Rigshospitalet
The Neuroscience Centre

PERNS
Personalised Neurosurgery

UNIVERSITY OF COPENHAGEN

REGION

# Innovations and the elusive quest for evidence

## The warrant
## The researcher or vendor
## The oversight


Tiit Mathiesen

Copenhagen University Hospital

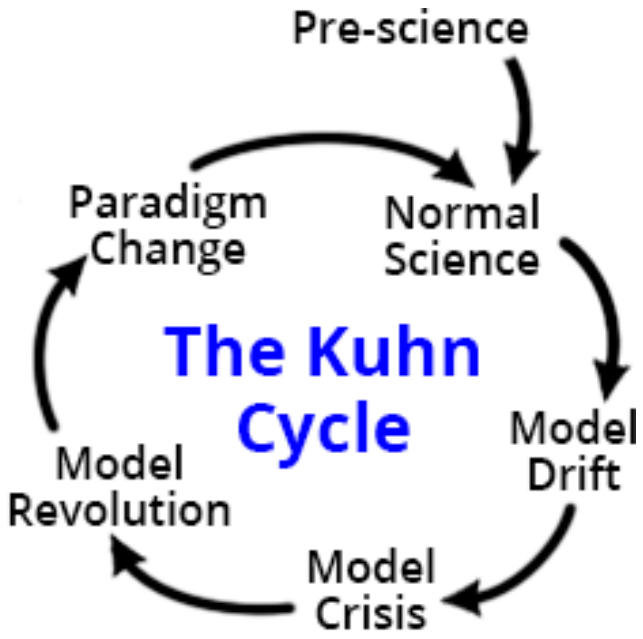
Personalized Neurosurgery Research Center

# Medical innovations

- Many similar definitions: “A novel idea, product, service or care pathway that has ***clear benefits*** when compared to what is currently done”
- Vaccination, Epidemiology, Anesthesia, Germ theory, 3D printing, Gene therapy, Medical imaging, Antibiotics, Organ transplants, Immunotherapy, Stem-cell therapy, ECMO…

**clear benefits - vague. subjective**

# Innovations - revolution


- ”Paradigm” = ”*shared theoretical beliefs, values, instruments, techniques and even metaphysics*” or “*community’s consensus on exemplary instances of scientific research in the field*”
- Paradigm shift implies fundamentally different *theoretical beliefs, values, instruments, techniques*
- *Innovations are often or are marketed as revolutions*

# “Successful innovations that have stood the test of time”

.”

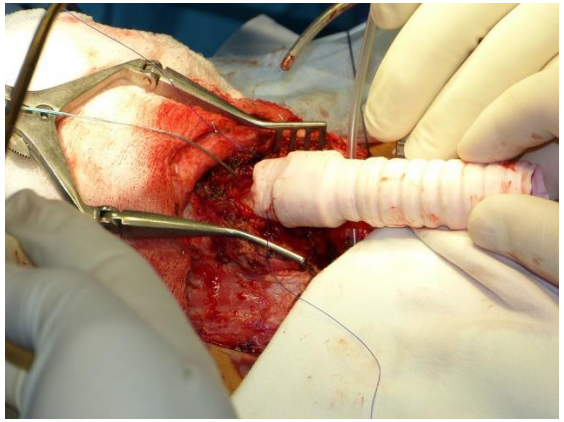
- The Wheel. Invented around 4000 BCE, the wheel is one of the earliest recorded innovations.
- Automobiles.
- Cellular Phones.
- ...


**what warrant?**

# One revolutionary innovation example

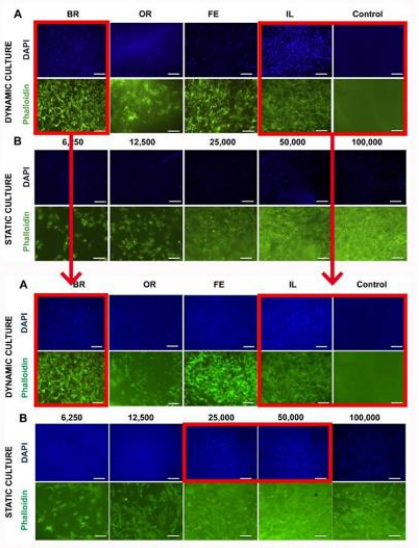
First tracheal nano-transplants: Lancet, NY Times, Times

