



## Standard Operating Procedures

### 4.7.1 Randomisation and allocation ©2008

History			
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1.1	21 <sup>st</sup> August 2007	B Fazekas	New procedure adapted from Oxygen study SOP V4.2.6
1.2	14 <sup>th</sup> December 2007	B Fazekas	Update after MAB review
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Approval				
Version	Author	Signature	Approval Name	Approval Signature
1.3	B Fazekas	<i>B. Fazekas</i>	David Currow (CI)	<i>David Currow</i>

Scheduled review

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Responsible person Project Officer

## Purpose

Rigorous methodology for randomisation, and for the allocation of people to study interventions, is a critical element of randomised trials.

Correct documentation of the randomisation and allocation process ensures that the study results can be verified and are able to withstand external examination. Errors in the randomisation procedure itself, or shortcomings in documentation of the randomisation and allocation procedures, would expose the study results to criticism; this critique could, in turn, render the results questionable. This situation should be avoided at all costs.

Poor allocation concealment is associated with bias, and the quality of a trial can affect the estimates of the efficacy of the intervention (Moher 1998). Therefore both design and reporting of studies should be accurate and complete (Schulz 1995). If PaCCSC trials are to be assessed as high quality, all stages (design, execution and reporting) must be of the best possible standard. One of the established mechanisms for assessing the quality of a trial via its report is through the use of a Jadad score. This score allows a score to be allocated to the study by external review. A maximum score of 5 indicates high quality randomisation and masking of allocation (Jadad 1996).

This Standard Operating Procedure (SOP) document details the procedures by which people are allocated to an intervention, and the roles and responsibilities of each party involved in these procedures.

This SOP does not describe the randomisation process by which the allocation codes were generated prior to distribution to each site. This process is described in the study protocol (i.e., blocks of 4 were used to generate allocation codes using standard random tables) and is recorded by the central randomisation service.

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### Related SOPs

5.14.1 Investigational Product Handling

4.7.2 Unblinding

5.5.1 Electronic Data Handling

5.5.5 Allocation of Identification Numbers

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### Appendices

- A: Prescription for study drug example
  - B: Stratum randomisation table example
  - C: File note example
  - D: Participant registration fax
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## References

Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled ClinTrials* 1996; 17:1-12.

Moher D, Jones A, Cook D et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; 352: 609-13

Notes for Guidance on Good Clinical Practice (GCP/ICH/135/95) annotated with TGA comments. July 2000.

Schulz KF, Chalmers I, Hayes RJ et al. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; 273: 408-412.

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## Acknowledgments

Trans-Tasman Radiation Oncology Group (TROG), for generous access to the Policy and Procedure Manual – the Red Book.

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## Definitions

**Allocation** – The assignment of an intervention to the person enrolled in a PaCCSC study according to the randomisation table.

**Allocation code** – The code which identifies the intervention to which the person is assigned; the code is the output from the randomisation process. This code (A=intervention 1, B=intervention 2, and C=intervention 3) does not change throughout the study or from one site to another.

**Blinding** – The procedure in which one or more parties in the study are kept unaware of the treatment assignment (i.e., medicine 1 vs medicine 2, study medicine vs placebo) or the allocation code (i.e., A or B). All studies in PaCCSC are double-blind, meaning that the person participating, investigators, and other study staff are unaware of the treatment assignment. This process is also called “masking”. The allocation code and person’s treatment assignment are known to:

- each Site Pharmacy involved in administration of blinded medicine as the study intervention; the site pharmacy holds the record of randomisation for that site;
- the Study Statistician who is responsible for reporting unblinded analyses to the Data Safety Monitoring Board (DSMB) and
- the Central Randomisation Centre where the schedules for each site were developed.

**CareSearch** – The web-based electronic data capture system used in the PaCCSC studies.

**Case Report Form (CRF)** - A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject. All events described within the study protocol should be captured the CRF.

**Central Randomisation Service** – The service where the allocation codes for the whole study, across all sites, are generated. The schedule for each site is prepared and sent to the coordinating site for distribution to the site pharmacies.

