Getting Reliable Evidence

Dr Simon Day

From ICORD 2007

“We need to stop always thinking about evidence based medicine”

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 control"

Also from ICORD 2007
"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.

“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 medicines at a very early stage of their development *deserve the right* to have a reasonable probability of being randomised *to the control group*

Or do patients have the right to try a new therapy?

109TH CONGRESS
1ST SESSION

S. 1956

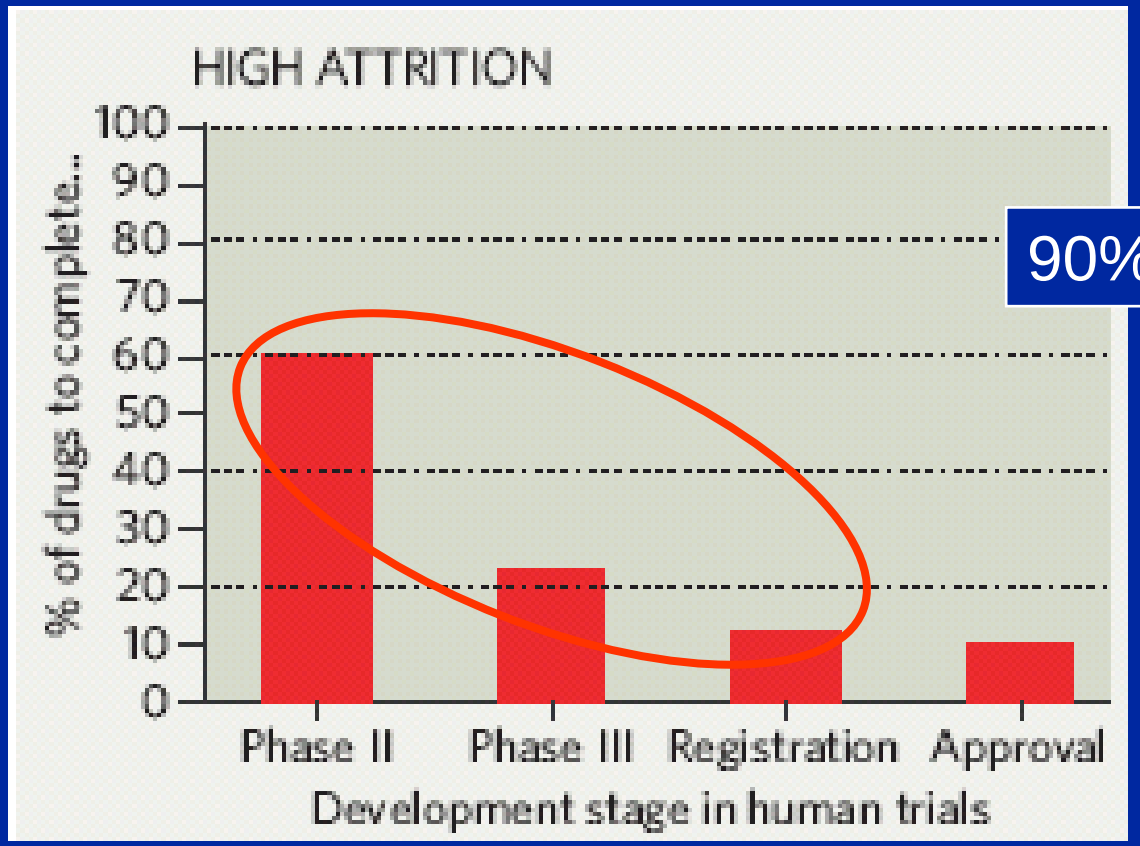
To amend the Federal Food, Drug, and Cosmetic Act to create a new three-tiered approval system for drugs, biological products, and devices that is responsive to the needs of seriously ill patients, and for other purposes.

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

How good are we at developing new drugs?



