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CAMERA – Combination Antibiotic treatment for MEthicillin Resistant
Staphylococcus aureus

STUDY PROTOCOL

Study Title: CAMERA – Combination Antibiotic treatment for MEthicillin Resistant *staphylococcus Aureus*: a pilot randomised controlled trial of vancomycin compared with vancomycin plus flucloxacilln for MRSA bacteraemia

Abbreviated Title: CAMERA

HREC ref: HREC-2010-1436 (Menzies School of Health Research and NT Dept of Health and Families)

Clinical Trial Registration #:   ACTRN12610000940077

Date and Version of Protocol: Version 5.0, 7 June 2012

Study Product/s: 1. Vancomycin
2. Flucloxacillin sodium for injection

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Study synopsis

TITLE:	CAMERA – **C**ombination **A**ntibiotic therapy for **ME**thicillin Resistant Staphylococcus **A**ureus. An open label randomized controlled trial to determine if 7 days of intravenous flucloxacillin in addition to vancomycin will lead to earlier clearance of *Staphylococcus aureus* bacteraemia (SAB) compared to standard therapy (vancomycin alone) in adult patients with methicillin-resistant *S. aureus* bloodstream infection.
BACKGROUND	MRSA bacteraemia has a mortality of 30-40%, exceeding that of sensitive *S. aureus* primarily due to the shortcomings of vancomycin, the standard therapy for MRSA bacteraemia. Whilst several new antibiotics have become available for MRSA, none have been shown to be superior to vancomycin. Although MRSA is by definition resistant to oxacillin, multiple *in-vitro* and animal studies have demonstrated synergy of vancomycin with β-lactams (including oxacillin) against MRSA and hVISA. This study aims to answer the following question: In hospitalised adults with MRSA bacteraemia, does combination therapy with vancomycin and flucloxacillin lead to a shorter time to clearance of bacteraemia than vancomycin alone?
RATIONALE:	This is a pilot study to demonstrate proof of concept and feasibility using duration of bacteraemia as an endpoint. If shown to be feasible, safe and possibly effective, this would justify the conduct of a larger, definitive trial to address the question of whether combination treatment with flucloxacillin reduces the mortality from MRSA bacteraemia.
PRIMARY OUTCOME MEASURE:	Duration of MRSA bacteraemia (in days)
SECONDARY OUTCOME MEASURES:	1. Combined safety endpoint of grade 2 or above nephrotoxicity or hepatotoxicity. 2. All cause 28-day and 90-day mortality 3. Metastatic complications during the first 10 days post randomisation 4. Composite endpoint of requirement for ICU admission OR development of septic shock (as a safety endpoint) 5. In-vitro analysis of *S.aureus* isolates for MICs and synergy to vancomycin and oxacillin and presence of heterogeneous resistance to vancomycin and oxacillin. 6. Relapsed bacteraemia during the index hospital admission
STUDY DESIGN: Group 1 Group 2	Open label randomized controlled trial (RCT) Standard therapy group: Intravenous vancomycin dosed as per Australian national guidelines (Therapeutic Guidelines antibiotic, 14th Edition, 2010) PLUS standard management of S.aureus bacteraemia as per ASID guidelines (IMJ, 2006) Combination therapy group: Intravenous vancomycin dosed as

