**Safety, tolerability and pharmacokinetics of subcutaneous administration of 2g ceftriaxone as an alternative to intravenous delivery**

**Version 2.2**

**03/04/2024**

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| Trial Details | | | | |
| **Protocol/Clinical Trial Title:** | Safety, tolerability and pharmacokinetics of 2g subcutaneous ceftriaxone as an alternative to intravenous delivery. | | |
| **Protocol Number (Version and Date):** | Version 2.2 03/04/2024 | | |
| **Amendment**  **(Number and Date):** |  | | |
| **Trial Start Date:** | 02/04/2024 | **Trial Finish Date:** | 31/10/2024 |
| **Coordinating Principal Investigator Name:** | A/Professor Laurens Manning | | |
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| **Sponsor Name (if applicable):** | South Metropolitan Health Service | | |
| **Laboratory Name (if applicable):** | School of Pharmacy and Biomedical Sciences, Curtin University | | |
| **Investigator List** | Dr Henco Nel  Dr Fionnuala Murray  Prof Sam Salman  Dr Edward Raby  Mr Matt Rawlins  A/Prof Brioni Moore | | |

## Trial Summary

There is an increasing body of evidence demonstrating the safety and efficacy of subcutaneous (SC) administration of antibiotics [1-4]. This practice has been successfully implemented at Fiona Stanley Hospital [5], both for inpatients as well as with the Infectious Diseases Ambulatory Care (IDAC) service delivering ceftriaxone (as a 1g dose), ertapenem and teicoplanin by this route in selected patients.

This is a prospective single arm cross over design study aims to extend our experience with subcutaneously administered antibiotics by determining the safety and tolerability of subcutaneous administration of 2g of ceftriaxone.

Inpatients already receiving ceftriaxone 2g to treat an infection will have dry blood spots collected immediately prior to an intravenous dose and at several time points subsequently over the dosing interval to measure the antibiotic concentrations in bloods. They will then have DBS collected at the same time points with a single dose of ceftriaxone 2g administered via subcutaneous infusion. Patients will be closely followed throughout the study with detailed safety and tolerability assessments completed.

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| Rationale / Background |

## Background summary

Subcutaneous administration of antibiotics has been practiced in Europe, particularly in France for many years [4, 6-8]. The SC route has garnered increasing attention in recent years as a practical alternative to intravenous delivery with increasing evidence of the safety and efficacy of this route being established in the literature [1, 2, 6, 8-10]. Subcutaneous administration offers an attractive alternative to other parenteral means of antibiotic administration such as intravenous or intramuscular. Intravenous administration requires sustained intravenous access which in turn requires an adequate venous network, staff experience and patient compliance, with delirium and cognitive impairment often serving as a significant barrier in the inpatient setting. Additional issues commonly encountered with intravenous access include tissue damage related to extravasation of medication, thrombophlebitis, and secondary blood stream infection as well patient discomfort from multiple attempts to secure access and the potential for missed doses during inpatient admissions due to inability to site access. Furthermore, for patients who require prolonged parenteral antibiotics, a long-term venous access device such as a peripherally inserted central catheter (PICC) is required which can often delay discharges and presents problems in the community with blockage, thrombosis and secondary infection which can result in readmission, all of which has significant cost implications for the healthcare system. IM administration is approved for numerous antibiotics however is infrequently used due to injection-related pain. Previous research has also indicated a preference for SC administration over IV from a patient perspective [11]. As our patient population continues to increase in both age and complexity, SC administration of antibiotics warrants thorough exploration.

Ceftriaxone is a third generation parenterally administered cephalosporin antibiotic used to treat a wide range of infectious diseases including as empiric therapy for several indications such as severe community acquired pneumonia, urinary tract infections, intra-abdominal infections, and meningitis. It is commonly used in the OPAT setting due to its safety profile and single daily dose for most indications outside of CNS diseases and critical care.

There has been increased interest in the use of SC administration of antibiotics due to the relative ease of administration and fewer local complications particularly in the outpatient setting. SC administration of various antibiotics, including ceftriaxone, ertapenem, teicoplanin, ampicillin and cefepime among others have been described in the literature with all demonstrating pharmacokinetic profiles that are comparable between SC and IV routes. Ceftriaxone is one of the most described SC administered antibiotics in the literature with numerous studies reporting that SC ceftriaxone is well absorbed with a bioavailability of 96-100% [3, 6, 7, 12-14]. Lower Cmax and longer Tmax are consistently reported with a comparable AUC for SC administration compared to IV [12, 15, 16].

