What Constitutes “Reliable Evidence”?
– Rare Diseases and Clinical Trials –

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RAY OF HOPE

RICHARD BROWNE

Sasha Browne, 3, has taken part in the first trial to treat cerebral palsy using stem cells taken at birth from the patient's umbilical cord. Her parents say her condition has improved *Stem cell first for cerebral palsy girl, page 4*

Sasha Browne, 3, has taken part in the first trial to treat cerebral palsy using stem cells taken at birth from the patient's umbilical cord. Her parents say her condition has improved *Stem cell first for cerebral palsy girl, page 4*

From ICORD, Brussels 2007

"We need to stop always thinking about evidence-based medicine"

"ICORD" … "International Conference on Rare Diseases [and Orphan Drugs]"

An example of convincing evidence

Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials. *BMJ* 2003; **327**:1459–61.

Cuello C (rapid response) http://www.bmj.com/cgi/eletters/327/7429/1459#44035
"...skydiving student Sharon McClelland, 26, who amazingly survived a 10,000-foot plunge in September 1994 near Queensville, Ontario, into a marsh when her parachute malfunctioned"

Temple R (rapid response) http://www.bmj.com/cgi/eletters/327/7429/1459#44035
Code of Federal Regulations. 21 CFR 314.126. Adequate and well controlled studies
"…placebo concurrent controls, dose comparison concurrent controls, no treatment concurrent controls, active treatment concurrent controls, historical controls"

The idea of "Randomise the first patient"

Chalmers TC. When should randomisation begin? *Lancet* 1968: 858.

Chalmers TC. Randomization of the first patient. *Medical Clinics of North America* 1975; **59**:1035–1038.

Chalmers TC. Randomize the first patient! *NEJM* 1977; **296**:107.

"…frequently, we have no scientific evidence that a particular treatment will benefit the patients and … we are often, willy-nilly, experimenting upon them. It may well be unethical, therefore, *not* to institute a proper trial."

Bradford Hill. The Clinical Trial. *Brit Med Bull* 1951; **7**:278–282.

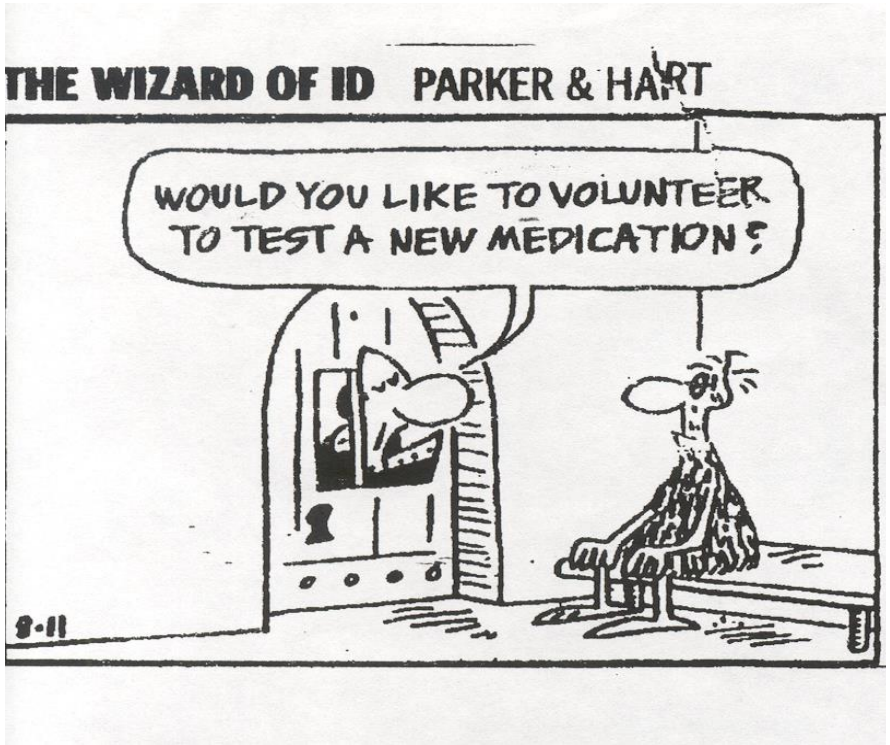
“Randomise the first patient”

Spodick DH. Randomize the first patient: Scientific, ethical, and behavioral bases.
The American Journal of Cardiology 1983; **51**:916–917.

“[it’s always possible to do a randomized trial]… in the search for a real answer, and ensures an ethical approach that gives every patient a 50–50 chance to get best treatment, that is, not to get the new medicine at a time when its precise effects and risk–benefit ratio are not understood.” (emphasis added)

This is saying (in my words):

Patients who volunteer to take potential new medicines at a very early stage of their development *deserve the right* to have a reasonable probability of being randomised *to the control group*



Conn HO. *Clinics in Gastroenterology* 1985;**14**:259–288.
“…hope to meet the inclusion criteria for a controlled trial, enter, and then refuse treatment”

Or should patients have the *right* to try a new therapy?

109TH CONGRESS
1ST SESSION

S. 1956

To amend the Federal Food, Drug, and Cosmetic Act to create a new three-tiered approval system for drugs, biological products, and devices that is responsive to the needs of seriously ill patients, and for other purposes.