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	above plus intravenous flucloxacillin 2g 6/24ly, PLUS standard management as above
STUDY DURATION:	November 2010 – December 2011
NUMBER OF PARTICIPANTS:	60 patients randomized 1:1 The primary aim is to demonstrate feasibility and gather data to inform study design of a subsequent larger study powered for mortality. For this pilot study, sample size was estimated for the aim of determining the duration of bacteraemia in each group. Using a 95% confidence interval of 2 days, and assuming a standard deviation of 5.1 days (derived from unpublished data from an RCT of daptomycin for MRSA bacteraemia), we would need 27 patients in each group=54, plus 10% correction factor for drop-out=60 patients.
INCLUSION CRITERIA:	1. Age >= 18 years. 2. ≥1 set of blood cultures positive for MRSA as determined by Gram positive cocci on Gram stain followed by rapid molecular testing 3. Able to be randomized within 48 hours of blood cultures being collected. 4. Likely to remain as inpatient for 7 days following randomization
EXCLUSION CRITERIA:	1. Previous type 1 hypersensitivity reaction to beta-lactams, vancomycin or other constituents of study medications. Definite history of rash or serious non-type 1 hypersensitivity reaction to flucloxacillin or any penicillin. 2. Renal failure with GFR<30 (because of uncertainty about flucox dosing, difficulty with Vanc dosing). 3. Polymicrobial bacteraemia. 4. Previous participation in the trial. 5. Known pregnancy 6. Patient on Beta-lactam therapy which cannot be ceased or substituted.
VANCOMYCIN DOSAGE	Intravenous vancomycin dosed as per Australian national guidelines (Therapeutic Guidelines antibiotic, 14th Edition, 2010) with subsequent adjustment to maintain trough levels at 15 +/- 3mg/L
FLUCLOXACILLIN ADMINISTRATION	Flucloxacillin 2g reconstituted in a 50ml bag of normal saline (0.9%) infused over 10-30 minutes every 6 hours.
RANDOMISATION	Eligible participants will be randomized 1:1. Randomization will be stratified by hospital and in permuted blocks of 4 or 6. Allocation concealment will be maintained by a research assistant not involved in patient care at each hospital who will hold a computer generated randomization list.
BLINDING	This will be a non-blinded, open label study. All patients will have daily blood cultures collected for 7 days and, if still positive on day 7, every 2nd day until negative (i.e., no difference according to group) and microbiology laboratory staff will be blinded to patient allocation. Analysis of the primary outcome measure will be performed in a blinded manner (with patients divided into group A and group B). The subsequent large phase 3 study will be double blinded and placebo controlled.

Contents

1   Introduction

1.1   Background to the study

Invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infection imposes a substantial burden on healthcare systems throughout the world [1]. A recent national Australian laboratory-based study conducted over 1 year found that 450 of 1,994 episodes (24.1%) of *S. aureus* bacteraemia were caused by MRSA [2]. More importantly this study found that the all-cause 30-day mortality was 30% for MRSA compared with 17.7% for methicillin-sensitive *S. aureus* (MSSA; p<0.001). Studies from elsewhere have also reported infection with MRSA to have a higher mortality than MSSA infection [3]. The reasons for this are unclear, but may relate to the limitations of vancomycin, the most commonly used antibiotic for invasive MRSA infections [4, 5]. Indeed, the ANZCOSS study found treatment with vancomycin but not MRSA infection itself to be an independent risk factor for 30-day mortality among all patients with *S. aureus* bacteraemia [2]. Compared with oxacillin and its derivatives for treatment of MSSA infections, vancomycin demonstrates slower bacterial killing [6], poorer tissue penetration [7], slower clearance of bacteraemia [8, 9] and higher mortality [10, 11]. In recent years, several alternative agents to vancomycin have become available for the treatment of MRSA bacteraemia, including linezolid, daptomycin and tigecycline. Each of these has been found to be non-inferior to vancomycin for MRSA infections, but none have been shown to be superior [12], and all are associated with a high cost and a substantial risk of adverse effects.

An alternative strategy to improve outcomes from MRSA bacteraemia is to combine vancomycin with a second agent, aiming for synergistic bacterial killing [13, 14]. Unfortunately, none of the three new agents mentioned have been shown to be synergistic with vancomycin against MRSA. In contrast, at least ten *in-vitro* studies have demonstrated synergy of vancomycin combined with various beta-lactams against MRSA and vancomycin-intermediate *S. Aureus* (VISA) (reviewed in [13, 14]). Climo et al found that vancomycin plus oxacillin were synergistic *in-vitro* against 30 of 59 strains of VISA, and showed no antagonism in the remainder [15]; they also showed this combination to be superior to vancomycin alone in sterilising cardiac vegetations and renal abscesses in a rabbit model [15]. Domaracki et al

found that vancomycin and oxacillin were synergistic in-vitro against 14 of 21 strains of MRSA, with time-kill studies showing enhanced killing [16].

The mechanisms for this observed synergy are unknown but may include an upregulation of cell-wall production induced by beta-lactams thus increasing vancomycin sensitivity. Potential concerns with the use of vancomycin with oxacillin are the possibility of antagonism, and the theoretical risk of the oxacillin inducing increased toxin production by the MRSA. Joukhadar et al looked for antagonism between vancomycin and oxacillin in 10 clinical isolates of MSSA in vitro, and found no evidence of either synergy or antagonism [17]. Increased toxin production has been observed in specific laboratory conditions [18], but there is no evidence of this occurring *in-vivo*.

