STUDY PROTOCOL

Investigation of nasal deposition using a nasal mesh nebuliser

Short title: Nasal Deposition by NMN
Protocol number: RT16-NMN-V01 / AFT-MD-01

Test device: Nasal Mesh Nebuliser
Study Sponsors: AFT Pharmaceuticals PTY Ltd

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Co-Investigators:	A/Prof Daniela Traini Prof Paul Young Prof Dale Bailey
Sponsors representative:	Dr Brendon Woodhead Dr Ioana Stanescu

Version :	2
Date:	27 July 2016

STATEMENT OF COMPLIANCE
This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

Investigator Agreement

Certain responsibilities devolve to the Principal Investigator (notably those of signing the Statutory Declarations related to the Ethics Committee, the requirement to retain records, and oversight and governance of the study). Other responsibilities apply to all named co-investigators.

I have read and understand the protocol and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will personally conduct the study as described, with the assistance of co-investigators and study personnel.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel responsible to me who will participate in the study. Together with the Sponsor, I will arrange briefing sessions and will discuss the protocol with them, to assure myself that they are appropriately informed regarding the investigational device, the radio-labelled saline, the efficacy and safety parameters and the conduct of the study in general. I agree to make all reasonable efforts to adhere to the attached protocol. I understand that this protocol will be submitted to the regulatory authorities by the Sponsor, as appropriate. I agree to allow Sponsor monitors and auditors full access to all medical records at the research facility for participants screened or randomised in the study. In return the Sponsor agrees to undertake audits regularly and assist me in identifying any deficiencies in the conduct of the study as early as possible, and in instituting appropriate measures to address these.

I agree to provide all participants with informed consent forms, as required by government and ICH regulations. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol and FDA regulation, 21 CFR 312.64.

Principal Investigator 's Name (printed)	Signature	Date
Name (printed)	Signature	Date
Name (printed)	Signature	Date
Name (printed)	Signature	Date

Contents

1.0 Investigators and facilities

1.1 Study locations

This project will be conducted at Royal North Shore Hospital (RNSH). Recruitment of patients will occur via the RNSH.

1.2 Study management

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1.3 Funding and resources

Project funding will be provided by the WIMR Respiratory Technology Group. AFT Pharmaceuticals will supply the Nasal Mesh Nebuliser (NMN) clinical prototype and provide technical assistance in operating and maintaining the device as well as site monitoring.

2.0 Introduction and background

2.1 Chronic Sinus Infection (CSI)

Chronic sinus infection (CSI) occurs regularly in patients with chronic rhinosinusitis. When the normal draining of sinuses is obstructed by swelling, excessive mucus, or an abnormality in the structure of the sinuses, aerobic and anaerobic bacterial 'set-up-shop' and establish biofilm colonies [1, 2] that are difficult to remove with current therapies. In many cases surgical intervention is required. CSI results in hyper-mucosal secretion, inflammation and severe discomfort and pain. Astonishingly, CSI affects a large percentage of the population with an estimated 1.9 million Australians being diagnosed in 2010–11 [3]. Symptoms are prevalent in 16% of the general population [4, 5], with acute sinusitis occurring in up to 4.6% of young adults [6].

Limitation of current therapies: There is no current marketed nasal aerosol medicine for the treatment of CSI, or an efficient device capable of specific targeting. Current non-surgical approaches to CSI treatment include the administration of bolus antibiotics, mucolytic and steroids. Administration is either conducted using nasal pumps or modified nebulisers; originally developed for 'lung-targeting'. These approaches result in virtually no access to the target site, and thus limited therapeutic efficacy.

2.2 Nasal Mesh Nebuliser device

The Nasal Mesh Nebuliser (NMN) device has been developed by AFT Pharmaceuticals and has shown to be highly efficient at generating an aerosol of suitable size for nasal drug delivery and therefore has the potential to be used as a delivery system to treat chronic sinusitis and other nasal infections. Furthermore, previous researchers have established that a pulsed aerosol is required for efficient nasal delivery [7, 8]. It has been demonstrated that it is possible to generate a pulsed frequency 'cloud' suitable for para-sinus targeting using the AFT NMN. The main competitor to the AFT NMN with this capability is PARI SINUS® (PARI, Starnberg, Germany), which only achieves ca. 6.5% sinus deposition [9], has long dosing times (4 min/nostril [10]) and a high potential for lung deposition. However, the

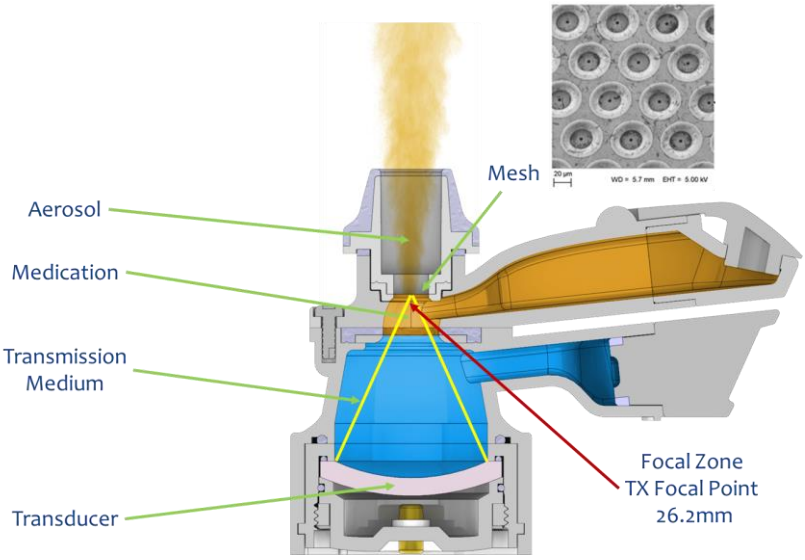


Figure 1: Operating principle of the CSI-NMN device. In-house prototype schematic.

NMN, can deliver a dose quickly (10mL/min) with a particle size suited for nasal deposition (i.e. ≥ 10 μm) and has the potential for a high sinus deposition. Furthermore, by varying the pulsation frequency (PF) sinus and nasal deposition may also be optimised.

The NMN (Figure 1) works on the principle of focusing ultrasonic energy via a 880 kHz transducer into a liquid formulation that is enclosed behind a thin palladium alloy film containing thousands of micron-sized holes. Cavitation within the formulation causes a 'sono-capillary effect' [11], essentially extruding droplets through the mesh orifices to produce a dense aerosol with particles of suitable size for nasal deposition. The device can operate over short time frames and has been designed to emit the aerosol during the patient's exhalation, via a mouthpiece actuator (Figure 2A); avoiding any potential lung inhalation of medicament. Importantly, the pulse frequency (1-500 Hz) of the device can be adjusted easily to help control dosing to enhance sinus delivery.

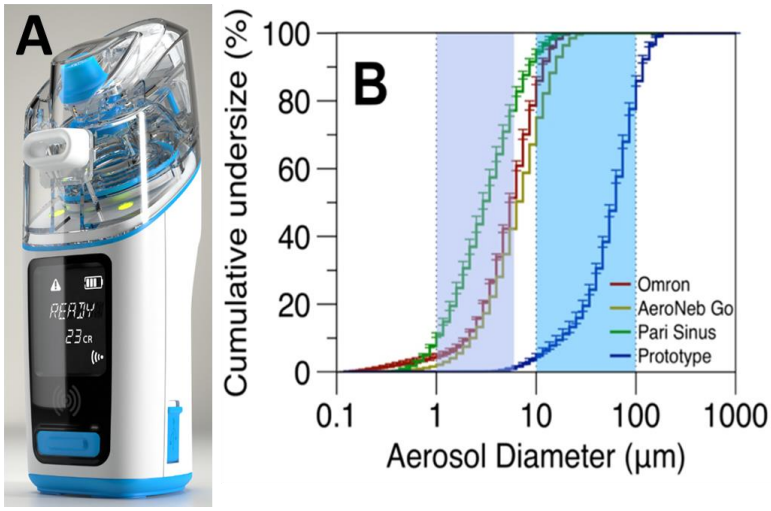


Figure 2: (A) concept of final clinical device prototype (B) cumulative aerosol particle size distribution of PARI SINUS and other commercially available nebulisers vs. the NMN prototype. Purple and blue regions correspond to optimal particle sizes for lung and nasal deposition, respectively. (n=5 ± StDev).