**Central Registry** – The location that holds the allocation codes for each person participating in a trial in the form of unblinding envelopes. This will vary from one study to the next, and is specified within the study protocol. This location may include; the site pharmacy, a central pharmacy (a pharmacy nominated to hold the unblinding envelopes), the lead investigator or, the central randomisation service.

**Coordinating Site** – The Coordinating Site for PaCCSC is Flinders University located at Southern Adelaide Palliative Services in Daw Park, South Australia (the palliative care program associated with Flinders University). The National Manager and Project Officer at this site work closely with the Lead Investigator, all Study Investigators, the local site staff, the Study Statistician, and the Central Randomisation Service to manage the day-to-day operations of the study procedures.

**Day 1** – The day that the intervention commences. Days are numbered according to the study schema (see the study protocols).

**Intervention** – The medicine, equipment or procedure being tested by the study protocol. The interventions vary according to each study protocol. In the PaCCSC studies, the interventions are medicines prepared so that the active and inactive (or active and comparator) medicine look, smell and taste the same as each other.

**Randomisation** – The process of allocating people to one treatment group or the other using an element of chance to determine the assignment. Randomisation is meant to reduce the chance of systematic bias that can be encountered when investigators, study staff, or study participants make decisions regarding which intervention is received by which participant. In most cases, blocks and standard random number tables are used to generate the allocation codes. An independent research group not associated with PaCCSC have been contracted to undertake the randomisation for PaCCSC.

**Site Pharmacy** – The local pharmacy who has been contracted to undertake the randomisation at the study site, maintain the allocation logs, and supply the study medicines. The Site Pharmacy is usually on-site and has the capacity, storage and procedures to undertake preparation of clinical medicine trial materials, but in some situations, there may be a pharmacy to manufacture the study medicine and another to dispense the study medicine.

**Stratum and Strata** - A “stratum” designates the study group within which an individual person is categorised (the plural term for stratum is “strata”). This may be by demographic (age group, gender, diagnosis) or by disease stage or some other parameter where the investigators decide that stratification is required. Not all studies will require stratification at the point of randomisation.

**Study Site** – The local site for person enrolment and study conduct. Each site has a local Site Investigator, local site study staff, and an associated site pharmacy.

**Study Statistician** – The lead statistician for the trial. The Study Statistician is responsible for all study analyses, and final trial reporting. The Study Statistician is also responsible for reporting unblinded data to the DSMB. The Study Statistician may vary between studies.

**Unblinding** – Unblinding is the process by which the allocation code is broken so that the investigator, clinical staff and/or the trial statistician becomes aware of the intervention for a person participating in a trial. The usual reason for unblinding in a study context is that a person participating in the study has encountered an urgent medical problem necessitating that the clinician know his/her intervention allocation. People are not unblinded at the end of their participation in the study.

## Randomisation and Allocation Procedures

This document is organised in sections corresponding to each of the parties actively involved in the study's randomisation and allocation procedures.

### 1. Study Site

When a person has provided consent for the study and is eligible for the study, they are then ready to enter the study and will need to be randomised.

The study nurse will need to determine the day a person is to begin the study (Day 1) to ensure that all study procedures, such as, medicine supply, and medical review, can be undertaken at the times specified within the study protocol. This can be via email, telephone, or fax, and is an informal request at this point.

When Day 1 has been determined a formal request for randomisation needs to be recorded. For most PaCCSC studies this formal request will be a signed prescription by the investigator, as the studies involve medicines and require a medical order (see 5.14.1 Investigational Product Handling SOP).

After confirmation of the randomisation from the Site Pharmacy, the study nurse will be provided with the randomisation strata letter and number (see 5.5.5 Allocation of Identification Number SOP). This string will be recorded in the Patient Master Index, and on all subsequent CRF's for that person. For example;

The explanation of the ID number structure can be

- Study code/Site code/ID number

In practice, the actual ID number will thus be

- 01/02/001

This number indicates the following participant details

- Ketamine study/Braeside/individual number 001

### 2. Site Pharmacy

Procedures for randomisation and allocation will be kept in the randomisation folder at each site; all documents related to the procedure are to be filed within the folder.