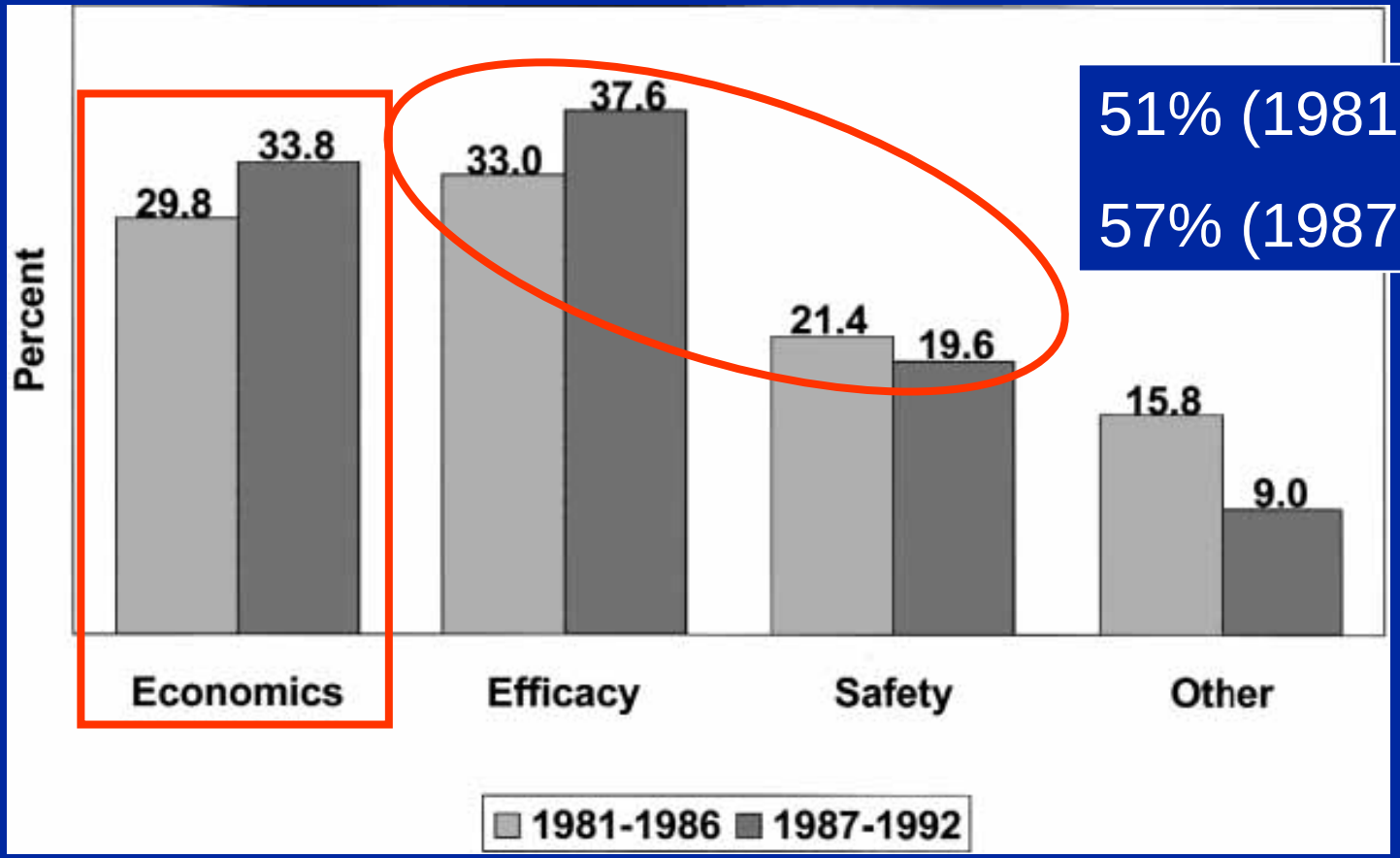
Pearson H. The bitterest pill
Nature 2006; **444**:532–533.

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.