IN THE SENATE OF THE UNITED STATES

NOVEMBER 3, 2005

Mr. BROWNBACK (for himself and Mr. INHOFE) introduced the following bill; which was read twice and referred to the Committee on Health, Education, Labor, and Pensions

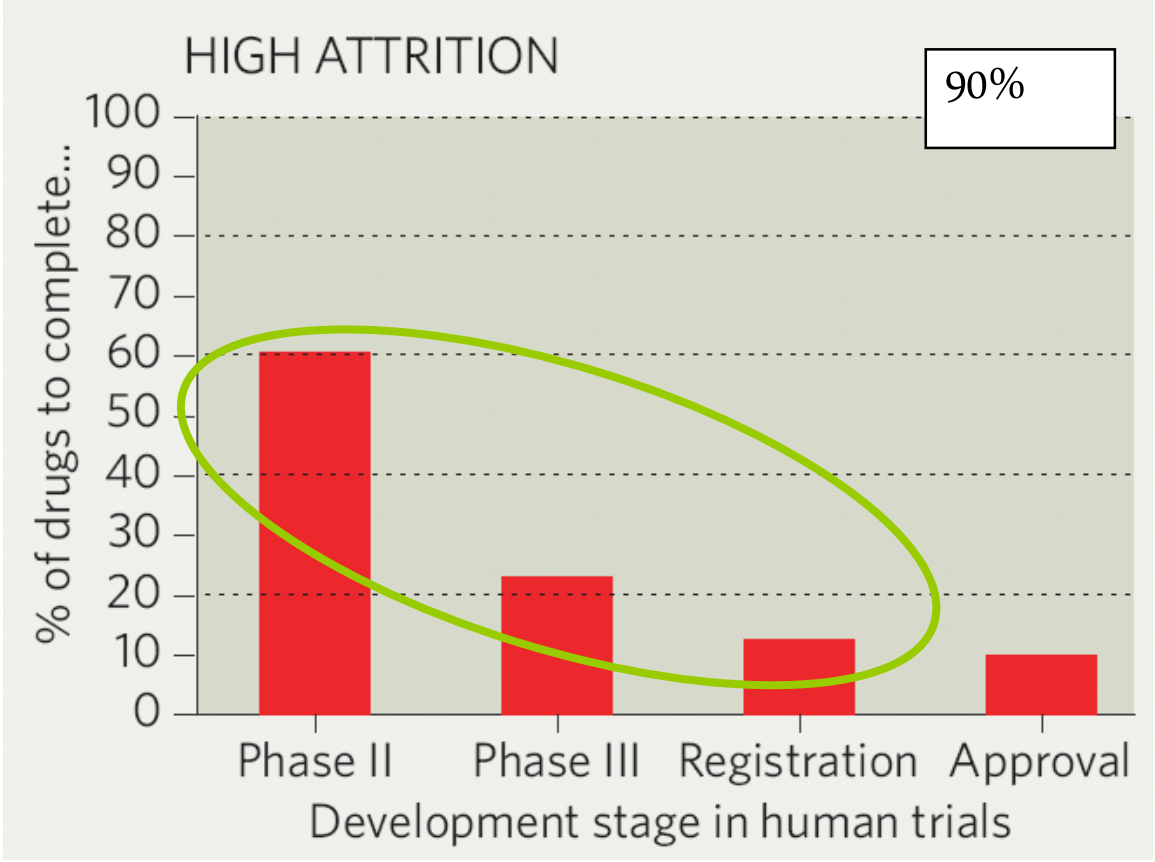
The “Saatchi” Bill
(“Medical Innovation” Bill)

Lord Saatchi and Josephine Hart

“EAMS”

- The early access to medicines scheme
- MHRA will give a scientific opinion on the benefit/risk balance of the medicine
- …the opinion from MHRA does not replace the normal licensing procedures for medicines

How good are we at developing new drugs?



