Trials in diabetes: issues past, present and future

Dr. Amanda Adler
Chair, National Institute of Care Excellent (NICE) Technology Appraisal Committee B
Physician, Cambridge University Hospitals Foundation Trust

Outline

1. Defining a trial
2. Issues in the past
3. Issues with current trials
4. Issues in the future

11. **Definition.**—A
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It is the subst

Clinical Trial Definition

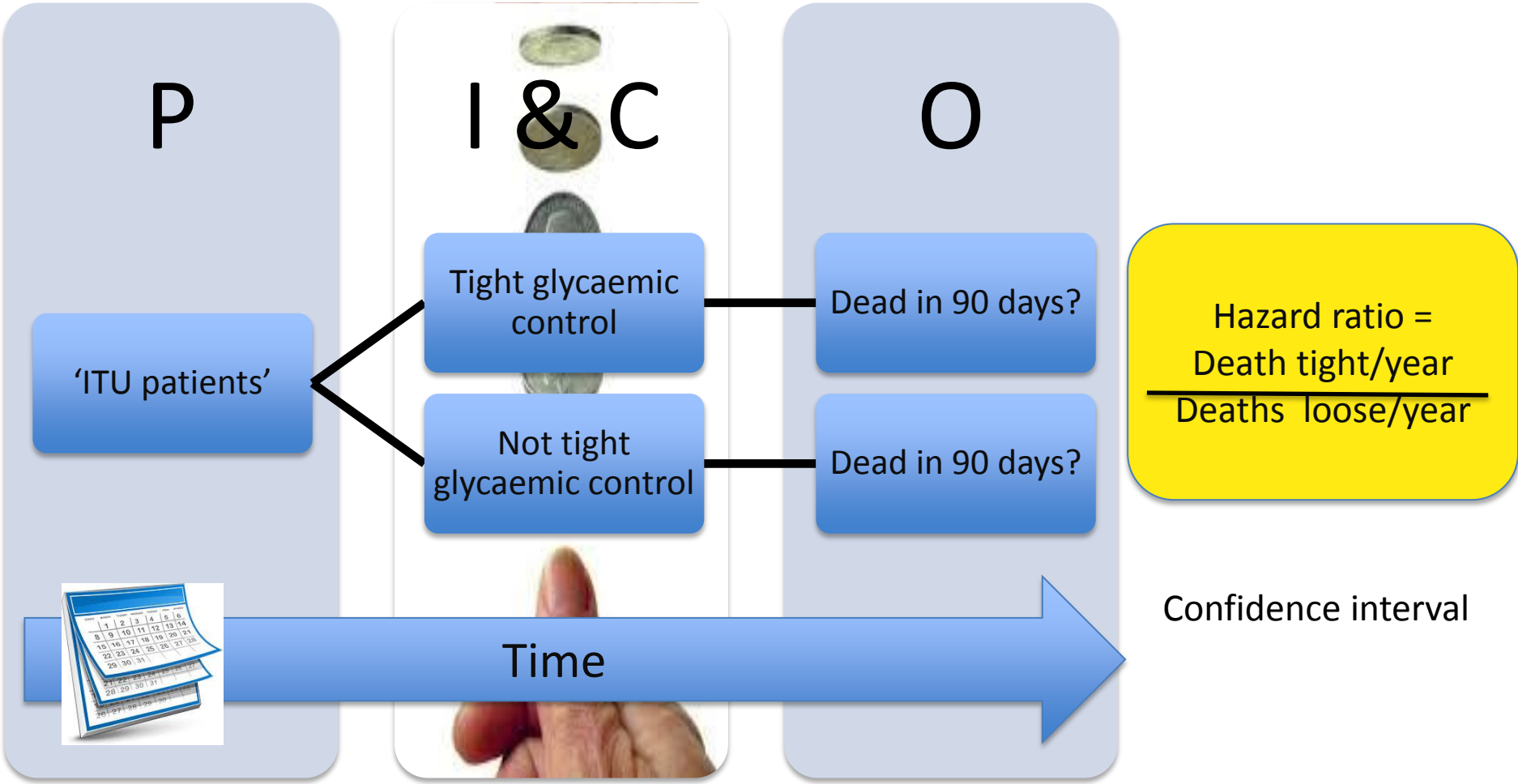
‘A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

Observational Study Definition

- ‘Observational studies are what we do when we cannot conduct a randomized trial’

