# PH 458/231
# Evidence & Policy
# Lecture 5

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Monday 13.30-14.30
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# Examples of worrying conceptual problems: ‘Statistically significant’ does not entail ‘significant’

- One reason is that it would be remarkable if there were really *zero* difference between two ‘treatments’
- That is , if a ‘null hypothesis’ were literally true
- But if there is a difference, no matter how tiny, then a statistically high-powered (large sample) test is very likely to “find it”
- The result would be SS but might be of no real significance at all
- Effect size (or ‘likely effect size’) and statistical significance are two quite separate things

# ‘Statistically significant’ does not entail ‘significant’

- And neither does non-SS entail ‘not significant’!
- Suppose you have very good reason to believe ahead of the test/trial that some new treatment is really effective
- Yet the test fails to refute the null
- That surely, again *pace* Fisher, gives you some reason to think that the null might be right
- And since that would be surprising, the result is surely significant in the general sense
- (Need for judgment)

# Lessons for ‘evidence savvy’ Policy makers

- 1.  Don’t be fooled by “impressive” (i.e. small) p values, you want to know whether the evidence is really significant , not just statistically significant.
- 2. Look at *all* the evidence, don’t ignore ‘negative’ (“insignificant”!) evidence.
- (so you should worry about meta-analysis)
- 3. Don’t fall for the tempting ‘ the evidence is significant at the x% level’ therefore ‘it’s x% likely that the null is false (and the ‘alternative’ true)’
- (a) there are lots of alternatives!
- (b) it’s a fallacy anyway

# Lessons for ‘evidence savvy’ Policy makers

- 4.However, it would also be a mistake to be *too* negative about the impact of SS results
- Suppose we accept
- (i) that ‘all’ an SS result tells you that p(e/h) is low; and
- (ii) that you really want to know p(h/e); and
- (iii) that you need further information to get to what you want to know
- STILL: that further information may be available
- Indeed you may reasonably think you have it!
- Blue cabs/yellow cabs again
- (Reason why Kahnemann and Tversky stuff may be questionable and the ‘base rate fallacy’ may not always be a fallacy)
- But still it is something else you MUST as an evidence savvy policy person think about.

# Ethics & evidence can get intertwined: a case study

- Suppose you are Chair of the Ethics Committee at some University Hospital
- A researcher is seeking permission to recruit patients for an RCT on some new treatment
- She appears before the committee and says ‘ We are really excited about this trial because we are sure that this new treatment marks a big advance.’
- Reaction 1: ‘Hold on, if you are sure that the treatment is a big advance, how about those patients in your trial who would be randomized to the control arm? Wouldn’t you be consigning them to a treatment you were sure was inferior? And isn’t that contrary to the Hippocratic Oath?’
- Reaction 2: ‘will you tell the patients that you are sure that the new treatment is a big advance (‘informed consent’)? If so, you may have recruitment problems!’

# “Equipoise”

- Generally assumed within medicine that the ethics of clinical trials is governed by a principle called ‘equipoise’
- That a trial is ethically acceptable if, and only if, some state of equipoise exists
- But what exactly does equipoise involve? And who is supposed to be in it??
- Initially supposed that it applies to the individual investigators
- The name suggests that to satisfy *equi*poise the investigators should be in a state of ‘maximum uncertainty’
- But generally taken that it means there should be at least some substantial uncertainty about the comparative effectiveness of the treatment
- ??
- In any event, many believed that this individual principle was too stringent and perhaps inappropriate →
- Freedman’s notion of ‘collective equipoise’

# “Equipoise”

- No surprise that ethics and epistemology are intertwined here
- But it is, perhaps, surprising just how *inter*twined they are.
- Will show this via a case-study: trials on ECMO

# Evidence and Ethics intertwined: The story of ECMO

- There is a condition called pulmonary hypertension of the new born which historically had a mortality rate, across hospitals in the US and Europe, of around 80%.

