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Introduction to the Legal Aspects of Clinical Trials in Australia

SOUL Conference
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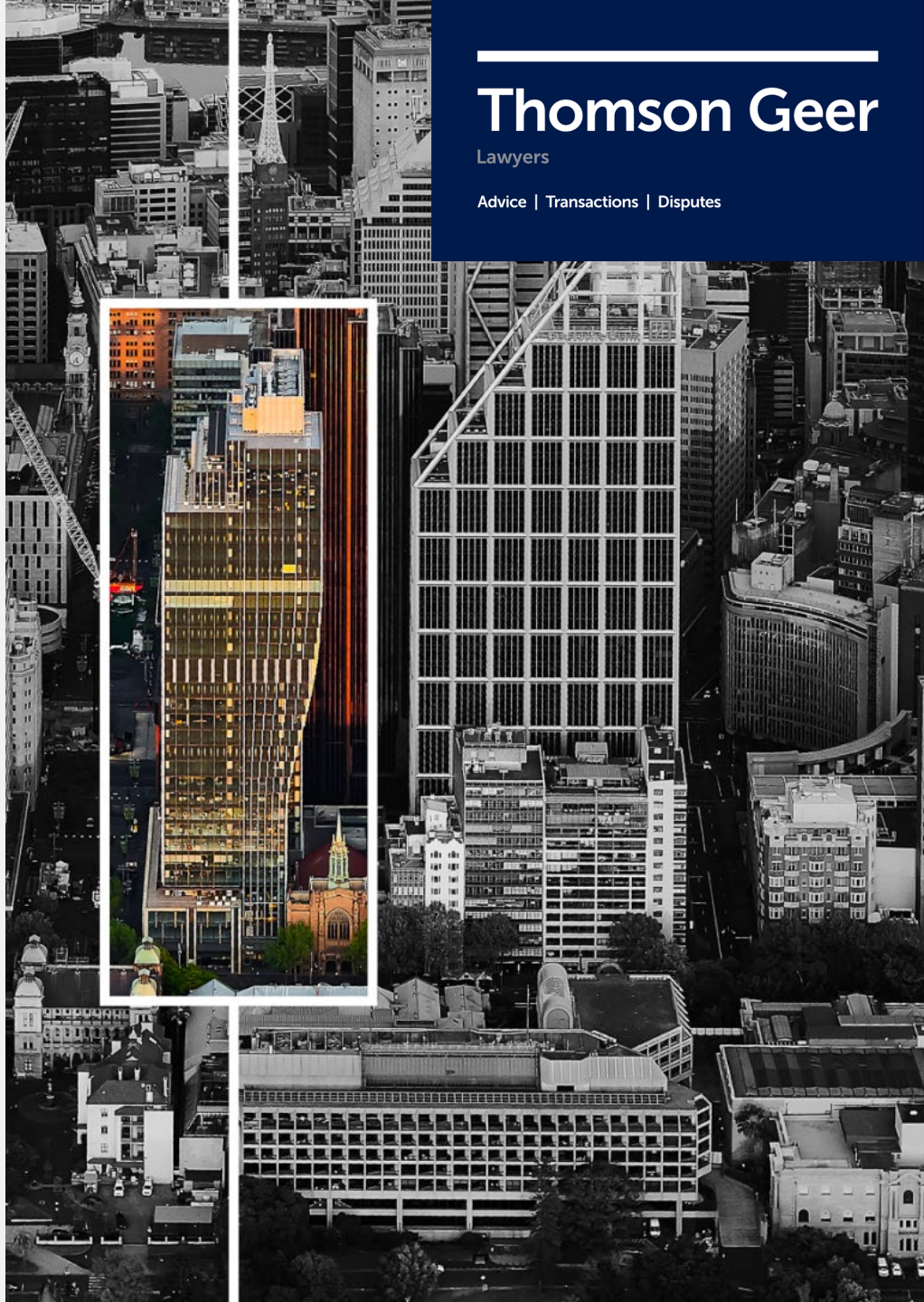

What is human research?