- *“PM dedicated his career to improving the outcomes of tracheal transplant patients”*
- *Macchiarini led an international team to successfully implant an artificial trachea, seeded with autologous stem cells, in a human patient, a world first.*
- *The patient, a 36-year-old man with late-stage tracheal cancer, has since made a good recovery.*
- *”Macchiarini (press conference po day 1): ”They get their lives back”*



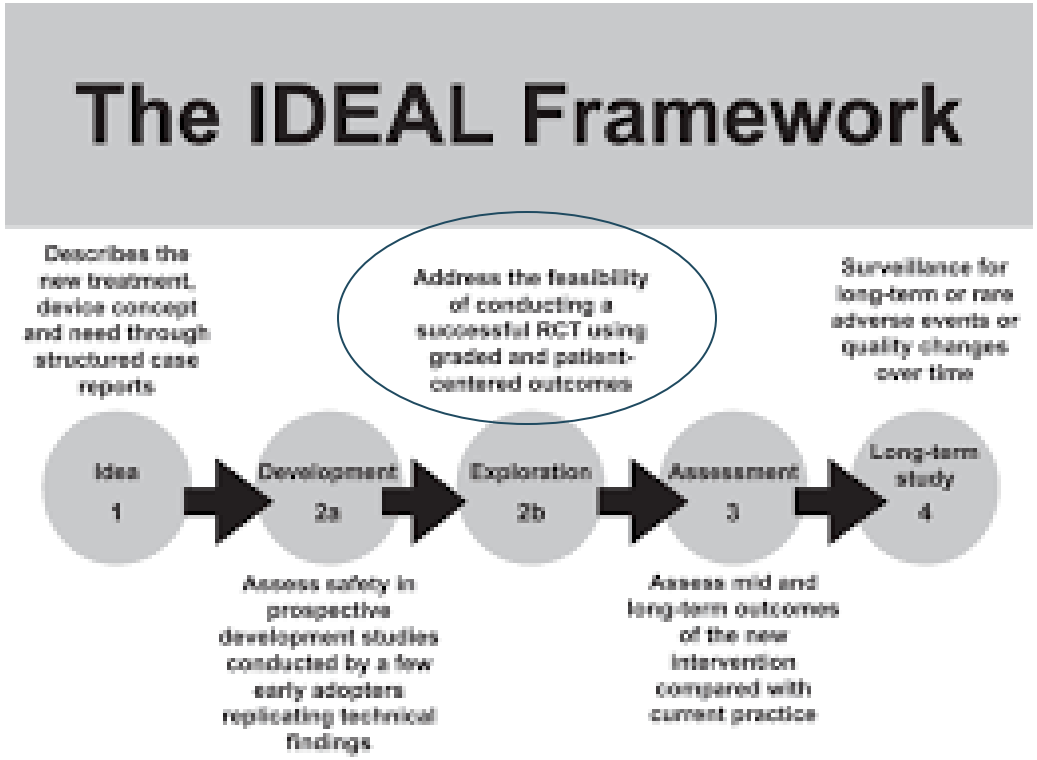
# Real story:

- All 3 patients at KI died
  - No ethics approval
  - Lab research (fabricated) published 3 y post-hoc
- PM: ”*patients too fragile”*
  - *operated healthier patients in Russia*
  - *Similar lethal outcomes…*
- Investigation at KI/KS
  - No objective critical assessment - critics ignored
  - ”chief physician” supported ”compassionate” indication
  - ”whistleblowers” punished
  - Managers very eager – week peer oversight or critcal assessment



## Need:

- Systematic implementation
- Systematic evaluation
- ”Evidence” & EBM
- Compare pharma-trials (phase 1-4 etc)