Pearson H. The bitterest pill

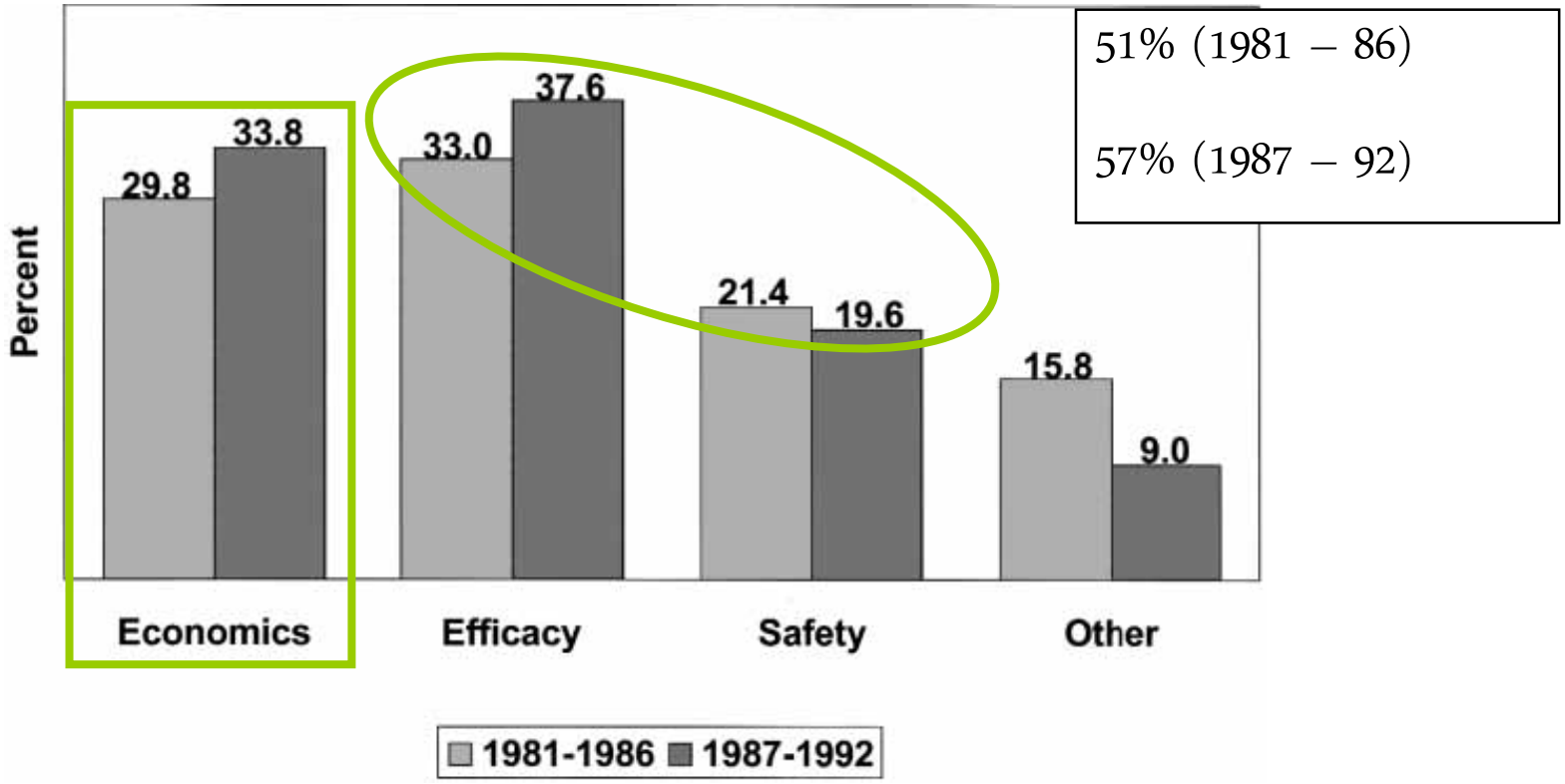
Nature 2006; **444**:532–533.

More on attrition rates in drug development…

Booth B, Glassman R and Ma P. Oncology's trials. *Nature Reviews. Drug Discovery* 2003;**2**:609–610.

"The dramatic unpredictability of single-arm, uncontrolled Phase II trials [in cancer]…"

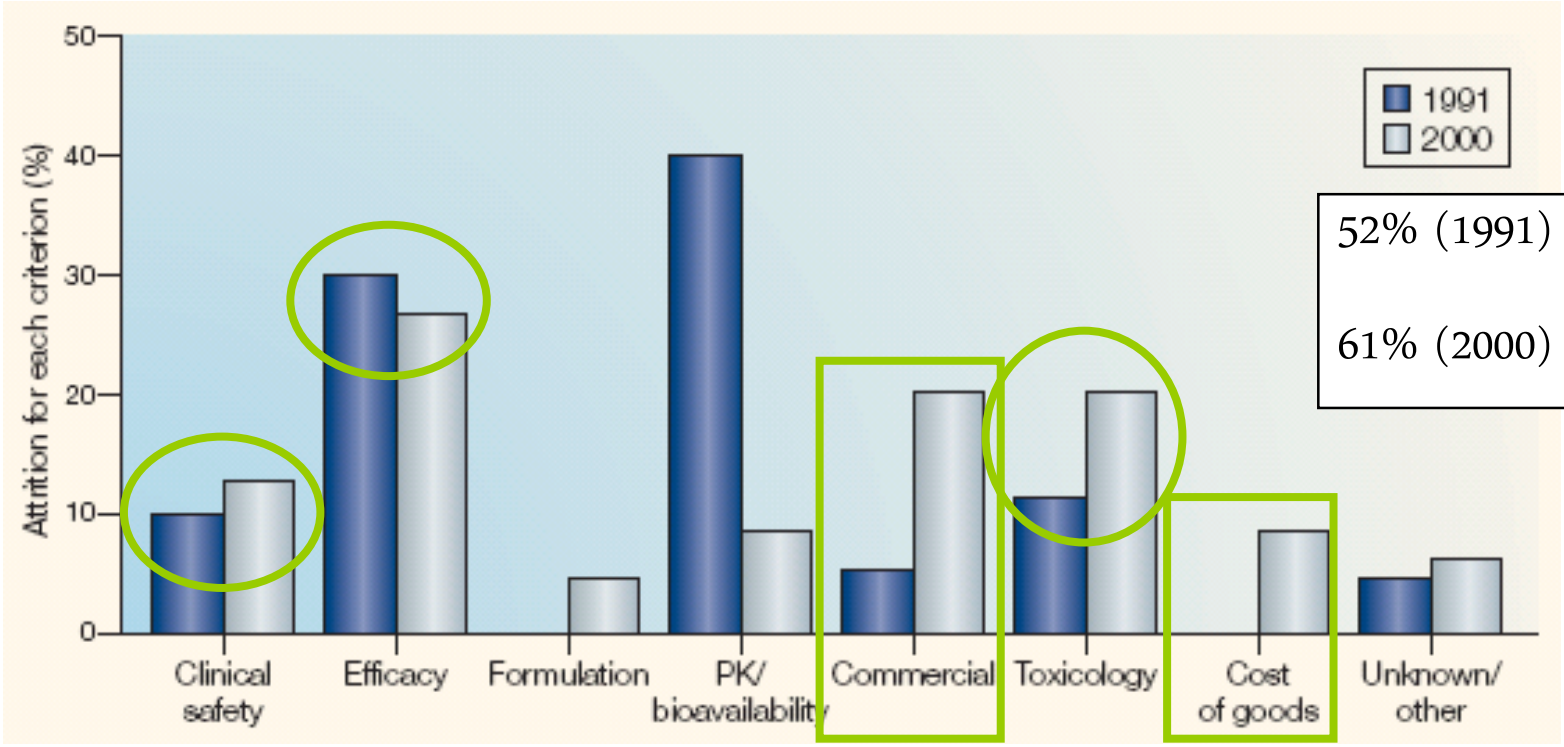
How good are we at developing new drugs?



