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Promoting Ethics and Education in Research

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THE UNIVERSITY OF SYDNEY

Ethics and method in conducting clinical research

(Disclaimer: Random change of title!)

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PRAXIS Australia, RNSH and
University of Sydney

Declarations

- Director (Sydney Uni) of *PRAXIS Australia*
- Haematologist/BMT Physician
- Laboratory Haematologist with *Pathology North*
- Investigator on Phase 1-3 Clinical Trials in BMT and Haematological malignancies
- Investigator on and recruit to investigator-initiated and industry-sponsored clinical trials
- No other research, education or consultancy-relationship with Pharmaceutical or Biotech industry.
- Rubbish dancer

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CHALLENGE OF CLINICAL TRIALS

In our quest to innovate, reduce costs and improve efficiencies in clinical trials, we risk failure to embed the fundamental ethical principles that underpin all research.

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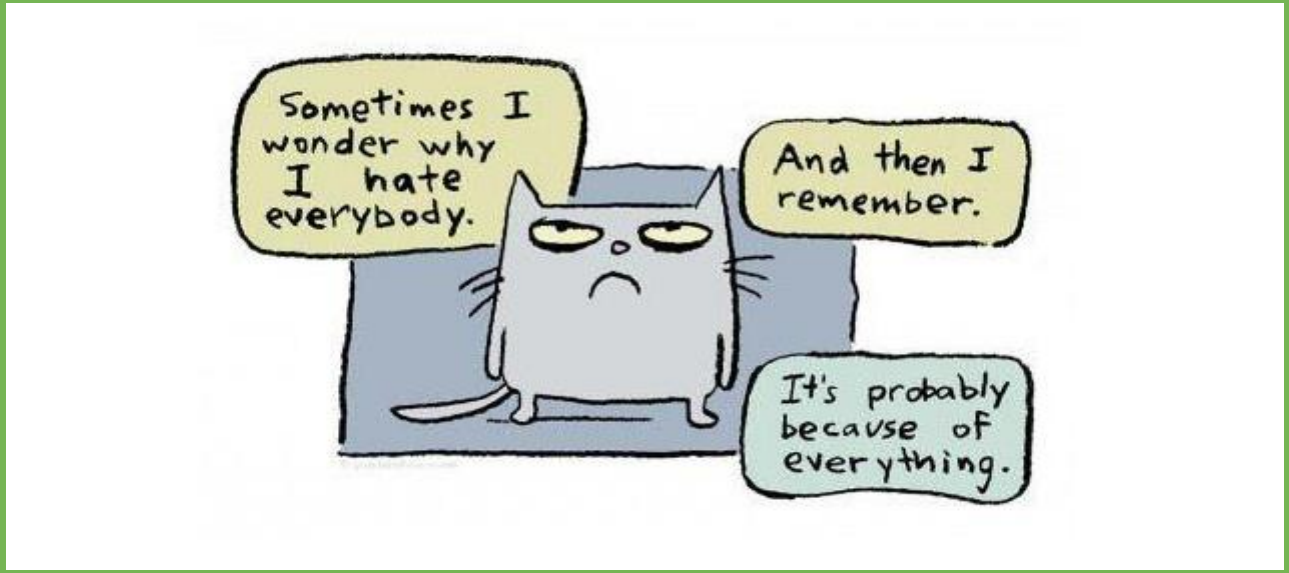

So……we have to think about ethics????

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What do you think of when you hear the term "Research Ethics"?

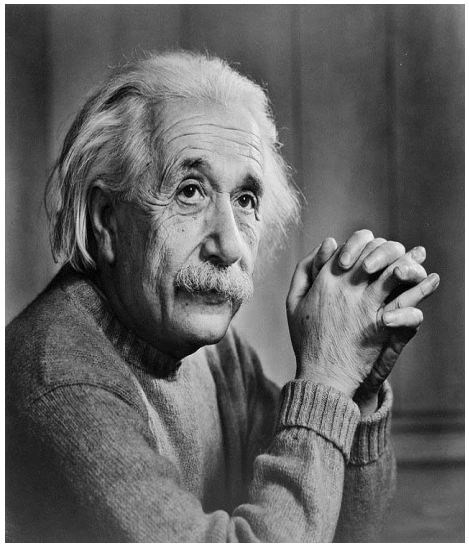
- Nothing
- Bureaucracy
- Delay
- Confusion
- A shotgun
- Interference with good science
- How high can fleas jump? Is Donald Trump a real person? Does Christopher Pyne really speak like that? I feel like a cheeseburger!
- All of the above (including the shotgun)
- .....ethics? (Hurrah!)