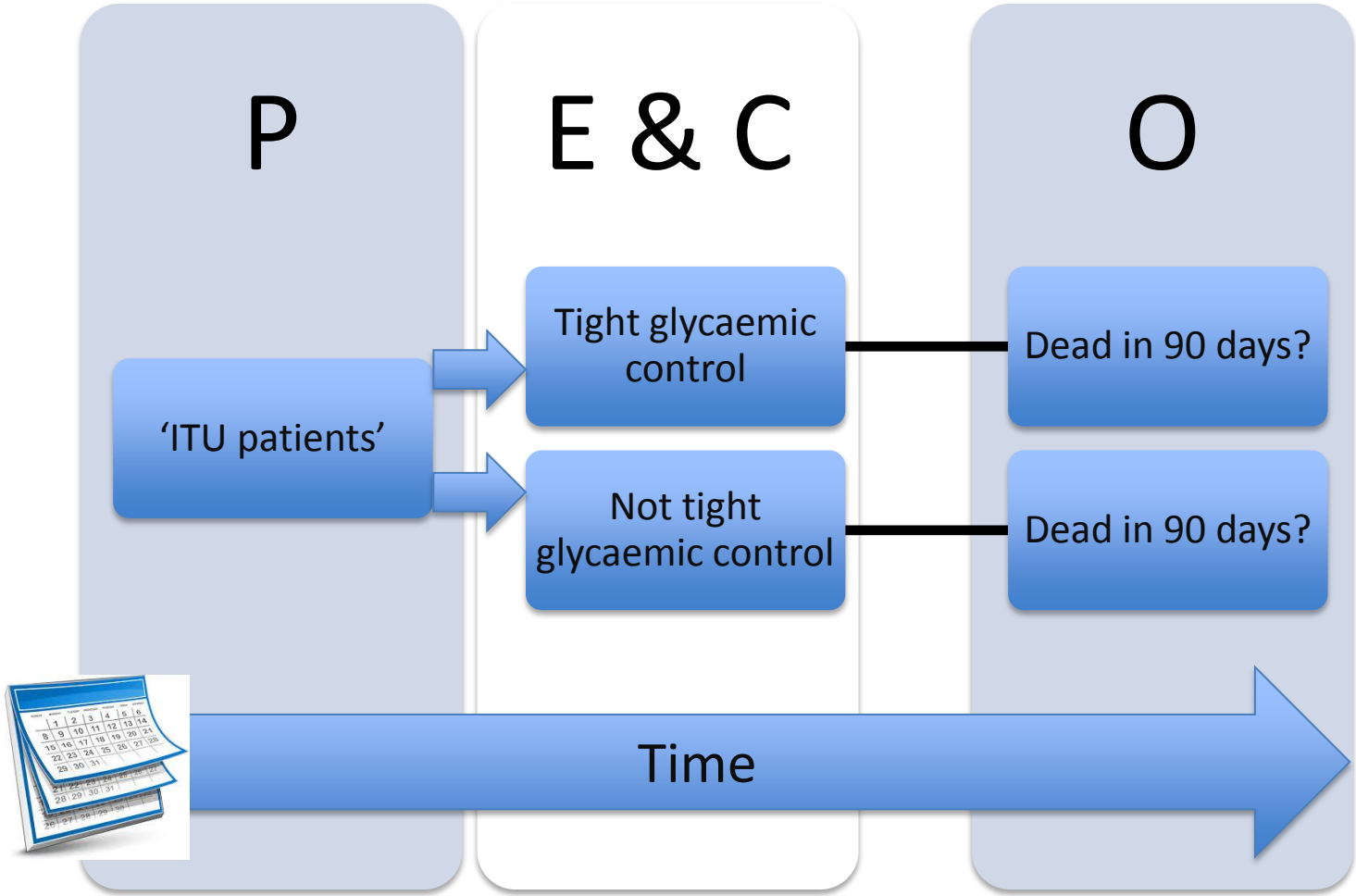
  – Miguel Hernan, Professor of Biostatistics and Epidemiology at Harvard, and James Robins, Professor of Epidemiology

Example Trial –'NICE Sugar'
Population/**Intervention**/Comparison/Outcome



New England Journal of Medicine, 2009

Example Observational Study – Population/**Exposure**/Comparison/Outcome



New England Journal of Medicine, 2009

Synonyms

Trial study

- Interventional study
- Experiment

Observational study

- Non-interventional study
- Epidemiological study
- ‘Non-randomized’ evidence
- ‘Real world evidence’