Thus there is considerable *in-vitro* and limited animal model evidence to suggest that the combination of vancomycin and flucloxacillin, which is commonly used in initial empiric therapy of staphylococcal bacteraemia, may be more effective than vancomycin alone for this common and devastating infection. However, although the majority of *in-vitro* studies support the use of this combination, no studies addressing this question have previously been performed in humans. Thus there is clinical equipoise sufficient to justify the performance of a pilot RCT, to assess feasibility, proof of concept and safety of this strategy.

2   Objectives of the study

2.1   Primary objectives

The principle aim of the study is to determine the duration of MRSA bacteraemia in hospitalised adults treated with either vancomycin alone or vancomycin plus flucloxacillin.

This is a pilot study to demonstrate proof of concept and feasibility using duration of bacteraemia as an endpoint. If shown to be feasible, safe and possibly effective, this would justify the conduct of a larger, definitive trial to address the question of whether combination treatment with flucloxacillin reduces the mortality from MRSA bacteraemia.

2.2   Secondary objectives

2.2.1 To determine the likely recruitment rate of a subsequent large phase III clinical trial with the same inclusion and exclusion criteria as the current trial.

2.2.2 To explore the effect of possible confounders on the impact of adding flucloxacillin to vancomycin for the treatment of MRSA bacteraemia. These include:
- Vancomycin MIC of the infecting organism
- Multiresistant versus non-multiresistant MRSA
- Other antibiotic use prior to study recruitment
- Endovascular infection

2.2.3 To determine the feasibility and clinical utility of using a rapid molecular test to screen relevant positive blood cultures for MRSA.

3   Study design

Experimental design: Open label, randomised (1:1), controlled, multi-centre pilot study.

4   Study flowchart
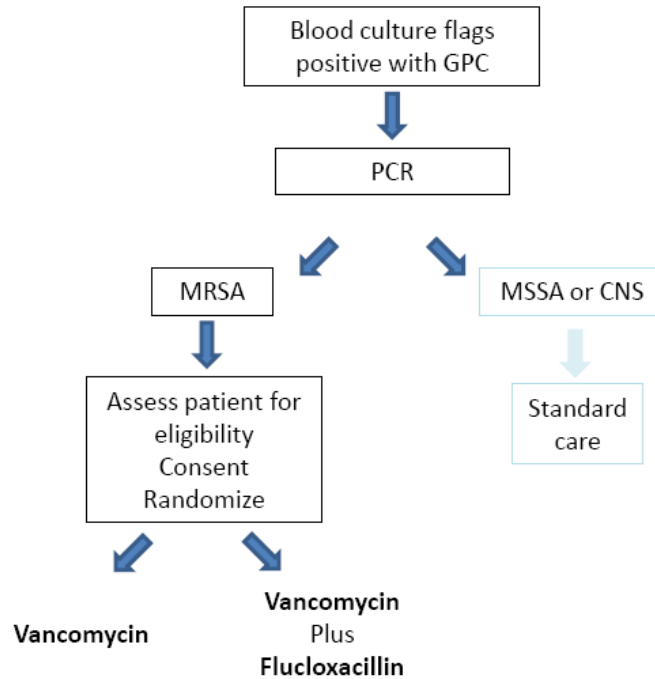
Notes: GPC=Gram positive cocci in clusters

At Royal Darwin Hospital, we will use GeneXpert for performing PCR testing. Other sites may use an alternative platform.

CNS=Coagulase negative staphylococcus

5 Study Procedures

5.1 Summary of study procedures

Visit day	Pre-screen	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	After Day 10
Microbiology laboratory finds MRSA in blood culture by rapid test	√											
Check inclusion criteria	√											
Check exclusion criteria	√											
Informed consent		√										
Demographic and clinical questionnaire		√										
Weigh		√										
Randomise		√										
Safety and monitoring bloods (LFTs, FBC, EUC, CRP)		√	√	√	√	√	√	√			√	
Blood cultures – For first 7 days in all, then 2nd daily until negativex2 at 48h.		√	√	√	√	√	√	√	(√)*		(√*)	(√)*
Group 1: Vancomycin standard dosing		√	√	√	√	√	√	√	√	√	√	**2-6 weeks**
Group 2: Vancomycin standard dosing		√	√	√	√	√	√	√	√	√	√	**2-6 weeks**
Group 2: Flucloxacillin 2g QID IVI		√	√	√	√	√	√	√				
Assessment of clinical progress		√	√	√	√	√	√	√	√	√	√	**Day 28**

*(√) If required

We will contact the participant, or their community health clinic, one and three months after beginning treatment to access their condition.