Human research is conducted with or about people, or their data or tissue. Human participation in research is therefore to be understood broadly, to include the involvement of human beings through:

- Taking part in surveys, interviews or focus groups;
- Undergoing psychological, physiological or medical testing or treatment;
- Being observed by researchers;
- Researchers having access to their personal documents or other materials;
- The collection and use of their body organs, tissues or fluids (e.g. skin, blood, urine, saliva, hair, bones, tumour and other biopsy specimens) or their exhaled breath; and
- Access to their information (in individually identifiable, re-identifiable or non-identifiable form) as part of an existing published or unpublished source or database.

NHMRC in collaboration with Universities Australia and the Australian Research Council - National Statement on Ethical Conduct in Human Research 2023

What is a clinical trial?

A clinical trial refers to human research designed to test the safety, efficacy or effectiveness of an intervention including therapeutic intervention (such as medicines, medical devices, procedures or preventative strategies) or diagnostic procedures.

Types of clinical trials include:

- Trials of treatment using therapeutic goods (medicines, medical devices, biologicals)
- Trials assessing a surgical, psychotherapeutic or behavioural intervention
- Trials assessing diagnostic tests or procedures
- Prevention trials
- Educational interventions

Regulation of therapeutic goods

Applicable legislation:

- *Therapeutic Goods Act 1989* (Cth)
- *Therapeutic Goods Regulations 1990* (Cth)
- *Therapeutic Goods (Medical Devices) Regulations 2002* (Cth)

Administered by the Therapeutic Goods Administration

The use of therapeutic goods in a clinical trial must be in accordance with the **National Statement on Ethical Conduct in Human Research 2023** and **Good Clinical Practice** (ICH Guidelines for Good Clinical Practice for medicinal products and biologicals, and ISO 14155 for medical devices).

What are therapeutic goods?

Section 3 *Therapeutic Goods Act 1989* (Cth):

"**therapeutic goods**" means goods:

- That are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be ….. for therapeutic use;"

"**therapeutic use**" means use in or in connection with:

- preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons; or
- influencing, inhibiting or modifying a physiological process in persons; or
- testing the susceptibility of persons to a disease or ailment; or
- influencing, controlling or preventing conception in persons; or
- testing for pregnancy in persons; or
- the replacement or modification of parts of the anatomy in persons.

Categorised by the TGA as medicines, medical devices or biologicals. Medical devices can include software and mobile medical "apps".

What is not a clinical trial?

- **Observational research** – The investigator observes and collects data on participants without manipulating any variables or intervening in their behaviour or environment. There is no active intervention. E.g. a long-term study tracking smokers and non-smokers to observe lung cancer rates.
- **Data collection and analysis** – Review and analysis of data about human subjects that has previously been collected, e.g. in a previous study or as a part of routine medical care. Data collection and analysis will occur during a clinical trial, but can also occur in studies that aren't clinical trials.
- **Quality assurance** – Routine review of clinical practices and processes to ensure that they meet certain standards rather than to generate new knowledge. Example: hospital audit of infection rates following surgery to ensure compliance with hygiene protocols.

The CTN and CTA schemes

- Therapeutic goods must be included in the Australian Register of Therapeutic Goods before those goods can be legally imported or supplied in Australia, subject to exemptions, approval and authorities under the *Therapeutic Goods Act 1989* (Cth). Goods included on the ARTG have been evaluated by the TGA for safety and efficacy.
- Therapeutic goods will also be "unapproved" if they are intended to be used for indications not covered by an existing entry in the ARTG.
- "Unapproved" therapeutic goods can be used for experimental purposes in humans pursuant to one of the following schemes:
  - Clinical Trial Notification (**CTN**); or
  - Clinical Trial Approval (**CTA**).
- The CTN scheme is designed for earlier-phase studies where there is adequate preclinical information available, particularly with respect to safety.
- The CTA scheme is designed for high-risk or novel treatments where there is no or limited knowledge of safety (certain class 4 biologicals must be submitted under the CTA scheme).
- Clinical trials that do not involve the use of "unapproved" therapeutic goods are not subject to CTN or CTA requirements. However all clinical trials require HREC approval before the clinical trial may commence. Forms of human research that are not a clinical trial also require HREC approval.

