On the necessity of embedding clinical equipoise in the Declaration of Helsinki

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Utrecht

Outline

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- Equipoise paradox
- What is equipoise?
- Perceived problems
- Answers
- Moral status
- Why embed equipoise?
- Conclusions

Equipoise paradox

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- Many regard it as a fundamental ethical concept of human subjects research
- Ethicists are criticial & not embedded in guidelines

Claim presentation:

- Time to focus on merits > weaknesses of the concept
- Sufficient reason to incorporate the concept in main ethical guidelines

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What is clinical equipoise?

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Freedman 1987

genuine uncertainty in the expert medical community about the preferred treatment

3 elements definition

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1. Expert medical community
2. Preferred treatment
3. Genuine uncertainty

1. Expert medical community

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- Uncertainty not in the mind of a single investigator, but in broader community of clinical experts

2. Preferred treatment

Standard drug (S)

2. Preferred treatment

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Standard drug (S)

Experimental drug (E)

2. If S is superior to E…

…participants have to be provided with S

“Must be offered best treatment known”

(Freedman)

Standard drug (S)

3. Genuine uncertainty

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- Equipoise not only grounded in therapeutic obligation, but also in scientific duties
  - Epistemic reasons to conduct a controlled trial
  - Focus trials on solving questions that may influence clinical decisions > theoretical questions

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Perceived problems

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- Expert community:
  - Who are the members?
  - How many?
  - Patient should be in equipoise
- Preferred treatment
  - May rule out many placebo-controlled trials
  - Impossible to always offer best proven care
  - Patients may still be harmed
- Genuine uncertainty
  - What does it mean?
  - When is it disturbed?

Equipoise controversy

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- “Rehabilitate the concept” (PB Miller/Weijer 2003)
- “Not yet time to give up on equipoise” (Ashcroft 2004)

- “Equipoise is fundamentally flawed” (F Miller/Joffe 2011)
- “Equipoise is bankrupt, pull the plug” (Gifford 2007)
- “Equipoise is a muddy concept, beyond rehabilitation” (Menikoff 2003)

Proposals of opponents: alternatives

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- Alternative conceptions that can justify why we allow compromises to individual interests patients

- Problems of alternatives:
  - Conceive equipoise as overarching justification of human subjects research
  - opponents of the concept '*resolve the ethical problems of equipoise by abandoning the need for equipoise*' (Freedman 1987)

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1. Expert medical community

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- Distinguish between
  - those who are uncertain (virtual community of experts)
  - those who have to determine whether experts are uncertain
    - IRB, researchers, sponsors (also experts!)

- Physicians and patients may have own treatment preferences ≠ clinical equipoise

2. Preferred treatment

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- Extensive debate whether clinicians have therapeutic duties as researchers
- Even proponents of the concept: unnecessary to always offer the “best possible care”
- Focus on what cannot reasonably be withheld > what should be provided

3. Genuine uncertainty: semantics

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- Semantics of equipoise creates confusion over the concept
- Alex London (2007):
  - Distinguish between ‘agnosticism’ (don’t know) and ‘conflict’

3. Genuine uncertainty: don’t know

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- Safe?
- Effective?
- Efficacious?

E

- No balance in this situation

3. Genuine uncertainty: conflict

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- Both E and S standard drugs for given condition

- Some experts favor E, others favor S

E

S

3. Genuine uncertainty: conflict

- In the case of a conflict experts are seldom “equally poised”

3. Genuine uncertainty: conflict

S E

- More experts favor E>S
- Researchers/IRBs determine whether experts are in equipoise

3. Genuine uncertainty: conflict

- Irrelevant how many
- Strength of the evidence matters

S E

Equipoise vs balance of trial arms

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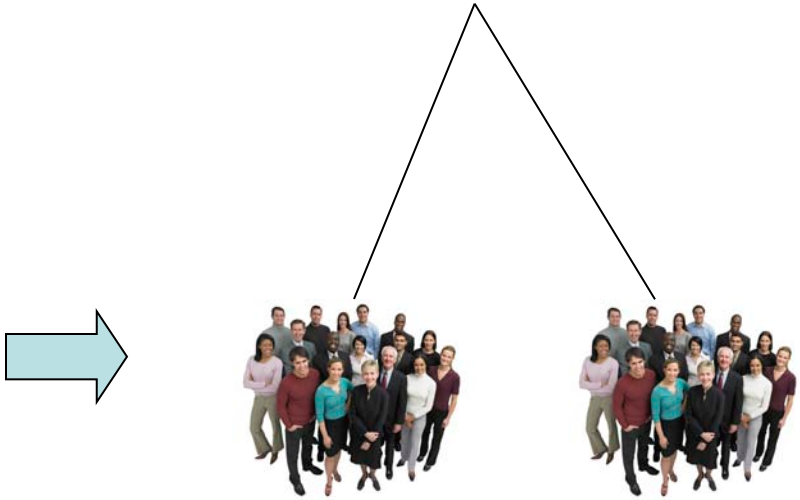
S E