Preliminary study: In-line laser diffraction studies, using the development-prototype NMN (Figure 2A), have shown that a narrow particle size can be achieved which is suitable for nasal drug delivery (Figure 2B). In general, the median particle diameter of isotonic saline after 3 seconds operation was 53.9 μm ± 2.6 μm. This is in comparison to 2.75 μm ± 0.15 μm for the PARI SINUS. Under these conditions, the output rate was 20x that of the PARI SINUS. Additionally, two other commercial nebulizers were tested (Omron® and AeroNeb-Go®) and it was shown that they were also not suitable for nasal deposition (Figure 2B). Subsequently, the effect of pulsation frequency (Hz) on aerosol generation and particle size using the NMN device has been investigated and shown that changing the pulse frequency had little effect on aerosol size, measured by laser diffraction (Figure 3A).

Using a commercially available silicon cast of the human upper respiratory tract (Koken LM005, Koken Ltd, Tokyo, Japan; also referred to in this study as 'Boris') (Figure 3B), the effects of pulsative frequency and orifice size of the mesh on nasal deposition were evaluated.

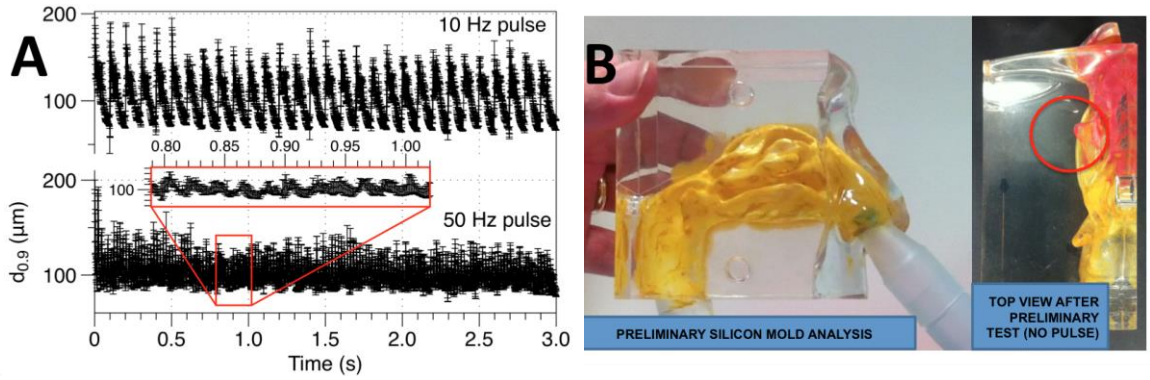


Figure 3: (A) Influence of pulse frequency at 10 and 50 Hz on aerosol particle size over a 3-second period. $D_{0.9}$ represents diameter of 90th percentile cumulative size distribution. (n=5± StDev). (B) Assembly (left) and testing of prototype NMN (right) in nasal cast model. Yellow water sensitive coating reacts with saline and turns red upon contact. The circled region in top view highlights the maxillary sinus inlet.

Preliminary studies using the Boris model (Figure 4) indicated these particles were deposited within the nasal cavity, with no observable oral-pharynx deposition. It also demonstrated that by applying different pulsative frequencies different nasal deposition profiles could be achieved but these observations need to be confirmed *in vivo*.

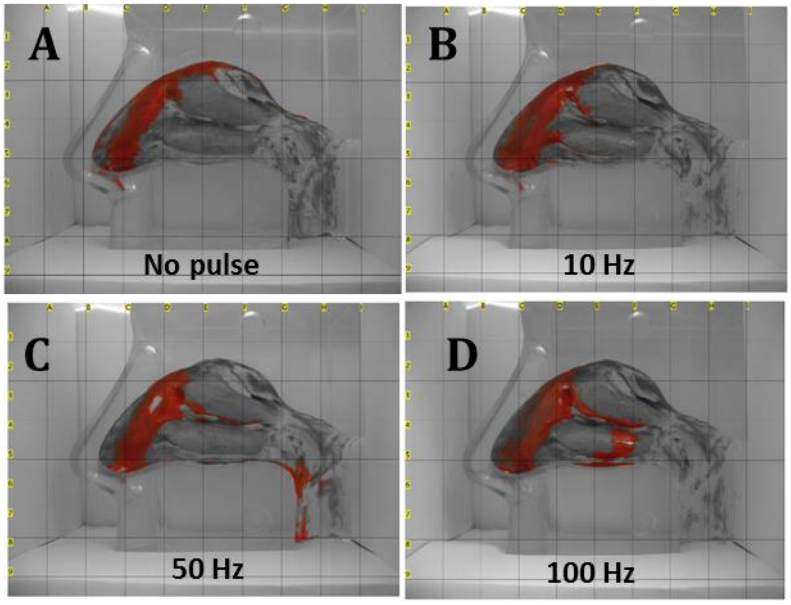


Figure 4: Assembly and testing of prototype NMN in nasal cast model with different pulsative frequency: (A) no pulse frequency (continuous delivery mode) (B) 10 Hz pulse frequency, (C) 50 Hz and (D) 100 Hz. Red areas indicate saline deposition from NMN device using a water indicating gel for a delivery volume of 0.33 mL

2.3 Rational for current study

The proposed study aims to investigate the regional deposition in the nasal cavity of aerosols generated from the clinical NMN prototype using different pulse frequency modes. Information from this study will be used to aid in determining the optimal

deposition settings for future targeting of medication to the sinuses and within the nasal cavity.

Once beyond the nasal valve, the deposition pattern within the nasal cavity is vitally important. Deposition on middle meatus is of particular significance as this is the location of the ostiomeatal complex, a group of structures that receive drainage from the anterior and medial ethmoid cells, the frontal sinus and the maxillary sinus. Other important sites include the ostia of the sphenoid and posterior ethmoid sinuses, which are located superoposteriorly to the ostiomeatal complex on the sphenoethmoid recess and superior/supreme meatus, respectively. Improving the deposition to these regions is of clinical importance as it would translate into improved therapeutic effects in CRS, including patients that have undergone Functional Endoscopic Sinus Surgery (FESS).

To evaluate this, radio-labelled aerosols of a saline solution will be delivered using the clinical NMN prototype and sequential imaging will be performed using Single-photon emission computed tomography (SPECT) or positron emission tomography (PET) (depending on accessibility and availability of equipment in the hospital) and gamma scintigraphy imaging. Simultaneously, hHigh resolution computed tomography (CT) scans of the nasal and sinus anatomy will be obtained from all participants and used as templates for overlaying subsequent deposition data to provide a detailed assessment of deposition characteristics.

Four different pulse frequency settings will be evaluated including: A) no pulse frequency (continuous delivery mode), B) a 10 Hz pulse frequency C) a 50 Hz pulse frequency and D) a 100 Hz pulse frequency based on preliminary *in vitro* studies and those investigated by other researchers [9].

Furthermore, the high-resolution head CT scan data from the participants will be used to generate an anatomically correct model of the upper respiratory tract that includes the sinus cavities. While there are several models of the upper respiratory tract available in the literature [12, 13] and commercially available cast models, such as the Koken LM005 silicon cast referred to as 'Boris' in our earlier studies, these models do not contain the sinus regions and are generally not suitable for routine deposition analysis to evaluate sinus delivery.