5.2 Number of subjects / centres

60 participants will be entered into the study. It is not planned to replace 'drop outs' or those lost to follow-up. The target enrolment will be 30 participants per group, which with an allowance for loss to follow-up, is anticipated to provide 54 evaluable subjects (27 per group). Enrolment will be terminated when 60 evaluable subjects have been enrolled.

Because MRSA bacteraemia is common Australia-wide, but less common at individual centres, subjects will be recruited from 7 study sites in order to complete the study in a timely fashion.

A maximum of 20 participants will be recruited from any one site.

5.3 Estimated duration of study
It is anticipated the recruitment will take 12 months in total, but we have allowed for a lower rate by making the study period October 2010 until the end of December 2011. The study

period will be extended if needed, following discussion with the sites involved and the relevant HRECs.

5.4 Ethics and regulatory approvals

The study will be conducted according to the declaration of Helsinki, the NHMRC criteria for the ethical conduct of research in humans and the NHMRC criteria for research in Indigenous Australians.

Although this is a clinical trial, we have not applied for TGA approval under the CTN scheme, as we are not using an investigational product. Flucloxacillin is a commonly used antibiotic and its route and manner of use in this study will be as per standard clinical use. Flucloxacillin has an approved indication to treat staphylococcal infections.

Institutional permission and endorsement will also be sought from each participating hospital prior to the commencement of recruitment at that centre.

The study protocol, information statements, consent forms, and any other documents required for ethics approval will be submitted to the relevant Human Research Ethics Committees for approval before the study commences. Each HREC reviewing the protocol must be properly constituted according to NHMRC requirements and have the capacity to review the study. Approvals must specify the study title, version numbers, and identify all documents reviewed and state the date of review. No amendments to, or deviations from, the protocol must be initiated without prior written approval from the relevant HREC. The exceptions to this are:
- administrative aspects that have no bearing on subjects;
- the need to address regulatory requirements; and/or,
- the need to eliminate immediate hazards to the subjects.

The investigator will inform the HREC of the following:
- all protocol amendments, informed consent changes or revisions of other documents originally submitted for review;
- serious and/or unexpected adverse events
- new information that may affect the safety of the subjects or the proper conduct of the trial;
- annual updates of study progress
- termination of the study including provision of a final study report.

5.5 Informed consent

Informed consent processes are to be consistent with the principles of GCP, the Declaration of Helsinki, the NHMRC requirements and cultural aspects of consent in Indigenous communities.

Freely given informed consent must be obtained from every participant or their surrogate decision maker prior to enrolment. This information should be provided in written and oral and formats that have been approved by the HREC and in a language fully comprehensible

to the potential participant or their surrogate decision maker parent/guardian. An independent interpreter should be available for those with limited English literacy skills and this person should witness the signed informed consent form. A copy of the information statement and informed consent form must be provided to the participant.

5.6   Screening and Subject identification

Subject numbers will be assigned sequentially to subjects at randomisation. These numbers will become study identifiers for the subjects and will be used on all study records.

Each study site will have its own individual code for identification.

5.7   Inclusion and Exclusion criteria

As described in study synopsis

Literature suggests no real safety concern when adding Flucloxacillin to a medication regimen already containing a beta-lactam with Vancomycin. Issue is one of efficacy, it will be impossible to see the result of Flucloxacillin if the patient is on other beta-lactams. Plan to try to enrol patient even if on other beta-lactams, using the following steps:

- If the beta-lactam can be ceased, encourage the treating team to cease it (e.g. most cases of MRSA bacteraemia).
- If the team feels that broader antibiotic cover is still needed, assess them from a general ID point of view and encourage cessation of beta-lactam unless truly necessary.
- If expanded cover is truly necessary, suggest an alternative regimen not including beta-lactams e.g. ciprofloxacin added to the Vancomycin.
- Only if all the above steps have been gone through, and the treating team still insist on continuing the beta-lactam, then the patient should be considered ineligible and not recruited (ie new exclusion criterion: Current beta-lactam therapy which can not be ceased or substituted.)