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Disturbance trial arms ≠ disturbance equipoise

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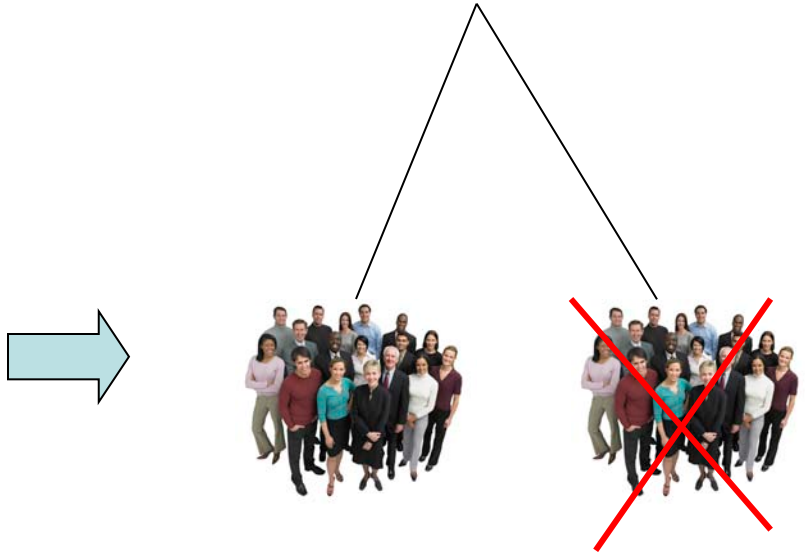

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Disturbance trial arms ≠ disturbance equipoise

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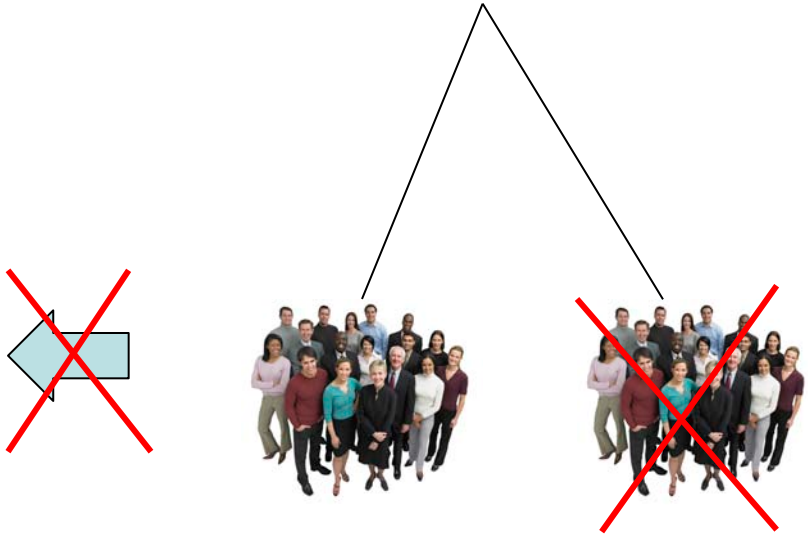

S E

3. Genuine uncertainty: disturbance

S E

- Freedman: trial must be designed to disturb clinical equipoise
- Unrealistic: often many RCTs, meta-analyses

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What does clinical equipoise require?

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- *Expert medical community should be in a state of genuine agnosticism or conflict about the net preferred medically established procedure for the condition under study*

- Those who consider initiating or continuing an RCT

1. Is there sufficient disagreement, or absence of agreement among experts? (scientific component)
2. Can standard of care reasonably be withheld all-things-considered (“therapeutic” component)

Moral status of equipoise

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- Fundamental > foundational concept of research ethics
- *Prima facie* obligation
- Deduced from scientific validity/social value and favorable risk-benefit
  - Adds substance to these norms
- Not a specific rule that determines comparator
- Threshold requirement

If equipoise cannot be met…

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- …trial not necessarily unethical, but

- Burden of proof on researchers/IRBs to explicate
  - Why it is necessary to conduct RCT (and not observational study e.g.)
  - Whether the control group can reasonably be withheld the standard of care

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§ 32 Declaration of Helsinki

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- “The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention”

- Applied rule focusing on testing of new interventions and on precise comparator

- Needs further grounding: why provide best proven care and when is it allowed to conduct controlled studies?

Conclusions

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- Weaknesses ≠ equipoise is flawed
- If we give up on equipoise we may lose a requirement that explicitly asks for:
  - scientific justifications of controlled trials
  - taking professional standards into account when considering these trials
- In order to protect the merits of equipoise and hence the interests of patient-subjects clinical equipoise should be incorporated in the Declaration

Some references

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