# Evidence and Ethics intertwined: The story of ECMO

- In the 1980s, Bartlett and colleagues at the University of Michigan hospital used a new technique in treating this condition - a technique called ‘Extra-corporeal membraneous oxygenation’ (ECMO).

# Evidence and Ethics intertwined: The story of ECMO

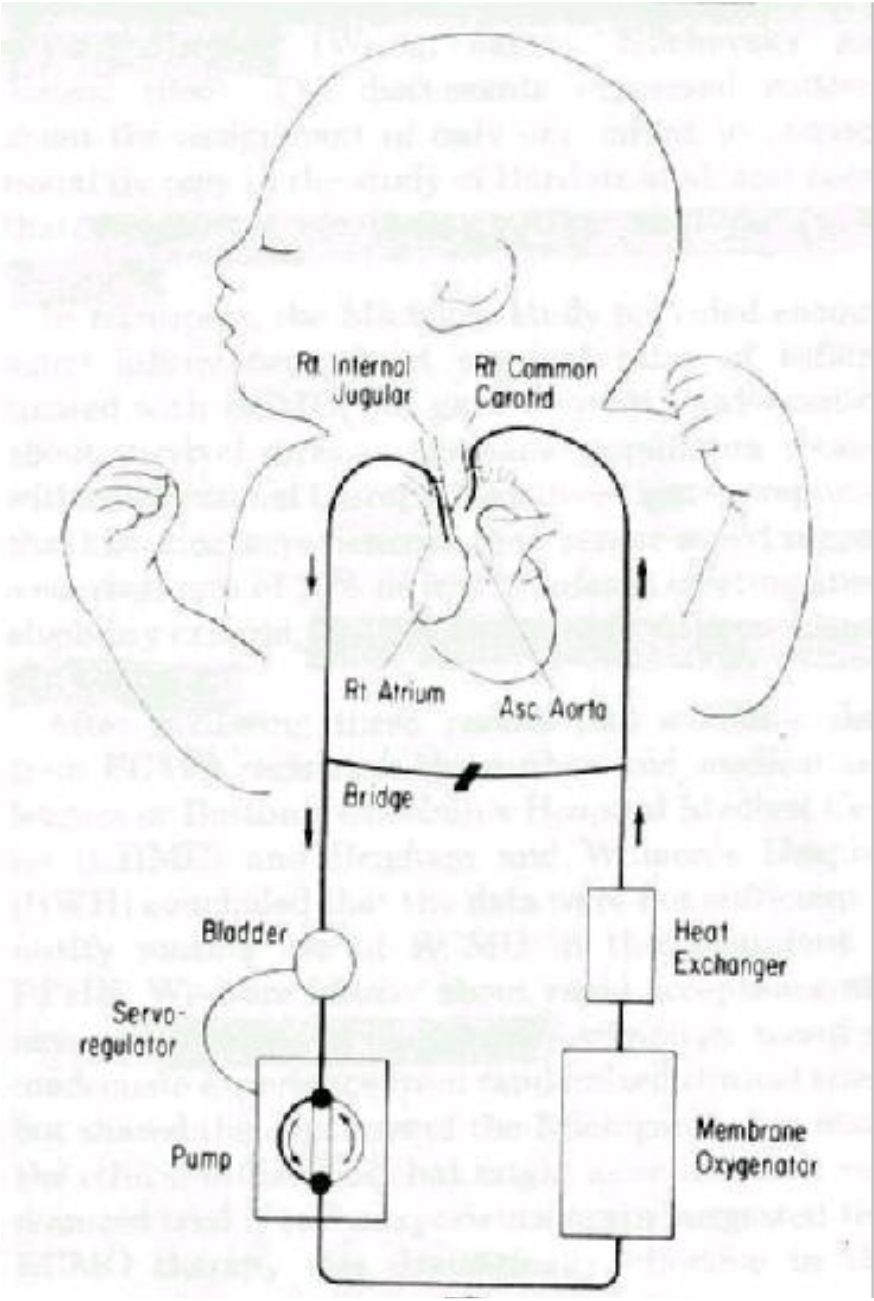
- It’s important background information, I think, that the etiology of the condition was known.
- The problem was that these otherwise fully mature babies had immature underdeveloped lungs.