DiMasi JA. Risks in new drug development: approval success rates for investigational drugs.

Clinical Pharmacology and Therapeutics 2001; **69**:297–307.

How good are we at developing new drugs?



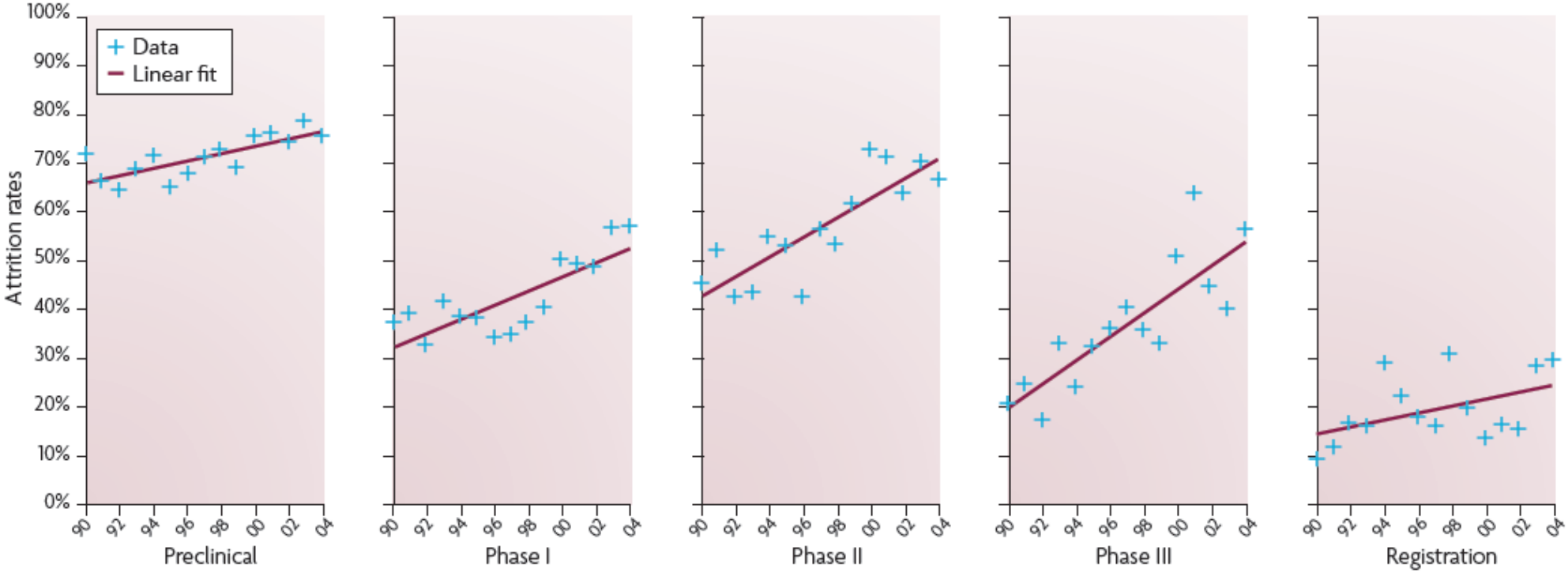
52% (1991)

61% (2000)

Kola I and Landis J. Can the pharmaceutical industry reduce attrition rates?

Nature Reviews. Drug Discovery 2004; **3**:711–715.

How good are we at developing new drugs?



Pammolli F, Magazzini L and Riccaboni M.

The productivity crisis in pharmaceutical industry R & D

Nature Reviews. Drug Discovery 2011; **10**:428–438.

“Randomise the first patient”

Hence, my statement:

Patients who volunteer to take potential new medicines at a very early stage of their development *deserve the right* to have a reasonable probability of being randomised *to the control group*

Most early “promising” / “hopeful” new molecules sadly *don’t work*; they actually have a *negative* benefit–risk ratio

You, your loved one, your patient, would be *better off taking placebo*

STATISTICS IN MEDICINE
Statist. Med. 2008; **27**:469–482
Published online 15 June 2007 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.2928

WILEY InterScience® DISCOVER SOMETHING GREAT

Bayesians in clinical trials: Asleep at the switch

Lemuel A. Moyé*, †, ‡

School of Public Health, University of Texas, 1200 Herman Pressler – E815 Houston, TX 77025, U.S.A.

"It is difficult for physicians [and others] to keep in mind how bad things may be with an untested intervention, in the face of the reality of how bad things are without it."

"…the more passionate the investigator [or other], the greater the protection the priors require from their strongly held opinion."