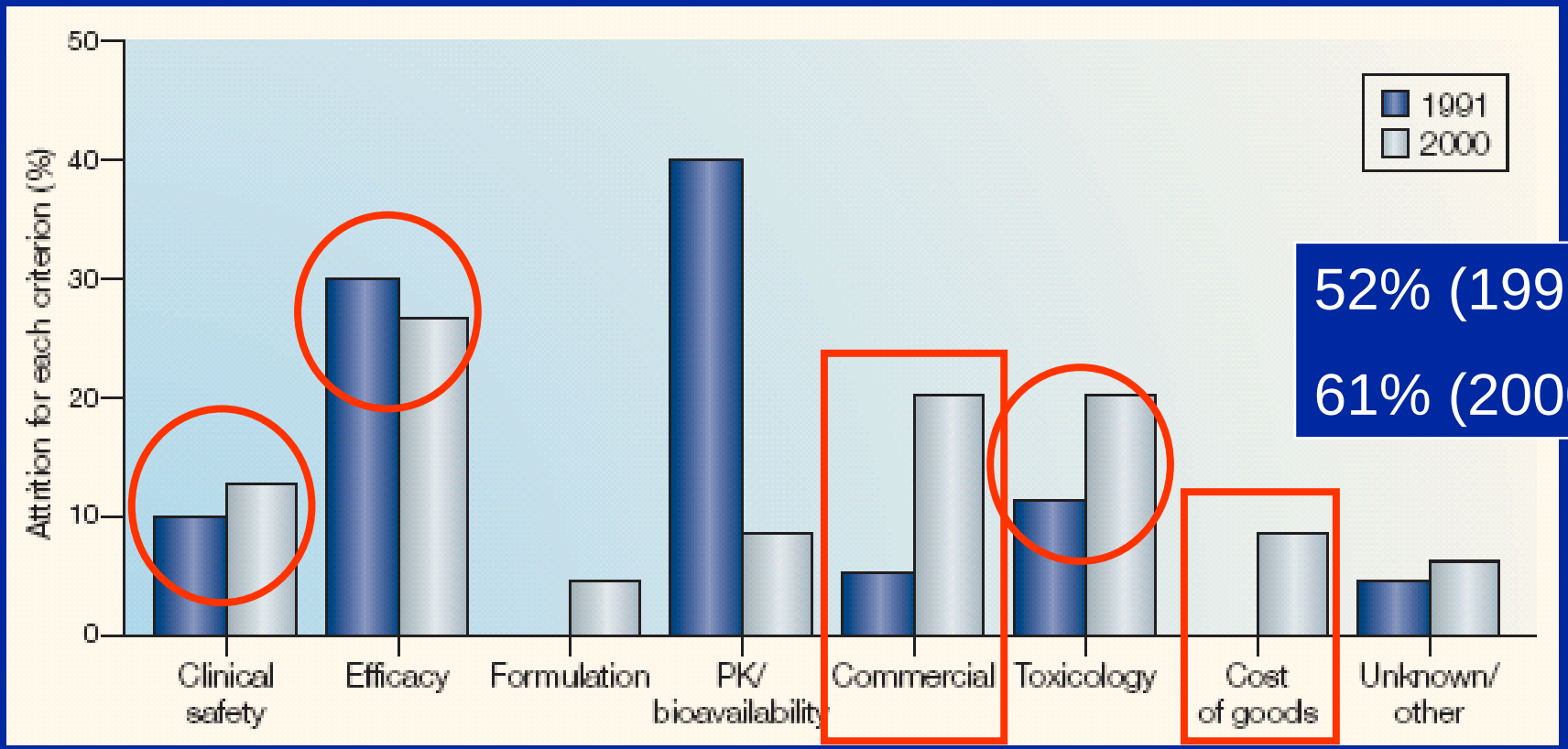
"The dramatic unpredictability of single-arm, uncontrolled Phase II trials [in cancer]…"

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?



Kola I and Landis J. Can the pharmaceutical industry reduce attrition rates?
Nature Reviews. Drug Discovery 2004; **3**:711–715.