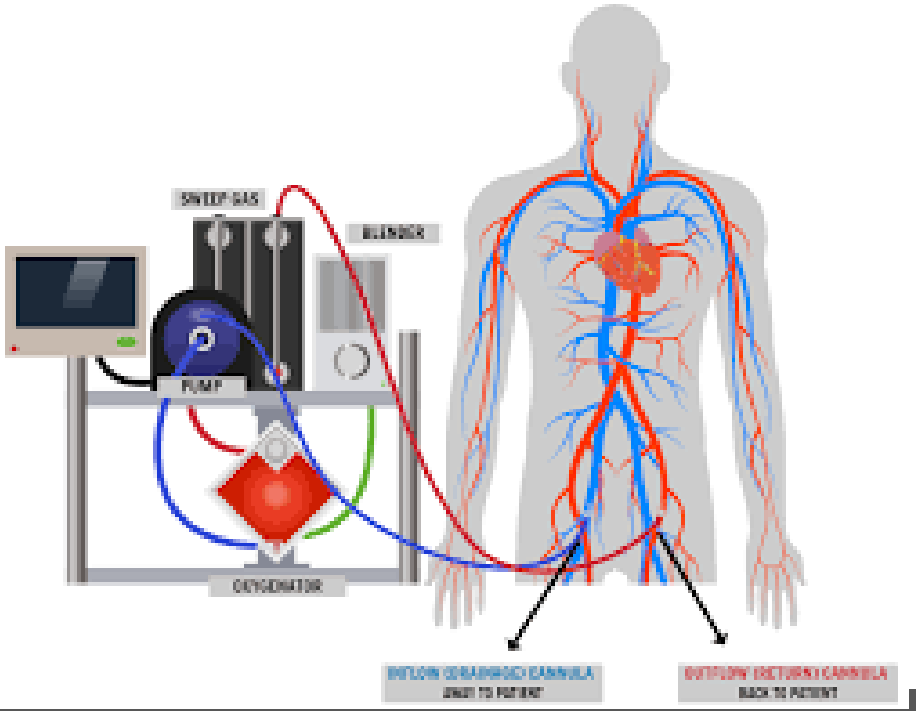



IDOL

**The unethical warrant**
The unethical researcher or vendor
The unethical oversight

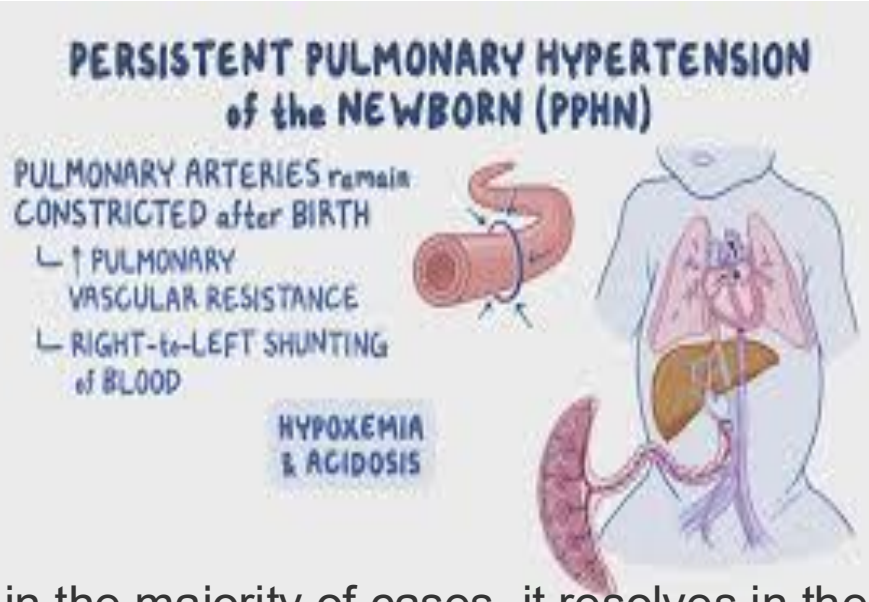
# The ECMO story and the search for evidence