The CT scan data will enable the development of a representative nasal cast that includes sinus structure allowing for realistic *in vitro* simulation and optimization for sinus delivery in the future.

Royal North Shore Hospital has a well-established research group using 3D imaging techniques (SPECT/PET) and gamma scintigraphy imaging to assess lung physiology and regional ventilation distribution and CT to determine morphological changes in the respiratory tract with multiple published studies in the field [14-16].

The intent of the present study is to provide evidence and demonstrate that the NMN device will be able to effectively and efficiently target the sinus region of the nasal

cavity. Results from the proposed study will be intended to support the registration of the device for use with a range of currently available medicaments that targets the nose.

3.0 Study objectives and endpoints

3.1 Study hypothesis

It is hypothesised that increasing the pulsative frequency (0-100 Hz) produced by the NMN device will improve deposition within the sinuses.

Statistical consideration

This is an exploratory study using a new clinical NMN prototype to determine the regional depositions in the nasal cavity of aerosols using different pulse frequency modes in healthy volunteers. It is also of interest to determine whether the new NMN prototype will achieve higher deposition (>6%) compared to previous similar clinical studies using other devices. Specifically, in a study by Moller et al [9], about 6.5% of activity deposited in the nasal cavity was detected in the sinus of five healthy volunteers using new PARI VibrENT nebulizer system.

A previous study that investigated the temporo-spatial deposition of saline delivered by a squeeze bottle, nasal saline spray and nasal gel, enrolled 5 healthy subjects [17]**.** Similarly, a PARI VibrENT nebulizer system that evaluated the pulsating aerosol (fixed frequency of 25 Hz) to the sinuses was conducted with five healthy volunteers [9]. Taking into account that four different pulse frequencies are evaluated, a sample size of minimum 10 subjects will be sufficient for this pilot study. It should be noted that all recruited participants will be randomised to receive radiolabelled saline generated with all four different pulse frequencies settings.

3.2 Primary objective and endpoint

The main objective of the study is to determine the optimal frequency for the NMN that will provide the basis for future *in vivo* sinus targeting of drug delivery systems. The primary endpoint of this study is the total area of distribution (mm^2) of radiolabelled saline immediately after administration by the NMN (T_0) in the different regions of the sinus cavity.

3.3 Secondary objectives and endpoints

The secondary objectives are:
1) To generate an anatomically correct model of the upper respiratory tract that includes the sinus cavities (maxillary, frontal, ethmoidal, sphenoidal) and that could be used for in vitro optimisation study of sinus delivery formulation in the future.

It is expected to obtain from all participants a high-resolution CT scan of their head at the first initial visit that includes sinus structure allowing for realistic *in vitro* simulation and optimization for sinus delivery in the future.

2) To assess the clearance of the radio-labelled saline over 1 hour (at 0, 20 and 60 minutes post-administration) after its administration with the NMN prototype at four different pulse frequencies.

3.4 Data analysis and interpretation

Defined volume of radiolabelled saline (2 ml) will be delivered using the NMN device through the nasal airways with four different pulse frequency settings in front of a single-head gamma camera using the NMN device to capture a planar images. Subsequently, serial images (2 frames per second) will be recorded from the anterior and lateral view using the SPECT/CT. This allows dynamic studies of filling and emptying of the nose, including the sinuses.

Image analysis
The CT scan image will be reconstructed to provide transaxial image using standard protocol and the deposition, retention and clearance evaluated. The image data will be assessed quantitatively (to meet primary objective and endpoint). In addition, high resolution CT-scan of their head at the first initial visit to generate an anatomically correct model of the upper respiratory tract that includes the sinus cavities (maxillary, frontal, ethmoidal, sphenoidal) (Secondary objective and endpoints)

Interpretation and assumption of quantitative data
The quantitative assessment of nasal deposition, retention and clearance will be determined as a percentage of total nasal deposition (quantified using the first planar image immediately after inhalation of the radioaerosol) as a function of intensity within defined areas of the nasal cavity, left and right of the maxillary, frontal, ethmoidal and sphenoidal sinuses using standard protocol as briefly described below. Count rates in the selected region of interests will be analysed using the MATLab Software or ImageJ Software packages (http://rsb.info.nih. gov/ij/). Count rates will be corrected for background activity and radioactive decay.

For analysis of the distribution of the radiolabelled saline into the different compartments, all serial images will be superimposed with regions of interest (ROI) of the nasal airways and sinuses defined as shown in Figures 6 and 7. The activity is obtained in these ROIs.

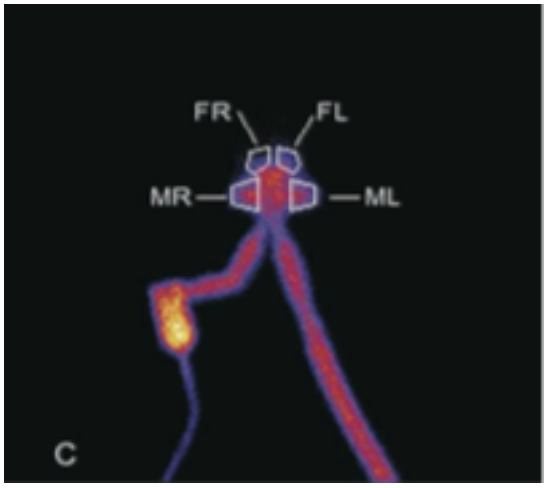


Figure 6. Regions of interest of the nasal cavity of the right and left maxillary and frontal sinuses (MR, FR, FL and ML). Image was taken from [9].

The primary endpoint of this study is the total area of distribution (mm^2) of radiolabelled saline immediately after administration by the NMN (T_0). This will be evaluated for each of subsites (surgically expanded ostia of the paranasal sinuses and oropharynx) and compared between treatments (A-D) which correspond to the different pulse frequencies tested. Between-treatment differences in total area of deposition of radiolabelled saline at each subsite will be compared by means of one-way analysis of variance (ANOVA) with application method as a factor.

Pairwise comparisons will be performed between each of the pulsed application methods and the continuous application (no pulse). Pairwise comparisons will be tested using a two-tailed p-value of <0.05.

Clearance will be calculated by the decrement in total radiolabelled saline between T_0, $T_{2\ 0}$and $T_{60.}$ Clearance will be evaluated for each subsite and compared between treatments (A-D). As with the primary efficacy endpoint, between-treatment differences in radiolabelled clearance will be tested by means of one-way analysis of variance (ANOVA) with application method as a factor. Pair-wise comparisons will be made between each of the pulsed application methods and the continuous application (no pulse).

The retention of radiolabelled saline will be evaluated as the Area Under the Curve between T_0 and T_{60} ($AUC_{0\text{-}60}$) of the following assessments:

- the total area of deposition of radiolabelled saline
- the intensity of radiolabelled saline

The AUCs will be evaluated for each subsite and compared between treatments (A-D). Between-treatment differences in AUCs will be tested by means of one-way analysis of covariance (ANCOVA) with application method as a factor and the value at T_0 as

covariate. Pair-wise comparisons will be made between each of the pulsed application methods and the continuous application (no pulse).

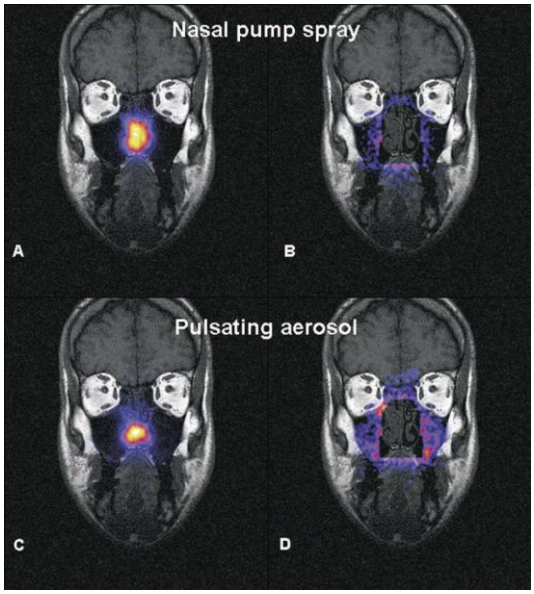


Figure 7. Example of superposition of anterior gamma camera images of radiolabelled aerosol after nasal delivery [9]. After deletion of the activity in the central nasal cavity, the aerosol penetration into the sinuses will be highlighted in B and D.