The Site Pharmacy will receive a folder from the Coordinating Site containing allocation code schedules (sealed), instructions, study protocols, medicine accountability logs, and documents related to the recording and reporting of study randomisation for each study. This folder is to be maintained by the clinical trials pharmacist in keeping with Good Clinical Practice.

At the time a person is to be randomised and allocated to an intervention, the Site Pharmacy receives a prescription (which will also confirm the stratum assignment). This serves as confirmation of the person's eligibility for the study, and specifies the day that the Site Pharmacy should deliver the intervention to the patient (Day 1). All prescriptions for the use of study medicine for clinical trials must be:

- a. Completed by a person authorised to do so
    - i. The site investigator
    - ii. Sub investigators
    - iii. Those medically authorised to prescribe the specific medicine under investigation
  - b. Completed on a hospital prescription form, which can include the inpatient medication chart, or study specific form approved by the local HREC
  - c. Include a full description of the
    - i. Details of the person participating that can uniquely identify them (including identification number, date of birth, address and stratum, if applicable)
    - ii. Study protocol number
    - iii. Medicine
    - iv. Dose
    - v. Frequency
    - vi. Routeas specified within the study protocol and/or study implementation procedures
  - d. In accordance with standard hospital prescription orders.
- c) The Site Pharmacy checks the prescription for completeness and legibility. The study site will be notified if the prescription does not meet requirements.
- e) The Site Pharmacy refers to the appropriate randomisation table in order to determine the allocation code the patient should receive.
- f) Site Pharmacy staff locate the next available randomisation number, taking into account any strata requirements that may apply.
- g) Should the Site Pharmacy receive more than one request in one day, it:
  - o Undertakes the randomisation procedure **in the order that the prescriptions were received;**
  - o Records each randomisation according to the prescription, and completes the procedure before undertaking the next randomisation.
- j) If the Site Pharmacy makes an error in recording data within a particular strata table or schedule, the Site Pharmacy should take following actions:
  - Strike out the error with a single line, then sign and date the randomisation log next to the error.
    - Use pen and ink, but not liquid paper.
    - Do not obliterate the original error; the original writing must remain intact and visible.
  - Prepare a file note (Appendix D) that includes the following details:

- Identification number
  - Original and new entry
  - Reason for the change
  - Date of the change
  - Signature of the person verifying the change
- File the file note in the Randomisation Folder.
  - The file note must be completed, and filed in the randomisation folder within one working day of realising the error.
  - If an entry is written in error and 'struck out' (has a line put through the entry), the randomisation number for that line is to be used for the next participant to be recorded within that stratum. The line is to be treated as if it was left blank.
  - There are to be no gaps in the table.
    - For example: Lines that have been left blank and missed (or struck out) are to be used for the next person and given the allocation according to that line. If a number of lines have been left blank, and an allocation recorded further down the page (in error), each line is to be used sequentially until all lines have been completed.
- k) The Site Pharmacy completes a participant registration fax and faxes this to the Coordinating Site on the day of the randomisation.
- m) The Site Pharmacy prepares the study medicine according to the allocation code for each individual person.
- n) The Site Pharmacy delivers the study medicine to the person participating in the study (or the ward if inpatient, or the study nurse if the study drug is to be delivered to the person at home) on the day specified within the study protocol (this might be the previous day in the case of people at home for the morning intervention doses) and as per the arrangements already confirmed with the study nurse.
- o) The Site Pharmacy performs internal checks and maintains records that make it possible to verify that the person actually received the intervention as determined by the allocation code.
- p) The Site Pharmacy maintains the stratum randomisation table until completion of the study. At the end of the study and after the close out monitoring visit, the study folder containing all of the randomisation records, instructions and related correspondence are passed to the Study Statistician by the most secure means possible (this might be registered and secure mail for example). The Site Pharmacy should receipt the postage cost and invoice the Coordinating Site for reimbursement of the cost.