D Spiegelhalter 1 August 2018 at 13:32

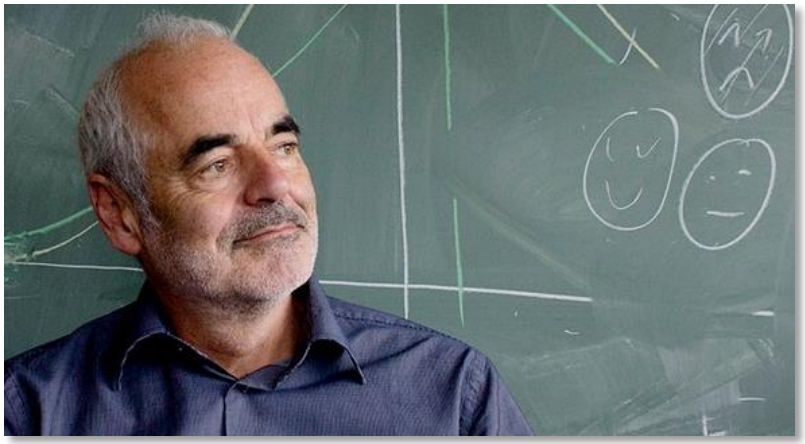
Re: the term 'real world evidence'

To: Amanda Adler, david@statslab.cam.ac.uk

Dear Amanda,

greetings from Vancouver (not the beach).

I dislike the term 'real-world evidence' as it strongly suggests that evidence from formal trials is somehow inferior to that obtained from simply observing what happens. I think 'found evidence' might be more appropriate.