Clinical trial registries

- **National Statement on Ethical Conduct in Human Research 2023 (section 3.1.7):**

  For any research project that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes, researchers must register the project as a clinical trial on a publicly accessible register complying with international standards (see information on the International Clinical Trials Registry Platform (ICTRP) on the World Health Organisation website) before the recruitment of the first participant.

- https://www.anzctr.org.au/

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Commonly used terms and acronyms

Sponsor	▪ Responsible for the initiation, management and financing (or arranging the financing) of the trial and carries the medico-legal responsibility associated with its conduct. The sponsor can be an Australian individual, company or institution and must submit the CTN or CTA to the TGA. The sponsor may be a commercial company (e.g. drug manufacturer) or a non-commercial institution (e.g. a university).
Institution	▪ Oversees and facilitates the conduct of a clinical trial within its facilities. Typically the university, hospital or research centre where the trial is carried out. It's responsibilities are set out in the Clinical Trial Research Agreement.
Investigator / Principal Investigator	▪ The lead researcher responsible on a day to day basis for the conduct of the study. The primary point of contact between the Institution and the sponsor for commercial studies. Usually employed or affiliated with the Institution.
Participant	▪ The individual who participates in trial. Must sign a Participant Information and Consent Form (PICF).
CRO	▪ Contract Research Organisation – A person or organisation (commercial, academic or otherwise) contracted by the sponsor to perform one or more of the sponsor's trial related duties and functions. The sponsor retains the ultimate responsibility for all delegated duties.
TGA	▪ Therapeutic Goods Administration
ARTG	▪ Australian Register of Therapeutic Goods
NHMRC	▪ National Health and Medical Research Council
HREC	▪ Human Research Ethics Committee. Assess research merit and integrity, justice, beneficence and respect.
Approving Authority	▪ The institution or organisation at which the trial will be conducted and that gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.

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Clinical trial phases

- **Preclinical** – no human participation
- **Phase 0 / Pilot Study / Exploratory Study** – very limited number of participants and reduction of risk, e.g. small doses, short timeframes
- **Phase I** – small number of participants (10 to 100) primarily to assess safety and tolerance
- **Phase II** – larger group of participants (100 to 300) to assess efficacy and safety
- **Phase III** – large group (from several hundred to several thousand) in intended patient population to determine the therapeutic effect
- **Phase IV** – after the therapeutic good has been included in the ARTG and marketed; monitors the effectiveness of the intervention in the general population.

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Sponsor responsibilities

- Quality management including risk identification, evaluation and control
- Trial design
- Trial management, data handling and record keeping
- Selection of investigator/institution
- Defining, establishing and allocating all trial-related duties and functions
- Compensation to subjects and investigators
- Financing
- Notifications/submissions to TGA
- HREC approval
- Supply of the investigational product and information in relation to the investigational product
- Safety evaluation
- Reporting including completion advice to TGA
- Monitoring
- Entry into a Clinical Trial Research Agreement with the Institution

Participant consent

Requirements for valid consent

- **voluntary**
  - no force, duress, fraud, deceit
  - consider vulnerability of the participant, e.g. poverty as a driver for access to free treatment; recruitment by treating physician or participant is in another dependent or unequal relationship
- **informed**
  - sufficient information requires an adequate understanding of the purpose, methods, demands, risks and potential benefits of the study
  - information must be adequately communicated in a way suitable for the relevant participant, e.g. in the face of any literacy or language barriers
  - there must be **comprehension** of the information
  - Requires an opportunity for participants to ask questions and to discuss the information and their decision with others if they wish
- the participant must have **capacity** to understand and communicate consent
- there must be **evidence** of obtaining valid consent (**PICF**)