5.8   Treatment allocation
- Randomised (1:1) using sealed, sequentially marked, opaque envelopes, stratified by site.

5.9   Additional Treatments and study withdrawal

The clinicians caring for the patients will be asked not to make unnecessary changes to the patient's antibiotic regimen. However, if clinically indicated, the patient's clinician may change the antibiotic regimen.

If this involved the addition of another drug, but continuation of study drug(s), this fact will be recorded and the study will continue

If either flucloxacillin or vancomycin are ceased by the treating clinician (because of adverse events), this will be recorded and follow up data will continue to be collected (including blood tests and clinical assessments)

The participant may choose to withdraw from the study at any time. If they do so, permission will be sought to use the data already collected. IF they refuse, these data will be destroyed and will not be further analysed.

5.10 Medication dosage and administration

Intravenous vancomycin will be dosed as per the Australian Antibiotic Guidelines version 14, as below:

Creatinine clearance [NB1]	Starting dose [NB2]	Timing of trough concentration measurement
(mL/min)		
greater than 90	1.5 g 12-hourly	before the fourth dose
60 to 90	1 g 12-hourly	before the fourth dose
30 to less than 60	1 g 24-hourly	before the third dose
NB1: Creatinine clearance is reported in the laboratory electrolyte results or can be approximated using the modified Cockcroft-Gault formula. NB2: **Individual doses of vancomycin should be infused at a rate not exceeding 10 mg/minute**. Shorter infusion times can be trialled and used if tolerated, but should not be less than 60 minutes. If 'red-man' syndrome occurs, the infusion time should be extended.		

Intravenous flucloxacillin will be dosed at 2g q6h IVI, each dose as a slow bolus over 10-30 minutes. This dose will be adjusted for renal function as per the Australian Antibiotic Guidelines version 14

5.10.1 Dispensing and administration
Vancomycin and flucloxacillin will be prescribed by the treating clinical team (after discussion with the research team) using standard hospital prescribing. They will be provided by the hospital pharmacy and administered by the registered nurse who is caring for the patient.

5.11 Sample collection

- o Blood cultures will be collected once per day into standard BacTec bottles, both aerobic and anaerobic, **with 8-10ml in each bottle**. This will occur for the first 7 days in all patients. If the day 7 blood culture is negative at 48hours, no further blood cultures will be taken unless clinically indicated. Otherwise, blood cultures will be collected every 2nd day till negative for MRSA after 48 hours of incubation.

- o In addition, an EDTA tube (4-6ml) and a Lithium Heparin tube (4-6ml) will be collected for FBC (EDTA tube) and LFTs, EUC, CRP (LiHep tube). The clinical team will be asked to arrange this as part of usual care, but if necessary, the research team will make sure this blood is collected and sent. These bloods will be collected for days 1-7 and on day 10.

5.12 Laboratory procedures and methods

5.12.1 Pre-recruitment

All blood cultures which flag positive will have a Gram stain done as per standard laboratory protocols. During the recruitment period, if the Gram stain shows Gram positive cocci in clusters (GPCC), a sample from the blood culture bottle will be tested by a rapid molecular test to confirm the presence of MRSA.

The particular test used may vary between sites. At RDH, the Cepheid GeneXpert platform will be used, and will give a result within 2 hours of the blood culture bottle flagging as positive. Other sites will use either the Cepheid GeneXpert platform or an internally validated PCR assay.

Once a patient has had MRSA identified in blood cultures, subsequent positive blood cultures from the same admission will NOT be tested by a rapid molecular test.

5.12.2 Post-recruitment

Blood cultures will be processed as per usual lab protocols. Further rapid molecular tests will not be done. All bacterial isolates will be frozen and stored as per standard lab practice.

6 Adverse events

All participants will be monitored for adverse events.

As the two medications are licensed with established safety profiles, monitoring of non-serious adverse events will not occur. It will be the responsibility of the investigators, with the help of an independent safety monitor, to ensure that all serious adverse events (SAEs) and medically significant adverse events are documented and accurately reported.

6.1 SAE definition

A SAE is defined as any experience that:
- o Results in death
- o Is life-threatening
- o Requires unexpected prolongation of existing hospitalisation
- o Results in persistent or significant disability/incapacity

The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically may have caused death, if it were more serious.