- Extra corporeal membrane oxygenation



**John Worrall :Perspectives in Biology and Medicine,** 51, 2008, 418-431

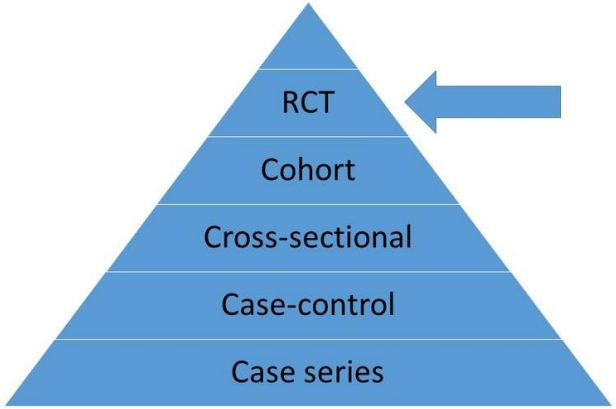
- In 1980, pulmonary hypertension of the newborn
  - 80% mortality
- In 1980s Bartlett et al (U of Michigan): extracorporeal membrane oxygenation (ECMO)
  - 80% SURVIVAL (Bartlett et al 1982)
- Switch to ECMO “historically controlled trial,”
  - controls provided by earlier (recent) patients treated under the old regime.



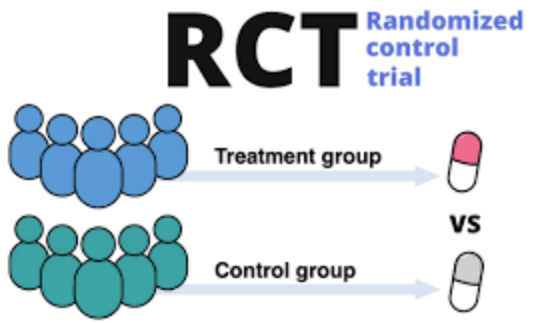

in the majority of cases, it resolves in the neonatal period following treatment of the underlying cause

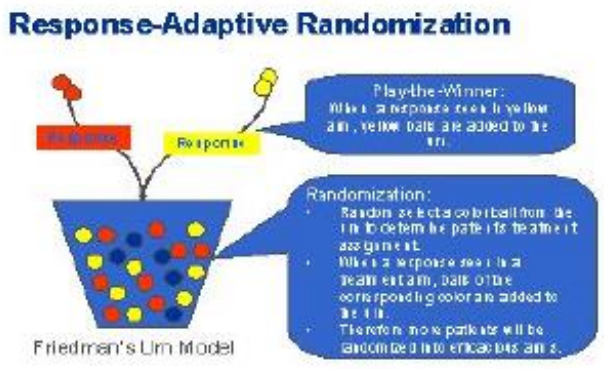
# Quest for evidence

- “felt compelled to conduct a prospective randomized study”
  - *if ECMO’s superiority was to be generally accepted by the medical community, the superiority of ECMO had to be demonstrated in a prospective randomized trial*
- Ethical qualms about assigning babies to the control arm when they could have treated those babies with ECMO
  - they felt driven to perform a trial that had a random element



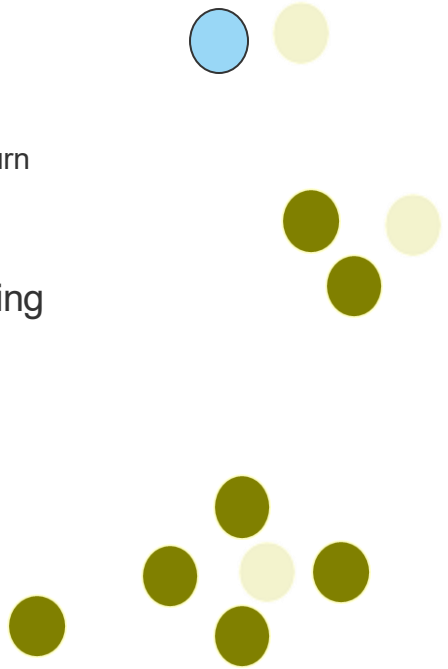



# “randomized play the winner” (Truog 1999).

- randomization of the first patient
  - by drawing a ball from an urn with one green (ECMO) and one white (control) ball
    - Suppose first patient is green - assigned to ECMO
  - Play the winner:
    - if first patient survives, a red (ECMO) ball is added to the urn
    - if first patient dies, a white (CT) ball is added to the urn
- As each new patient enters the trial, the chances of being assigned to the “better” treatment are improved
- Results (Bartlett et al. 1985).
  - First – ECMO, lived (2+1 marbles)
  - Second – control, died (3+1 marbles)
  - Total: 11 ECMO lived, 1 control died