Arguments against small (efficacy) trials

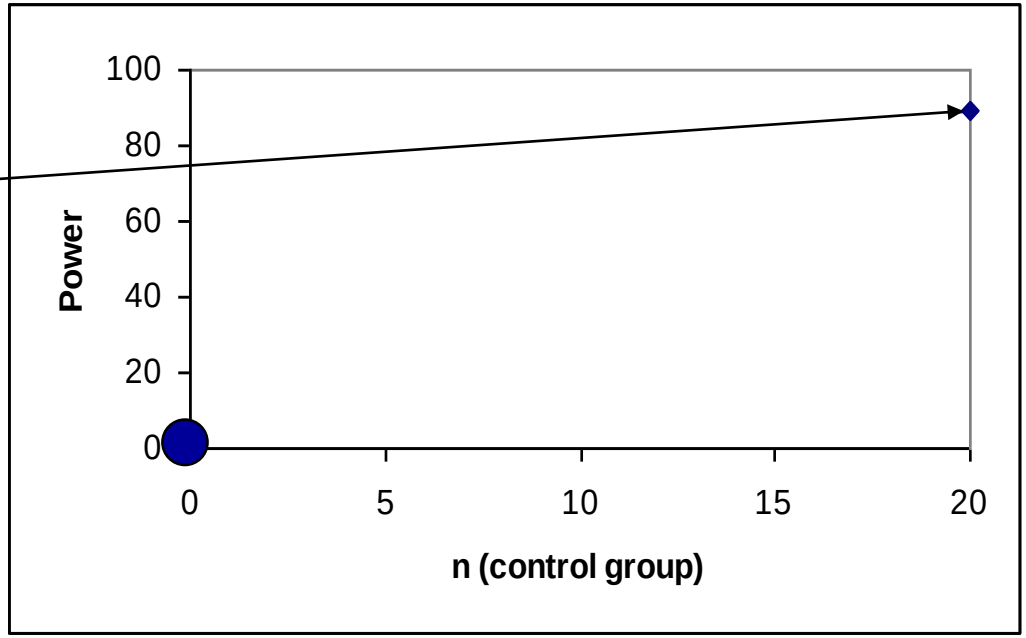
- “Can’t do randomised trials because we haven’t got enough patients”
- “No point in having a control group because the trial would be severely underpowered”
- “No point in having a control group because there’s no chance to show any treatment benefit”

Control group “not worth it” An example

Event rates 50% *vs*. 10%

Two (equal size) groups of 20 patients gives 85% power for a 1-sided test at α=5%

What happens if the control group gets smaller and smaller?
15, 10, 5, 2



What if the control group falls to size of *zero*?
– An “uncontrolled” study

Control group “not worth it”

“I’m sorry but your study has zero percent power to demonstrate *any* treatment effect, of *any* magnitude. At least my study of 20 patients *vs.* 20 patients has 20% power, which is a lot better than nothing”

Response:

“Well, but I would get all of those 20 (or 22) patients with the active treatment, and I would be able to compare them to historical controls”

“But your small trial has 20% power (even on its own) and I can compare the results to historical controls as well”

And 2 equal-sized groups of 10 (or 11) give us about 50% power

Concurrent controls *or(?)* historical controls

Why the dichotomy?

THE COMBINATION OF RANDOMIZED AND HISTORICAL CONTROLS IN CLINICAL TRIALS

STUART J. POCOCK

- 1975 (“Bayes without computers”)

“Randomise the first patient”…

and even small randomised trials are not in vain

Recent Results in Cancer Research, Vol. 111

The Value of Small Clinical Trials

K. D. MacRae

Charing Cross and Westminster Medical School, St. Dunstan's Road,
London W6 8RP, Great Britain

Type I errors, Type II errors, … Type III errors

“Randomise the first patient”…

and even small randomised trials are not in vain

STATISTICS IN MEDICINE, VOL. 14, 115–126 (1995)

SMALL CLINICAL TRIALS: ARE THEY ALL BAD?

JOHN N. S. MATTHEWS

Department of Medical Statistics, University of Newcastle upon Tyne, The Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, U.K.

Large trials, “mega-trials” (aka “large simple trials”)

- What justifies a [new] study?
  - Peto and colleagues…
    - Well known for “mega-trials”
    - ISIS 1 – 4 (etc.)
    - *n* = 20,000; *n* = 30,000; *n* = 40,000; where next…?
  - Why do they do trials that large?
  - How large does a new trial [study] have to be to usefully add to the existing evidence?

Large trials, “mega-trials” (aka “large simple trials”)

- A new study should usefully add to the existing evidence base
  - If there is a lot of evidence already, new studies need to be big!
  - If there is very little evidence existing, even small studies will add useful information
- Examples:

  Tan S-B, Dear KBG, Bruzzi P and Machin D. Strategy for randomised clinical trials in rare cancers. *Brit Med J* 2003; 327:47–49.

  Phillips CV. The economics of ‘more research is needed.’ *Intl J Epid* 2001; **30**:771–776.

Large trials, “mega-trials” (aka “large simple trials”)

- A new study should usefully add to the existing evidence base
  - If there is a lot of evidence already, new studies need to be big!
  - If there is very little evidence existing, even small studies will add useful information
- The caveats:
  - “How much evidence already exists” does *not* equate to the current *sample size* of all existing studies (but it’s related!)
  - But there probably *is* an ethical obstacle if a “small” study is planned when a “usefully bigger” one *could* be achieved

Clinical trials, gold standards and levels of evidence

CHMP. Guideline on clinical trials in small populations. London: EMEA, 2006.

- Meta-analyses of good quality randomised controlled trials that all show consistent results
- Individual randomised controlled trials
- Meta-analyses of observational studies
- Individual observational studies
- Published case-reports
- Anecdotal case-reports
- Opinions of experts in the field

Let's turn back about 20 years

Clinical trials, gold standards and levels of evidence

Green SB, Byar DP. Using observational data from registries to compare treatments: the fallacy of omnimetrics.
Statistics in Medicine 1984; **3**:361–370

- Anecdotal case reports
- Case series without controls
- Series with literature controls
- Analyses using computer databases
- Case-control observational studies
- Series based on historical control data
- Single randomized controlled clinical trials
- Confirmed randomized controlled clinical trials

Let's turn back another 20 years

Clinical trials, gold standards and levels of evidence

Hill AB. The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine* 1965; **58**:295–300

1. Strength of association
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

"None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer which is more likely than cause and effect?"