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Legal documentation

- Confidentiality Agreement/NDA
- Funding Agreement
- Multi-Institutional Agreement for NHMRC Funded Research
- Clinical Trial Research Agreement / Clinical Investigation Research Agreement
- Supply/Service Agreement
- Local Representative Agreement
- Participant Information and Consent Form
- CRO contract

CTRAs/CIRAs

- Conduct of the study
- Obligations of the Principal Investigator
- Institution's obligations and responsibilities
- Sponsor obligations and responsibilities - including (for commercial sponsors) indemnity, insurance and compensation to participants
- Payments
- Provision of equipment and software
- Supply and use of the investigational product
- Confidentiality
- Privacy
- Publications
- Intellectual property
- Medicines Australia template CTRAs: https://www.medicinesaustralia.com.au/policy/clinical-trials/clinical-trial-research-agreements/
- Medical Technology Association of Australia template CIRAs: https://www.mtaa.org.au/clinical-investigation-research-agreements

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Insurance and indemnities

- ICH Guidelines for Good Clinical Practice - Section 5.8 Compensation to Subjects and Investigators:
  - If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.
- Evidence of appropriate insurance and indemnity arrangements should be provided as part of HREC review.
- Medicines Australia Standard Form of Indemnity mandated by Medicines Australia CTRA for commercial sponsors: https://www.medicinesaustralia.com.au/policy/clinical-trials/indemnity-compensation-guidelines/
- Medical Technology Association of Australia Standard Form of Indemnity: https://www.mtaa.org.au/clinical-investigation-research-agreements
- For investigator-initiated trials, whether an indemnity is required by the institution depends on the specific institution's policy. Not mandated in the Medicines Australia CTRA for collaborative or cooperative research groups.

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Useful resources and links

- **Australian Clinical Trial Handbook:**
  https://www.tga.gov.au/sites/default/files/australian-clinical-trial-handbook.pdf
- **National Statement of Ethical Conduct in Research 2023:**
  https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2023
- **Australian Clinical Trials website:**
  https://www.australianclinicaltrials.gov.au

Contacts

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Advice | Transactions | Disputes

Clinical Trial Fundamentals

THE UNIVERSITY OF MELBOURNE

SOUL 2024 Conference

15 November 2024

Challenges in university setting

- Most sponsorship obligations discharged to the sponsor-investigator
  - Principal Investigator has multiple roles as clinician / academic / trialist
  - Collaborations with hospitals – which hat is the Principal Investigator wearing?
- Researcher capacity building
  - Investigators may not be experienced in clinical trials
  - Collaborating sites/practices may not be experienced in clinical trials
- Residual systematic sponsorship obligations eg validation of data systems
- Funding constraints
  - Who pays for shortfalls and additional costs eg overseas insurance
  - Breach of flow-down contracts if funding runs out
- Complexity in complying with international funding and regulatory environment

Diversity of trial design

- Single-site trials
- Hospital-based trials
- Multinational trials
- Drug trials
- Process-of-care changes
- Education interventions
- Mental health
- Wellness app
- Physiotherapy
- AI
- Dietary supplements
- Exercise
- Community-based trials
- Devices
- In-house developed devices
- Teletrials
- Platform trials
- Musical therapy