# Wade and Epstein 1985:


- the historically controlled trial **scientifically non-telling**
- this first prospective trial was not a properly randomized study, also **scientifically non-telling**
- *no scientifically telling evidence of the superior effectiveness of ECMO*
- *“the only source of reliable evidence . . . Is that obtained from . . . carefully conducted randomized trials” (Tukey 1977, p.679).*

# a 3d properly randomized trial was performed

- orthodox randomization, p <0.05
- “stopping rule”
  - trial halted once four deaths occurred on either of the treatment arms
- Outcome (O’Rourke et al. 1989
  - 9 babies allocated to ECMO survived
  - 10 babies assigned to control, four died
  - fourth death triggered stopping rule.
  - p = 0.054 if there is no difference between the two treatments (>0.05)
- *even this second trial* failed to provide proper scientific evidence (Pocock 1993) (Although 20 subsequent allocated to ECMO, 1 died)

# 4th randomized trial (UK ECMO trial group 1996)

- ECMO for respiratory failure in general ( not just pulmonary hypertension)
- 185 neonates
- Stopped early –for deaths on control arm by safety committee

# Innovation

- the process of bringing about (1) new ideas, methods, products, services, or solutions that have a (2) significant positive impact and value
- the process of developing or (1) renewing a technique or product to (2) create or improve value
- novelty and divergence from standard or accepted practice identified as key elements of surgical innovation
- It involves transforming creative concepts into tangible outcomes that improve efficiency, and effectiveness, or address unmet needs
- To *invent* something is to discover a new thing. Meanwhile, to *innovate* means “to use a new idea or method”
  - Yet, inventions and innovations overlap
- Surgical research, invention, experimental surgery - overlap

# Evidence

- facts, information, documents, etc. that give reason to believe that something is true
- Wide term – subjective element – no qualifying criteria –
- Evidence based Medicine defined as best external evidence applied with clinical expertise
  - Hierarchy of external evidence – RCTs

# Ethical impact of ”evidence”

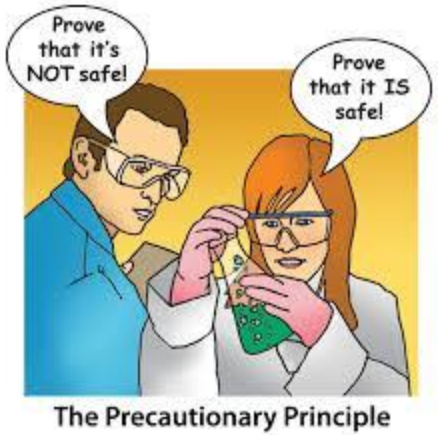
- One can always request more evidence
- Risk of not deciding

- Can we defend a dogmatic request for RCTs to support all innovations?
- RCTs false idols under some conditions

# Christian Munthe: two dimensions of balance

- Responsible balancing of chances of benefits and risks
  - Failure ➔ irresponsibly reckless behaviour (e.g., taking needless or disproportionate risks)
  - Success ➔ Design of intervention to balance chances and risks responsibly
- Responsible handling of ”knowledge gaps”: more or less pronounced uncertainty of the information used to estimate chances and risks
  - Failure ➔ irresponsibly negligent behaviour (e.g., taking chances when information could have been improved)
  - Success ➔ Delay decision on intervention while updating information basis for risk analysis.