Alternative ways to frame the question (and encourage researchers to think about ethics review of clinical trials)

- Have you ever been in research?
- Has your partner or mother or father or child ever been involved in research?
- Did you worry?
- Did you worry about them?
- Did you (or they) want to know anything about the study?
- Would you have wanted the researchers to do as they pleased?
- Consideration of the ‘Other’

Rethinking ethics in research

- ***Research is a moral enterprise***
- ***Research = research ethics***
- ***Or at least there is an iterative relationship between ethics and method…….and so must be thought through prospectively!***
  - **Research question**
  - **Research design**
  - **Research size and sample**
  - **Recruitment and selection and consent**
  - **Analysis**
  - **Conduct**
  - **Publication, dissemination and translation**



Outline

1. Ethics and method in clinical trials
2. Therapeutic misconception and clinical equipoise
3. Consent to research
4. Why ethics and what ethics?

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Ethics, method and science

Research is good…..Right?

- **No**
- Good research is good
- Research may be useless, pointless, wasteful, expensive, self-interested, designed not to advance knowledge but to gain market-entry.
- Research may also not actually be research (eg many registries ASC therapies)

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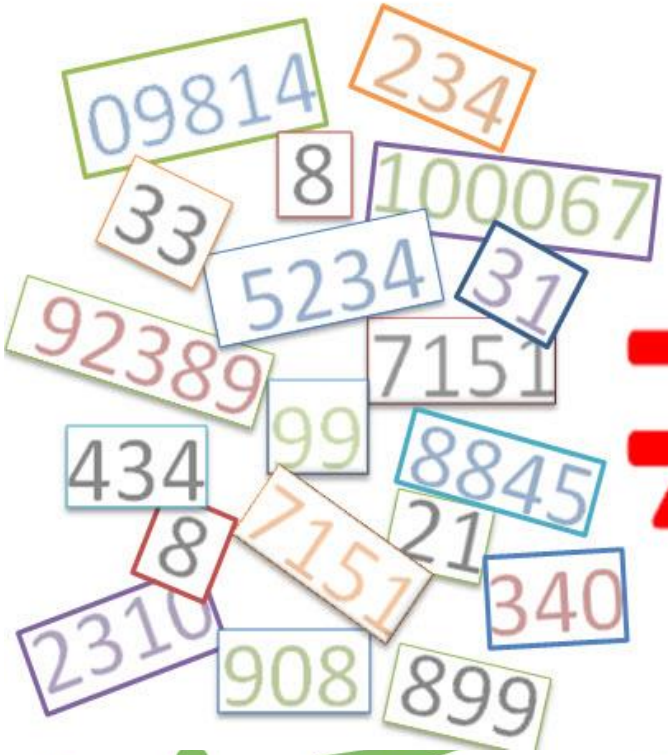
And research may just create ‘noise’



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But research is not *ipso facto* 'Good'. What is 'Good' research

- *Important* (to the community)
- Builds upon knowledge rather than simply repeating it. *Novel*
- Asks the 'right' question (reflect community values and needs eg for security, flourishing etc)
- Asks a question that can be answered
- Uses a design/method that enables the question to be answered
- Uses the appropriate design (dying = not an RCT)
- Is ethically justifiable and conducted ethically
- Is at least aware of the context in which the results may be interpreted (Homosexuality genetics, mouse-pox synthesis etc)
- Other?

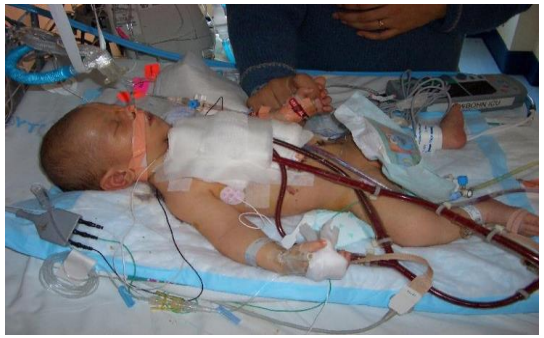
How do we ensure ‘good’ science is done and ‘bad’ science doesn’t?