Not one size-fits-all

Current risk issues

Recruitment & consenting practices – privacy compliance/ethics interface

Migration to higher risk activities

First in human

Human challenge trials

Sponsor of last resort

Pregnancy trials

Psychedelics

Psilocybin

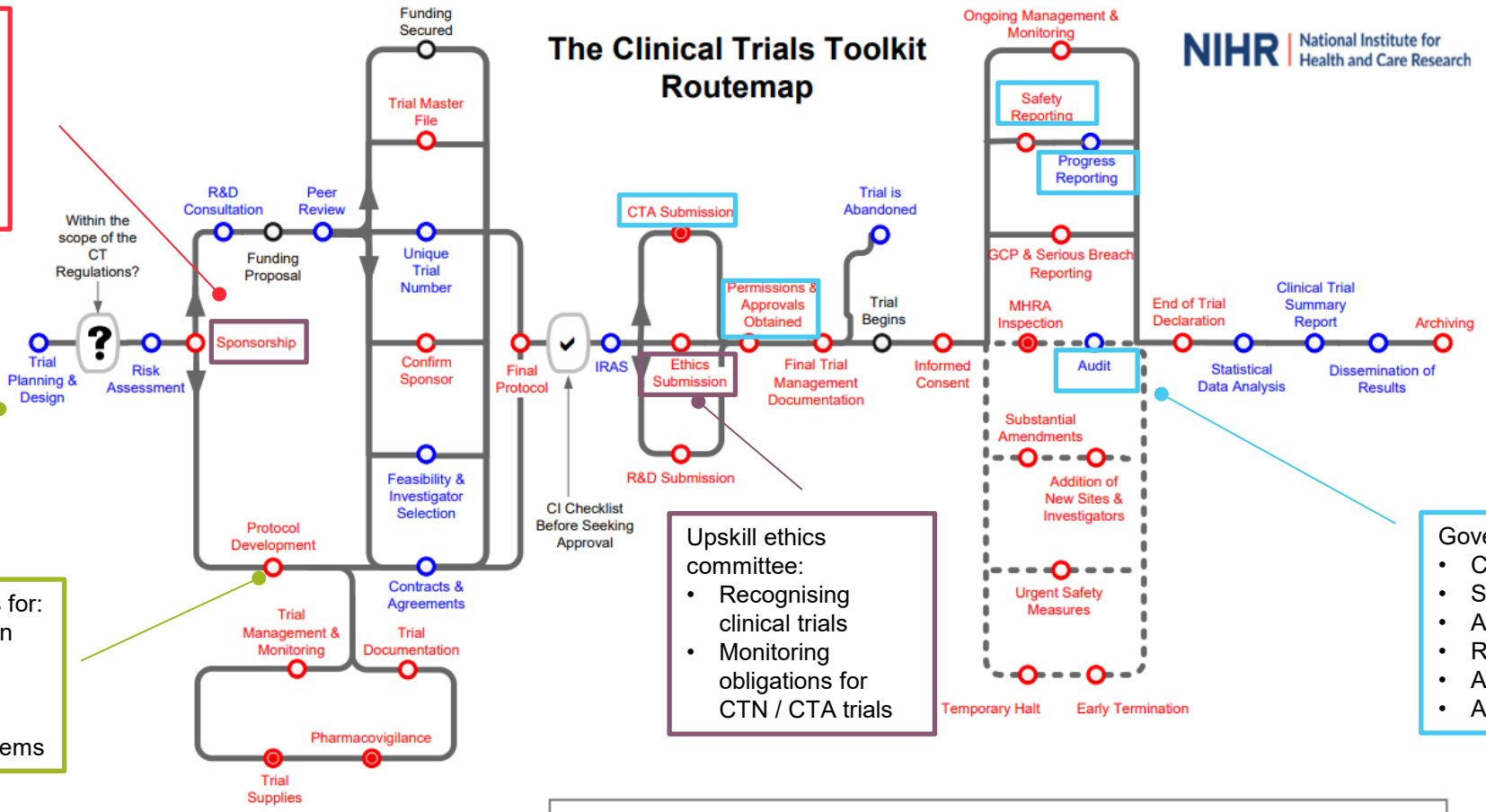
MDMA

Research integrity and quality

Decline in Acronym quality!!