# Evidence and Ethics intertwined: The story of ECMO

- Hence it was known what happened in the 20% of survivors –
- somehow keep them alive long enough for the lungs to mature.

# ECMO

- Extra-corporeal membraneous oxygenation



# Evidence and Ethics intertwined: The story of ECMO

- Bartlett and Colleagues found that, using the new technique, 80% of babies with this condition survived.
- Nonetheless they “felt compelled to conduct a prospective randomized study”.
- This, despite the fact that they “anticipated that most ECMO patients would survive and most control patients would die”
- (What is a prospective randomized study?)

# Evidence and Ethics intertwined: The story of ECMO

- First trial
- Protocol: “Randomized play the winner”
- Result: 11 babies assigned ECMO and lived
- 1 baby assigned standard treatment and died

# Evidence and Ethics intertwined: The story of ECMO

- Should this trial have been done at all?
- Some people thought that, on the contrary, the 'historically controlled' "evidence" was scientifically worthless AND that
- This first trial was not a properly randomized study and hence produced no real evidence for the extra efficacy of ECMO
- (Since 'the only source of reliable evidence … is that obtained from … carefully conducted randomized trials" (Tukey))
- And so if *real* evidence was to be obtained, *another* trial was necessary

# Evidence and Ethics intertwined: The story of ECMO

- A second trial was performed
- Protocol: orthodox randomisation with $p<0.05$
- (with stopping rule – stop after 4 deaths in either arm)

# Evidence and Ethics intertwined: The story of ECMO

- RESULT: 9 babies assigned to ECMO, all survived
- 10 babies assigned to standard treatment, 4 died

# Evidence and Ethics intertwined: The story of ECMO

- If you had qualms about the first trial, then you will certainly have qualms about this one
- (in particular about the deaths on the control arm)
- But orthodox statistical analysis says that the stopping rule messes up the power calculations
- AND may lead to a trial being stopped without a ‘significant’ result having been achieved
- And that in fact neither the first nor the second trial provided any real scientific evidence of the extra effectiveness of ECMO

# Evidence and Ethics intertwined: The story of ECMO

- (Pocock) ".. a decision was taken to halt randomization when the data disclosed four deaths among ten infants receiving conventional medical treatment compared with none among nine infants having ECMO (p= 0.054). [R]andomization was stopped early on the basis of a fairly small amount of data…

# Evidence and Ethics intertwined: The story of ECMO

- ..However, with only 19 patients this does not represent strong evidence of the superiority of ECMO and provides little scope for making reliable judgments on the benefits of this treatment for universal use in such newborn infants in the future."
- Thus a third trial was recommended and performed.
- Outcome: stopped early because of large number of deaths on the 'control arm'.

# So: Epistemology affects ethics

- Want now to look at 3 ethical/policy issues raised by the case study.
- And show how this case-study reveals that the ethical judgments concerned are strongly interconnected with evidential judgments.

# Epistemology affects ethics

- 3 issues are:
- 1. Whether or not performing a trial at all is ethical
- 2. Are ‘Stopping Rules’ ethically-required?
- 3. What’s involved in ‘informed consent’?

# When is a trial ethically permissible?

- Which, if any, clinical trials are ethical (in general)?
- In placebo controlled trials, it is hoped that the doctor is in fact assigning (roughly) half the patients to an inferior treatment.

# When is a trial ethically permissible?

- How then it this compatible with?
- ‘the health of my patient will be my first consideration’
- (Physician’s oath, Declaration of Geneva)
- Usual response: ok so long as the doctor is in EQUIPOISE
- The objective state of affairs is one thing, what the physician *knows* is another

# When is a trial ethically permissible?

- The physician is not contravening her ‘oath’ so long as
- She *does not know* which treatment in the trial is more efficacious.
- ‘know’???????