3.5 Safety Assessment

Adverse events (AEs) will be collected for all randomized participants and will be listed with type of AE, severity and relationship for each treatment group, using the safety population. Adverse events data will be summarized for each treatment groups using frequencies and percentages (% of participants with each specific AE)

4.0 Study design

4.1 Type of study

This is a single centre, randomised, controlled, cross-over clinical study investigating the deposition of aerosols generated by the NMN prototype into the nasal cavity using different pulse frequencies.

4.2 Study design

This study will be performed in healthy Caucasian male participants with no history of sinusitis or chronic respiratory diseases.

Informed consent will be obtained for participants prior to the initiation of any study-specific procedures including screening. All participants will receive a head CT scan on their first visit.
The treatment sequence for the study participants will then be randomly applied with at least a 72-hours washout period between treatments (Table 1). The potential carry-over effect of the applied radiolabel is considered negligible since Technetium has a half-life of 6 hours, consequently a 'rest' minimum period of 72 hours is considered sufficient between imaging study days.

Table 1. Treatment types to applied in the proposed study

Treatment	Device	Application method
A	NMN	No pulsing (continuous mode)
B	NMN	10 Hz pulse
C	NMN	50 Hz pulse
D	NMN	100 Hz pulse

Each participant will receive a radio-labelled saline dose of 2.0 mL per visit by one of the application methods (Table 1), the order of which will have been randomly selected.

Nasal deposition, retention and clearance of radiolabelled saline solution will be measured using serial imaging of SPECT/PET and gramma scintigraphy. The study does not involve the use of novel treatments and is restricted to investigating the ability of the NMN device to target the paranasal sinuses.

4.3 Number of participants

Employing a cross-over design enables each participant to act as its own control, and reduces the overall number of patients needed to assess aerosol deposition.

For this investigational study, participants who meet all the eligibility criteria will be enrolled and randomised into the study until 11 participants who complete the study are met.

4.4 Number of centres

All testing and recruitment will be performed at RNSH.

4.5 Expected duration of the study

Participant recruitment is expected to be completed within 6 months of approval from the relevant HRECs. The testing phase will begin right after the participant-screening visit, and all testing will be completed within 60 days of commencement. In all, the anticipated finish date will be December 2017- No ongoing follow-up will be conducted.

5.0 Study population

5.1 Sample size calculation

A previous study that investigated the temporo-spatial deposition of saline delivered by a squeeze bottle, nasal saline spray and nasal gel enrolled 5 healthy subjects (**Bleier et al. 2011**). Similarly, a PARI VibrENT nebulizer system that evaluated the pulsating aerosol (fixed frequency of 25 Hz) to the sinuses was conducted with five healthy volunteers (**Moller et al 2010**). Taking into account that four different pulse frequencies are evaluated a sample size of minimum 10 subjects will be sufficient for this pilot study.

5.2 Recruitment and screening

Potential participants will be identified from the RNSH database of trial participants. Each of these volunteers has previously consented to be included in the database, and to be contacted for future studies.

The study will also be advertised through the WIMR website and social media pages where brief description of the study will be posted. No other media advertising is planned. The WIMR media officer will coordinate advertisement of the trial. However, recruitment will still be performed at the RNSH.

Initial pre-screening will be made via telephone, where the volunteer will be provided with verbal information about the study and the inclusion/exclusion criteria. If the volunteer is willing to participate in the study, they will be invited to attend an enrolment visit at RNSH.

5.3 Eligibility criteria

5.3.1 Inclusion criteria

Signed informed consent will be obtained before any study procedure. Patients must be able to understand and be willing to sign a written informed consent.

Inclusion criteria, which must be met at the time of study screening, are:

- Healthy Caucasian male
- Aged >20 years
- No history of smoking
- No history of chronic lung diseases including asthma, cystic fibrosis, tuberculosis, chronic obstructive lung disease
- Normal lung function with stable and reproducible baseline FEV1 of > 80% of predicted value following adjustment for height, age and gender according to the Global Lung Initiative equation [18].
- No history of chronic sinusitis or rhinitis
- Agree that CT scan data can be used post-study to generate an anatomically correct model of the upper respiratory tract

5.3.2 Exclusion criteria

Exclusion criteria are:

- Significant upper and lower respiratory infection within the previous 4 weeks
- History of chronic sinusitis or rhinitis
- History of recurrent lung infections.
- History of chronic lung diseases
- History of severe or multiple allergies, including hay-fever and perennial rhinitis
- History of nasal fracture, nasal deformities or nasal polyps
- History of disease, surgery, or abnormality of the upper respiratory tract, especially the nasal cavity.
- History of significant nose bleeds
- Participants using topical nasal medication e.g. decongestant, within the last 14 days of the first study day
- Participants unable to perform pulmonary function test according to ATS/ERS criteria
- Participants with documented or suspected, clinically significant alcohol or drug abuse
- Current malignant or cardiovascular disease
- Any serious or active medical or psychiatric illness
- Current smokers, i.e. those who had smoked within the last 12 months and 6 hours prior to the scan. A negative Cotinine test must be demonstrated at each visit.
- Participants who have any non-removable metal objects such as pacemakers, insulin/infusion pumps, cochlear and ear implant, metal plates, screws etc. in their head, neck, chest or abdominal area that may interfere with the /PET/SPECT/CT.
- Nasal jewellery or nasal piercing
- Participants with tattoos or permanent makeup above shoulder
- Participants for whom participation in this study will exceed the limit of total radiation exposure allowed in any 12 months period (5 mSv), or will exceed 10 mSv over the last five-year period [19].

5.4 Informed consent process

Participants will be presented with written information on the study process, the study device and assessments, and potential side-effects. If the study investigator judges them capable of providing informed consent, the participant will be asked to provide written consent. The ability to understand written and verbal English is included in this assessment.

5.5 Enrolment

If written informed consent is provided, the participant will be allocated a unique participant identification number, which will be recorded in the WIMR Respiratory Technology, Airways Physiology and Imaging Group list of trial participants. This number will appear on all study documents and computer files, and will be used as the identifier during data analysis until the study is completed.

5.6 Randomisation

Randomisation will occur once participant eligibility is confirmed.

Participants will be randomly assigned to one of the four possible study treatment frequencies in a fashion that ensures: that each individual receives each treatment.

The randomisation sequence will be generated by computer, prior to the study, by an independent statistician. The statistician will maintain a schedule of participant numbers and drug sequence allocation.

5.7 Blinding

The study is an open-label study in terms of the investigational solution (2 mL radio-labelled saline) and the NMN pulse frequencies used where all participants will receive the same parameters but randomised at different study visit.

5.8 Incidental findings

Although unlikely, making incidental findings on medical imaging and during screening can occur and may warrant further investigation. For example, lesions may be detected on the CT scan that may represent early, asymptomatic cancers. In the event of such a finding, the study investigators will inform both the participant and, with permission, their primary care physician. An assessment as to the significance of the finding will be given to the participant/physician. If immediate investigation is thought to be necessary, this recommendation will be made by the study investigators and the participant removed from the study. If immediate investigation of the lesion is not considered to be necessary, the participant will be reminded that they may withdraw from the study at any time in order to pursue further investigation.

5.9 Participant withdrawal

In accordance with the Declaration of Helsinki, the Investigator must explain to the participant that they have the right to withdraw from the study at any time, and that this will in no way prejudice their future treatment.

