Clinical Equipoise: “Do We Really Need Another Study?”

CAEP 2012

John M Tallon MD MSc FRCPC
VP Medical Programs, Emergency and Health Services Commission, Province of British Columbia
No Disclosures, No Conflicts of Interest
Research and Emergency Medicine

"an undertaking intended to extend knowledge through a disciplined inquiry or systematic investigation."

Trauma Association of Canada
Association Canadienne de Traumatologie
Objectives:

- Define (and explore) “clinical equipoise”
- Elaborate on why clinical equipoise is important
- Controversies of clinical equipoise
- Demonstrate relevance (to EM) of clinical equipoise with examples
Key Words, Documents and Concepts in Medical Ethics and Research

- TCPStatement
- Fiduciary
- Beneficence
- Common Rule
- Belmont Report
- Nuremberg Code
- Nazi Experiments
- Helsinki Declaration
- Epistemology
- Agnosticism
- **Clinical Equipoise**
- National Research Act
- Tuskegee Syphilis Study
- Willowbrook Hepatitis Experiments
Clinical Equipoise: Origins

- 1974: C Fried
  - Original elucidation of concept
  - A neo-Kantian ethical justification for doctrine of equipoise (therapeutic mandate/optimal care)

- 1987: B Freedman
  - Nails it: see final definition...

Fried C: Medical Experimentation: Personal Integrity and Social Policy, New York; Elsevier Publishing: 1974

“Equipoise and the ethics of clinical research”

“The ethics of clinical research requires equipoise--a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. Should the investigator discover that one treatment is of superior therapeutic merit, he or she is ethically obliged to offer that treatment.”

“Equipoise and the ethics of clinical research”

“I suggest an alternative concept of equipoise, which would be based on present or imminent controversy in the clinical community over the preferred treatment. According to this concept of "clinical equipoise," the requirement is satisfied if there is genuine uncertainty within the expert medical community--not necessarily on the part of the individual investigator--about the preferred treatment.”

Clinical equipoise

- “…means that there is genuine uncertainty in the expert medical community over whether a treatment will be beneficial.”

- “Once a certain threshold of evidence is passed, there is no longer genuine uncertainty about the most beneficial treatment…”

Miller and Joffe NEJM 2011
Is Clinical Equipoise Important?

- Yes!
- Used and taught in TCPS!
- Used every day by REBs!
- Used by all clinical researchers!
- Used to predicate decisions on study design and legitimacy!
TRI-COUNCIL POLICY STATEMENT 2010

- “The existence of a genuine uncertainty on the part of the relevant expert community about what therapy or therapies are most effective for a given condition”
- For this reason, clinical equipoise may be considered as a starting point for the design and review of clinical trials

Parachutes and Equipoise

“Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials”

Smith GC, Pell JP. Parachute use to prevent death ...randomised controlled trials. BMJ. 2003 Dec 20;327(7429):1459-61.
OBJECTIVES:
To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

DESIGN:
Systematic review of randomised controlled trials.

DATA SOURCES:
Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

STUDY SELECTION:
Studies showing the effects of using a parachute during free fall.

MAIN OUTCOME MEASURE:
Death or major trauma, defined as an injury severity score > 15.

RESULTS:
We were unable to identify any randomised controlled trials of parachute intervention.

CONCLUSIONS:
As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.
CONCLUSION: Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Smith GC, Pell JP. Parachute use to prevent death ...randomised controlled trials. BMJ. 2003 Dec 20;327(7429):1459-61.
The Parachute Paradigm:

- Are RCTs evil?
- Are RCTs ethical?
- Are RCTs with placebo ethical?
- In a RCT/study of 2000 patients does equipoise disappear at patient enrollment #1500...#1700?
- Is violation of equipoise always “unethical”?
Issues with Clinical Research:

- How can a clinician offer their patient optimal medical care (the *therapeutic obligation*) at the same time that their treatment (the *scientific obligation*) is selected by chance in the context of an RCT???
Problems with Clinical Equipoise:

- Imprecision in definition
- Reliance on expert opinion
- Efficacy determination limitations based upon surrogate outcomes
- High cost of new treatments and lack of population health focus
- Interim analysis study terminations
- Challenges of geography and resources
NY Times Article: Show me the Equipoise? NOT!

- “New Drugs Stir Debate on Rules of Clinical Trials”
  - Metastatic melanoma drug, PLX4032 versus usual chemotherapy
  - Results of phase 2 testing and observational data show dramatic improvement with PLX4032 (versus usual care)
  - FDA demands RCT; patients and oncologists disagree!