# Downsides of precautionary measures
# Christian Munthe




- Immediate cost, harm or risk resulting from the precautionary measure
  - Risks or costs due to research in order to update information on which risk analysis is based,
  - Cancelling of possible benefits of an intervention

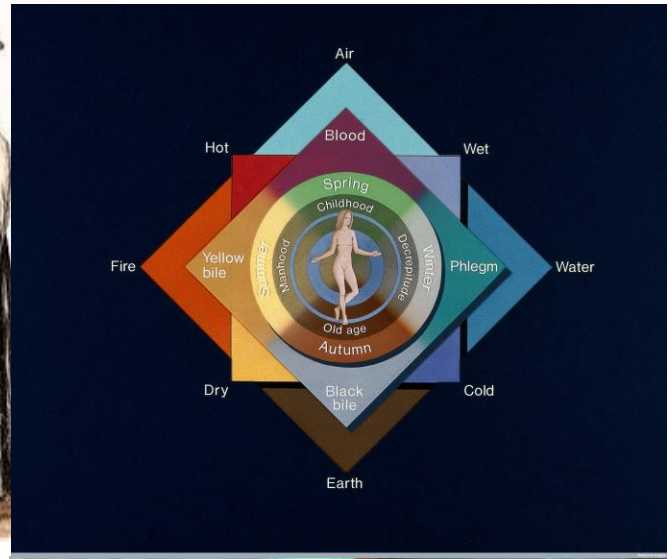
*Recurring argument in debates on new interventions, drugs, ”fast track”, ”compassionate use”*

## Therefore:

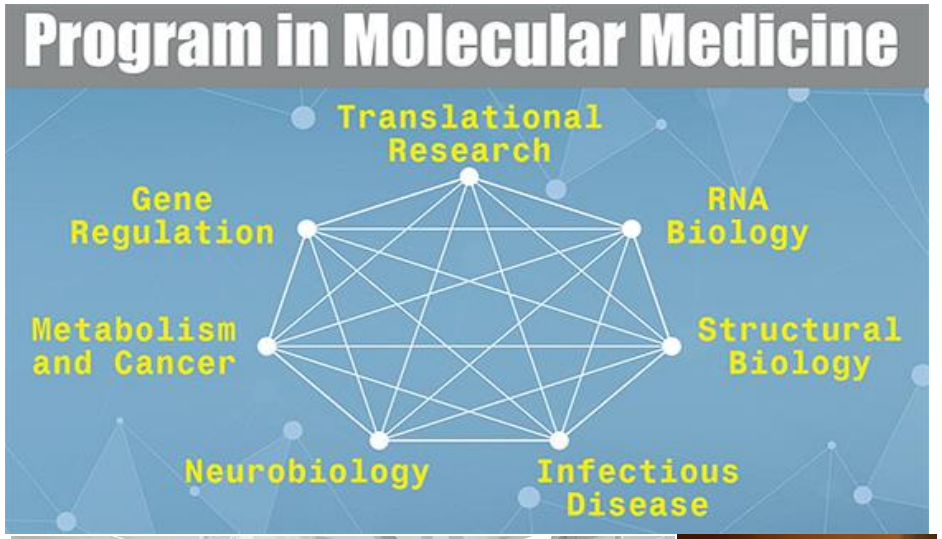
- Precaution ”cuts both ways”: the price of precaution must not be too high, or it turns into reckless or negligent exagerration.
- Professional responsibility requires to mind about this price whatever we do or ***do not*** **do**.

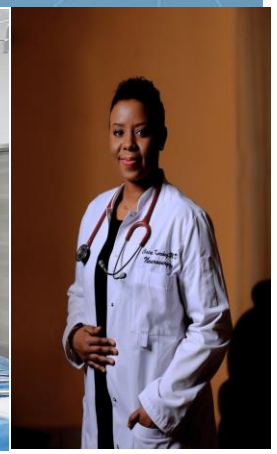
**The unethical warrant fails to balance cost of obtaining more evidence with risk of delaying innovation**