Clinical trials, gold standards and levels of evidence

Hill AB. The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine* 1965; **58**:295–300

1. Strength of association
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

"What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect."

This seems (to me) what gets forgotten. One size does *not* fit all.

Levels of evidence might be consistent but *methods of evidence* need not be.

Clinical trials, gold standards, levels of evidence

Cochrane levels of evidence

Level	Description
1++	High quality meta-analyses or systematic reviews of randomised controlled trials (RCTs) or of RCTs with very low risk of bias
1+	Well conducted meta-analyses or systematic reviews of RCTs or of RCTs with very low risk of bias
1–	Meta-analyses or systematic reviews of RCTs or of RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding, bias or chance, and a significant risk that the relationship is not causal
3	No analytic studies; only case reports, case series
4	Expert opinion

Clinical trials, gold standards, levels of evidence

Cochrane levels of evidence

Level	Description
1	Randomised Controlled Trials
2	Case-control or cohort studies
3	No analytic studies; only case reports, case series
4	Expert opinion

Clinical trials, gold standards, levels of evidence

Cochrane grades of recommendation

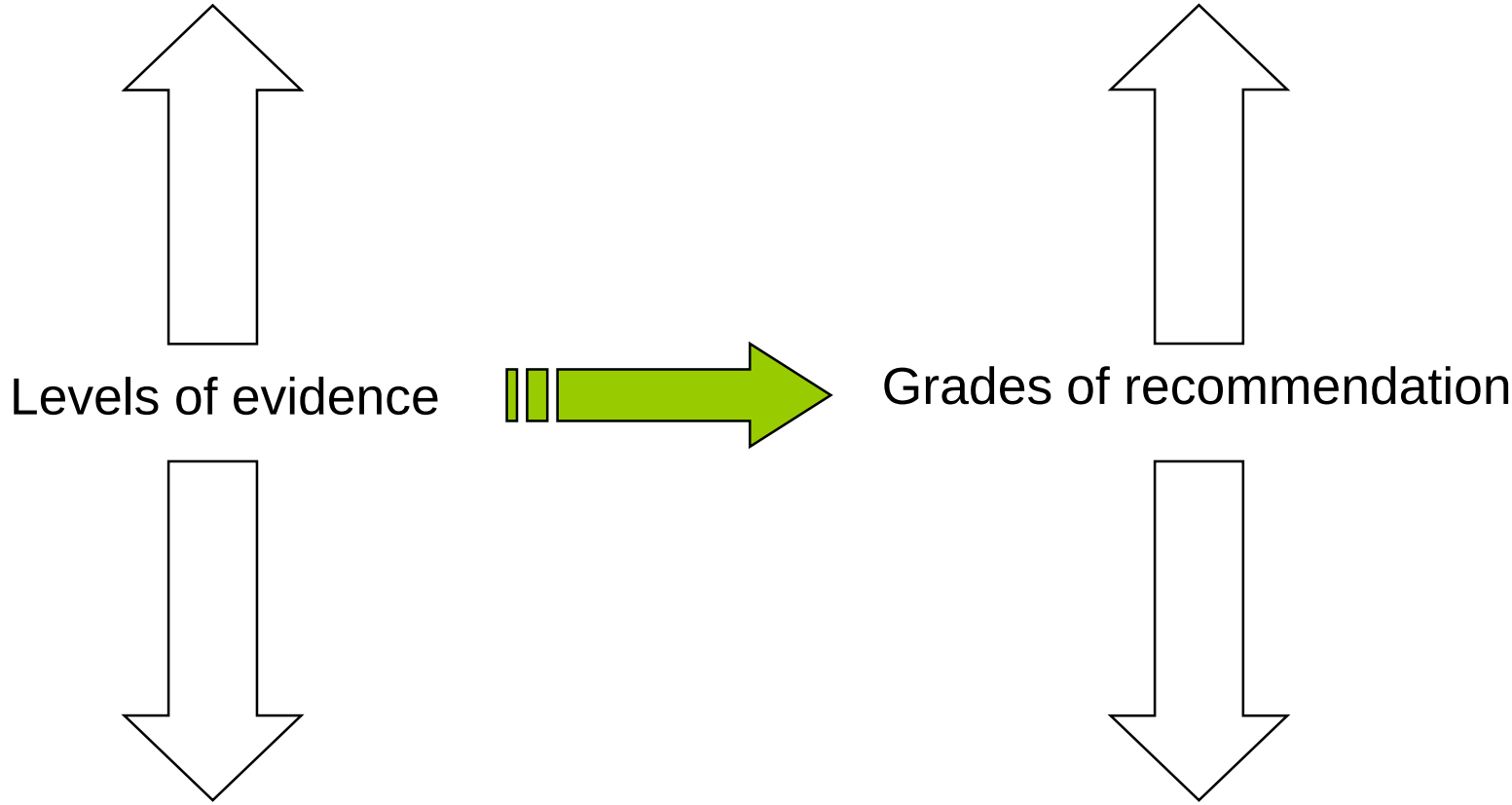
Grade	Description
A	At least one meta-analysis, systematic review or randomised controlled trial at 1++ and directly applicable to the target population; Or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated 1+, directly applicable to the target population and demonstrating overall consistency of result
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; Or Extrapolated evidence from studies rated 1+ or 1++
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results Or Extrapolated evidence from studies rated 2++
D	Evidence level 3 or 4; Or Extrapolated evidence from studies rated 2+