(NOTE: final RCT just published late 2011 showed positive results)
TRI-COUNCIL POLICY STATEMENT
2010: Placebo Controlled Trials

- **Article 11.2 (a)** A new therapy or intervention should generally be tested against an established effective therapy
- The use of an active treatment comparator in a clinical trial of a new therapy is generally the appropriate trial design when an established effective therapy exists for the population and clinical indication under study

Solutions to Equipoise Issues:

- Component Analysis in ethics assessment process:
- “When are research risks reasonable in relation to benefits?”
- Therapeutic risk versus non-therapeutic risk
- Therapeutic risk: Still use Clinical Equipoise
- Consistent with competent care?
- Risks reasonable?

Weijer and Miller, Nature Medicine, 2004
Bayesian Concepts:

- Shifting beyond 50%
- Utilizing LRs in clinical practise
- Credibility intervals (CrI) versus confidence intervals (CI)
- Concept of Marginal Informativeness
- Ethical advantages in interim analysis

Clinical Example:

- **Disease:** Appendicitis
- **Intervention:** Surgery versus antibiotics/RCT.
- **Does this proposed RCT possess the appropriate elements of clinical equipoise?**

What is the Role of Observational Studies?

- Set the stage for RCTs
- Inform the equipoise argument
- Serve as a means of avoiding an RCT?
- Inform expert opinion
- Inform public policy (tobacco and cancer)
- Contribute to the marginal informativeness of any research question...
Do Observational Studies Fail to Provide “the Truth”?

- Anti-arrhythmic studies
- HTS saline in trauma
- HTS in major head injury
- HRT and ischemic cardiac disease
- Arthroscopic surgery for knee OA
- ALS for trauma?

Definitive Results via RCT
Clinical Research Example

- EMS ETI for major head injury
- 12+ observational studies showing “harm”
- One small RCT showing “good outcomes”

- You, as REB, as asked to consider a larger RCT
- Does clinical equipoise exist?
Are RCTs Always Needed? Example

- Tacrolimus (FK 506) story
- Pittsburgh group “knew” that FK 506 worked
- FDA mandated that RCTs begin....
- Pittsburgh refused to join the RCT and randomize patients to placebo
- Same issue held for sulfonamides in the 1930’s and 40’s
What Can EMS ALS do for Trauma or Cardiac Arrest Patients?
ALS Versus BLS

**Interventions – ALS**
- Intubation
- IV drugs
- Training
- RSI?

**Interventions – BLS**
- BMV
- IV (fluids)
- Training
- Other meds?
Advanced life support versus basic life support in the pre-hospital setting: a meta-analysis.

Summary- Results

- 18 articles of 1081 reviewed were included
- 9 trauma studies (16,857 patients)
  - OR for survival in ALS treated: 0.892 (95% CI 0.775, 1.026)
- 9 cardiac arrest studies (7659 patients)
  - OR for survival in ALS treated: 1.468 (95% CI 1.257, 1.715)
  - OR for survival if physician-ALS: 2.047 (95% CI 1.593, 2.631)

Advanced life support versus basic life support in the pre-hospital setting: a meta-analysis.

- **Summary-Discussion**

- ALS care does not improve survival in *trauma* vs. BLS \([p=0.005]\)

- ALS care improves survival in *CA*, more so with physician-ALS
You are the REB

- Will you grant “ethics approval” for ALS versus BLS RCT study?
- Does equipoise exist?
- What is your impression of the literature?
- Of the therapeutic mandate?
- Of the current standard of care?
ROC: Resuscitation Outcomes Consortium

https://roc.uwctc.org/tiki/tiki-index.php
ROC: Amiodarone, lidocaine or placebo for out-of-hospital cardiac arrest due to ventricular fibrillation or tachycardia (ALPS)

The goal of ALPS is to determine if survival to hospital discharge is improved with early (and if necessary) repeated therapeutic administration of a new Captisol-Enabled formulation of IV amiodarone (PM101) compared to no antiarrhythmic drug (placebo) or lidocaine.
ROC: Amiodarone, lidocaine or placebo for out-of-hospital cardiac arrest due to ventricular fibrillation or tachycardia (ALPS)

- “No pharmacologic agent has ever been demonstrated to improve survival to hospital discharge after cardiac arrest. It is not known whether these drugs may cause more harm than good.”

- You are the REB? Ethics approval?
Conclusions:

- “Clinical Equipoise” concept here to stay
- Integral component of current Canadian REBs
- Component analysis of research (therapeutic versus non therapeutic paradigms) assists the ethical assessment.
- Controversy continues around specific issues of equipoise ie expert opinion, geography etc
- Know your REB approach!
“Wisdom is knowing what to do next, skill is knowing how to do it, and virtue is doing it”

David Starr Jordan
Special Thanks to Departments of Emergency Medicine, Dalhousie University and UBC and Dr. KS Joseph, UBC

jtallon@dal.ca
john.tallon@gov.bc.ca