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

Dr Rieke van der Graaf
Prof dr Hans van Delden
Julius Center, Dpt Medical Humanities
UMC Utrecht, Netherlands

WMA Satellite Meeting during the 11th World Congress of Bioethics, 26 June 2012
Outline

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

- Many regard it as a fundamental ethical concept of human subjects research
- Ethicists are critical & 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
Outline

• Equipoise paradox
• **What is equipoise?**
• Perceived problems
• Answers
• Moral status
• Why embed equipoise?
• Conclusions
What is clinical equipoise?

Freedman 1987

genuine uncertainty in the expert medical community about the preferred treatment
3 elements definition

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

- 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

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

- 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
Outline

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

• 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

- “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

- 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)
Outline

• Equipoise paradox
• What is equipoise?
• Perceived problems
• **Answers**
• Moral status
• Why embed equipoise?
• Conclusions
1. Expert medical community

• 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

- 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

• 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

- Safe?
- Effective?
- Efficacious?

- No balance in this situation
3. Genuine uncertainty: conflict

• Both E and S standard drugs for given condition

• Some experts favor E, others favor S
3. Genuine uncertainty: conflict

• In the case of a conflict experts are seldom "equally poised"
3. Genuine uncertainty: conflict

- 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
Equipoise vs balance of trial arms
Disturbance trial arms ≠ disturbance equipoise
Disturbance trial arms ≠ disturbance equipoise
3. Genuine uncertainty: disturbance

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

• Equipoise paradox
• What is equipoise?
• Perceived problems
• Answers
• Moral status
• Why embed equipoise?
• Conclusions
What does clinical equipoise require?

• **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

- 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...

• …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
Outline

• Equipoise paradox
• What is equipoise?
• Perceived problems
• Answers
• Moral status?
• Why embed equipoise?
• Conclusions
§ 32 Declaration of Helsinki

• “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

• 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

- Pictures: Istockphoto
- Van der Graaf R, Van Delden JJM. Equipoise should be amended, not abandoned. Clinical Trials 2011;8:408-416.
- Van der Graaf R, Van Delden JJM. On what we will lose in giving up on equipoise: a reply to Miller. Clinical Trials, forthcoming.