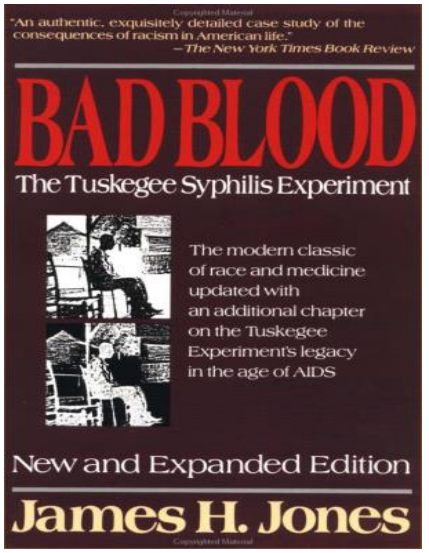
- Reflection – whose interests are being served? Why this research?
- Knowing literature
- Trials register
- Community involvement in setting research agenda
- Conflict of interest processes
- Commitment to publish
- Research methods and research ethics training.
- Audit
- Peer Review of grants, publications etc.
- Open work environment: honest, transparent, collegial
- Stress on the values of the researcher
- SAC and HREC review
- Granting process (competitive distribution of funds)
- Sponsorship of creative, low yield research.
- Researchers aware of social context of research.
- Codes of Research Practice and Ethics (Universal)
- Punishments

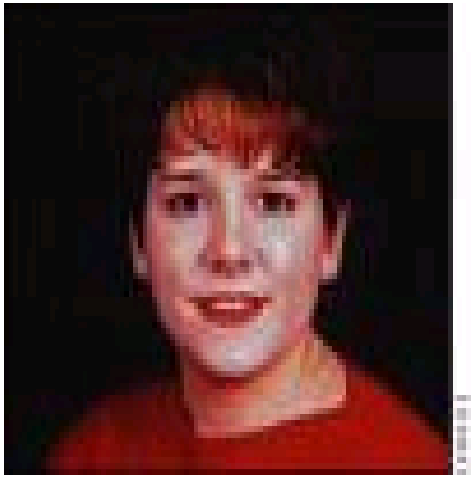
Research design and ethics

- **Valid question**
- **Valid design (must be able to answer the question posed) –**
  - What research design would you choose for a study of a new (untested) therapeutic agent?
  - What if you had a new agent but already had another that was proven to be efficacious?
  - What if you wanted to understand a patients experience of cystic fibrosis?
- **Appropriate starting point/decision**
- **Adequate monitoring processes**
- **Stopping rules**
- **Unbias** (bias = systematic difference between the results from a study and the 'truth') **(Challenge: Results may be influenced by question, method, design, analysis, researcher and sponsor. Contamination of the 'evidentiary water-source'?)**

Crucial to recognise that ALL trial designs have potential problems, and ALL types of research may provide benefit but also cause harm







Choice of research participants

- Computer models or tissue models (?embryo)
- Animal studies (pre-requisite or epistemologically invalid and ethically suspect)
  - If do; Animal species and number
- When to do first human studies
- Human population: type, inclusions, exclusions, vulnerability and power (What groups are relatively excluded from research?)
- Human population (number)
- **Match of study population to target population**

When to test – and on whom?