Participants will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The Investigator will provide a written report on the appropriate CRF page describing the reason for discontinuation and included in a final study report to the HREC.

A participant may be removed from the study for the following medical or alternative reasons:

- Adverse event
- If a participant suffers an adverse event that, in the judgement of the Investigator or the Sponsor, presents an unacceptable consequence or risk to the participant, the participant may be discontinued from further participation in the study.
- Intercurrent illness
- A participant may also be discontinued from the study if, in the judgement of the Investigator, he or she develops an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies his or her withdrawal from the study.
- Failure of participant to comply fully with protocol required safety and/or efficacy assessments or general protocol non-compliance (in the opinion of the investigator at his/her discretion)

If a participant withdraws:

- prior to treatment but after CT scans, the CT scans data of the participant can be utilised for developing an anatomical model and another participant enrolled.
- After initial treatment (visit 1) but before final treatment (visit 4) then the participant's data will be placed in a subsidiary file and a replacement participant enrolled.

6.0 Trial procedure

6.1 Research plan

The study will have a cross-over design with each participant completing 4 different device settings over a period of 4 visits with at least a 72 hour wash-out period in between visits.

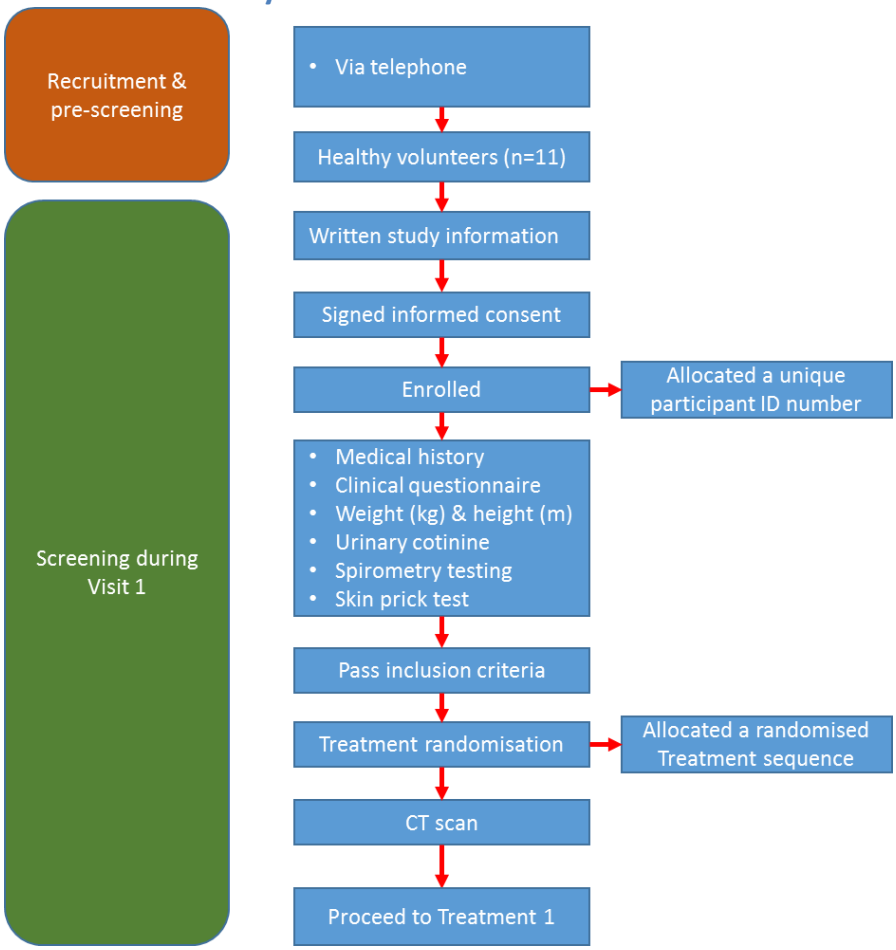
In the first visit, participants will sign a written informed consent, undergo lung function, urinary cotinine and skin prick tests, as well as completing 2 standard and validated clinical questionnaires: Woolcock's Clinical questionnaire and SinoNasal Outcome Test (SNOT) 22 [20] on medication use, medical history and smoking history. Participants will then undergo a full head high-resolution CT scan of the upper respiratory tract before being subjected to 1 of 4 randomised treatments of radio-labelled saline by using the NMN: A) no pulse frequency (continuous delivery mode), B) 10 Hz pulse frequency, C) at 50 Hz pulse frequency, or D) at 100 Hz pulse frequency. Immediately following administration of the radio-labelled aerosol, deposition of aerosols will be measured via gamma camera and dynamic SPECT/PET images for the first 20 minutes and finally at 1 hour to assess deposition, retention and clearance.

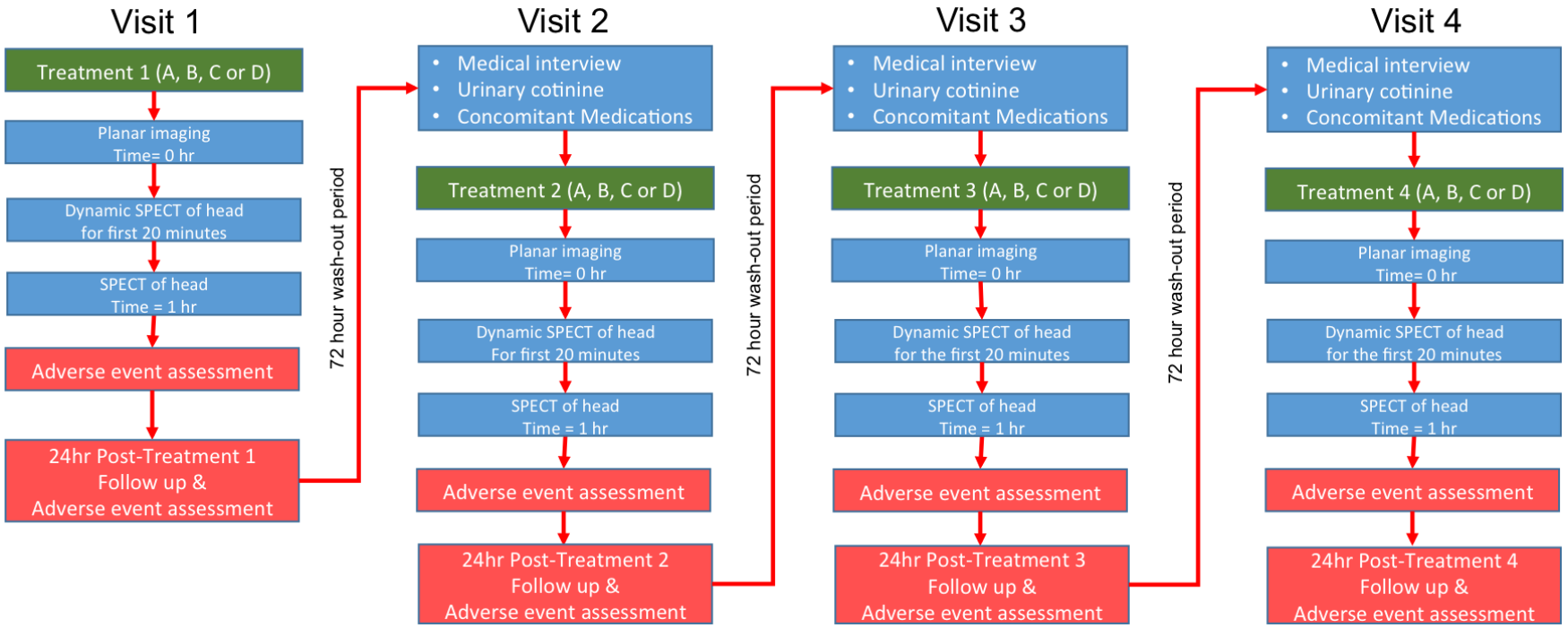
In subsequent visits (2-4), participants undergo a brief medical interview as well as repeating the urinary cotinine tests to confirm non-smoking status before further administration of radio-labelled aerosol via one of the four treatment processes as defined by the randomisation sequence.