“Randomise the first patient”

Hence, my statement:

Patients who volunteer to take potential 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*

Arguments against small (efficacy) trials

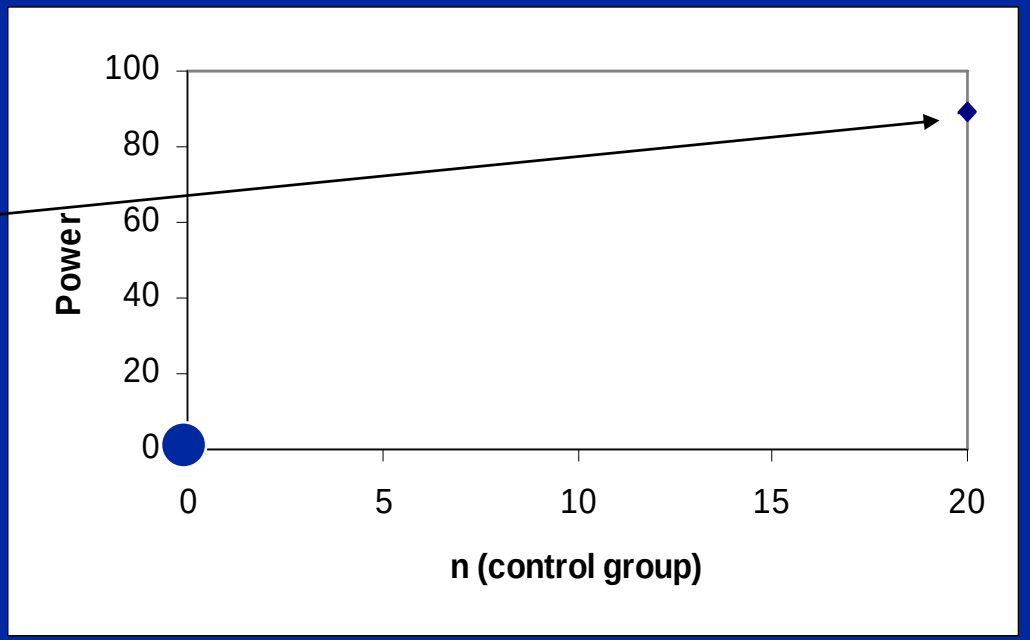
- “Can’t do randomised trials because we haven't got enough patients”
- “No point in having a control group because the trial would be severely underpowered”
- “No point in having a control group because there’s no chance to show any treatment benefit”

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 d[illegible]strate *any* treatment effect, of *any* magnitude
At least my study of 20 patients *vs.* 2 patie[illegible]s 20% power, which is a lot better than nothing”

Response:
“Well, but I would trea[illegible] those 20 (or 22) patients with active[?] treatme[illegible] I would be able to compare them to historical con[illegible]

“But m[illegible]l trial has 20% power (even on its own) *and* I can co[illegible] the results to historical controls as well”

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

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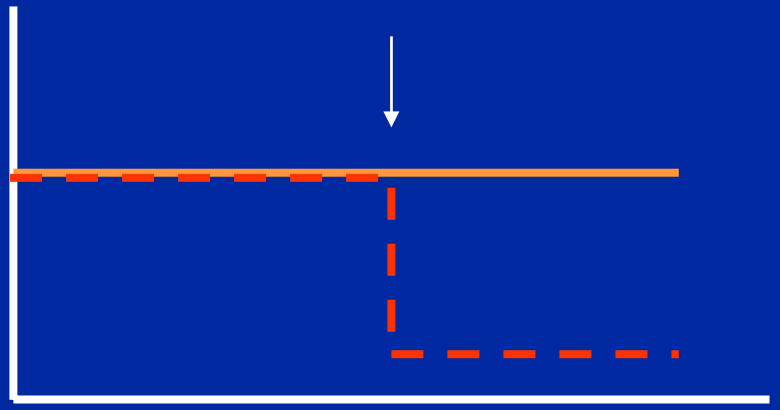
"What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect."