Early – more benefit and more to lose

Late – less benefit and less to lose

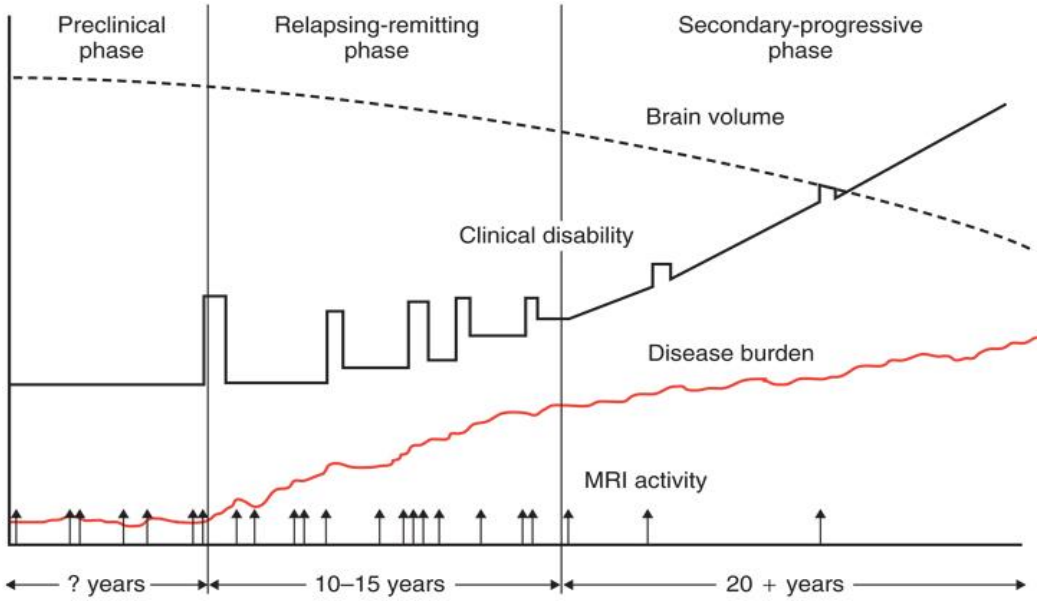
Matching the target population or establishing benefit?

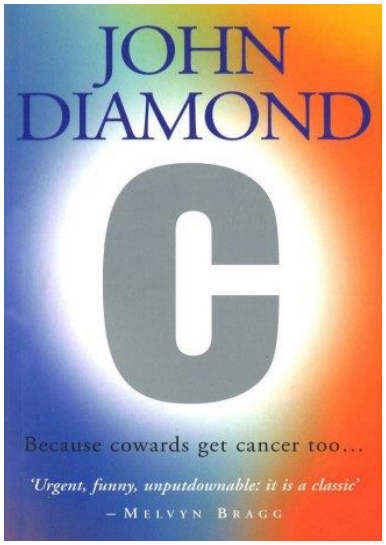
Illness – unlike research – persists!

When is research done?

What benefit is gained over time?

Early benefit and late catch-up?





Even statistical analysis is an ethical issue. It is a choice!

Consider

- New lipid-lowering agent
- New drug for neurodegenerative disorder in children
- Antiviral for SARS, Ebola etc

Ie Statistical end-points: p values, confidence-intervals, SD are all **choices**.

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Participation in clinical trials and the 'therapeutic misconception'

Why *don't* patients participate in clinical trials?

- Not offered
- Not available
- Not available there
- Direct risk (MUST be acknowledged) eg radiology
- Easier to just have standard of care/best practice.
- Too much to think about – esp when newly diagnosed
- Onerous (more tests, more visits etc)
- Depersonalised (at least in terms of link with clinician) – but is this true?
- Who really benefits? Sponsor or me? Will I get access to this drug afterwards? (More an issue in developing world eg Imatinib)
- Creates a conflict of interest (Will it drive therapy beyond the point at which a patient would 'normally' be treated?)

Why do patients participate in clinical trials?

- Hope
- Fear
- Direct benefit:
  - from experimental therapy
  - outcomes better even where treatment identical
- Benefit to ‘medicine’ and science (altruism) – likely <5%
- Benefits future patients (speeds development of effective therapies)
- Benefits institution (ensures trial completion, ensures work on trials is productive, and provides income to the unit – for each patient recruited)
- Access to therapies not available on PBS.

THERAPEUTIC MISCONCEPTION

Definitions of the Therapeutic Misconception (TM)

"The belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge."

"It is not a misconception to believe that participants probably will receive good clinical care during research, but it is a misconception to believe that the primary purpose of clinical trials is treatment…"