We need warrant – what is a good warrant
Innovative paradigm shift in medicine





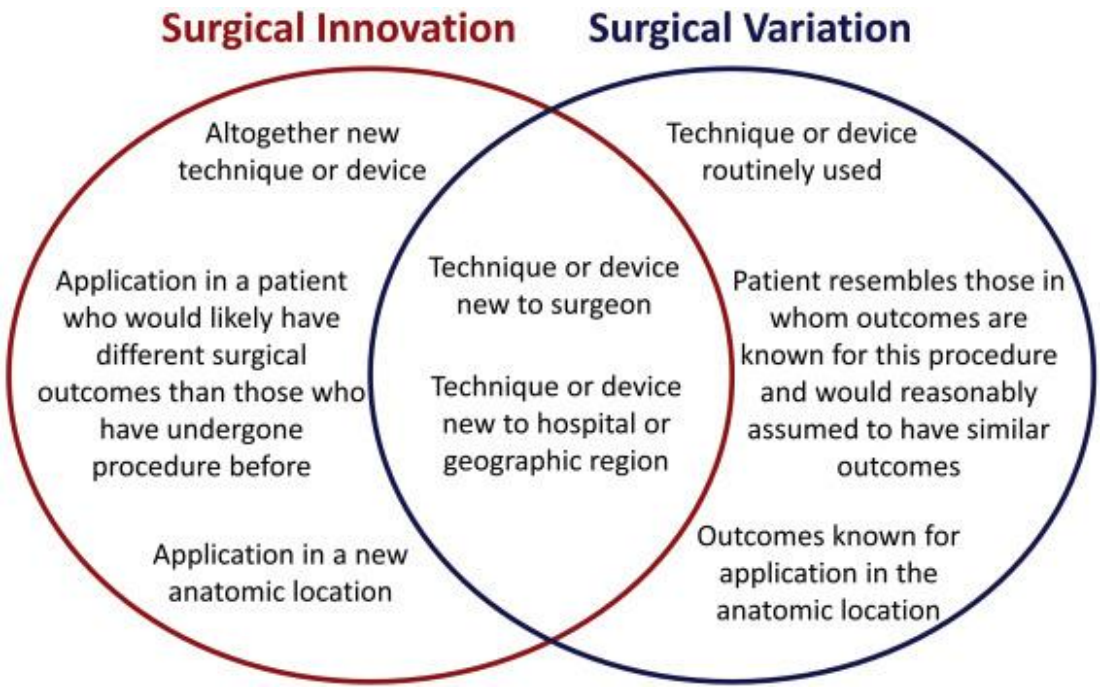


# Two kinds of medical innovations – need of what warrant?

- **Paradigm shift**
- Vaccination, Epidemiology, Anaesthesia, Germ theory, 3D printing, Gene therapy, Medical imaging, Antibiotics, Organ transplants, Immunotherapy, Stem-cell therapy, molecular medicine ….
- **Organic development, gradual refinement with experience and skill**
- Surgical techniques, refined approaches – extradural clinoid removal, adjuncts, better bipolar, Kamiyama microscissors, optimal lateral surgical position…

# Innovations:
# Organic development vs. Scientific revolution




- RCTs never made
- Selective proximal vagotomy vs. Antibiotics for duodenal ulcer
- Microscope vs macro-surgery for aneurysm
- Surgery with / without bipolar
- Aneurysm clipping with para-magnetic vs. non-magnetic clips

# An RCT may lack meaning to evaluate an innovation if

- Paradigmatic shift (micro- vs microsurgery)
  - Fundamental difference makes trial design weird
  - Frequently unethical to randomize patients to dated methods if researchers have *good reasons to believe* new method is superior
  - Unethical to select outcomes with redundant mechanistic causality
- Gradual, organic refinement (gradually refined aneurysm microsurgery)
  - Endless regression of RCTs for each minute improvement

**Many misguided surgical RCTs**
**External evidence from RCT is one component of evaluation**

# Redundance of causality
# Device to measure brain oxygenation in neonatal care

- Innovation – but what is the value?
- RCT w / wo device
- Outcome: school performance age 7

- Claudius: io imaging and navigation
- RCT for patient outcomes?

# Misguided RCTs

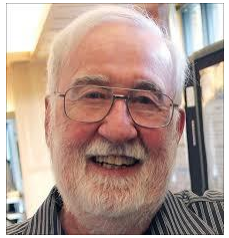
- Result:
  - There was/was not a detectable difference between treatment and control
- Underlying research questions incompletly answered
  - Coss, STA-MCA, Aruba, STICH, ICP guided TBI care (biased inlcusion, change underways, meaningless endpoints, endpoints affected by redundance (icp measurement – mortality))
  - Senft et al. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol. 2011 (strawman controls)
  - Pradilla et al. Trial of Early Minimally Invasive Removal of Intracerebral Hemorrhage. N Engl J Med. 2024 (merger of central and lobar ICH, device driven)
  - Roberts et al. Tranexamic acid to reduce head injury death in people with traumatic brain injury: the CRASH-3 international RCT. Health Technol Assess. 2021 (post hoc subgroup)

