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Evidence and Reasons in Clinical Trial Design and Regulatory Approval

Dr. Mark Sheehan and Dr. Mackenzie Graham

The Ethox Centre, University of Oxford

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Disclosure

We have no conflicts of interest to disclose in relation to this presentation

Outline

The key tradeoff:

- Obligations to research: ‘scientific duties’
- Obligations to participants: ‘clinical duties’

The role of evidence generation methodologies…

Making decisions about evidence within the key tradeoff…

- Reasons and evidence
- Evidence supports reasons – limited evidence gives us reason too
- For each decision, what matters are the reasons, justification rather than simply, the evidence

The Obligation to Conduct Research

Purpose of research: ‘clinical’ duties to the patient vs. scientific duties to provide care

- Strong ethical argument for research: Without research, we cannot know what counts as care, so we cannot deliver on our duty to provide care.
- Weaker case: We have a duty not to harm patients, but without research, we do not know what will harm and what will not (this connects interestingly to the idea that for us to learn something must fail or not work)

There are some important complexities here about how we design trials so that we can and do learn. For example, the more we give up on comparison the less we can learn (for the benefit of future patients)

- Adaptations are always for the benefit of participants?

The Obligation to Patients

'Clinical' duties to current patients: Those patients who are in front of us now require our attention and care – if there is a chance, we should act for their benefit…

- Parachute trials: 'Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials.' (Smith G, Pell, J. BMJ 2003;327:1459)

Common sense judgements: what are the kinds of considerations that might be relevant – aside from trial evidence?

- Detecting noise from signal: 'When are randomised trials unnecessary? Picking signal from noise.' (Glasziou P, Chalmers I, Rawlins M, McCulloch P. BMJ. 2007 Feb 17;334(7589):349-51)

Clinical questions vs. scientific questions

Levels of Evidence

Levels of Evidence and Grades of Recommendations

Grade of recommendation	Level of evidence	Interventions
A	1a	Systematic review of randomized controlled trials
	1b	Individual randomized controlled trial
B	2a	Systematic review of cohort studies
	2b	Individual cohort study
	3a	Systematic review of case-control studies
	3b	Individual case-control study
C	4	Case series
D	5	Expert opinion without explicit critical appraisal or based on physiology or bench research

Evidence and Reasons

The decision-making which matters here (regulatory approval and related trial design) requires that we have reasons which provide justification

Reasons justify decisions (provide grounds for thinking that we ought to X)

- A ought not to X because doing X is likely to harm B
- That X is likely to harm B is a reason not to X

Evidence provides support for reasons of a certain sort

- X involves an 80% chance of permanent physical injury to B
- This gives us evidence that X is likely to harm B

Evidence and Reasons

- The process of having and giving reasons is distinct from the process of having evidence
- Evidence provides support for reasons
  - The quality of the evidence requires a value judgement (albeit a largely scientific one)
  - The value of the evidence requires a value judgement (not clearly a scientific one)
  - Note: Even this distinction is hard to keep distinct everywhere – e.g. outcomes/biomarkers/methodology

Evidence and Reasons

- Often, the quality of the evidence is contested/contestable. But, on this account, this is not the end of the matter (a decision is still required)
- Even ‘lesser quality’ evidence gives us some reason, i.e. provides some support
  - Reasons can get a grip even when the evidence is weaker because reasons involve the incorporation of value and hence are judged in the light of other competing reasons
  - When we are balancing clinical trial design with our obligations to participants and our obligations to learn, this matters.

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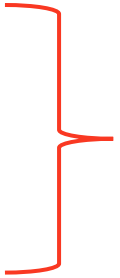

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Evidence and Reasons

Examples

- Parachute: the physics is clear, extrapolation…
- Experience – ‘case series’: clinician judgement…
- Proton Beam therapy

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