---National Bioethics Advisory Committee (NBAC), 2001

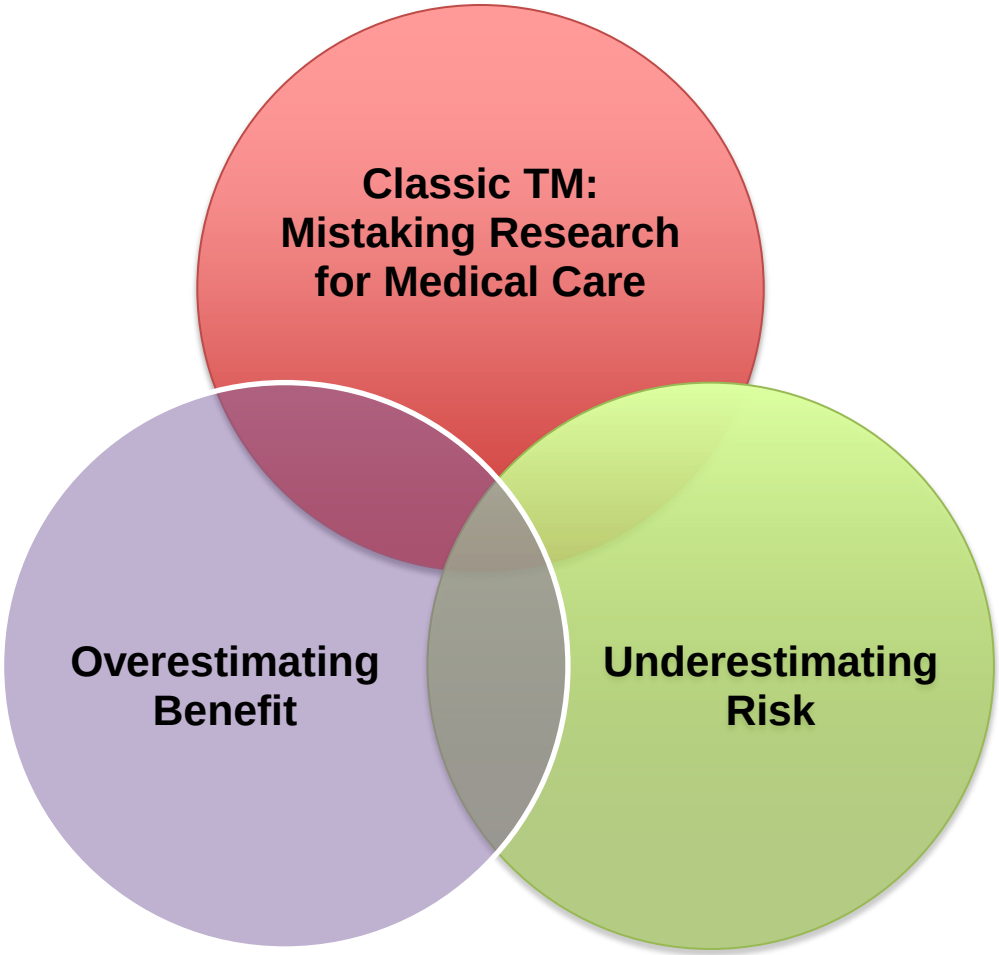
"When a research subject *fails to appreciate the distinction between the imperatives* of clinical research and of ordinary treatment, and therefore inaccurately attributes therapeutic intent to research procedures." (italics added)

---*Lidz and Appelbaum, 2002*

How prevalent is the TM?

Most empirical studies of clinical trials, predominantly early stage Cancer trials, indicate that participants are often motivated to participate in research by expectation of direct medical benefit, and when asked, blur the distinction between research and treatment.

TM and Risk/Benefit Perception



Consent

And this (the TM) is a problem because it may not be true and may invalidate consent

.....

But it may be unavoidable.

Voluntariness in consent

"Incapacitated and hospitalised because of illness, frightened by strange and impersonal routines, and fearful for his health and perhaps life, he (the patient-subject) is far from exercising a free power of choice when the person to whom he anchors all his hope asks, 'Say, you wouldn't mind, would you, if you joined some of the other patients on this floor and helped us to carry out some very important research we are doing?" *Ingelfinger FJ. Informed (but uneducated) consent. NEnglJMed 1972;287:465-6*.

Misleading Consent Forms

- Consent forms may be a cause of confusion.
- King et al: Analysis of 321 consent forms for gene transfer research, 1990-2000; all early phase:
  - ❑ **'research' and 'treatment' used as interchangeable terms**
  - ❑ **surrogate endpoints (e.g., tumor shrinkage, immune response) discussed but not distinguished from clinical endpoints (e.g., survival time, improved quality of life)**
  - ❑ **benefits to society and inclusion benefits not distinguished from possible medical benefits for participants**

N. King, G. Henderson, L. Churchill, et al., "Consent Forms and the Therapeutic Misconception: The Example of Gene Transfer Research," IRB (2005); 27,1:1-8.

