Research Ethics and Governance

PREDICT Research Study Meeting

Tuesday 16th February 2016

Overview

- Ethics vs governance
- Roles and responsibilities for multi-site research
- Consent
- Indigenous considerations
- Adverse event reporting

Ethics Vs Governance

- Research ethics and governance are often assumed to be one and the same - but it is important to recognise the differences between them.
- **Research ethics** refers to the ethical considerations and dilemmas that apply to research in line with the principles of respect for human beings, research merit, integrity, justice, and beneficence.
- **Research governance** is the framework used to manage research through regulation and assurance. This includes risk management, compliance (with legislation, institutional policies, and best practice standards), quality management and ongoing monitoring (such as audit).
- In practice, this means research will receive an ethical review to ensure the rights, safety and welfare of participants, **and** a governance review to ensure institutional acceptability. A project will always receive both types of review, irrespective of whether the proposed research is single or multi-site.

The Guidelines

Ethics:

- The National Statement on Human Research (2007)
- Declaration of Helsinki
- ICH Good Clinical Practice
- Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research (NHMRC 2003)

Governance

- The Australian Code for the Responsible Conduct of Research (2007)
- Research Governance Handbook (2011)
- ICH Good Clinical Practice
- Institutional Policies and Procedures

Multi-site Research

- Multi-site research can be ethically approved under the National Mutual Acceptance Scheme (NMA)
- NMA enables human research that is to be conducted at multiple sites to undergo a single ethical review by a certified Human Research Ethics Committee (HREC).
- Once obtained the ethics approval can be accepted by the other participating sites who need only seek institutional governance authorisation. This reduces duplication associated with multiple ethical reviews.
- NMA is currently restricted to public health sites in VIC, NSW, ACT, QLD and SA.
- Mutual acceptance of ethics approval outside of NMA is at the discretion of each site.

Scope of NMA

- On the 13th December 2015, the scope of NMA expanded.
- NMA is now available for all human research, including low and negligible risk research (LNR).
- All NMA applications must be submitted using the National Ethics Application Form (NEAF) which is accessed via Online Forms.
- There are a number of state-specific exclusions from NMA to note. These include:
  - Phase I studies (ACT, SA)
  - Studies that specifically target Aboriginal and/or Torres strait islanders (ACT, NSW, QLD)
  - Studies that involve incarcerated persons and/or the use of coronial information (ACT, NSW, QLD, VIC)

Roles and Responsibilities for Multi-site Research

- All multi-site research **must** have a Coordinating Principal Investigator (CPI)
  - The CPI is the conduit between participating sites and the HREC.
  - The CPI is responsible for coordinating:
    - The development of study documents
    - Submitting the ethics application on behalf of all participating sites (master documents)
    - Annual progress reports to the HREC (by gathering reports from all sites and collating this into a single report for the HREC)
    - Safety reporting to the HREC (reporting adverse events from all participating sites)

- All participating sites **must** have a Principal Investigator (PI)
  - PI's are responsible for the conduct of the study at their site, including:
    - Applying for governance authorisation at their site prior to commencement (this includes preparing and submitting site specific documents including PICFs, and regulatory documents including research agreements, indemnities, eCTN etc.)
    - Submitting site specific annual progress reports to the governance officer
    - The CPI assumes the role of PI at their site and must also undertake the above governance activities.

Roles and Responsibilities - Delegations

- The PI may delegate study related tasks to suitably qualified, trained and experienced study staff (including associated investigators, study coordinators, RA's and other non-investigators) (GCP 4.1.5)
- A detailed account of all delegations issued by the PI must be recorded using a delegations log (GCP 4.1.5).
- **Even though a task may be delegated, the PI retains ultimate responsibility for all study related activities.**

Informed Consent

- Informed consent is required for all human research (where practical).
- Consent should be voluntary and should be based on a sufficient understanding of both the research itself and any implications that participation may have.
- The obtainment of informed consent is governed by:
  - National Statement 2007 (including all updates)
  - Australian Code for the Responsible Conduct of Research 2007
  - Privacy Act 1988 and Australian Privacy Principles 2014
- Consideration should also be given to relevant state based legislation and institutional policies when designing a study i.e. the Health Records Act (Vic) 2001.

Who can provide consent for paediatric research?

- When the participant is under the age of 18:
  - A parent or legal guardian must provide informed consent for that person to participate in research.
  - Where the participant is deemed as having sufficient competence and maturity to provide informed consent, consent should also be sought from the participant in addition to parent/guardian consent.

- When the participant is over the age of 18
  - The participant should provide informed consent if they are able to do so. Additional consent by the parent/guardian is not usually required.

- For longitudinal studies where a participant may reach the age 18 part-way through the study:
  - It may be appropriate to seek consent from the participant so there is no longer a need to rely on parent/guardian consent.