Prior to the initiation of the screening assessments, potential participants will be given a complete explanation of the study.

Once an individual has agreed to participate and signed a copy of the Informed Consent documents, information will be obtained from the participant to determine their eligibility for enrolment in the study

6.2 Study flow chart




Visit 1
Treatment 1 (A, B, C or D)
Planar imaging
Time= 0 hr
Dynamic SPECT of head
for first 20 minutes
SPECT of head
Time = 1 hr
Adverse event assessment
24hr Post-Treatment 1
Follow up &
Adverse event assessment
72 hour wash-out period
Visit 2
Medical interview
Urinary cotinine
Concomitant Medications
Treatment 2 (A, B, C or D)
Planar imaging
Time= 0 hr
Dynamic SPECT of head
For first 20 minutes
SPECT of head
Time = 1 hr
Adverse event assessment
24hr Post-Treatment 2
Follow up &
Adverse event assessment
72 hour wash-out period
Visit 3
Medical interview
Urinary cotinine
Concomitant Medications
Treatment 3 (A, B, C or D)
Planar imaging
Time= 0 hr
Dynamic SPECT of head
for the first 20 minutes
SPECT of head
Time = 1 hr
Adverse event assessment
24hr Post-Treatment 3
Follow up &
Adverse event assessment
72 hour wash-out period
Visit 4
Medical interview
Urinary cotinine
Concomitant Medications
Treatment 4 (A, B, C or D)
Planar imaging
Time= 0 hr
Dynamic SPECT of head
for the first 20 minutes
SPECT of head
Time = 1 hr
Adverse event assessment
24hr Post-Treatment 4
Follow up &
Adverse event assessment

6.3 Schedule of study assessments

Table 2. Schedule of assessments

Assessment	Screening+ Visit 1*	Visit 2	Visit 3	Visit 4
Informed consent	x			
Inclusion/exclusion criteria	x			
Medical history	x			
Brief medical Interview		x	x	x
Concomitant medications	x	x	x	x
Weight and height	x			
Skin prick test	x			
Urinary cotinine	x	x	x	x
Spirometry	x			
Treatment randomisation*	x			
Head CT Scan	x			
Intervention (A-D)	A or B or C or D	A or B or C or D	A or B or C or D	A or B or C or D
Radiation Dose (mSv)	1.9 + 0.24	0.24	0.24	0.24
Deposition and clearance study (SPECT or PET and gamma scintigraphy)	x	x	x	x
Adverse event assessments & monitoring	x	x	x	x

* Screening and first treatment performed on same day

** Randomisation of treatment to define order of administration

6.2.1 Medical history and pre-treatment reviews (All visits)

A complete review of the participant's past medical history including exercise, smoking habits and alcohol intake, demographic data, concomitant diseases and medication will be undertaken by the Investigator at Screening (Visit 1). This will be captured by evaluating previous medical records and using the standard Woolcock respiratory and the SNOT-22 questionnaires.

At subsequent visits (Visits 2-4) the participant's medical history, concomitant medication will be re-reviewed to assess any new findings since the first visit.

6.2.2 Screening assessments and pre-treatment monitoring

- Demographic data: age, ethnicity, height (cm), weight (kg) (Visit 1 only).
- Urinary cotinine to confirm non-smoking status. (All visits)
- Baseline lung function tests will be performed including spirometry (FEV_1 and FVC). (Visit 1 only)
  - Spirometry testing will be conducted according to the American Thoracic Society/European Respiratory Society guidelines [21, 22].
  - Participants will be asked to breathe through a mouthpiece from which air flow is measured. Some manoeuvres will require maximal effort e.g. spirometry may be uncomfortable for some participants, but not painful for the participant.
  - Spirometry will be measured in triplicate with at least 2 values in which FEV1 and FVC are within 150ml.
  - The value to be recorded should be taken from the manoeuvre that produces the highest sum of FVC plus FEV_1 values.
  - Spirometry testing carries negligible risk.

6.2.3 Skin prick test (Visit 1 only)

A skin prick test to common aeroallergens (histamine, 24lycerine/saline control, house dust, D. pteronisinus, D farina, cat hair, alternaria, aspergillus fumigatus, grass mix #7, Rye grass (perennial rye) will be performed to determine atopic status according to previous published protocols [23]. A small droplet of allergen will be placed on the participant's forearm and the skin will be pricked lightly through the droplet. If participants are allergic to the tested allergen, a small itchy lump (wheal) surrounded by a red flare will appear within 15-20 minutes. The test is generally well tolerated and is relatively low risk.

6.2.4 CT scan (Visit 1 only)

A high-resolution head CT scan will be performed only at the initial first visit.

6.3 Treatment processes and Imaging

Participants will receive the following treatments in accordance to their allocated randomised sequence.

Treatment	Device	Application method	Radio-labelled saline dose
A	NMN	No pulsing (continuous mode)	2 mL
B	NMN	10 Hz pulse	2 mL
C	NMN	50 Hz pulse	2 mL
D	NMN	100 Hz pulse	2 mL

The NMN prototype the device is actuated by the participant's exhaled breath. Each actuation lasts 1 second. For all treatments and for the initial actuation at all visits participants must positioned the nose piece on the left nostril, after first exhalation patients may alternate between nostrils until the total dose volume (2mL) has been administered.

6.3.1 Radiolabel and radiation dose

An isotonic saline solution (0.9% w/v) will be mixed and delivered together with the technetium labelled diethylene triamine pentaacetic acid (^{99m}Tc-DTPA). DTPA is a nano-colloid of 492 Dalton size. In nuclear medicine, DTPA aerosols are used for ventilation imaging and for measurement of alveolar transmembrane permeability. ^{99m}Tc-DTPA is cleared from the lungs into the circulation by passive diffusion through the paracellular junctions of the alveolar capillary barrier with a half-life of approximately 70 minutes in a healthy non-smoker participant [9, 24, 25]. DTPA was selected due to its saline solubility and the ability to easily measure clearance either through mucociliary or absorption through the sinuses and nasal cavity.

Technetium will be provided by the radiopharmacy department at the Royal North Shore Hospital. A solution of ^{99m}Tc-DTPA will be prepared immediately before administration using a commercially available kit (TechneScan DTPA; Mallinckrodt Medical BV). A total of 2 mL of saline -^{99m}Tc-DTPA (approximately 0.24 mSv) will be added to the device drug reservoir of the NMN prototype.

Each 2mL dose contains a radiolabeled saline solution which equates to a radiation dose of approximately 0.24 mSv.

During the first visit participants are subjected to a high-resolution head CT scan which equates to a radiation dose of 1.9 mSv. Therefore, the total radiation dose that each participant would be exposed to is estimated to be up to 2.86 mSv. This calculated radiation exposure is classified as low as it is markedly lower than the dose constraint of5 mSv/year, it is therefore within the acceptable limits as per the ARPANSA Code of Practice *Exposure of Humans to Ionizing Radiation for Research Purposes* 2005 [19].

6.3.2 NMN Device orientation

Both, the device and the participant's head will be positioned in a straight and upright position as shown in Figure 5.

Figure 5: Position of head and NMN device during the clinical study

6.3.3 SPECT/PET Imaging

The imaging protocol commences immediately after the inhaled radiolabelled aerosol is administered. The following images are performed:

1. Planar imaging (anterior/posterior) of head and upper respiratory tract with participants sitting in front of the gamma camera head.

