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Clinical Trial Research Agreements (CTRA): Guidance for anaesthesia research teams and investigators

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Purpose of document:

This document provides guidance for ANZCA Clinical Trials Network (CTN) members on the development, review, and management of Clinical Trial Research Agreements (CTRAs). It incorporates practical insights from experienced project manager Belinda Howe, addressing both Australian and New Zealand contexts. It includes updates based on the 2024–2025 template revisions issued by Medicines Australia and Medical Technology Association of Australia (MTAA).

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Version	Contributors	Reviewed/Approved	Date Approved by ARCN Sub-Committee & CTN Executive	Changes
1.0	Belinda Howe Paige Druce Gillian Ormond Karen Goulding	Samantha Ryan Samantha Bates A/Prof David Highton	1/8/25	Creation

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1. Overview of CTRAs

CTRAs are legally binding contracts that govern the conduct of clinical trials. They outline the responsibilities, obligations, and expectations of all parties involved, including investigators, hospitals, universities, research institutes, and sponsors.

CTRAs must be aligned with the trial's ethics approval to ensure both legal and ethical consistency. Discrepancies between legal agreements and ethics approvals can lead to non-compliance and jeopardise trial integrity.

2. CTRA templates and use

- Australia: Use Medicines Australia CTRA templates:
  - Sponsor-Initiated: Medicines Australia Standard CTRA.
  - Contract Research Organisations: Contract Research Organisation CTRA.
  - Investigator/Academic-Led: Collaborative Research Group (CRG) CTRA.
  - Phase 4 Clinical Trial (Medicines).
  - Phase 4 Clinical Trial (Medicines) Contract Research Organisation acting as the Local Sponsor.
  - Teletrials Subcontract.
- Device studies: Use the MTAA Clinical Investigation Research Agreement (CIRA).
- New Zealand: Use templates from the New Zealand Association of Clinical Research (NZACRes), including helpful guidance documents and addendum templates.

Note: NZ templates were modelled on Australian versions but often contain clearer and more user-friendly language.

3. Structure of the CTRA

- Main body: Standardised and should not be altered.
- Schedules (e.g., Schedule 4/7 in AU, Schedule 5 in NZ): Contain trial-specific modifications known as "special conditions". These override the main body in case of conflicts.

4. When to modify CTRAs

Changes should be made using the appropriate schedules. Some common scenarios include:

- Opt-out consent or emergency recruitment where prior written consent is not possible.
- Centralised follow-up requiring transfer of identifying data.
- Multi-national or tripartite agreements where local templates are not accepted.

It is generally recommended to use standard templates to avoid legal review delays and additional costs. Non-standard CTRAs often prolong start-up timelines.

5. Guidance for collaborative clinical trials supported by a grant funding agreement

There are a set of clauses that can be used when a non-commercial sponsor receives grant funding for a trial through a Funding Agreement (from NHMRC, MRFF or Cancer Australia) and wishes to pass through some of those obligations onto the institution. The variations consist of clauses for each funder with the CRG CTRAs.

You can find these standard clauses on the Medicines Australia website – your institution may also have CTRA templates with these clauses inserted.

6. Key clauses for research co-ordinators to review

a. Consent clause

Standard language requires written consent from participants prior to enrolment. This is not always feasible in critical care settings. Recommended action:

- Add a generic clause allowing for consent scenarios approved by HREC (e.g., delayed or opt-out consent).

b. Identifiable data Clause

Standard clauses may not permit transfer of identifying data to central follow-up sites. Recommended action:

- Include a clause permitting transfer of limited identifiable data to a coordinating centre for follow-up, if ethically approved.

c. Ineligible participant reimbursement

Some clauses state sponsors need not pay for participants later found to be ineligible. While rarely enforced, coordinators should:

- Be aware of the clause.
- Ensure rigorous eligibility screening to avoid disputes.

d. Data collection by CRG or Sponsor

Newer clauses allowing sponsors or CRGs to directly collect data at sites are problematic:

- Breach GCP (data collection is a PI-delegated responsibility).
- Undermine site-level data integrity and independence.
- Require HREC approval if implemented.

Recommended action: Avoid or modify such clauses.

7. Best practice tips

- Always read the special conditions schedule for each CTRA.
- Use generic clauses that cover multiple scenarios to avoid needing future amendments.
- If a clause is not relevant, it falls silent. Do not insert “Not Applicable” repeatedly.
- Schedule 2: For observational studies or no investigational product, list “nil” under product descriptions.

8. National Clinical Trial Agreement (NaCTA) Panel (previously known as SEBS Committee) Role (AU Only)

This panel reviews Australian clinical trial agreements, is a national panel and has representatives from all states and territories in Australia.

Changes to the existing clauses in the body of the template CTRA’s should go to NaCTA Panel for review. Although not mandatory to do, this can assist with a timely standardised review, where only one negotiation is required expediting RGO approvals.

Further guidance can be found on the Medicines Australia website.

9. Recommendations for the CTN

- Maintain a library of approved, flexible generic clauses that cover:
    - Consent (including opt-out/delayed).

- Identifiable data transfer.
- Data access and delegation responsibilities.

- Share templates and guidance with investigators and research coordinators.
- Align ethics and legal documentation during protocol development.
- Encourage site investigators and coordinators to review CTRA schedules carefully.

10. Budget and contract negotiations

- Non-commercial trials (Investigator Initiated Trials (ITT)): Limited negotiation due to fixed budgets. Clarify reimbursements (e.g., governance fees) case-by-case with project managers.
- Commercial trials: Budget negotiation usually done by site coordinators or trial managers, with PI sign-off. Budget templates should include:
  - Per participant costs
  - Screening time
  - Governance and regulatory costs
- Withholding fees: Clauses to hold back partial payments until database lock or close-out of a trial (can be common for commercial trials). As example, 10% withholding of scheduled visit fee. This strategy is used to ensure full and accurate data is completed before payment in its entirety is made. Be cautious in accepting this clause and consider the effect on your income flow during the trial.

11. Amendments and addendums

An amendment is when substantial changes to the original agreement are needed such as:

- Modifications to the protocol such as study endpoints or scheduled visits.
- Changes to payment terms.
- Changes to research personnel such as principal investigator, or change of site address.
- Changes to trial periods such as extension of recruitment timeline or trial duration.

An addendum is attached to the original trial contract and is used to add new terms or provisions to the contract without altering the core terms, such as:

- Clarification of language or terminology of a specific clause.
- Adding a new study site such as satellite site or another hospital site within the same health network.

12. 2024–2025 CTRA updates to note

a. Updated standardised templates

Medicines Australia released revised CTRA templates in late 2023, with continued relevance into 2025. Key updates include:

- Alignment with data privacy laws and international data sharing practices (e.g. GDPR-style protections)
- Standard clauses for remote monitoring and teletrials.
- Electronic consent (eConsent) and digital signature support.
- Expanded guidance on publication and data retention.

b. Digital signatures

Templates now explicitly allow for digital signatures, provided they comply with Australian and New Zealand electronic transaction legislation.

c. Remote access and Teletrial language

Templates now contain:

- Clauses for remote data monitoring and virtual site access
- Recognition of decentralised trial models

d. Updated device study templates (CIRA)

The MTAA CIRA templates now align with ISO 14155:2020. These revisions are essential for sponsors and sites conducting device-related studies.

13. Conclusion

CTRAs are essential for the governance, compliance, and smooth operation of clinical trials. For ANZCA CTN trials, ensuring consistency between legal and ethical documents, using standard templates, and proactively addressing problematic clauses protects both trial integrity and research coordinators.