### **3. Coordinating Site**

The role of the Coordinating Site is to manage the day-to-day operations of the study.

The Coordinating Site:

- a) Receives automatic notification when the Study Site has entered eligibility and baseline data (including any stratum data) into CareSearch.
  
- b) Upon automated email notification of data entry from CareSearch, checks;
  - a. the randomisation data against the expected stratum assignment based upon the predetermined characteristics. For example,
    - i. the patient will have been recorded as strata 'V' in the Ketamine study if the LANSS is more than 12
  - b. all eligibility have been met prior to the randomisation process
- c) Maintains a log of those enrolled in the study as per the data entry and compares the participant registration faxes received from the Site Pharmacies,
- d) If discrepancies are identified the Coordinating Site contacts the Study Site.

#### **4. Central Randomisation Service**

The primary responsibility of the Central Randomisation Service is to develop the schedules for each site for each study, and to provide a mechanism by which the code can be broken (unblinding envelopes).

#### **5. Contact details**

Any problems with completion of the allocation table should be directed to;

Ms Vicki Beal  
Data Associate  
Centre for Pharmaceutical Research  
Sansom Institute  
University of South Australia  
Phone +61 8 8302 2034  
Fax +61 8 8302 2501  
Email : [victoria.beal@unisa.edu.au](mailto:victoria.beal@unisa.edu.au)

Any problems with materials, procedures, timeframes or other questions should be directed to;

Ms Belinda Fazekas  
Project Officer  
Palliative Care Clinical Studies Collaborative  
Flinders University  
700 Goodwood Road  
Daw Park, SA 5041  
Telephone; +61 08 8275 1396  
[Belinda.fazekas@rgh.sa.gov.au](mailto:Belinda.fazekas@rgh.sa.gov.au)

## Prescription sample – Ketamine study



**PaCCSC**  
Palliative Care Clinical Studies Collaborative

**001/07**

**Ketamine for cancer pain**

The prescription for requesting study medicine must be;

- Written by an appropriately qualified person
- Written on the hospital prescription forms,
  - either the inpatient medication forms or
  - a negotiated prescription form
- Written in the doctors own handwriting,
  - Signed
  - Dated
  - In black ink pen
  - Written in full as shown below.

001/07 STUDY
KETAMINE OR PLACEBO 100MG, 300MG OR 500MG
PLEASE SUPPLY 12 (TWELVE) SYRINGES FOR S.C. INFUSION
5(FIVE) X 100MG KETAMINE IN 15MLS NaCl 0.9% OR PLACEBO
4(FOUR) X 300MG IN 15MLS Na Cl 0.9% OR PLACEBO
3(THREE) X 500MG IN 15MLS Na Cl 0.9% OR PLACEBO
TOTAL QUANTITY 3200 MG (THREE THOUSAND TWO HUNDRED MG) OF KETAMINE OR PLACEBO



## **File note.**

### **Purpose**

File notes are to ensure that any changes or actions taken regarding the study are documented and are able to be authenticated by any member of the study team and monitors.

Any changes to data and study related documentation that does not have an associated file note is subject to suspicion and doubt, leading to possible exclusion of the participants data from the analysis.

Complete one of these forms for each and every change made to the recording of data that does not have a data query form.

### **Instructions**

All of the following sections are to be completed by the person who made the change or another who can authenticate the change. The original is to be stored at the site of origin, a copy is to be forwarded to the Coordinating site.

### **Note:**

**Date of change:**

**Changed from:**

**Changed to:**

**Changed by:**

**Date of File note:**

**Signature of person completing file note.**



# Participant Registration Fax

To: **National Project Officer** From: \_\_\_\_\_

Fax: **+61 8 8374 0350** Fax: \_\_\_\_\_

Phone: **+61 8 8275 1396** Phone: \_\_\_\_\_

Pages: **1** Date: \_\_\_\_\_

## Dear Coordinating site

The following patient has been randomised for a PaCCSC clinical study.

Study ID Number:	
Strata:	
Site Name	
Randomisation date	
Date of treatment commencement	

Yours sincerely

Site Pharmacy: