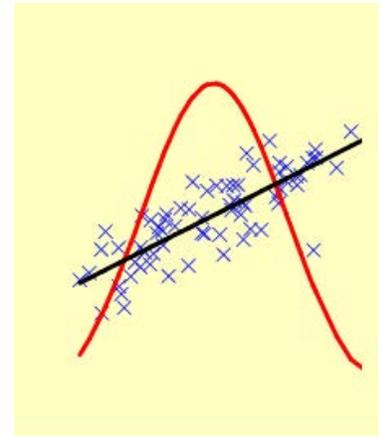


# In search of the lost loss function

ethics, equity and rationality in rare disease research

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# Basic thesis

- Rare diseases present a challenge when traditional models of drug development are considered
  - Similar issues apply to small subgroups
- I think we need a fundamental examination of what we need to do
  - But I am not capable of providing it!
- The value of information is central
- This requires thinking about the losses associated with
  1. Imperfect decisions
  2. Delays in taking action

# Warning: a ragbag of thoughts

## **An apology**

- This talk is very confusing
- In fact, it is even confusing to me
- You have little hope of finding any structure
- The outline on the right may help

## **An outline**

- Conventional power calculations
- The value of information approach
- The philosophy of John Rawls as it may or may not apply to drug development
- Some examples
- Lessons for ethics and perhaps rare diseases

# Approximate Formula for Sample-Size Determination

$$n = 2 \left( z_{\alpha/2} + z_{\beta} \right)^2 \left( \frac{\sigma}{\Delta} \right)^2$$

substitute  $k = z_{\alpha/2} + z_{\beta}$ ,

$$n = 2k^2 \left( \frac{\sigma}{\Delta} \right)^2 \rightarrow$$

$$\left| \frac{\Delta}{\sqrt{\left( \frac{2\sigma^2}{n} \right)}} \right| = k$$

## Primitives

$\alpha$  : probability of type I error given no effect.

$\Delta$ : the relevant difference.

$\beta$  : probability of a type II error given that the true treatment effect is relevant.

$\sigma$  : the standard deviation of the outcome.

## Functions of primitives

$Z_{\alpha/2}$  : value of standard Normal corresponding to right hand tail probabilities of  $\alpha/2$ .

$Z_{\beta}$  : value of standard Normal corresponding to right hand tail probabilities of  $\beta$ .

## Derived

$n$ : the number of units in each treatment group.

## Alternative interpretation

$k$ : targeted signal to noise ratio or, equivalently, precision in units of clinical relevance

Alternative view of conventional power calculations is that they target a given degree of 'data precision'

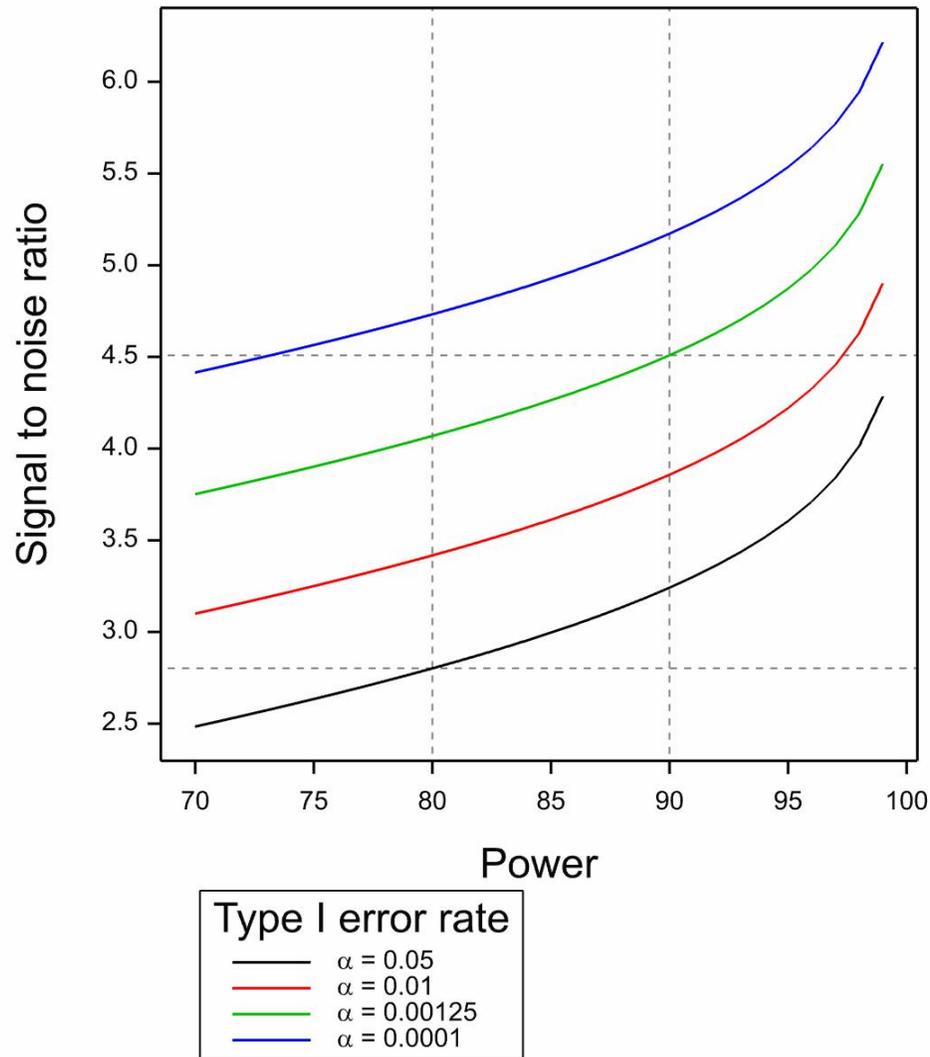
Typically between about 2.8 and 4.5

So they can be regarded as providing a given amount of information

**Exception: frequentist sequential trials do not do this**

**In my opinion, stopping early for efficacy is rarely a good idea**

Signal to noise ratio for various type I error rates



$\alpha = 0.00125$  is 'two trials rule' equivalent

# A trap for the unwary

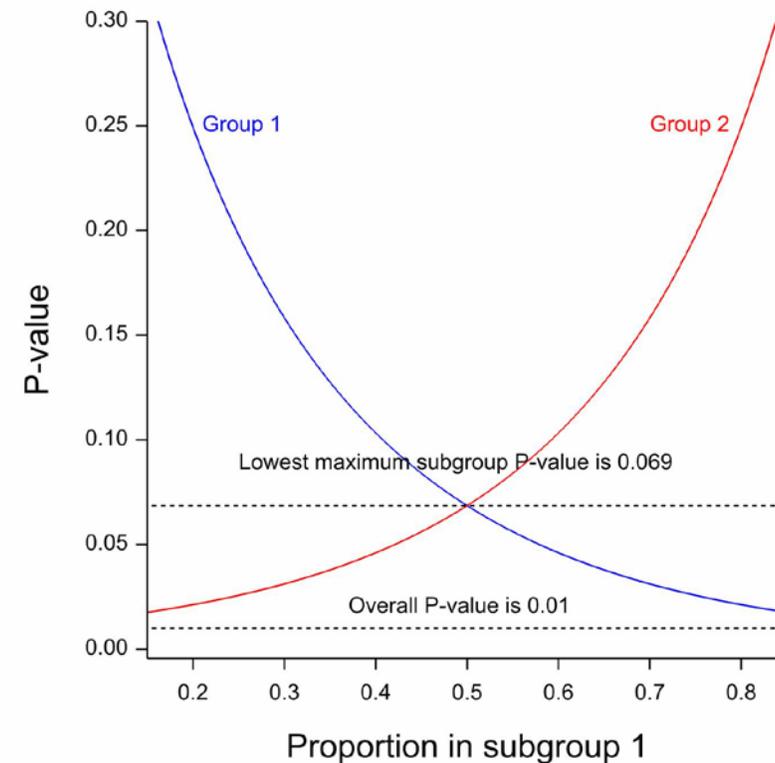
- It is sometimes suggested that only large trials (adequate power etc) are worth doing
- However, consider the case of a fixed budget and many possible projects
- Now think of the problem in terms of the *average size* of the trials for *all* projects
- ***All those projects that are not funded have, from one point of view, trials with zero patients***
- Where else would a statistician think it was acceptable to calculate averages ignoring the zeros?
- So, making sure that only big trials are run may not be information efficient from a wider perspective

# What is missing?

- Cost
  - In £,€, \$, CHF
  - In patients' lives and quality
  - In other consequences of delay
- Conventional power calculations have no cost dimension
- This means that for any degree of targeted data precision two trials with the same value of  $\Delta/\sigma$  will give the same answer, whatever the cost
- What is needed is a *value of information* perspective

# Subgroups (an aside)

- In a sense small subgroups are similar to rare diseases
- However, information may carry over between subgroups rather more plausibly than between diseases
- Suggests that bias-variance trade-offs be considered
- Also each sub-group investigation should perhaps be regarded as competing for funds and hence as a mini-project
- Is it worth doing?



# Value of information

## The basic idea

- There are three choices facing you
  - Choose A
  - Choose B
  - Pay to find out more about the relative values of A and B
- You may currently believe that B is better than A
  - If you had to act now, you should choose B
- If you can delay action with the possibility of acquiring new information, it might be worth doing this
  - Depends on the losses involved
  - Depends on cost of information

# Various historical approaches (selection)

## **Fixed**

- Raiffa and Schlaifer, 1961
- Lindley, 1997
- Stallard, 1998
- Burman and Senn 2003
- Etc, etc

## **Sequential**

- Anscombe 1963
- Chernoff 1966
- Gittins various, starting 1979
- Etc, etc
- Pertile et al 2013
- Jobjörnssen and Christiansen 2017

# Lindley's approach: a double optimisation

**Optimal action for any given result for any sample size**

You must know what the optimal decision would be (say choose A or choose B) for any given result for any given sample size

You then have to calculate the expected value of the optimal decision

**Optimal sample size using expected value of optimal decision per sample size**

Associated with each sample size there is a cost

This has to be subtracted from the expected benefit of the optimal decision

You have to search amongst the sample sizes to find the maximum expected benefit net of information cost

# I am not going to go into this theory

- It's complicated
- I don't think that advancing this theory is the main problem
- I think that the problem of deciding on appropriate loss functions and also various perspectives , patients, society, is more important
- I am too stupid to understand let alone explain the theory fully
- So I am now going to consider a basic perspective and provide some examples to help raise some issues

# A Rawlsian View (John Rawls 1921-2002)

- You are about to be born into the world
  - The original position
- You don't know who you will be
  - The veil of ignorance
- How would you like society to be organised?
- Ethical arrangements require long-term perspectives
- Something similar is required in the world of insurance
  - You can't insure against a calamity that has already happened
  - Utmost good faith is required

# Example 1: spending priorities in society

- Try your hand at this one.
  - The spending priorities of Great Britain Ltd
    - Currently spend millions on frivolous holidays for the young in Ibiza
    - We have lots of deserving elderly on the waiting lists for hip replacement etc.
    - Shouldn't we tax the young and single to pay for these operations?
- You are about to start your life
- But you don't know who you will be
- Do you want society to be
  - For "ants" only
    - No holidays
    - High taxes for eventual old age
  - Or for "grasshoppers"
    - Let's have fun while we are young

# The Original Position and Medical Research

## Short termism

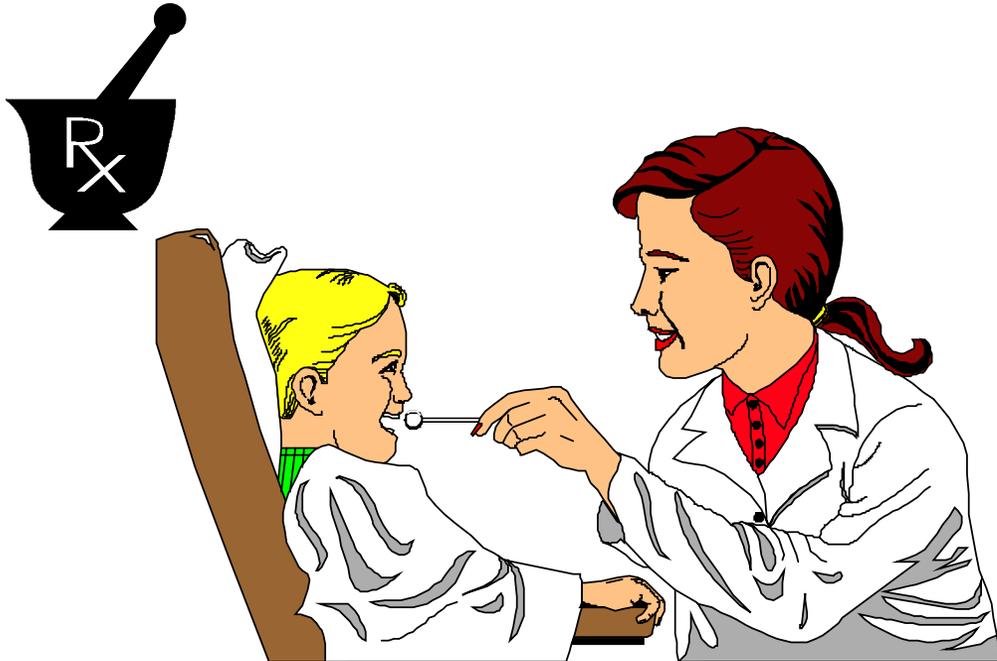
- Doctors back their hunches as to what they think is best
  - “Right to Try” law USA
    - Signed off by president Trump 30 May 2018
  - Medical Innovation Bill UK (Saatchi bill)
    - Failed to pass senate

## Long termism (The regulatory system)

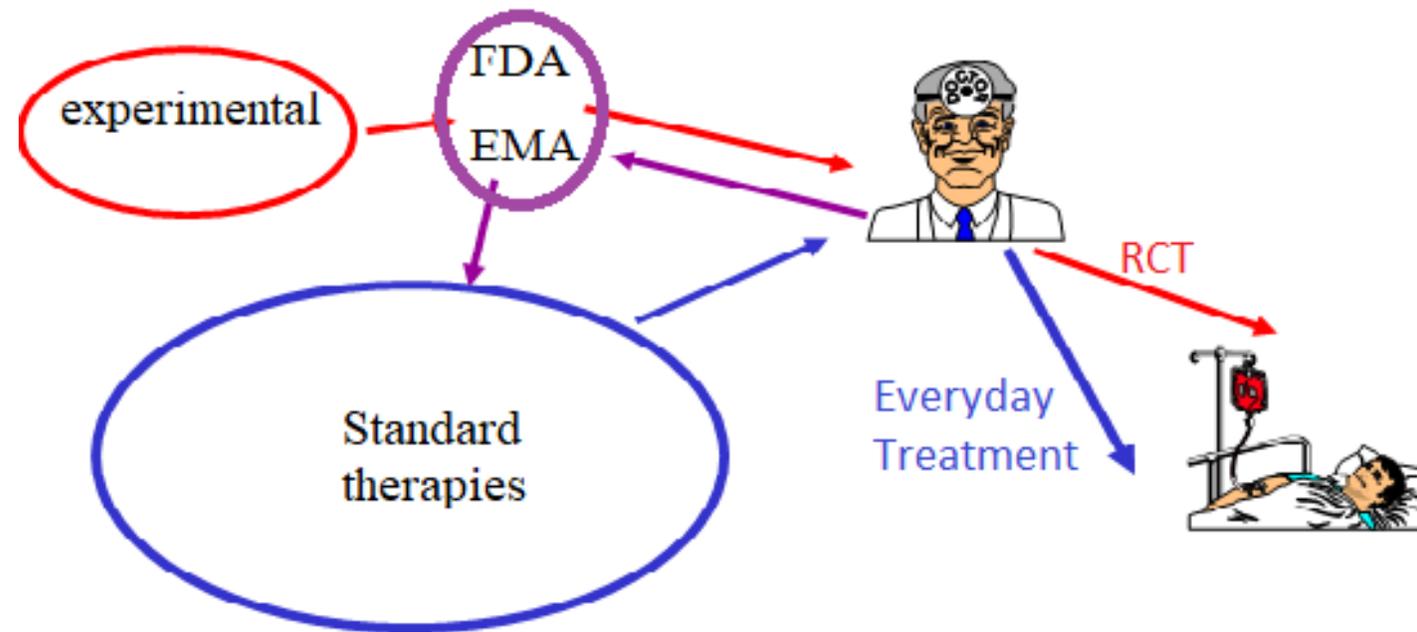
- You don't know whether and in what era you fall ill
- It is in your interest that drugs are evaluated scientifically
- You benefit from previous research
- Patients have the right to approved medication
- The only access to unapproved medication is through clinical trials

# The two systems

A closed world of Dr and Patient



A wider world with 'society' as a third player



# Example 2: O'Quigley's Continuous Reassessment Method CRM

- Example of a one-step-ahead optimisation problem
- You are trying to target the best dose for the patient you are just about to treat
  - Once that patient has been treated you repeat the process for the next patient
- It is possible that you could do better for later patients by allocating some of the earlier patients sub-optimally for them
  - This is usually regarded as unethical
- However, there is one problem
  - How do you decide when to stop?

# Example 3 Childhood melanoma

- This disease had its waiver for EMA Paediatric Investigation Plans revoked in 2008
  - As far as I am aware the situation has not changed
- So you have to study children if you want to get a license
- A blow for the rights of children has been struck
- Or has it?
- But the results of such trials will only benefit (if at all) children who are not yet ill and perhaps not yet born
- How will melanoma most plausibly affect their lives?
  - As a paediatric patient?
  - Because their parents become patients?
  - Because they get melanoma as young adults?
- So if such legislation delays research into melanoma in adults it may actually be against the interests of children

## Example 4 First in Man Studies

- Suppose that the acceptable risk to an individual is 1 in 2000
- But we believe it is 1 in 1000 for this drug
- By having one placebo for every active treatment and randomising we can reduce the risk to 1 in 2000
- Does this make it acceptable?
- Such a device reduces the risk to the individual to acceptable levels
- However, it does not reduce the expected number of side-effects per trial
  - Nor the risk to the insurer
- Suggests a dual perspective
- Acceptable to an individual AND to society

## Example 5 Funding rare disease research?

- Suppose that we know that the most effective total impact for good on the health of children would be to spend all our research budget on the most common diseases?
- Should we abandon research in rare diseases for the foreseeable future?
- This is a really difficult case
- At first sight the long term broader view seems to suggest 'yes'
- But maybe the even longer Rawlsian view suggests 'no'
- This is a very difficult issue

# Trials in rare diseases

- We have to accept that the classical model is inappropriate
  - Can be defended when we have a long time horizon of future patients compared to patients in the trial
- Patients have to make choices even if we have no provided information for them
  - Pragmatic framework of Schwartz and Lellouch 1967
  - Type III errors should be controlled
    - Choosing the worse treatment
- We may have to accept weaker standards of evidence
- WP9 IDEAL project [https://www.ideal.rwth-aachen.de/?page\\_id=342](https://www.ideal.rwth-aachen.de/?page_id=342)

# Conclusions

- It is often very misleading to make decisions at the point of sickness
  - Young holidays versus old hip replacements
- Sometimes, however, we concentrate on the short term
  - CRM
- Sometimes longer and wider perspectives might be appropriate
  - Childhood melanoma
- Nevertheless, single perspectives may not be enough
  - First-in-man example (societal and individual)
  - Rare diseases example
- We need more debate about what we are trying to achieve with clinical trials

# Final thought

Statistical calculation of consequences is not the be all and end all of ethics

Nevertheless, those who ignore statistical considerations in coming to decisions about resource allocation and information gathering in medicine are likely to make bad decisions and this is unethical