Why consent will always be challenging

- Consent is not about forms (which are often/increasingly good)
- It is a process, an iterative discussion.
- In regards Phase 1 studies involving patients it makes sense only when one also knows ones prognosis – and this sometimes isn't made clear
- Large volume of research that shows that patients over-estimate benefit and minimise risk.
- Hope is supreme, uncertainty a reality and fear ever present
- Illness (and hospitals) do create vulnerability
- Benefit = number + value (even a remote possibility of benefit may be sufficient)
- Navigating between paternalism and advocacy always problematic

- *Broad/Blanket consent*
- *Dynamic consent*
- *Waiver of consent*
- *Opt out consent*
- *eConsent*

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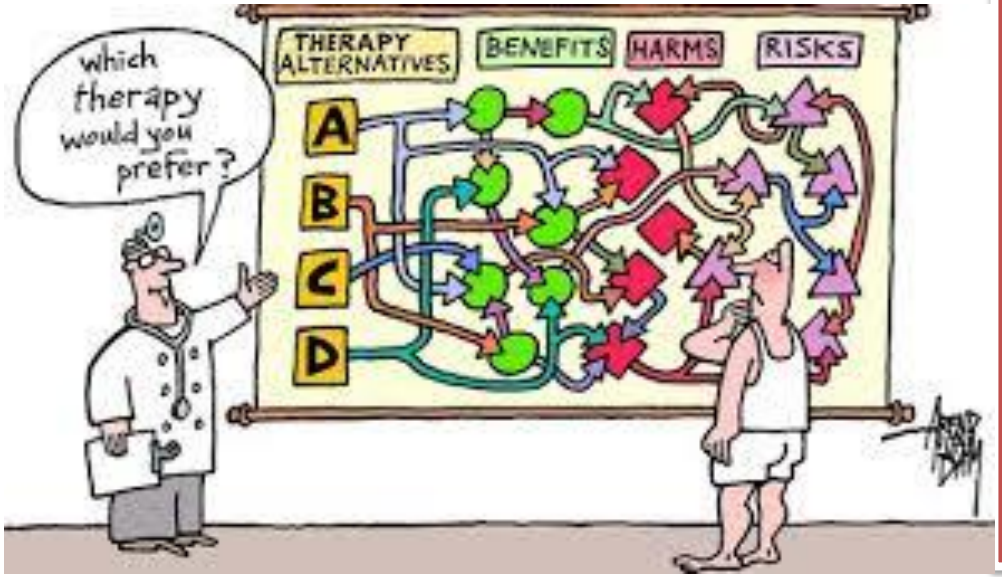
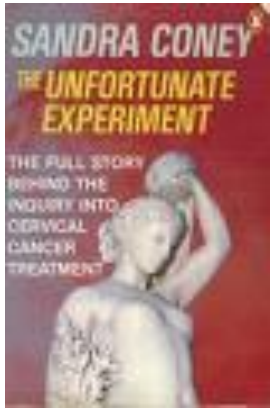


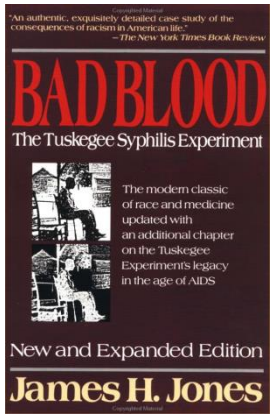
Other approaches to consent

ETHICAL CONSIDERATIONS

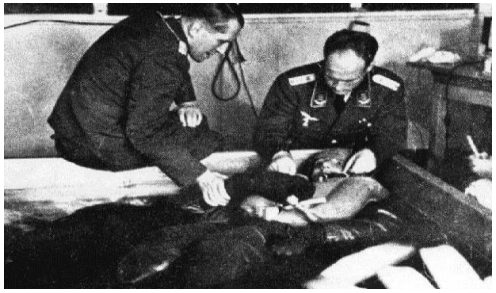
- Autonomy (respect)
- Voluntariness
- Literacy levels and readability
- Cultural competence
- Length and complexity
- Disclosure and balance
- Capacity
- Privacy (eConsent)
- Authentification of identity (eConsent)

Why is research ethics necessary?