2. Dynamic SPECT or PET imaging of the head is performed with participants in the supine position for the first 20 minutes

3. Final repeat head SPECT or PET scan at 1 hour.

6.4 Follow-up period

The clinical study staff will phone the participants to identify any adverse and serious adverse events and if these events required any further intervention within 24 hours of each study period.

The monitoring and reporting of adverse events during this study will be conducted in accordance with the NH&MRC National Statement on Ethical Conduct in Human Research 2007 [26].

Participants experiencing adverse events will be followed clinically until their health has returned to baseline status or until all abnormal values have returned to normal or have otherwise been explained. The investigators will provide or arrange appropriate supportive care for the participant if necessary.

Adverse events will be monitored throughout the study along with a 24 hour follow-up after each treatment.

7.0 Adverse events

7.1 Definitions

7.1.1 Adverse event

An adverse event (AE) is defined as any unintended, unfavourable clinical sign or symptom, any new illness or disease or deterioration of existing illness or disease, or any clinically relevant deterioration in laboratory variables (e.g., haematological, biochemical, hormonal) or other clinical tests (e.g., ECG, X-ray), whether or not considered treatment related.

Note that the devices used during this study are clinical investigational devices and therefore not all adverse events maybe known at this stage.

The anticipated adverse events related to the NMN may include only mild discomfort during testing (such as mild nose irritation and/or stinging). Any severe device adverse events will be reported immediately to the IEC. The Principal investigator will assume responsibility for reporting and communicating with the Sponsor (AFT Pharmaceuticals) regarding any adverse or seriously adverse events.

Planned hospital admissions and/or surgical operations for an illness or disease which existed before using the device by a participant or before the participant was randomized in the clinical study will not be considered adverse events.

The severity of an adverse event and the relationship to the use of the device will be assessed by the Investigator (see Appendix 1: Grading of adverse events).

7.1.2 Serious Adverse Event

A serious adverse event is an AE that:

- results in death;
- is life-threatening (i.e., the participant was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred; this does not include an event that, had it occurred in a more severe form, might have caused death);
- results in persistent or significant disability/incapacity;
- requires participant hospitalization or prolongs hospitalization;
- is a congenital anomaly/birth defect; or
- is another medically significant event that, on the basis of appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

An adverse event fulfilling any one or more of these criteria must be reported as a serious adverse event, irrespective of the interventions given, and even if it is the result of an interaction or drug abuse.

A distinction should be drawn between serious and severe adverse events. Severity is an estimate or measure of the intensity of an adverse event, while the criteria for serious are indications of adverse participant outcomes for regulatory reporting purposes. A severe adverse event need not necessarily be considered serious and a serious adverse event need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not a serious adverse event. On the other hand, a myocardial infarction that may be considered minor could also be a serious adverse event if it prolonged hospitalization, for example.

7.1.3 Suspected Adverse Drug Reactions (ADR)

According to ICH GCP 1.1, "all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions."

7.1.4 Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information.

7.2 Procedure for adverse event reporting

All adverse events (non-serious and serious) spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded.
All adverse events (non-serious and serious) must be recorded on the source documents and case report forms provided by the Sponsor. The following information shall be included:

- nature of the adverse event
- the onset date of adverse event
- the end date of adverse event (if applicable)
- the outcome of the AE
- the frequency of the AE
- action taken with the investigational device
- whether this adverse event was serious
- relationship to the investigational device
- whether any treatment was received for this adverse event

Any adverse event or abnormal laboratory result evaluated as clinically significant by the study investigator shall be followed until satisfactory resolution: it becomes stable, or it can be attributed to other causes (existing conditions) and in the opinion of investigators that further follow-up is not required.

A sample of the SAE form for reporting is presented in Appendix 2: SAE Reporting Form.

7.3 Procedure for Serious Adverse event Reporting

In addition to entering each serious adverse event irrespective of causality on the appropriate page of the case report form (CRF), the Investigator must complete a Serious Adverse Event Report (SAER) for each serious adverse event regardless of causality to the investigational device (Appendix 2: SAE Reporting Form). The SAER must be faxed to the Drug Safety Officer at the CRO and then to AFT Pharmaceuticals Ltd (+64 94880234) within 24 hours from the point in time when the SAE is realized. The Drug Safety Officer will contact the Investigator should it be necessary to clarify any of the event information. The Investigator should provide any additional follow-up information for the event to AFT Pharmaceuticals Ltd as soon as it becomes available and up to the point the event has been resolved.

This reporting requirement is applicable to serious adverse events that occur during the designated study period. If the Investigator is notified of a serious event post Day 7that he or she determines to be causally related to study medication, the event should also be reported through this process.

7.3.1 Reporting to the Sponsor

Serious adverse events will also be reported to the local ethics committee and the relevant health authority as per the requirements.

In addition to entering each serious adverse event irrespective of causality on the appropriate page of the case report form (CRF), the Investigator must complete a Serious Adverse Event Report (SAER) for each serious adverse event regardless of causality to study drug (Appendix 2: SAE Reporting Form). The SAER must be faxed to the Drug Safety Officer at the CRO and then to AFT Pharmaceuticals Ltd (+64 94880234) within 24 hours from the point in time when the SAE is realized. The Drug Safety Officer will contact the Investigator should it be necessary to clarify any of the event information. The Investigator should provide any additional follow-up information for the event to AFT Pharmaceuticals Ltd as soon as it becomes available and up to the point the event has been resolved. This reporting requirement is applicable to serious adverse events that occur during the designated study period. If the Investigator is notified of a serious event post Day 7 that he or she determines to be causally related to the investigational device, the event should also be reported through this process.

7.3.2 Reporting to Local IEC and Regulatory Authorities

Serious adverse events will also be reported to the local ethics committee and the relevant health authority as per the requirements.

7.3.2.1 Local Ethics Committee

There is no general requirement for applicants to submit individual or expedited reports of SAEs or suspected unexpected serious adverse reactions (SUSARs) to local ethics committees who do not have the expertise or resources to review them. In the case of intervention studies involving a new medicine, the researcher is required to submit an annual summary of safety information.

7.3.2.2 Fatal or Life-Threatening Unexpected ADRs

An ADR is considered "fatal or life-threatening" if, in the review of either the investigator or sponsor, its occurrence places the participants at immediate risk of death. It does not include an adverse events of adverse drug reaction that, had it occurred in a more severe form, might have caused death.

Fatal of life-threatening ADRs occurring in clinical investigations is subjective to expedited reporting. Regulatory agencies should be notified (e.g., by telephone, facsimile, transmission, or in writing) as soon as possible but no later than 7 calendar days after the first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible with 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same of similar medicinal products.

7.3.2.3 All other serious, unexpected ADRs

Serious, unexpected reaction (ADRs) that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

7.4 Protocol deviations

This study will be conducted, within reasonable limits, as described in this protocol, except for emergency situations in which the protection, safety, and well-being of the participant requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the Sponsor, or the Sponsor's agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the best way to proceed with the study. It is expected that all consenting participants will at least continue to be followed up for adverse events). The investigator and the Sponsor will document this decision. The Institutional Review Board (IRB) or Ethics Committee (EC) will be informed of all protocol changes by the investigator in accordance with the IRB or EC established procedure. No significant planned or deliberate deviations from the protocol of any type will be made without the Sponsor's agreement and complying with all the IRB or EC established procedures.

7.5 Quality control and quality assurance (Monitoring & Auditing)

The Sponsor has ethical, legal, and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and applicable regulations. As part of a concerted effort to fulfil these obligations the Sponsor's monitor will visit the centre(s) during the study in accordance with the Monitoring Plan set forth for this trial as well as maintain frequent telephone and written communication. The investigator expects that the Sponsor will fulfil this obligation, and provide early opportunity for the investigator to correct any deficiencies identified in the data.

The Sponsor can conduct audits at the study centre(s). Audits can include, but not be limited to: drug supply, devices supplied, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with regulatory authority audits conducted at a reasonable time in a reasonable manner.