Types of Consent in Emergency Research

- Section 4.4.1 of the National Statement states that:
  - Research involving people who are highly dependent on medical care may be approved where: (a) it is likely that the research will lead to increased understanding about, or improvements in, the care of this population;
  - (b) the requirements of relevant jurisdictional laws are taken into account; and
  - (c) either (i) any risk or burden of the proposed research to this particular participant is justified by the potential benefits to him or her; or (ii) where participants have capacity to consent, any risk or burden is acceptable to them and justified by the potential benefits of the research

- If consent can be obtained prior to participation, it may be:
  - Written, verbal or implied (i.e. returning a questionnaire); or
  - Specified, extended or unspecified.

- If consent cannot be obtained prior to participation, it may be:
  - Delayed (to support immediate sampling or therapeutic intervention, but obtained as soon as possible afterward); or
  - Waived by a fully constituted HREC.

The type of consent chosen for a research study must be legally compliant, ethically defensible, and approved by a fully constituted HREC.

Indigenous Considerations

- Indigenous populations are considered a vulnerable group (GCP 1.6.1) (NS 4.7)

- The National Statement describes six additional key principles that must be upheld when conducting research involving indigenous persons:
  - Reciprocity
  - Respect
  - Equality
  - Responsibility
  - Survival and protection
  - Spirit and integrity

- Ethical considerations for indigenous research are largely based on whether recruitment is targeted or incidental.

Targeted vs Incidental Recruitment

- Incidental recruitment of indigenous persons does not require specialist ethical review, and cases should be treated by the study team in the same way as a non-research case.

- Projects with targeted recruitment must be justified and must demonstrate cultural sensitivity by:
  - Demonstrating consultation with individuals or groups who are part of, or who are heavily engaged with local indigenous groups (most large public hospitals have dedicated resources to assist with this);
  - Ensuring that participant materials are culturally sensitive and have been developed in consultation with local experts;
  - Ensuring appropriate ethical review. Most states participating in NMA exclude studies targeting the recruitment of indigenous populations. Instead, these applications should be reviewed by an Aboriginal HREC (such as the South Australian Aboriginal Health Ethics Committee, NSW Aboriginal Health and Medical Research Council Ethics Committee or Menzies), or a HREC with suitable specialist expertise.

Adverse Event Reporting

Adverse Events (AEs)

Any untoward medical occurrence to a participant which does not necessarily have a causal relationship with the treatment.

Serious Adverse Events (SAEs)

Any untoward medical occurrence, whether it is considered related to the study or not, that:

- results in death;
- is life threatening*;
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly / birth defect.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

- An SAE for which there is some degree of probability that the event is related to the study drug and the adverse reaction is unexpected, i.e. the nature or severity of which is not consistent with the applicable product information.
- SUSARs must be reported to the Therapeutic Goods Administration (TGA). For commercially sponsored studies the commercial sponsor may take on this responsibility, however for Investigator driven studies SUSAR reporting is the Principal Investigator's responsibility.

When and what to report

Event	CPI Responsibilities	PI Responsibilities
AE's/SAE's occurring in research participants on site	Report to approving HREC within 24-72 hours of study staff becoming aware of the SAE	Report to CPI and sponsor as soon as possible. Report to local RGO as soon as practicable.
Line listings of SUSARs occurring with a compound, including sponsor and investigator comment as to whether action is planned for the trial on the basis of the reports	Report to approving HREC at least six-monthly	
Updated Investigator Brochure or approved Product Information or other reports consistent with section 5.5.5 of the National Statement and Good Clinical Practice (GCP) as adopted by the Therapeutic Goods Administration (TGA).	Report to approving HREC at least annually	

**If the study is single site, the PI assumes the role of the CPI and reports directly to the HREC and/or sponsor.*

Sponsor Responsibilities

- The sponsor must report all fatal or life-threatening unexpected adverse drug reactions to the TGA as soon as possible, but no later than 7 days. All other serious, or unexpected adverse drug reactions should be reported no later than 15 days.

- Sponsors must continue to monitor safety throughout the trial.

- Safety data should be regularly assessed by an independent DSMB where possible.

- Any new safety information should be formally communicated to participants. Participants may need to be re-consented.

Summary of key points

- Ethics is concerned with the rights, safety and welfare of participants, whereas governance is the management framework to ensure institutional accountability.
- Multi-site research is reviewed in Australia using the NMA scheme, which is now open to all human research, including low risk.
- Multi-site research requires a CPI to coordinate the study, and a PI at each site.
- Delegations are permitted, but ultimate responsibility remains with the PI.
- There are multiple types of consent that are considered legal and ethical. If consent can be obtained, it should be. If not, a waiver of consent may be sought from a fully constituted HREC.
- There are special considerations when undertaking research that targets the recruitment of indigenous persons.
- Adverse events should be reported to the reviewing HREC and the sponsor within 24-72 hours. Adverse drug reactions should also be reported to the TGA.

The Royal Children's Hospital Melbourne

Questions?

When in doubt – always contact your local Research Ethics and Governance Office for advice.