# When is a trial ethically permissible?

- We are here obviously into epistemology
- Clearly ‘know’ in the standard sense too strong
- (If you really (objectively) knew already, the trial would be (objectively) pointless;
- And if you *believed* you knew, why would you want to do the trial?)
- So how much weaker should it be? What sense of ‘know’ or ‘have (good?) reason to believe’ is the right one?

# When is a trial ethically permissible?

- Usual construal: has no reason to think that one treatment is more effective than the other
- Understood subjectively, a clinician very seldom is totally indifferent between the 2 treatments
- In particular those involved in organising the trial will often be positive about the new treatment under test
- (encouraged by all the preliminaries required before ‘ Phase 3 trials’.)

# When is a trial ethically permissible?

- ‘Clinical equipoise’? (Benjamin Freedman)
- ‘It is not necessary for a physician to be in personal equipoise to ethically enroll a patient .. so long as there is genuine uncertainty within the medical community …’

# When is a trial ethically permissible?

- BUT surely something to the “hardliners’” reaction:
- Doesn’t matter what anyone subjectively believes, it’s a question of *objective evidence*.
- And indeed several studies have shown that optimism tends to evaporate when controlled trials are performed

# When is a trial ethically permissible?

- E.g. Gilbert, McPeek and Mosteller (1977) looking at new therapies in surgery and anaesthesia found that only 49% of new therapies when tested proved superior to standard treatments
- (including as superior treatments that were only equally as good so far as the target disorder goes but were judged to have a more acceptable side-effect profile)
- Remarkable given that they were looking only at *published* studies

# When is a trial ethically permissible?

- Reasonably remark that:
- “when assessed by randomized clinical trials, innovations in surgery and anaesthesia are successful about half the time. Since innovations brought to the stage of randomized trials are usually expected by the innovators to be sure winners, we see that .. . the evidence is strong that the value of the innovation needs careful empirical checking.”

# When is a trial ethically permissible?

- So no argument from me that we need to look at the objective evidence rather than anything purely subjective
- Does ‘clinical equipoise’ help?
- Surely not if achieved via ignorance or failure to take on board the objective evidence
- BUT the issue surely is the (too ready?) identification of ‘objective evidence’ with ‘results of RCTs’.

# When is a trial ethically permissible?

- Gilbert, Shafer, Baum and many many others could be quoted as claiming that:
- Without RCT-evidence, there is no evidence but only ‘guesswork’ (Baum) or ‘hunches’ (Shafer).
- Herbert: “Uncontrolled studies may point in a direction, but they never provide *evidence* – only RCTs can tend to prove or actually prove.”

# When is a trial ethically permissible?

- Surely seems intuitively (and I would argue also from a ‘first principles of evidence’ perspective) too polarised.

# When is a trial ethically permissible?

- Thinking about the ECMO case:
- Certainly don't want to be carried away uncritically by the enthusiasm of the ECMO proponents;
- But we also don't want to say that because it was 'uncontrolled', the initial results (80% mortality rate turned into 80% survival rate) *can't* constitute any sort of proper evidence.
- Two aspects of this case need emphasis

# When is a trial ethically permissible?

- 1. The *size* of the effect
- 2. The fact that it's extremely difficult to see any difference that might plausibly *make a difference* between the babies who were earlier treated with CT and those who were now being treated with ECMO.
- Admittedly some allowance needs to be made for the fact that all the ECMO babies were known to be 'on the experimental arm'
- But is it plausible that 'attention effects' could make such a difference?

# When is a trial ethically permissible?

- Summary:
- Taking it as a given, that it is unethical to perform a trial when you have good evidential reason to think one of the ‘arms’ involves an inferior treatment, then
- IF you hold that ‘proper evidential reason’ can only be supplied by the results of RCTs, THEN you will NOT find the 2nd (and 3rd) trials unethical.

# When is a trial ethically permissible?

- Whereas IF you hold that ‘proper evidential reason’ can be supplied by sophisticated properly controlled historical trials, THEN
- You will judge both the 2nd and 3rd trials unethical.
- SO: epistemology affects ethics.

# Ethics and Stopping Rules

- 2. The ethics of ‘stopping rules’
- (Remember in ECMO case: 2nd ‘properly randomized’ trial to be stopped once there were 4 deaths on either arm.)
- Aimed presumably at preventing an ethical clash:
- how can a clinician continue with a trial if s/he has come to believe on the basis of results so far that one treatment arm is superior?

# Ethics and Stopping Rules

- Ian Kennedy sketches a related problem and takes a very definite view:
- “ As a trial progresses, a trend in the evidence may appear, suggesting that it would be harmful to continue with [the treatment on one ‘arm’]… Such a trend may appear, of course, before any statistically valid conclusion can be drawn … “
- Is it then ethically justifiable to continue with the trial?

# Ethics and Stopping Rules

- “In my view, … the trial must cease, despite the unfortunate consequences this may have for medical science. To argue otherwise … is hard to defend in any ethical system which takes seriously the principle of respect for autonomy. It would put the interests of others, at present unknown, and the interests of science … above the interests of the patient whom the doctor has undertaken to treat.”

# Ethics and Stopping Rules

- Again some epistemology/philosophy of science here:
- For one thing, a ‘trend’ does not ‘appear’ (at least not if this is taken to involve some sort of permanence or generality)
- Why would it be ‘putting the interests of science … above the interests of the patients’ if the first few results constituted no real evidence – as the statisticians will insist?

# Ethics and Stopping Rules

- Everyone has to accept that the first few results *may of course* be unrepresentative of the population result.
- Surely again subjective views are irrelevant.
- There is objective reason to feel that continuing a trial is unethical only if the trial results so far provide objective, and presumably strong, evidence that one of the two treatments involved is superior.

# Ethics and Stopping Rules

- Statisticians will insist that such ‘objective reason’ is supplied only by a properly powered RCT
- (Though even they will admit that sometimes stopping is ethically mandated.)
- Do we then want to take the strong line advocated by Pocock that in the 2nd ECMO trial the stopping rule was unjustified?

# Ethics and Stopping Rules

- And indeed made the trial itself ethically questionable –
- NOT because there was already evidence that ECMO is superior, BUT because it meant that this second trial could not supply such evidence
- And HENCE meant that patients were involved in a trial that had no epistemic purpose.

# Ethics and Stopping Rules

- Pocock: ".. a decision was taken to halt randomisation when the data disclosed four deaths among ten infants receiving conventional medical treatment compared with none among nine infants having ECMO (p= 0.054). [R]andomization was stopped early on the basis of a fairly small amount of data, all subsequent patients being allocated to ECMO."

# Ethics and Stopping Rules

- [Notice that there were in fact 20 of these, 19 (!!)of whom survived. But they could not count as part of the trial since they were not randomized.
- But had they been randomized and all been lucky then this would have been a highly significant result even in classical statistical terms!
- Classical statistical orthodoxy gone mad??]

# Ethics and Stopping Rules

- “The investigators were sensitive to the individual ethics of seeking parental consent and randomization for the next newborn infant .. However, with only 19 patients this does not represent strong evidence of the superiority of ECMO and provides little scope for making reliable judgments on the benefits of this treatment for universal use in such newborn infants in the future.”

# Ethics and Stopping Rules

- “Thus collective ethics may have been compromised by such early stopping…. [I]f ECMO really is effective the prolonged uncertainties maintained by lack of really substantial evidence may well have led to fewer newborn infants worldwide receiving it than would have been the case had the trial continued longer.”

# Ethics and Stopping Rules

- Two points:
- A. WHY were “the investigators sensitive to the individual ethics of seeking parental consent and randomization for the next newborn infant”?
- B. An implicit further argument here of a ‘social epistemological’ kind, that is interesting and well worth teasing out.

# Ethics and Stopping Rules

- Re A: Surely the investigators had this ‘sensitivity’ because they believed that
- the historical evidence *plus*
- the earlier trial result *plus*
- the 0 deaths out of 9 on ECMO compared to 4 out of 10 on CT in this 2nd trial
- Provided reasonably compelling OBJECTIVE evidence of the superiority of ECMO.

# Ethics and Stopping Rules

- In other words they implicitly rejected the orthdox, frequentist statisticians' view that the only objective, scientific evidence is that garnered from officially sanctioned RCTs.
- Were they right?

# Ethics and Stopping Rules

- Re B: Implicit in Pocock's treatment (and made explicit elsewhere) is the claim that:
- Whatever the objective rights and wrongs of the epistemic situation, it is just a matter of fact about the medical community that it will only accept that a new treatment is really superior (and therefore agree to its general introduction and use) if that superiority has been 'established' by a ' proper' RCT.

# Ethics and Stopping Rules

- Hence the argument that application of the stopping rule “may well have led to fewer newborn infants worldwide receiving it than would have been the case had the trial continued longer.”
- BUT this is extraordinary – it seems to concede that there may at least sometimes be some good evidence that a treatment is effective that is not produced by a fully accredited RCT;

# Ethics and Stopping Rules

- Yet in order to *convince* the medical community, a ‘proper’ RCT should still be performed
- even though there is already - objectively good but intersubjectively unappreciated - evidence that the new treatment is superior; and therefore
- even though there is good evidence ahead of the trial that those in the control arm are being given a decidedly inferior treatment

# Ethics and Stopping Rules

- Surely an alternative that is both ethically and epistemologically more attractive would be
- To stop teaching medics that RCTs are the ‘gold standard’ and stop encouraging the view that only they provide real scientific evidence; and
- Encourage a more sensible view of objective evidence.

# Ethics and Stopping Rules

- In any event clear that there's lots of work to be done here; but
- Surely clear, as I claimed, that you can't develop a serious ethical view about the matter of stopping rules without getting seriously involved in epistemic, evidential issues

# Ethics and Stopping Rules

- IF you hold that you really don't know anything objectively about a new treatment unless it has been validated in a ' proper' RCT – one with acceptable power
- THEN the stopping rule used in the 2nd ECMO trial was certainly obfuscatory and arguably itself unethical

# Ethics and Stopping Rules

- WHEREAS
- IF you hold that there can be real evidence short of a ‘proper’ RCT and that in the ECMO case the interim results of the 2nd trial (at the latest) provided it, then you would regard it as unethical to have continued the trial

# The ethics of ‘informed consent’

- In the 2nd & 3rd trials, the ‘Zellen method’ of obtaining “informed” consent was used.
- This involves seeking informed consent only after randomization and only if a patient is randomized to the experimental arm.
- The justification being that the normal treatment that a patient could expect was CT – so no need to ask for informed consent if actually assigned to CT

# The ethics of ‘informed consent’

- Was this ethical?
- Again much will depend on your attitude to an epistemological issue

# The ethics of ‘informed consent’

- IF statistical orthodoxy is correct that the results of the initial ‘historically controlled’ trial and the first ‘play the winner’ trial represent no sort of genuine information,
- THEN you may not find any ethical problems in not telling the ‘control’ parents about the possibility that their baby could have been assigned to the ECMO arm
- (Some issues about paternalism here.)

# The ethics of ‘informed consent’

- BUT IF you think that these earlier results did supply at least some sort of objective evidence, THEN
- In so far as you think that it is an ethical requirement that patients give genuinely informed consent
- You will definitely regard these trials as ethically questionable.

# Summary

- You won't do biomedical ethics/health policy properly unless you dig into epistemological/philosophy of science issues.
- I argued this by considering 3 questions arising from the ECMO case:
- 1. When is it ethical in general to perform a trial?
- 2. Are 'stopping rules' ethically mandated?
- 3. When should patients be regarded as having given their *informed* consent?