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

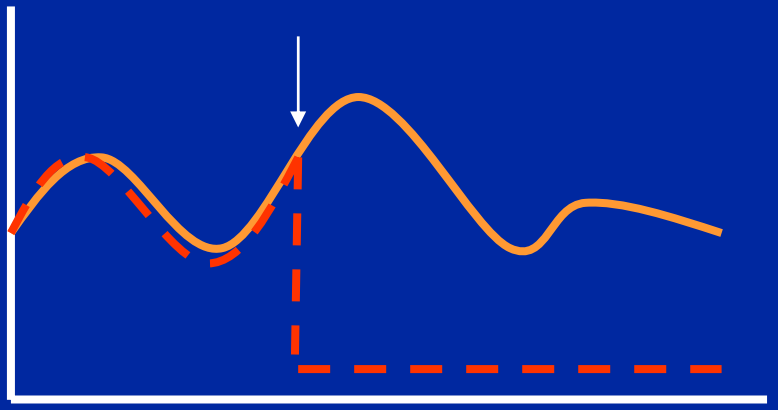
Levels of evidence might be consistent but *methods of evidence* need not be.

Context-specific evidence

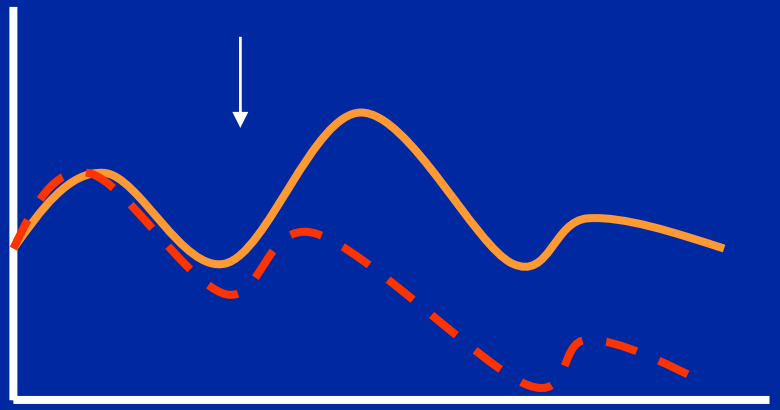
Stable disease, with sudden effect



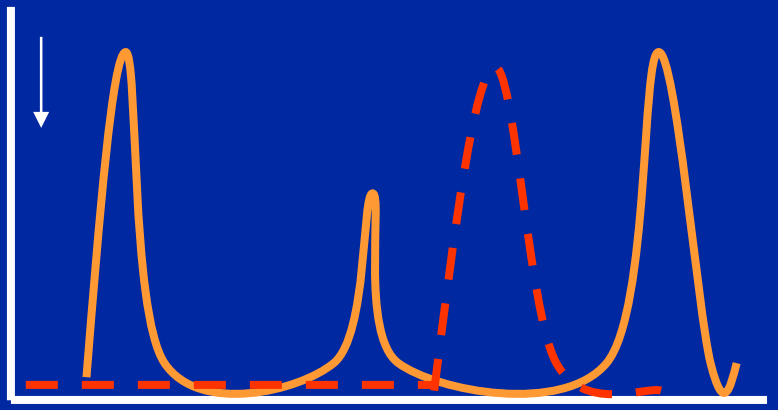
Fluctuating, with sudden effect



Fluctuating, with gradual effect



Episodic, with partial effect

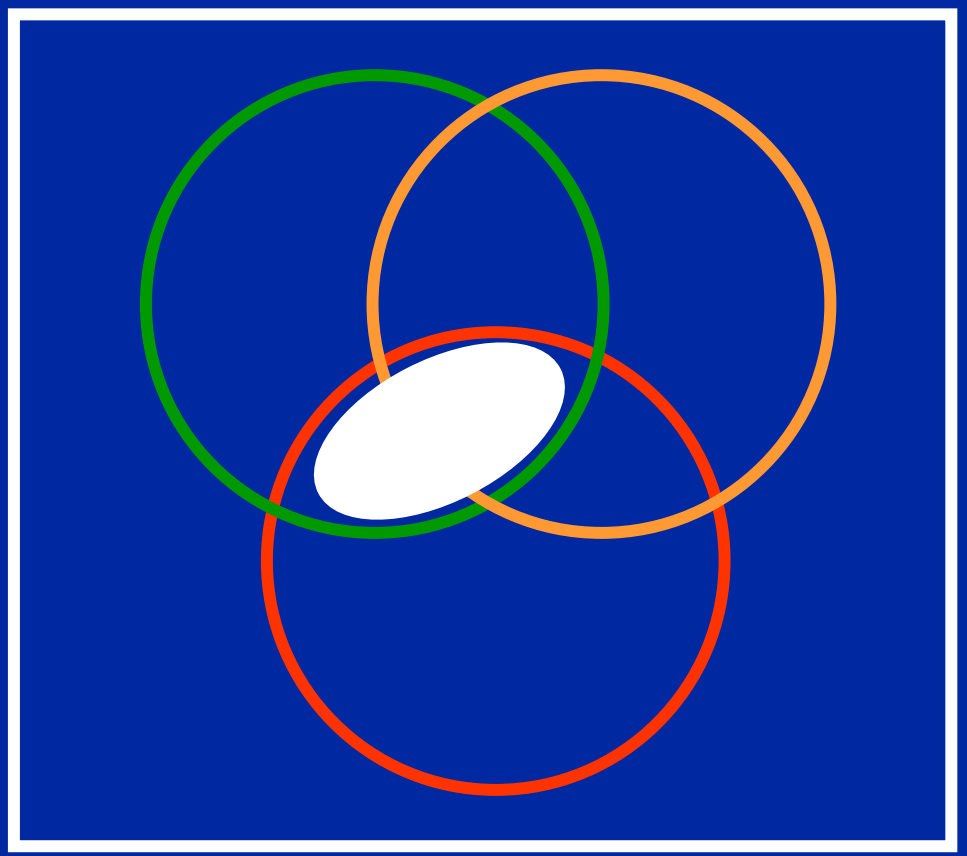


Adapted from Glasziou *et al.* (2008