Clinical trials, gold standards, levels of evidence

Cochrane grades of recommendation

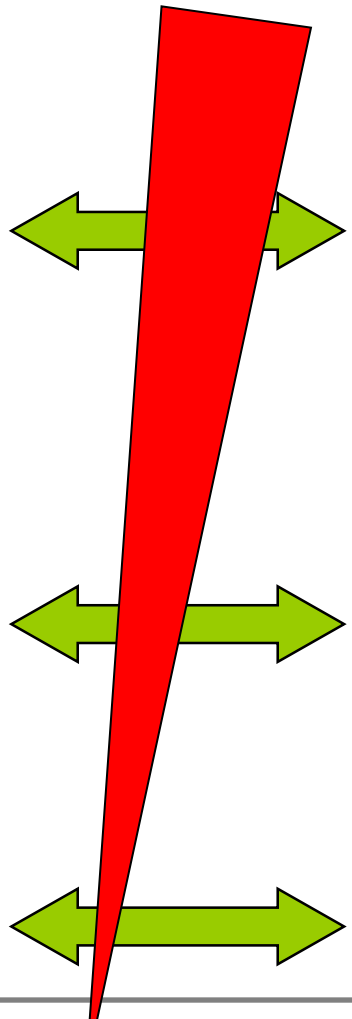
Grade	Description
A	1++ or 1+ studies
B	Directly applicable 2++ studies Or Extrapolated evidence from 1+ or 1++ studies
C	Directly applicable 2+ studies Or Extrapolated evidence from 2++ studies
D	Evidence level 3 or 4; Or Extrapolated evidence from studies rated 2+

Clinical trials, gold standards, and levels of evidence



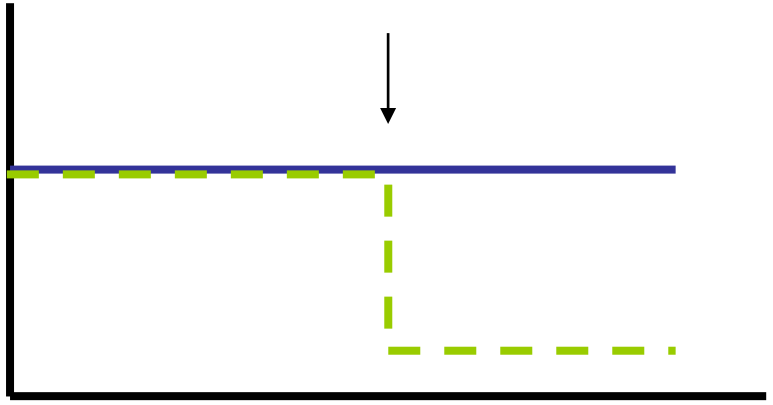
Clinical trials, gold standards, and levels of evidence

Level	Description		Grade
1	Randomised Controlled Trials		A (B)
2	Case-control or cohort studies		B (C)
3	No analytic studies; only case reports, case series		D
4	Expert opinion		D

