Standard Operating Procedure

4.7.2 Unblinding

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Introduction / Background

Unblinding is the process by which the allocation code is broken revealing the intervention allocated to the participant. Unblinding is undertaken by a pre-determined process to ensure that participants are not unblinded unnecessarily and study results are not compromised.

Emergency unblinding occurs when clinically indicated, in the following circumstances:

- When clinical treatment decisions require the intervention to be known;
- When an unexpected Serious Adverse Event occurs, and the intervention must be made known.

Other circumstances when unblinding occurs are:

- When an (unblinded) interim analysis is required, in accordance with the study analysis plan;
- When requested by the PaCCSC/CST/ITCC Data Safety Monitoring Committee;
- At the conclusion of the study, to determine the effect of the intervention.

Objective

This SOP describes the timing and process for unblinding to ensure correct unblinding procedures are followed.

Scope

This SOP applies to all staff involved in clinical studies conducted by the by the IMPACCT Trials Coordination Centre (ITCC), including Palliative Care Clinical Studies Collaborative (PaCCSC) and Cancer Symptom Trials (CST) irrespective of individual organisational employment, role or position.

Ownership and Responsibility

Responsibilities of the Coordinating Principal Investigator (CPI)

- To approve unblinding for safety reasons (emergency unblinding), for unblinded analysis and on study completion
- To inform the ITCC that unblinding has been approved

Responsibilities of the Principal Investigator and/or other designee(s) as documented in the Staff Signatures and Delegation Log (refer SOP 4.2.4 Delegation of Duties)

- To assess the need for unblinding
- To request approval for unblinding from the Coordinating Principal Investigator
- To record participant withdrawal in case of unblinding

Responsibilities of the ITCC

- To coordinate between the Coordinating Principal Investigator, Lead Statistician, Site Pharmacies/Contracted External Third-Party Pharmacy.
- To contact the Central Randomisation Service to request unblinding of individual participants
- To obtain randomisation schedules from study sites and site pharmacies or contracted external third-party pharmacy

Responsibilities of the Lead Statistician

- To merge the randomisation schedules and allocation schedules
- To merge main study data with the allocations in preparation for analysis
- To complete the unblinded analysis as determined by the PaCCSC/CST/ITCC Data Safety Monitoring Committee

Responsibilities of the PaCCSC/CST/ITCC Data Safety Monitoring Committee (DSMC)

- To determine when an unblinded analysis is required

Procedure

1. Individual participant – emergency unblinding

- If a Serious Adverse Event occurs (where the participant's wellbeing may be compromised), the Principal Investigator, in consultation with the clinical team, assesses the need for unblinding.
- If unblinding is indicated, the Principal Investigator contacts the Coordinating Principal Investigator to discuss the clinical situation and request approval for unblinding
- If approval to unblind is confirmed, the Coordinating Principal Investigator contacts the ITCC Central Randomisation Service, or the ITCC National Project Officer (as described in each study protocol) and provides the following information:
    - Caller details (own name and position)
    - Study site
    - Principal investigator
    - Study protocol number or identifier
    - Participant Identification Number
    - Randomisation number
    - Date of birth of participant
    - The reason for unblinding
- Upon receipt of an unblinding request, the Central Randomisation Service:
    - Completes an Unblind Request Form (Template 18) and obtains the unblinding contact details (Guidance 7) (this is filed for future auditing)
    - Discusses the unblinding authorisation with the Coordinating Principal Investigator if appropriate
    - Identifies the unblinding information (envelope, schedule or similar) associated with the specific randomisation number (Guidance 8) provided by the Coordinating Principal Investigator and determines the intervention allocation.
- The Central Randomisation Service contacts the site and informs the Principal Investigator and the Site Pharmacy of the intervention allocation.
- The Central Randomisation Service completes an Unblind Report Notification (Template 19) and emails this to the ITCC.
- When a participant is unblinded, the Principal Investigator (or delegate) records the participant withdrawal and allocation in their clinical and study notes along with the appropriate clinical notations.
- The ITCC logs the Unblind Reports and periodically reports unblinding rates to the Study Sub-committee and relevant Scientific Advisory Committee (SAC).
    - Aggregated assessment of unblinding for each study will be provided by the ITCC appointed Medical Monitor and/or the relevant SAC every six months (*refer* SOP 5.17.1 Medical Monitor).