What's the link between "rare" diseases and "dramatic" treatment effects?

Of all diseases:

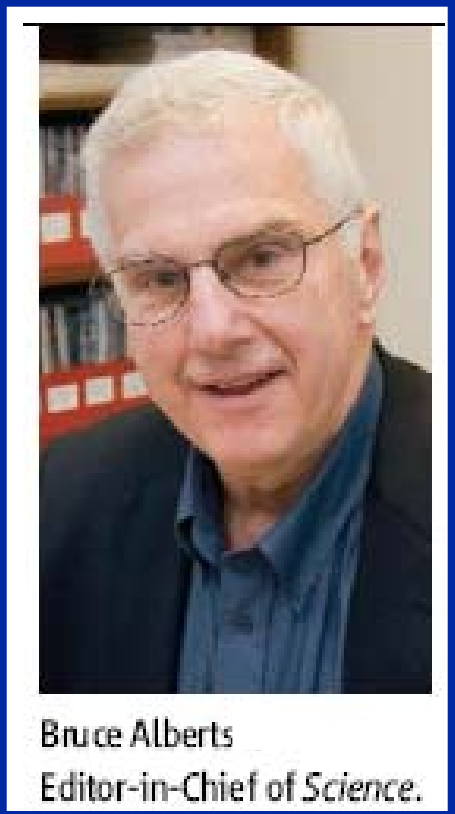
- Rare diseases
- Serious diseases
- "Dramatic" treatment effects



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

Sufficient evidence in one setting may be insufficient in another, or may be excessive in others

Sackett DL and Wennberg JE. Choosing the best research design for each question. *BMJ* 1997; **315**:1636.

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