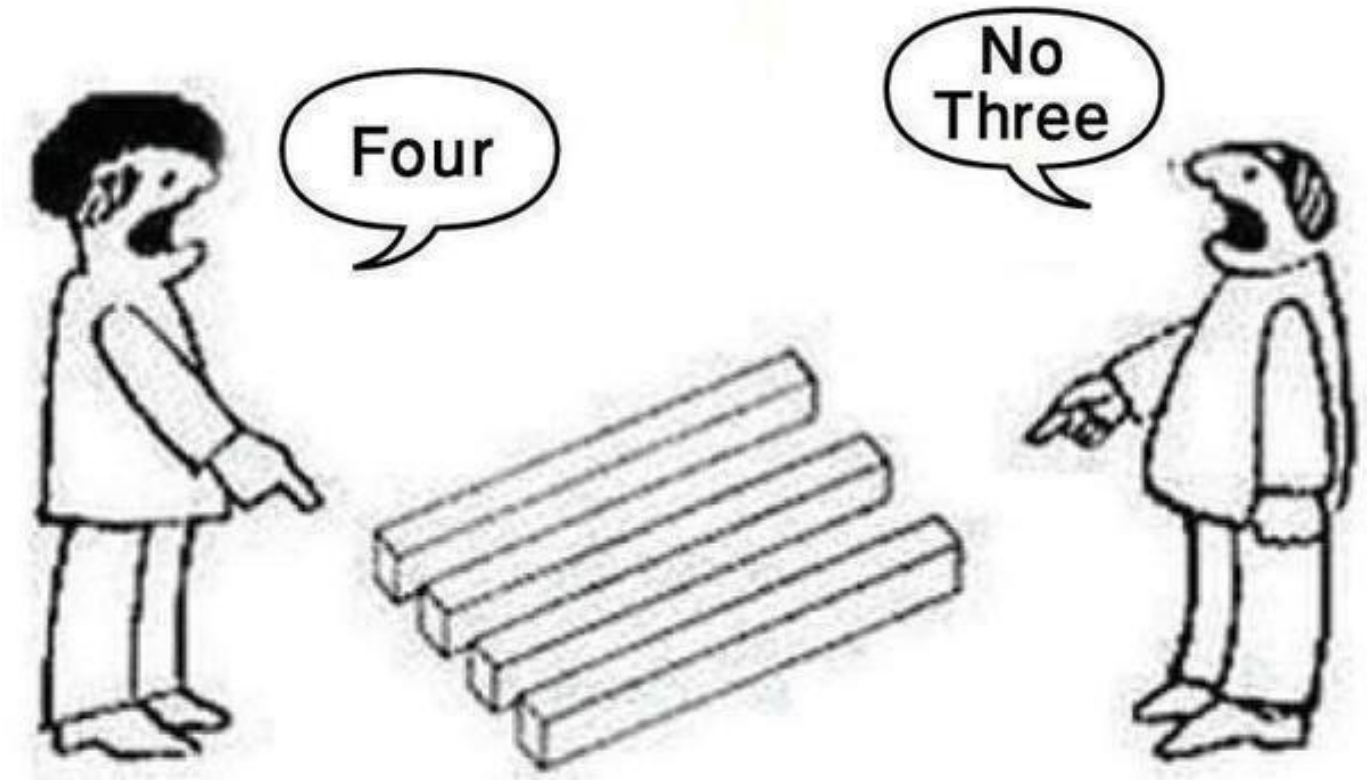
- *Prevent abuses*: (big: Nazi, China, Tuskegee etc, and small – micro-ethics)
- *Protect vulnerable* (science and medicine are powerful)
- *Care important*
- *Desire to get good, important research*
- *Respect*



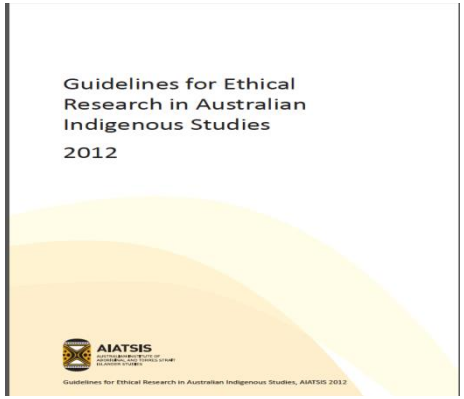
It is also to remember why we do research – and that this is about creating good (ethics) not about governance and compliance (which serve ethical ends)