6.2 Causality

The principle site investigator will make a judgement regarding whether an adverse event is clinically significant and whether or not it is related to the allocated treatment. The degree of certainty with which an adverse event is attributable to treatment or an alternative cause will be determined by how well the event can be understood in terms of:
- o Temporal relationship with the administration of the treatment or cessation of treatment
- o Reactions of a similar nature previously observed in the individual or others following treatment.

The relationship of the adverse event to treatment will be specified as follows:

Not related   In the PI's opinion, there is not a causal relationship

Unlikely   The temporal association between treatment and the adverse event is such that treatment is not likely to have any reasonable association.

Possibly   The adverse event could have been caused by treatment.

Probably   The adverse event follows a temporal sequence from the time of treatment and cannot be reasonably explained by the known characteristics of the subject's clinical presentation/history.

Definitely   The adverse event follows a reasonable temporal sequence from the time of treatment or reappears when the treatment is repeated.

6.3 SAE and medically significant event reporting.

An Independent Study Monitor will be appointed. This person will be a medical specialist with expertise in the treatment of infections, who is not an investigator on the study.

Any SAE and medically significant event must be reported to the Principle Site investigator within 24 hours of becoming aware of the event. The delegated PSI will complete the SAE form with as much information regarding the event that is available to them at the time.

SAE's are to be reported to the Chief Investigators within 1 week of notification. The Chief Investigators will pass all SAE reports to the Independent Safety Monitor (ISM) for evaluation. The ISM will decide if any immediate action needs to be taken, including whether the HREC should be notified immediately. The ISM will compile all SAE reports and submit a summary every 3 months to the HREC of the Menzies School of Health Research and the Northern Territory Department of Health and Families.

If the SAE is considered related to the study medication and unexpected, the event must be reported by the Chief Investigator to the Therapeutic Goods Administration (TGA) within the required reporting timeframes of the event occurring and/or being aware of the event (7 days for fatal or life-threatening conditions, 15 days for all others).

7   Statistics

7.1   Sample size estimation

The primary aim is to demonstrate feasibility and gather data to inform study design of a subsequent larger study powered for mortality. For this pilot study, sample size was estimated for the aim of determining the duration of bacteraemia in each group. Using a 95% confidence interval of 2 days, and assuming a standard deviation of 5.1 days (derived from unpublished data from an RCT of daptomycin for MRSA bacteraemia), we would need 27 patients in each group=54, plus 10% correction factor for drop-out=60 patients. This was calculated using the t-distibution.

7.2   Data analyses

7.2.1   *Participant groups for analysis*

All subjects randomised will be eligible for inclusion in the intention-to-treat analyses (ITT). All subjects randomised who complete all study visits and procedures and for whom complete data are available will be eligible for inclusion in the per-protocol analyses (PPA).

7.2.2   *Primary endpoint analyses*

To allow for possible early deaths due to MRSA bacteraemia, duration of bacteraemia in the two groups will be compared using a survival analysis approach.

If necessary, multivariate linear regression analysis will be used to adjust for important baseline differences between the two groups.

7.2.3   *Secondary endpoint analyses*

For analyses of secondary outcomes, mortality rates and treatment failure rates will be compared using the difference between two proportions.

A separate analysis will also be conducted using survival analysis, with Kaplan Meier Curves, and bacteraemia-free survival as the outcome.

7.2.4 Interim analysis

No interim efficacy analysis will be conducted.

Interim safety analyses will be conducted at 3-monthly intervals by the ISM, who will report these to the Chief Investigators and HREC.

8 Data management

Paper CRFs will be completed for all participants

Scanned copies of the paper CRFs will be sent to the central study site (the Menzies School of Health Research) for entry into a password protected database. They will then be kept at Menzies for 15 years in a locked filing cabinet.

All paper CRFs will be checked by the Chief Investigators, and data queries will be resolved with the relevant site PI before data entry.

Data will be analysed by JD and ST at Menzies, with help from Adrienne Kirby. Raw data and analysis logs will be available to all authors of the manuscript.

9 Publication

The data will be owned by the CAMERA management committee

The first draft of the manuscript will be written by JD and ST, and subsequent drafts will have input from the rest of the management committee.

The Australian Society for Infectious Diseases Clinical Research Network (ASID CRN) steering committee will be asked to provide feedback on the manuscript prior to submission for publication. The decision where and whether to publish will be made by the management committee.

The authorship of the paper will be all of the management committee " . . .and the ASID Clinical Research Network".

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