



# Statistical Topic: Ethics and Trial Design\*

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\* Thanks to my colleague Steve Goodman!



# Outline

- Ethics in medical research
- Equipoise
- Informed consent
- Sunitinib RCT



# Shalala Statement

- Bill Clinton's Secretary of Health and Human Services
- ***Protecting Research Subjects – What Must Be Done*** (NEJM, 9/14/2000)
- The Problems
  - Informed consent is not perfect
  - Too many researchers not adhering to good clinical practice
  - IRBs under pressure – oversight inadequate
  - Increasing conflicts of interests in CTs



# Shalala Statement (cont.)

- The Solutions

- NIH/FDA aggressive effort to improve education and training
- Guidelines for informed consent
- NIH requirement for trial monitoring plans for small trials and FDA guidelines for DSMBs
- Clarification of conflict of interest regulations
- Legislation to penalize in cases of violations of “important research practices” (\$250K/investigator and \$1M/institution)



# Important Message

- Ethical tensions pervade every aspect of design, execution, interpretation, and use of clinical research
- Every choice we make about a study has ethical implications, regardless of whether or not we explicitly consider them.



# Ethical Theories

- **Utilitarianism** – We should aim for “the good” of a world with collectively great happiness
  - *Morality concerns objective assessments of states of the world and not individual acts*
- **Deontology** – We should aim for “the good” of treating people properly: the golden rule of “do unto others...”
  - *Morality concerns the rightness of individual acts, regardless of the states of the world they entail*



# The tension

- Utilitarian

- *One's chance of getting the best treatment is highest if one lives in a society where treatment choices are governed by RCTs*

- Deontologic

- *You want your physician to give you the treatment s/he and you decide is most likely best for **you***



# However....

- Helsinki Declaration

- In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society



# Most Important Principle: **Equipoise**

- Equipoise is the concept that a clinical trial (esp. an RCT) is motivated by a collective uncertainty about the superiority of one treatment versus its alternative (Piantadosi, 2005)
- Satisfies the requirement that study participants not be *disadvantaged*
- “At the start of the trial, there must be a state of clinical equipoise regarding the merits of the regimens to be tested, and the trial must be designed in such a way as to make it reasonable that if it is successfully conducted, clinical equipoise will be **disturbed**.” (Freedman, 1987)



# Equipoise

- Once equipoise is “disturbed”
  - It is no longer ethical to randomize (or otherwise assign) patients to less effective therapy
- If trial is done well:
  - lack of efficacy should be clear
  - efficacy should be clear
  - should NOT have a situation where we are unsure!
- When is it disturbed?
  - In sunitinib RCT, WHEN was it disturbed?
    - Upon analysis of data?
    - At the time when the balance was definitively in favor of the sunitinib arm (i.e., prior to analysis)?



# Informed Consent

- Clinicians, PIs, Co-Is, CTOs, etc.
  - Understand the CTs (for the most part)
  - Understand the risks and benefits
  - We are very used to the idea of trials (RCTs and others)
- Patients, generally
  - Are unfamiliar with clinical research
  - Put trust in their doctors
  - Assume that they will get “the best” treatment when it is known
  - Do not understand “chance” and “randomization”
  - Assume a trial will help (even Phase I)



# Informed Consent: 4 criteria

- Is patient capable of giving consent?
  - Protection for those with diminished capacity (children, prisoners, developmentally disabled, elderly(!))
  - Recognition of patient vulnerability due to anxiety, or effects prior to treatment
- Is consent given freely? “Coercion”
  - Refusal to offer certain therapies outside of study settings
  - Change in caregiver due to refusal of consent
- Is patient given ALL necessary information, including alternatives?
- Can patient UNDERSTAND information?



# Informed Consent

- 6<sup>th</sup>-8<sup>th</sup> grade reading level
  - No “big” words
  - Short sentences
- Short and sweet vs. long and tiresome?
- Conflicts:
  - PI and caregiver?
  - Accrual goals



# Ethical issues in RCT of Sunitinib in advanced GI stromal tumor

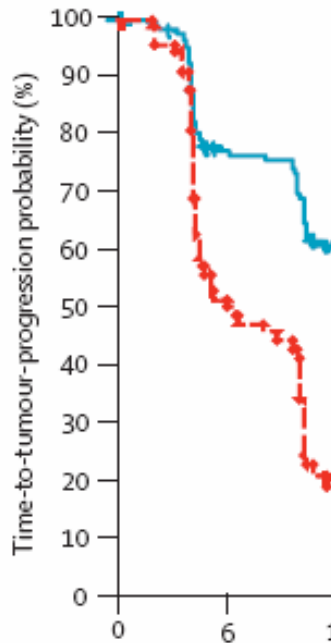
- 2:1 ratio of Sutent vs. placebo
  - Does that make us question equipoise?
  - Is it for patient accrual?
- Phase I/II study showed “promising activity”
  - Little response
  - Significant stable disease



# Ethical issues in RCT of Sunitinib in advanced GI stromal tumor

- Cross-over included (but didn't help)
- Double-Blinded: maintains equipoise
- Interim analyses after 141 and 211 progressions
  - Valid design
  - Prevalent problem in “frequentist” statistics: need to wait
  - At what point COULD we have stopped?

# Observed Data



What if they had looked at the data earlier in the study?

#### Number at risk

Sunitinib	207	106	6
Placebo	105	36	1

**Figure 2: Kaplan-Meier estimates of time to tumour progression**  
Results represent central radiology assessment of ITT population.



# Why not single arm?

- What is standard of care?
- No 2<sup>nd</sup> line treatments after failure of imatinib
- Was this ethically designed?
- Revised Helsinki Declaration (section 29)
  - The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, where no proven prophylactic, diagnostic or therapeutic method exists.
- **What design would you have felt most comfortable with?**
  - as a researcher, which is the best design?
  - would you encourage your family member to go on this trial?