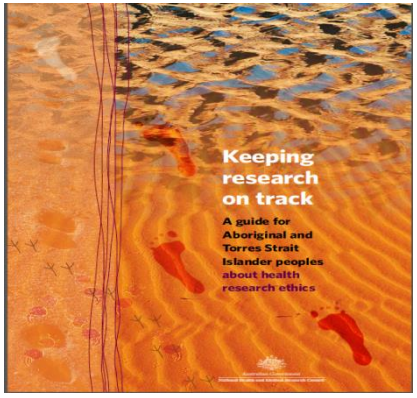
SO WHAT'S THE ANSWER?

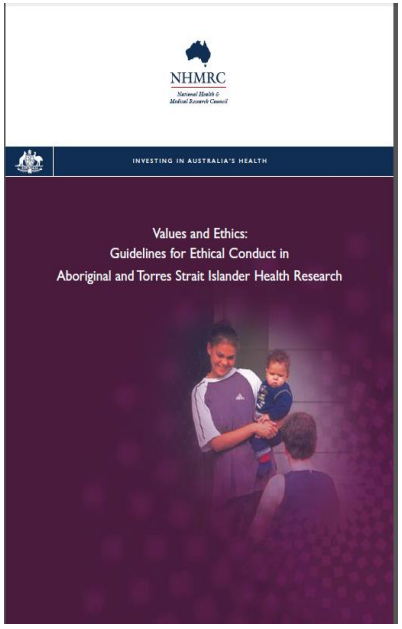
It is really confusing!!!

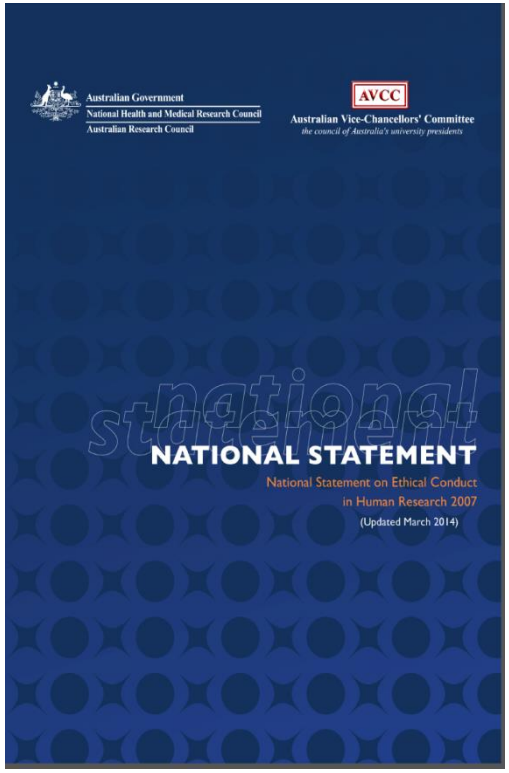


- ***A web of guidelines (now a continual process of review)***
- ***Emerging issues – uncharted territory***
  - ***Gene therapy***
  - ***Stem Cell Research***
  - ***Xenotransplantation***
  - ***Omics***
  - ***Synthetic biology***









Seven constant ethical requirements

- social or scientific value
- scientific validity
- fair subject selection
- favourable risk-benefit ratio
- informed consent
- respect for potential and enrolled subjects
- independent review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RESEARCH ESSENTIALS
DEVELOPING EXCELLENCE IN RESEARCH DESIGN AND PRACTICE
STEP 1. SELECT YOUR CORE AREA OF RESEARCH
STEP 2. NOMINATE YOUR CURRENT ROLE
GENERATE THE PATHWAY TO YOUR LEARNING
CLINICAL TRIALS
BENCH / BASIC / LABORATORY
PUBLIC HEALTH
SOCIAL SCIENCES
HUMANITIES RESEARCH
RESEARCH GOVERNANCE / INTEGRITY
RESEARCHER
RESEARCH MANAGER
RESEARCH CO-ORDINATOR
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