# warrant depends on innovation

- New statin expected NNT 80
  - RCTs
- Asystolic patient:
  - Probably difficult to conduct t rcts of CPR vs placebo
  - Will probably risk losing patients while conductiong trials, collecting evidence
  - know that procedure is potentially beneficial, risk harm if postpone
- Body transplant
  - Todays medical paradigm makes success unlikely
  - Ethical concerns
  - Risk of har if proceed without much more scientific background
  - know that procedure is potentially harmful, no knowledge of benefit

# Evidence and clinical expertise

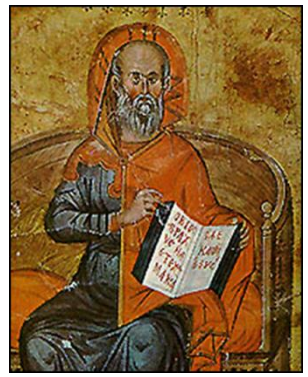
- The story – our first case and our cases
  - What explanations fit – create a theory
  - Adhere to theory, observe
  - Seek critical testing of theories
- The black swans:
  - The unexpected complications
  - Patients who did not improve
  - Seek opportunities to refine/reformulate hypotheses

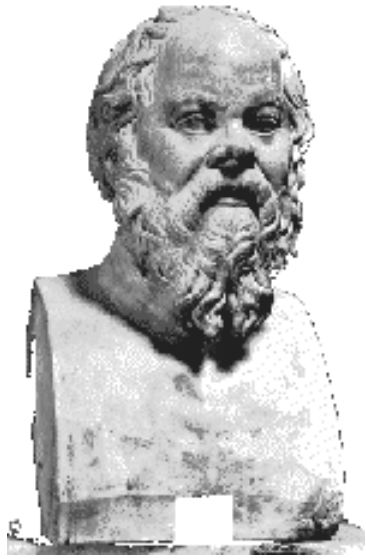


*However, some questions about therapy do not require randomised trials (successful interventions for otherwise fatal conditions) or cannot wait for the trials to be conducted. And if no randomised trial has been carried out for our patient's predicament, we must follow the trail to the next best external evidence and work from there. Sackett 1996)*

*Simply by keeping systematic records of how some treatment fares and whose effectiveness varies as it evolves, and by trying hard to eliminate other plausible causes of difference between treatments by suitable post hoc matching, we are likely to get evidence that is much more telling and relevant for how to treat current patients than that provided by an RCT on treatments which, as Truog suggests Troug 1992, Clinical Research 40, 519), may be out of date before the result is achieved. (Worrall J)*

# Moral agency





- Dogma and guidelines will not do the job
- Individual ethical responsibility – researchers are ethical agents
  - Lars Leksell (1962): ethics committees fundamentally unethical
- Skills in critical analysis and professional knowledge
- Support and help to do the right thing – formal and informal oversight
    - Academic ethics (2500 year history), training in critical analysis (what do we mean, which warrant…)
    - Checklists: Professional ethics, Helsinki declaration, professional rules of conduct
    - Profesisonal bodies, peer oversight, ethics committees
- Right and wrong are basic elements in of ethics and in all human projects
- Respect for individual responsibility and agency paired with peer oversight

# It takes three

- The warrant
  - Warrant is necessary but depends on the innovation
  - Balance between cost and benefit of better warrant

The researcher or vendor

  - Individual moral agency

- Peers and oversight
  - Professionalism and professional ethics
  - Evolution: time will tell



- Asking for too much or too little warrant for a treatment decision cause harm/loss of benefit
- Relying on a formal hierarchy of quality is treacherous – no substitute for proffessional knowledge
- "*at least some light can be shed on some facets by returning to the basic ideas about theory-testing studied in the philosophy of science*"
- John Worrall Evidence: philosophy of science meets medicine J of Evaluation in Clinical Practice 16 (2010) 356–362