2. Unblinded analysis

- The individual trial Data Safety Monitoring Committee (DSMC) or Medical Monitor (MM) determines when an unblinded analysis is required. This decision is documented within the DSMC meeting minutes or email correspondence.
- A written request for unblinding analysis is made by the DSMC/MM to the Coordinating Principal Investigator.
- Upon receipt of the request, the Coordinating Principal Investigator requests the ITCC to provide the randomisation schedules to the Lead Statistician or the DSMC.
- The ITCC makes requests to all Site Pharmacies or the contracted external Third-Party Pharmacy to copy the table of allocation schedules and email to the Lead Statistician or DSMC, or requests that the Central Randomisation Service provide the list of intervention allocations to date.
- If via pharmacies, each Site Pharmacy or the contracted Third-Party External Pharmacy checks their allocation logs for completeness and the pharmacist must date and sign the last entry on in the allocation log with a note to indicate the request. The table of allocation schedules is then copied and emailed to the Lead Statistician or DSMC:
    - Email subject line must clearly indicate that unblinding information is contained in the email (e.g. UNBLINDED INFORMATION: [Protocol ID] _ [Site ID] _Intervention Allocation Schedules)
- Upon receipt of all the allocation schedules from the study sites, the Lead Statistician merges the study data with the table of allocation codes as per the data transfer instructions (*refer* SOP 5.5.2 Electronic Data Transfer).
- The Lead Statistician completes the unblinded analysis as determined by the DSMC.

3. Unblinding on study completion

- The Coordinating Principal Investigator determines that study recruitment is complete and unblinding is required for analysis.
- The Coordinating Principal Investigator (or Lead Statistician) makes a written request to the ITCC to proceed with study unblinding.
- Upon receiving the written request to unblind the study, the ITCC either:
    - contacts each Site Pharmacy or the contracted Third-Party External Pharmacy and requests a copy of the randomisation schedule for the study to be sent by registered mail, or to be scanned and emailed. Upon receipt of a request from the ITCC, each Site Pharmacy/ contracted Third-Party External Pharmacy:
        - checks the randomisation schedule for completeness;
        - signs and dates the last entry;
        - provides the Coordinating Centre with the randomisation schedule;
        - ensures all invoicing is completed; *or*
    - collates the Randomisation Record held by the Central Randomisation Service and;

- requests the return of all unblinding envelopes (if used) for the study by registered mail;
- enters all Participant Identification Numbers and intervention allocations into an Excel file;
- sends the Excel file via email to the Lead Statistician (*refer* SOP 5.5.2 Electronic Data Transfer).

- Upon receipt of the Excel file from the ITCC, the Lead Statistician:
  - Confirms receipt of the Excel file containing the Participant ID numbers and intervention allocations (to the Coordinating Centre);
  - Merges the main study data with the new Excel file in preparation for analysis.

Related SOPs

4.2.4 Delegation of Duties
4.7.1 Randomisation and Allocation
5.5.1 Electronic Data Handling
5.5.2 Electronic Data Transfer
5.5.5 Allocation of Participant ID Numbers

Related documents

Template 18: Unblind Request Form
Template 19: Unblind Report Notification
Guidance 7: Unblind Contact Numbers
Guidance 8: PID Number Sequencing

References

Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Annotated with TGA comments 2000 (accessed 17/10/2017)
https://www.tga.gov.au/sites/default/files/ich13595an.pdf

Acknowledgments

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

History			
Version	Date	Author	Reason
1.1	21/08/2007	B Fazekas	New procedure
1.2	14/12/2007	B Fazekas	Update after MAB review
1.3	19/02/2008	B Fazekas	Update after David Currow review
1.4	7/06/2010	B Fazekas T Shelby-James	Periodic review
2.0	3/02/2011	B Fazekas	Changes ratified by MAB
2.1	28/10/2013	B Fazekas L Devilee	Review of procedure following unblinding
2.2	18/05/2015	C Hope	Periodic review
2.3	28/02/2018	B Fazekas, S Kochovska	Periodic review Publication of the ICH GCP E6 (R2)
2.4	16/03/2020	C Strauss	Periodic review
2.5	06/01/2022	C Strauss	Periodic review

Approval		
Version	Approval Name	Approval Signature
2.5	Meera Agar