Although pharmacological bioequivalence has been established for SC administered ceftriaxone compared to IV administration, most of these studies have used the lower dose of 1g of ceftriaxone, with relatively limited data on the tolerability of 2g dosing. While 1g was historically the standard dose, contemporary guidelines recommend 2g daily for a range of indications including urinary, intra-abdominal and musculoskeletal infections. Our hospital has an established protocol for the subcutaneous administration of ceftriaxone 1g diluted in 50ml of 0.9% NaCl via a 30-minute gravity feed infusion [17]. The aim of this study is to determine the feasibility of extending this experience to the higher 2g dosing.

## Intervention

In this prospective, single arm cross-over design study, we aim to extend our experience with SC ceftriaxone administration to include 2g dosing.

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| Trial Aims / Objectives / Hypotheses |

Given the increasing evidence to support SC antibiotic administration and the established utility and safety of SC administration of ceftriaxone 1g dosing in our centre, we propose to investigate the safety and tolerability of SC delivery of ceftriaxone 2g. There is an established protocol for SC delivery of 1g ceftriaxone in our hospital which has been utilised in the OPAT setting with excellent tolerability. We hypothesise that ceftriaxone 2g delivered via SC route will be well tolerated with a PK profile demonstrating equivalent bioavailability to IV delivery at the same dose.

This prospective, longitudinal PK study will help us to establish whether SC administration of 2g of ceftriaxone can be instituted as part of our clinical practice in managing difficult-to-treat infections in the hospital and through FSH ambulatory care program.

## Primary objective:

To establish tolerability of SC administration of 2g of ceftriaxone using a numerical rating score for pain, local erythema and local oedema.

## Secondary objectives:

To establish if SC ceftriaxone 2g has equivalent bioavailability to IV. That is a point estimate not more than 10% lower (i.e. 0.9) and the lower bound of the 90% confidence interval of bioavailability (compared with intravenous dosing) estimates for SC administration being within no less than 0.8. This is based on FDA/EMA guidance for bioequivalence where the 90% CI should fall between 0.8-1.25 for assessed parameters.

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| Trial Design |

## Study Endpoints

The primary endpoint will be the safety and tolerability of subcutaneous administration of ceftriaxone 2g, based on objective clinical evaluation of adverse events and subjective numerical rating scores for pain, erythema and oedema.

The secondary endpoint will be equivalent bioavailability, defined based on the lower bounds of the 90% confidence interval of the point estimate of bioavailability for SC administration being >80% of that of IV. This will be calculated after sample collection and processing has been completed for the pre-determined number of patients specified below.

## Study Design

This will be a prospective cross-over self-controlled trial, with PK data collected for both SC and IV administration for each patient.

## Intervention/Product Description

For patients already receiving ceftriaxone 2g as part of their infection management plan the intervention is delivering one dose of the patient’s prescribed antibiotic via the SC rather than IV route.

The antibiotic will be administered intravenously accordance with packaging and local guidelines. A dry blood spot blood sample will be collected immediately prior to infusion (T0), then 0.75-1, 2-3, 4-5, 8 hours (or as late as possible on the day) and 12 hours post-initiation (but before the next dose for those on twice daily dosing) of infusion for patients on twice daily dosing. For the majority of patients on once daily dosing regimens, an additional sample at 24 hours post initiation of infusion will be collected (which will also be the pre-dose sample timepoint for the SC administration.

The patient’s next dose will be administered via the SC route, adopting the existing protocol for ertapenem, 1g ceftriaxone and teicoplanin:

* The charted dose of antibiotic will be prepared to a 50mL volume with normal saline
* A flexible subcutaneous needle (23G) will be inserted
* The dose will be delivered over 30 minutes via gravity feed or infusion pump
* The needle will be removed after the SC dose is delivered.
* Dry blood spots will be collected at the same time points as for the IV dose (prior to the infusion (T0), then 0.75-1, 2-3, 4-5, 8 hours (or as late as possible on the day) and 12 hours post-initiation (but before the next dose) of infusion for patients on twice daily dosing. For patients on once daily dosing regimens, an additional sample at 24 hours post initiation of infusion will be collected.
* After the single SC dose, patients will revert to the IV route for their next scheduled dose.

## Laboratory Procedures

Capillary dry blood spots (DBS) will be collected from finger prick samples at the pre-specified timepoints. At least two DBS will be collected at each timepoint. The DBS cards will then be air dried for one hour before being placed into an airtight foil bag with two desiccant sachets before being stored at -80°C. Laboratory analysis will be performed at Curtin University. Ceftriaxone concentrations from DBS will be measured using a validated liquid chromatography-tandem mass spectroscopy (LC-MS/MS) assay with a limit of quantification of 0.1mg/litre as previously described [18].

Data will be reported in excel format and include assay performance and methodology details.

## Trial Duration/Schedule

Each participant will be part of the trial across 2 doses (one intravenous dose and one subcutaneous dose) of ceftriaxone 2g. We plan to begin patient recruitment collection soon after ethics and governance approvals are obtained: from April 2024 to October 2024. We estimate at least 5 FSH inpatients per week would meet eligibility criteria, so anticipate that recruitment and sample collection can be completed in this time frame.

Once collected, the DBS samples will be air dried for 1 hour before being placed in an airtight foil bag with two desiccant sachets and stored at -80°C until recruitment is completed, prior to transportation to Curtin University to undergo analysis.

The pharmacokinetic analyses and simulations will take between 3-6 months and the final write up and publication is planned for early to mid-2025.

## Trial Termination

The trial will be completed once the predetermined number of patients has been recruited and samples collected and processed. Any individual patient may choose to cease participating in the trial at any stage. If participants withdraw consent during the research project, additional information will not be collected, although personal information and blood samples already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law.

## Data identification

The confidentiality of participant information will be maintained at all times. Participant information will be identified only by a unique study number generated on enrolment. Dry blood spots will be tagged using the appropriate unique bleed codes and study number. The participant bleed codes will be recorded on the case reporting form to link to UMRN. At no time will personal information of study subjects be released to laboratory staff.

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| Source and Selection of Participants |

## Source of Participants

Fiona Stanley Hospital inpatients prescribed IV ceftriaxone at a dose of 2g per dosing interval by their treating team for an appropriate clinical indication will be identified through routine infectious diseases consultations and antimicrobial stewardship rounds. The patients will be anticipated to continue ceftriaxone 2g for at least 48 hours from enrolment. Inpatients from all relevant inpatient admitting units meeting the above criteria will be invited to participate. Potential participants will be approached by the investigating team and invited to participate in the study and provided with a copy of the PICF to review. Investigators responsible for obtaining informed consent will screen patients for eligibility based on the inclusion and exclusion criteria below.

## Participant inclusion criteria.

Must meet all of:

* Age ³ 18 years.
* Inpatient at Fiona Stanley Hospital
* Capacity to provide informed consent.
* Prescribed ceftriaxone 2g as part of their infection management plan.

## Participant exclusion criteria.

Patients will not be eligible for participation if any of the following criteria are met:

* Patients deemed to be clinically unstable (defined as requiring HDU/ICU level care or having had a MET call within the preceding 24 hours)
* Patients with a history of cognitive impairment, intellectual disability or a mental illness that leads to the inability to provide informed consent
* Children < 18 years.
* History of anaphylaxis or serious adverse reaction to cephalosporins in past.

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| Treatment of Participants |

## Description and justification for treatments, interventions, or methods to be utilised

Prospective participants will be identified through the routine clinical work of the Infectious Diseases team: through Antimicrobial Stewardship rounds, the Infectious Diseases Pharmacist, and Infectious Diseases clinical consults. Participants who satisfy any of the exclusion criteria will not participate in the study.

Once informed consent is established from the patient, baseline characteristics including age, sex, weight, serum creatinine, liver function tests, full blood count, full medications list and the presence of co-morbidities will be recorded for each participant using bloods at the nearest time point prior to enrolment.

Capillary dried blood spot (DBS) samples will be collected via finger prick using a single use safety lancet.

Ceftriaxone 2g will be administered intravenously accordance with packaging and local guidelines. A capillary DBS will be collected immediately before the infusion (T0), then 0.75-1, 2-3, 4-5, 8 hours (or as late as possible on the day) and 12 hours post-initiation (but before the next dose) of infusion for patients on twice daily dosing. For patients on once daily dosing regimens, an additional sample at 24 hours post initiation of infusion will be collected.

The patient’s next dose will be administered subcutaneously, as described above with DBS collected at the same specified time points before and after commencement of the infusion.

After a single SC dose, patients will revert to the IV route for their next scheduled dose.

## Permitted medications/treatments

All other regular medications prescribed to participants will be permitted during the study period.

## Monitoring of participant compliance

We will record whether either studied dose was not delivered in its entirety, and if so for what reason.

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| Assessment of Efficacy |

## Outcomes

Given that there has been previous data to support bioequivalence of SC administration of ceftriaxone compared to IV, the primary outcome in this study is the safety and tolerability of the higher 2g dose of ceftriaxone administered SC. Secondary outcomes will include demonstrating equivalent bioavailability, defined as the lower bounds of the 90% confidence interval of the point estimate of bioavailability for SC administration being >80% of that of IV.

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| Assessment of Safety |

## Risks and benefits

Potential Risks:

The participants in this study will be inpatients currently prescribed IV ceftriaxone 2g for serious infections.

The main concern in the literature is that localised skin necrosis has been reported following SC injection. This phenomenon has not been reported in our experience to date with >100 patients with SC ertapenem, teicoplanin or ceftriaxone at FSH. Similarly, it was not reported in a recent study at our site in which a further 24 patients (including 19 patients with type 2 diabetes, 8 of whom had a HbA1c > 10%) received meropenem or cefazolin via subcutaneous infusion into their flank (unpublished data).

Although published experience suggests that SC ceftriaxone will have equivalent bioavailability to IV, there is a risk that if that is not the case, the patients will be under-treated for only one dosing period. We will minimise this risk by including only patients who are clinically stable (not in intensive care, no MET calls in 24 hours before enrolment) and have already received at least 24 hours of ceftriaxone treatment.

Obtaining dry blood spots from finger prick may cause local pain, bruising, and very rarely, infection at the site of the blood draw.

Known Potential Benefits:

There are no anticipated immediate benefits to the participants in this study.

This study will allow for the identification of the pharmacokinetics of high dose ceftriaxone (2g) administered subcutaneously. It is possible that this study could allow a broader repertoire of antibiotic doses for SC administration in the future in selected patient groups.

## Safety and Tolerability

The tolerability of SC infusion will be assessed immediately after the infusion and then at each scheduled sampling time point by recording patient reported pain on a 0 - 10 point scale with 0 representing “No Pain” and 10 representing to the “Worst Pain Imaginable.” Additionally, the skin at the SC infusion site will evaluated for local erythema and oedema at various time points. Erythema will be scored on a 0 - 4 point scale with 0 representing “No Erythema” and 4 representing “Severe Erythema to Slight Eschar Formation.” Oedema will be scored using a 0 - 4 point scale with 0 representing “No Oedema” and 4 representing “Severe Oedema (raised more than 1 mm and beyond exposure area).” If concerning reactions such as skin necrosis are noted, the HREC and treating team will be informed, and patients will be managed in consultation with appropriate inpatient teams.

## Data and Safety Monitoring Board

NA

## Adverse event reporting

Any severe adverse events (such as skin necrosis) will be reported to the HREC.

## Follow-up of Adverse Events

Clinical follow-up will be through the respective specialty teams at FSH.

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| Data Management, Statistical Analysis and Record Keeping |

## Statistics and Interim Analysis

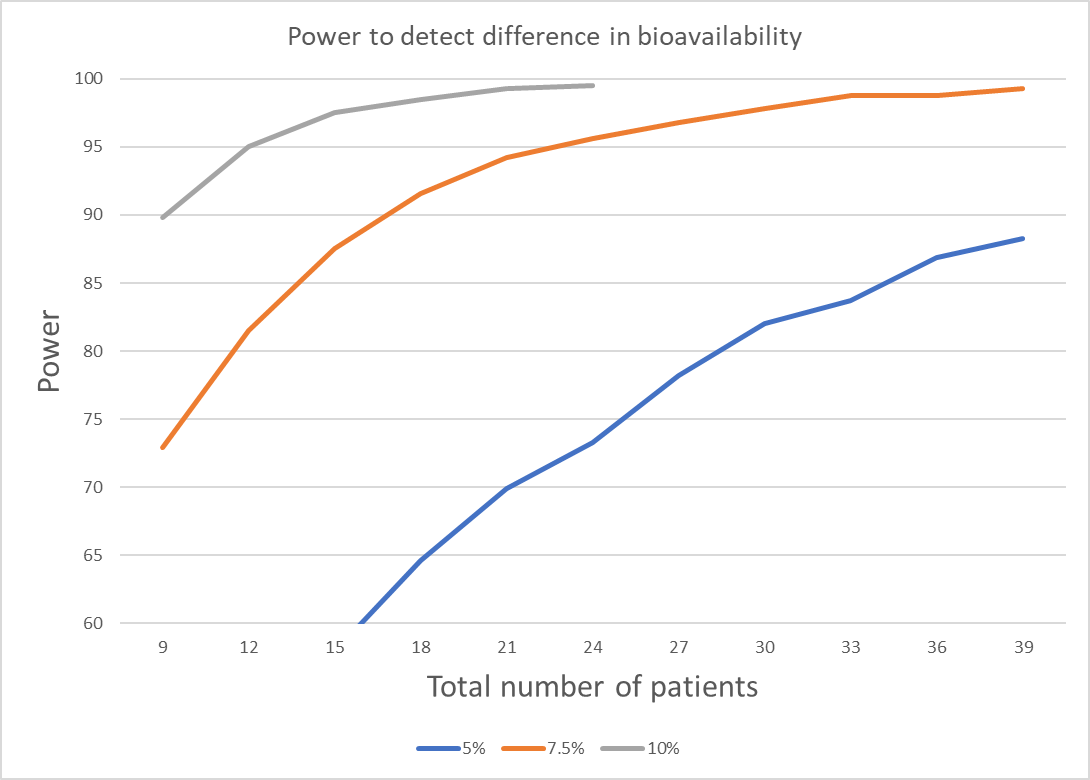
NONMEM (version 7.2.0, ICON Development Solutions, Ellicott City, MD, USA) with an Intel Visual FORTRAN 10.0 compiler will be used for nonlinear mixed-effects modelling of all predicted plasma concentrations of ceftriaxone measured from DBS concentrations using a previously validated method [18]. The first-order conditional estimates method with interaction will be used, with the minimum value of the objective function value (OFV), goodness-of-fit plots, and predictive checks used to arrive at suitable models during the model-building process.

The models will be used to obtain population estimates of conventional PK parameters including ka (rate of absorption for SC doses), VC (central volume of distribution), CL (clearance), VP and Q (peripheral volumes of distribution(s) and their respective inter-compartmental clearance(s)). A significance level of P<0.05 will be set for comparison of nested models and allometric scaling will be employed a priori, with volume terms multiplied by (weight/70)1.0 and clearance terms by (weight/70)0.75.

An additional parameter will be included to estimate the bioavailability of SC administration compared to IV doses (where, by definition, bioavailability is 1). While the potential influence of other covariates (in particular renal function and also age, other measures of size, co-morbidities etc.) will be assessed in the model, identifying covariate relationships is not the aim of the study and, given the cross-over design, will not influence the estimate of SC bioavailability. Model evaluation will include a non-parametric bootstrap to evaluate model parameter precision as well as goodness of fit plots and visual predictive checks to assess for any bias.

## Sample Size, Study Power and Significance

For the sample size calculation, we applied a modelling approach described in our previous studies. The key targets were i) to have power to detect a 10% lower bioavailability of SC vs. IV dosing and ii) to be able to demonstrate equivalent bioavailability between the two routes of administration. This was defined to be a lower 90% CI of the estimate of SC bioavailability no less than 0.8 and derived from FDA/EMA guidance for bioequivalence where the 90% CI should fall between 0.8-1.25 for assessed parameters (8). We assumed comparable data from a study of SC vs IV ertapenem for the rate of SC absorption and population variability of relative bioavailability of SC vs IV (9). In the first step the sample size required to detect a 10% lower bioavailability with SC dosing, noting IV dosing has a bioavailability of 1. A Monte Carlo Mapped Power simulation was performed using Perl speaks NONMEM (PsN).



As evidenced from the simulations, >20 patients would have >95% power to detect a 10% difference in bioavailability. Secondly, based on our experience with widespread administration of SC ertapenem and SC ceftriaxone (1g dosing) as well as our unpublished trial of SC meropenem and cefazolin, we expect the pain scores to be low. As such, a modest sample size of at least 20 participants should confirm the tolerability of SC ceftriaxone delivered as a 2g dose. To account for drop-out during the various infusions, we aim to recruit a **total of 24 participants**.

## Statistical plan deviations:

Nil.

## Selection of participants for analyses:

All participants with partial or completed datasets for SC and IV administration will be analysed.

## Data management

Study data will be collected, managed, and stored using WA Health REDCap (Research Electronic Data Capture) and merged with sample analysis data by study identification number. WA Health REDCap is a secure, web-based application designed to support data for capture for research studies. Paper records, such as consent forms, will be stored in a locked office in the Harry Perkins Research Institute, only accessible by the study team. Electronic records will contain only deidentified information which will not be re-identifiable, in a password protected format. In the present plan, data will be available only to the PIs apart from de-identified data related to drug concentrations measured at Curtin University which will be retained by them for audit purposes for 15 years. It is also acknowledged that the PIs are also responsible for compliance with the confidentiality agreement by data support staff with subsequent access to the data. Any information will be used solely for the research relating to this application and will not be shared or merged with other datasets. The information will not be used to contact individuals.

It is acknowledged that the PIs are responsible for all breaches and ensuring the Security Plan is followed.

Data Analysis will be performed using R. No identifying data will be maintained with the code, or from the R outputs.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval.

Participant anonymity will be maintained. Participants will not be identified in any publications of the study data.

The health information will be retained for 15 years at the study site, following the publication date. The expected date of data disposal will be December 2040. This is in accordance with UWA data retention guidelines. During this period the Security Measures detailed above will be strictly maintained. At the end of this period, all personal health information will be destroyed. The PIs will follow the guidelines on data sanitisation and deletion outlined in the Practice Code.

We understand the obligations for data retention and disposal along with notification of the DOHWA Data Services Office when health information has been destroyed.

## Procedures for missing, unused, and spurious data:

Given the use of a population pharmacokinetic model, participants with partial datasets can still be included in the analysis.

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| Monitoring / Audit |

## Monitoring, Audit and Regulatory Inspections Statement

Trial investigators will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents. This may include, but are not limited to, review by, Human Research Ethics Committees, and institutional governance review bodies.

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| Quality Control and Quality Assurance |

## Compliance statement

The investigators will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonisation Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever affords the greater protection to the subject.

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| Ethics |

This protocol and the consent form will be submitted to the South Metropolitan Health Service Human Research Ethics Committee. Patients will be offered participation in this study according to best practice.

A researcher will go through the study with the participant, ensuring all aspects of the study including, the purpose of the study, what is involved in the study, what their role in the study is, what the potentials risks and benefits are to themselves and the wider community and be given the opportunity to ask any questions they may have.

It will be emphasised and articulated clearly to the participants that they are free to decline to participate and that this will not impact on their current or future treatment in any way.

The participants may withdraw consent at any time throughout the course of the study.

At any time of the study, the principal investigators will be available to answer questions regarding any aspect of the present study.

Informed consent documents and information sheets will be submitted to the South Metropolitan Health Service HREC for approval prior to the start of the study.

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| Budget, Financing, Indemnity and Insurance |

This study will be supported by existing infrastructure, in-kind support and financial support established by A/Professor Laurens Manning. There are no cost implications for South Metro Health Services. Recruitment of patients will be in-kind as part of training activities for Dr Nel (as a registrar within the department of infectious diseases) and will therefore have no cost. Consumables and sample transportation will be funded by A/Prof Laurens Manning. Sample processing and analysis will also be on an in-kind basis, at an estimated cost of $100 per sample through Curtin University. Prof Sam Salman’s time is covered in-kind as a SMHS employee. The in-kind funds to support the analytical and components are held by A/Prof Manning and A/Prof Moore through various grants held at Curtin and Telethon Kids Institute.

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| Publication |

This study will be published in a peer-reviewed journal. Study participants will not be identified in publications. Authorship will be inclusive and offered to all people who significantly participate in the study.

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| Appendices |

## Participant information sheet and consent form.