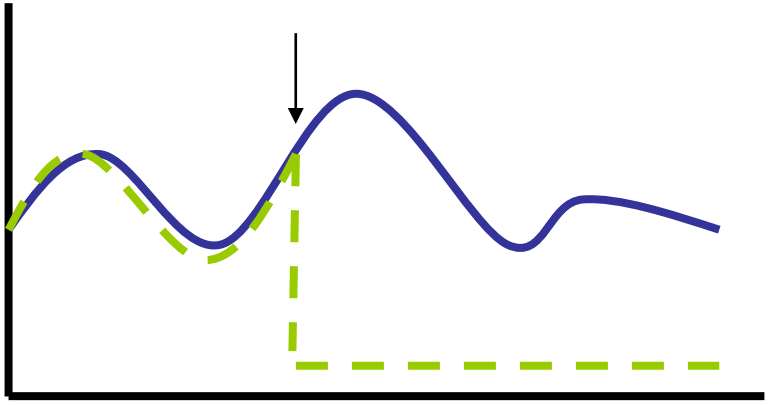


Context-specific evidence

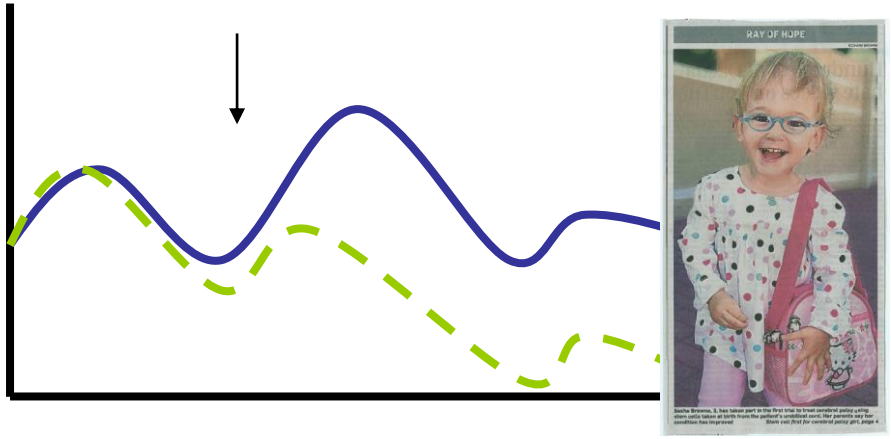
Stable disease, with sudden effect



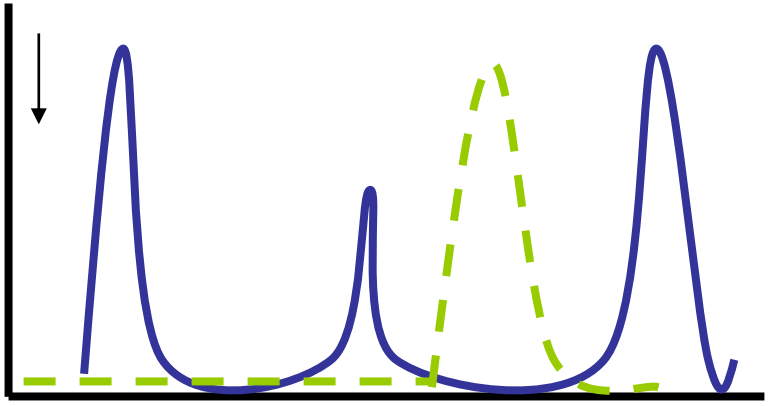
Fluctuating, with sudden effect



Fluctuating, with gradual effect



Episodic, with partial effect

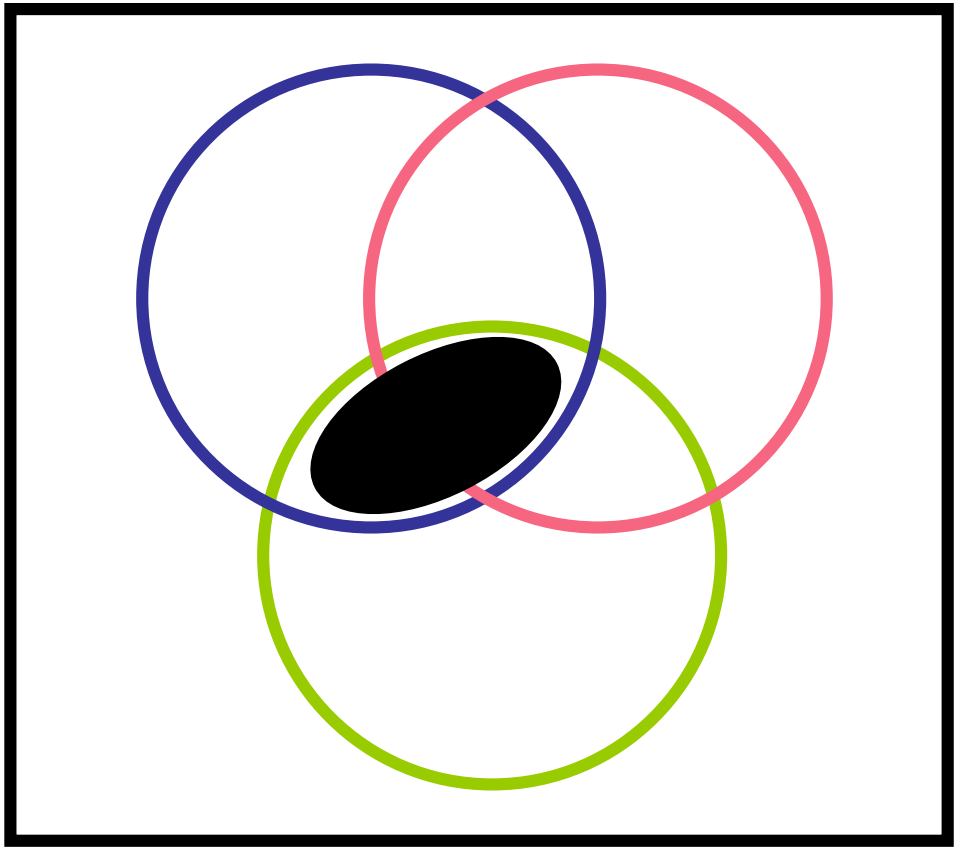


Adapted from Glasziou *et al.* (2008)

Is there a link between “rare” diseases and “dramatic” treatment effects?

Of all diseases:

- Rare diseases
- Serious diseases
- “Dramatic” treatment effects



Braiteh F, Kurzrock R. Uncommon tumors and exceptional therapies: paradox or paradigm?

Molecular Cancer Therapeutics 2007; **6**(4):1175–9.

If we know how the disease operates and how the treatment works…

Bruce Alberts
Editor-in-Chief of *Science*.

"If I were the czar of cancer research, I would give higher priority to recruiting more of our best young scientists to decipher the detailed mechanisms of both apoptosis and DNA repair…"

Alberts B.
The promise of cancer research.
Science, 4 April 2008; **320**:19.

Do we “need to stop always thinking about evidence-based medicine”?

- My strong belief is that we need evidence based decisions (which is something similar to evidence based medicine)
- But, we need to think widely – and *critically* – about what constitutes:
  - Evidence
  - *Best* evidence
  - Adequate (or *necessary*) evidence

Do we “need to stop always thinking about evidence-based medicine”?

- Sufficient evidence in one setting may be insufficient in another, or may be excessive in others
- The ethical argument of “last chance therapy” may not be sensible under the doctrine of individual ethics and is disastrous under the doctrine of collective ethics

Please let's keep evidence-based medicine

But let's acknowledge different sources of evidence

Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials. *BMJ* 2003; **327**:1459–61.

What causes death or major trauma?

Speed of hitting the earth.

Parachutes slow you down.

So they probably reduce incidence of death and major trauma.