Clinical trial process

Clinical Trials Review Committee
- Institutional approval of sponsorship
- Conditions of sponsorship



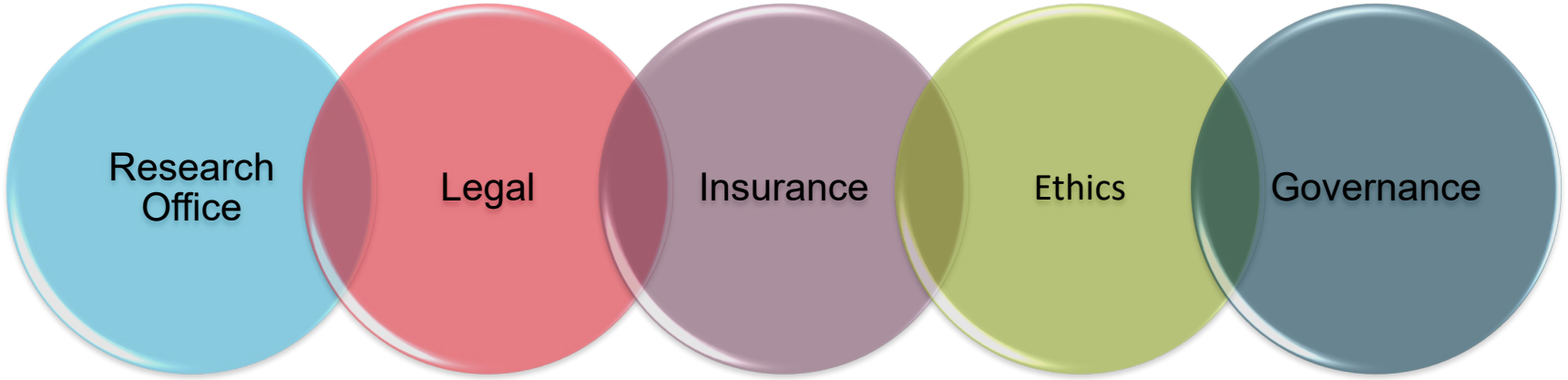
Support networks for:
- Protocol design
- Biostatistics
- Consumer engagement
- Database systems

Upskill ethics committee:
- Recognising clinical trials
- Monitoring obligations for CTN / CTA trials

Governance office:
- CTN submission
- Site-specific assessment
- Adverse event reporting to TGA
- Receive annual reports
- Annual insurance renewal
- Audit

Source: NIHR Clinical Trials Toolkit | EuroGCT

Make compliance easy



Further enhancements?

- Early-stage feasibility assessment
- Formal authorisation by Faculty

Considerations for sponsorship

- Participant characteristics ie alignment with insurance coverage, risk profile
- Location and collaborators (international, commercial)
  - In most jurisdictions a local sponsor is required
- Intervention ie applicability of CTN / CTA scheme, deviation from standard of care
- Experience level of investigator and currency of GCP training
- Conflicts of interest
- Trial phase, scale
- Adequacy of funding
- Insurance coverage
- Ethics approval status

What will you not sponsor?

Compliance program

- Policy including criteria when assessing sponsorship requests
- Clinical trial governance office
  - Central visibility (black box to glass box)
- Internal checks embedded in researcher journey
  - Post-award checks, contracts, ethics
- Education initiatives and support networks
- Management-initiated audit on clinical trial governance program

The role of university lawyers

- Part of an integrated ecosystem of risk controls and oversight
- Policy development
- Process design
- Member of Clinical Trial Review Committee
- Attend Mapping Meeting
- Contractual risk controls
- Advice on legislation eg Advertising Code

Ecosystem of risk controls – some take-aways

- Governance by Institution and HREC
- Explicit allocation of sponsorship responsibilities to PI/partner (via letter/contract)
- Annual reporting
- Monitoring program
- Insurance
- Training (GCP)
- Expert advice (protocol design/quality by design)
- Risk escalation (reputational, financial exposure)
- Reporting and visibility

Thank you

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