerns.
c. Dispensing or dosing error of IMP.
d. Not reporting SAEs.

When a major protocol deviation occurs, it will be discussed with the site investigator(s) and site PI and a Protocol Deviation Form detailing the deviation will be generated. This form, outlining the major protocol deviation, will be signed by the site investigator. A copy of the form will be filed in the investigator site file and details of the deviation will be entered onto the study database.

8.1.2.1 Reporting Requirements

Minor protocol deviations do not need to be reported to the lead IRB/IEB/HREC at the time they occur. All minor deviations must be recorded in the protocol deviation log and reported to the Sponsor (if applicable).

Major protocol deviations may need to be reported to the lead IRB/IEC/HREC and to the Sponsor (if applicable) as per local requirements and a protocol deviation form detailing the event completed. The protocol deviation CRF is to be completed, signed by the site investigator, and entered in the database.

All protocol deviations (major or minor) must be recorded in a protocol deviation log and reported as per local ethical and regulatory requirements.

8.2 CONFIDENTIALITY

The Investigator must ensure that a participant's anonymity will be respected throughout the study and that their identities are protected from unauthorised parties. A participant's privacy and confidentiality will be maintained by the assignment of a unique identification number. On CRFs and other documents submitted to review committees and the Sponsor participants will not be identified by their names, rather their unique identification number. These numbers will be used to collect, store and report participant information, including in the trial database. The local site should keep a Subject Identification Log showing codes, names and dates of birth of the participants. Confidentiality and protection of data will be maintained according to local regulatory requirements. All information disclosed or obtained during the trial is confidential. The site PI and any person under his/her authority must maintain this confidentiality and must not disclose the information to any third party without the prior written approval of the CI.

8.3 SITE REIMBURSEMENT

Sites will be reimbursed according to each participating site's contract. Please see the relevant appendix for further information.

8.4 DATA SHARING

All de-identified raw data measured during the trial will be made available on request to relevant regulatory authorities, recognised academic institutions and clinical teams. Deidentified, aggregated data sets will be hosted on an approved public research data platform. Data requests must be made in writing with a proposal for data usage to the CI. Upon the approval for data sharing by the CI, the requester will be required to sign a data agreement.

8.5 PUBLICATION POLICY

The results of this trial (positive, negative and/or inconclusive) will be published and/or presented at scientific meetings. The preparation and submission for publication of manuscripts containing the trial results shall only be done if prior consent is obtained by the CI. Any manuscript requests can be submitted to the FOR*Ma*T Trial

Management Team. Authorship will be granted according to the recommendations from the International Committee of Medical Journal Editors (ICMJE)(50).

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