The sponsor agrees to meet all reasonable costs that arise out of such audits, including reasonable remuneration of staff involved in complying with the requirements of such audits.

8.0 Data management

8.1 8.1 Confidentiality

Study participants will be made aware of their rights to privacy and confidentiality as part of the informed consent process.

Each participant will be allocated a unique study participant identification number, which will be stored in a separate, locked master spreadsheet on a secure server. Participant data, contact details and medical information will be stored securely (*see section 8.3 Data storage*).

8.2 8.2 Data collection

Data on individual participants, including demographic information, contact details and medical history, will be recorded in a paper file. The results of medical interviews, skin prick test and adverse events will also be recorded in the paper file at each study visit. Participants will have their unique identification number recorded on each sheet.

For lung function measurements, an electronic file will first be generated by the computer software for subsequent analysis. The file will be labelled with the participant's unique identification number. This data, once analysed, will be collated into a spreadsheet. The spreadsheet will identify participants only by their identification number.

Any imaging files taken off-site will be de-identified by removing identifying data from the images themselves, and by naming the electronic files by the participant's unique identification number only. However, the original files will remain stored on the RNSH Department of Nuclear Medicine servers in identifiable form, as per the requirements for clinical record keeping.

8.2.1 Safety Data

The definitions and requirements in relation to adverse events are described in Section 7.

All adverse events, including serious adverse events, will be assessed and documented on the Day of the study.

8.3 Data storage

All paper files will be stored in a locked filing cabinet at WIMR. All electronic files will be stored on a network drive, housed at WIMR that requires authentication to access. Medical imaging files retained on the RNSH clinical system will be stored on a secure network drive.

8.3.1 Banking of health information

The following health information is aimed to be collected and stored in a database (banking of health information):1) All imaging obtained from CT scans and gamma scintigraphy imaging
2) Results obtained from the lung function, skin prick and urine tests
3) Responses obtained from questionnaires
All data will be anonymised prior to its use. In addition to the informed consent form, a data banking consent form will be also provided to the participants to review and sign .

8.4 Study record retention

All data and participant information from this study will be retained at WIMR for a period of 15 years after the completion of the study, as per the requirements of the University of Sydney Code for Responsible Research Conduct [26].

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10.0 Appendix 1: GRADING OF ADVERSE EVENTS

Severity:

Mild	Discomfort noticed but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect daily activity
Severe	Inability to work or perform daily activity

Relationship:

Not related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is unlikely or not reasonable. Or where another cause can explain the occurrence of the event by itself
Unlikely	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is unlikely but cannot be ruled out.
Possibly related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable, but the event could have been due to an equally likely cause.
Probably related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable and the event is more likely to be explained by the medicinal product than by another cause.
Definitely related	A temporal (timely) relationship of the onset of the event, relative to the administration of the product is reasonable and there is no other cause to explain the event. Cause to explain the event, or a re-challenge is positive.

11.0 Appendix 2: SAE REPORTING FORM

Protocol : AFT-MD-01 **SAE Number:** _____ **Fax to:** + 64 9 488 0234	**Site:** _____	**Report Type:** ☐ Initial Report ☐ Follow-up ☐ Revised / additional information ☐ Final Report		**Date of Initial Report:** ____ / ____ /____ *dd mmm yyyy* **Date of Follow-up Report:** ____ / ____ /____ *dd mmm yyyy*
	PATIENT INFORMATION			
Patient Initials: _____ **Patient #:** _____	**Gender:** ☐ Male ☐ Female	**DOB:** ____/ _____ / ___ *dd mmm yyyy*		**Weight:** _____ ☐ lbs ☐ kg
	STUDY Device INFORMATION			
Study Device & Treatment administered:			**Start Date and Time:** _____/ _____ / ____ *dd mmm yyyy* _____: _____ *(24 hr clock)*	**Stop Date and Time:** ____/ _____ / ____ *dd mmm / yyyy* _____: _____ *(24 hr clock)*
Blind broken? ☐Yes ☐No ☐ N/A If yes, please specify the treatment: _____				
	ADVERSE EVENT (AE)* * List only one adverse event. Additional serious AE are to be reported separately.			
Adverse Event: (diagnosis)			**Date and Time of Event Onset:** ____ / _____ / ____ _____ : _____ *dd mmm yyyy (24 hr clock)* **Date and Time of Last Dose Prior to Event Onset:** ____ / _____ / ____ _____ : _____ *dd mmm yyyy (24 hr clock)*	

Serious Criteria (check <u>all</u> that apply):

☐ Death
☐ Life-threatening
☐ Hospitalization – initial or prolonged
☐ Persistent or significant disability
☐ Congenital anomaly or birth defect

☐ Medically significant (specify) _____
(i.e. may require intervention to prevent permanent impairment / damage or one of the other outcomes listed)

Protocol: AFT-MD-01	Site Name: _____ Patient No: _____ Patient Initials: _____

Relationship to Study Device and Medication used:	**Outcome of AE: (check only one)**	**Action Taken with Study Drug:**
☐ Unrelated , possible etiology: _____ ☐ Remotely Possible ☐ Possible ☐ Probable	☐ Death (*dd/mmm/yyyy*): ____/ ____ / ____ ☐ Resolved (*dd/mmm/yyyy):*____ / _____ / ____ ☐ Permanent sequelae (specify in description) ☐ Ongoing ☐ Unknown/Lost to follow-up	☐ None ☐ Discontinued permanently ☐ Temporarily interrupted ☐ Dose adjusted ☐ Not applicable

Description of Event* (including symptoms, diagnosis, chronology, treatment, re-challenge / dechallenge):**

* List only one adverse event. Additional serious AE are to be reported separately.
** Attach additional sheet if necessary

Relevant Tests/Laboratory Data (including dates, lab units):

If lab reports are attached, please tick here: ☐

Other Relevant History (including pre-existing medical conditions):

Protocol : AFT-MD-01	**Site Name:**________________________ *Patient No:* ________ *Patient Initials:* _______

CONCOMITANT MEDICATION(S)* *(List all administered at onset of SAE, attach additional sheet of necessary)*

Name & Indication	**Dose & Regimen**	**Route Of Administration**	**Start Date/Time & Stop Date/Time *(dd/mm/yyyy, 24 hr clock)***	**Causal Relationship to AE**
Name (generic): **Indication:**	____ dose ____ units ____ regimen	☐ iv ☐ sc ☐ im ☐ oral ☐ sublingual ☐ inhalation ☐ other (specify) _______	**Start:** ____/ ____ / ____ *dd mmm yyyy* _____: ____ *24 hr clock* **Stop:** ____/ ____ / ____ *dd mmm yyyy* _____: ____ *24 hr clock*	☐ Unrelated ☐ Possible ☐ Probable
Name (generic): **Indication:**	____ dose ____ units ____ regimen	☐ iv ☐ sc ☐ im ☐ oral ☐ sublingual ☐ inhalation ☐ other (specify) _______	**Start:** ____/ ____ / ____ *dd mmm yyyy* _____: ____ *24 hr clock* **Stop:** ____/ ____ / ____ *dd mmm yyyy* _____: ____ *24 hr clock*	☐ Unrelated ☐ Possible ☐ Probable
Name (generic): **Indication:**	____ dose ____ units ____ regimen	☐ iv ☐ sc ☐ im ☐ oral ☐ sublingual ☐ inhalation ☐ other (specify) _______	**Start:** ____/ ____ / ____ *dd mmm yyyy* _____: ____ *24 hr clock* **Stop:** ____/ ____ / ____ *dd mmm yyyy* _____: ____ *24 hr clock*	☐ Unrelated ☐ Possible ☐ Probable

INVESTIGATOR'S SIGNATURE

_____

Name

_____ **Date** _____/ ____ / _____

Signature *dd mmm yyyy*