Best wishes

d

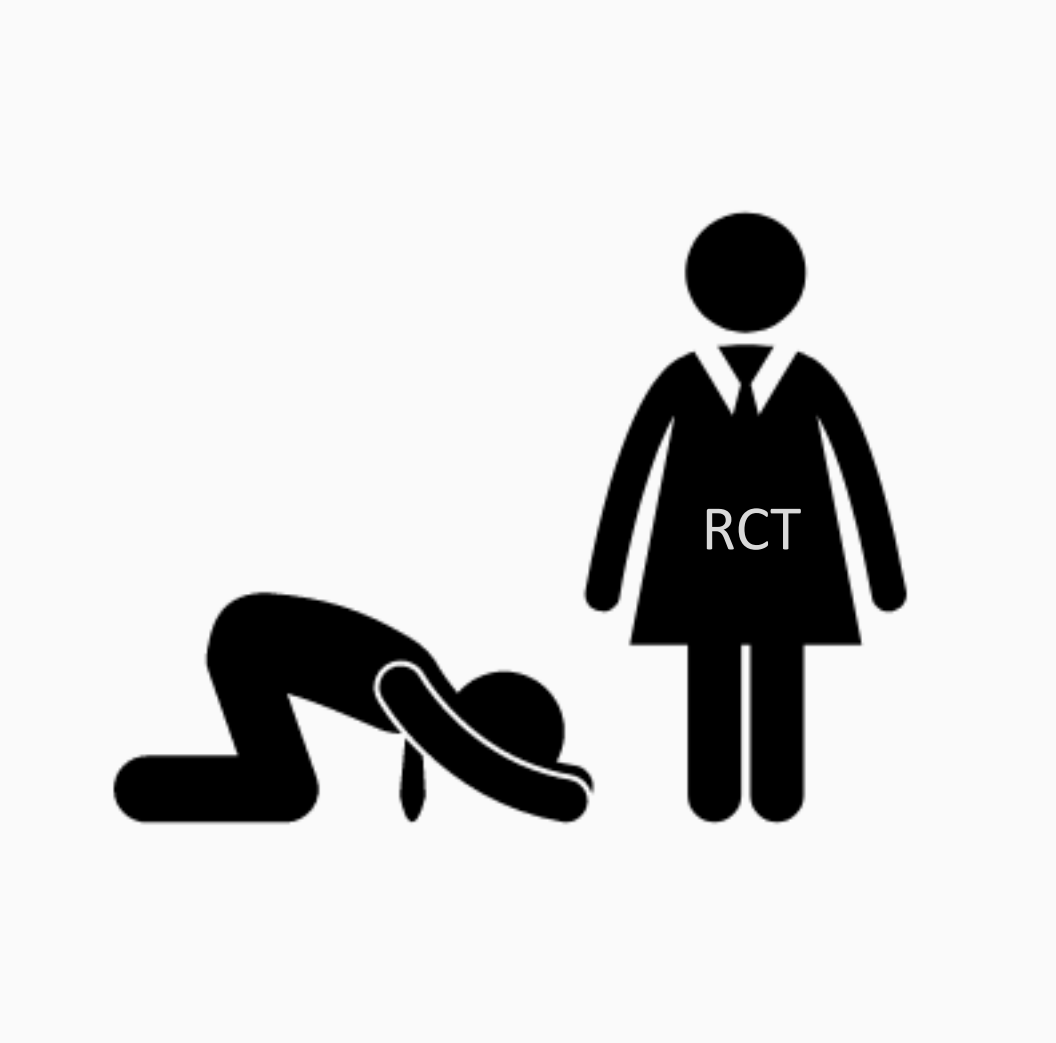
See More from Amanda Adler

--

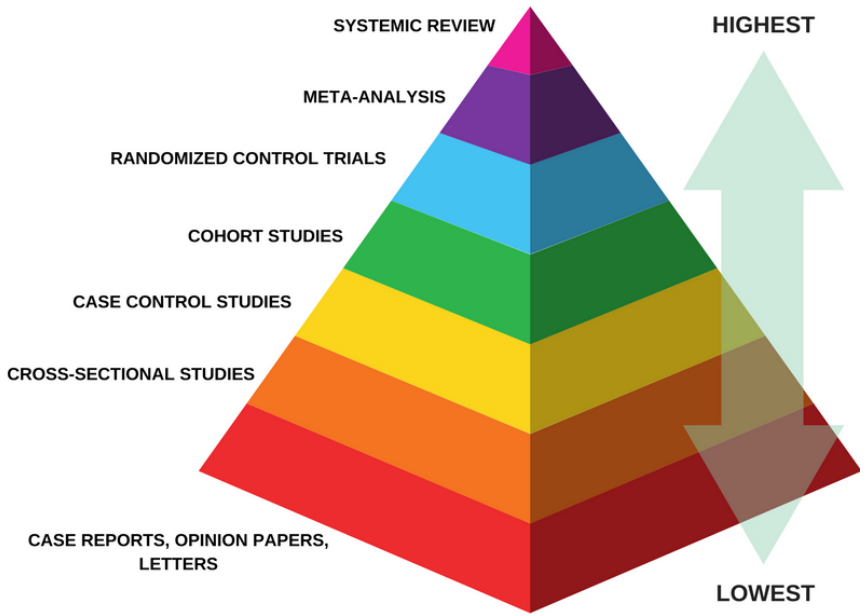
David Spiegelhalter
Winton Professor for the Public Understanding of Risk
Chair, Winton Centre for Risk and Evidence Communication
President, Royal Statistical Society 2017-2018

Statistical Laboratory
Centre for Mathematical Sciences
Wilberforce Road
Cambridge
CB3 0WB
UK

And yet, do we over-rate evidence from RCTs?



RCTs sit above all observational studies



The pyramid of evidence

From a company to NICE:

- "RCT evidence exists for the relationship between **surrogate measure** and outcomes in patients with **X** and is supported by observational data"
- Was an observational analysis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Nobel Lecture 1923 Banting
Early mention of near normal glycaemia

"..carefully adjusting the diet and the dose of insulin, all patients may be maintained sugar-free. This is advocated because we have abundant evidence for the belief that there is regeneration of the islet cells of the pancreas when the strain thrown upon them by a high blood sugar is relieved."

Banting FG in Nobel Lectures in Medicine and Physiology 1922 - 1941

Kroc Multicentre Trial

BLOOD GLUCOSE CONTROL AND THE EVOLUTION OF DIABETIC RETINOPATHY AND ALBUMINURIA

A Preliminary Multicenter Trial

THE KROC COLLABORATIVE STUDY GROUP *

Background:

The hypothesis that “correcting hyperglycemia would prevent microvascular complications” has become “one of the most debated and important issues in diabetes, but it has never been rigorously tested”

Kroc Trial

P: Type 1 diabetes

I: Insulin pumps, lots of testing, blood glucose goals

C: No more than 2 injections of insulin daily, little testing, no goals

O: Complications

Results:

HbA1c decreased 10.3% to 8.2% in continuous group

HbA1c did not change from 10.1% in conventional group

More serious hypos in continuous group (p=0.106)

More DKA in *continuous* group (9 vs 0) ($p<0.01$)

Albuminuria – not prevented

Continuous infusion associated with improved albuminuria

Retinopathy- continuous infusion associated with *greater* deterioration

Need longer term trials

Diabetes Control and Complications Trial
Epidemiology of Diabetes Interventions + Complications

Diabetes Control and Complications Trial (DCCT)

In type 1 diabetes, does improving metabolic control lower incidence of diabetes-related complications over 5 to 10 years?

P: No retinopathy or retinopathy (n=1,441, aged 13-39, USA/Canada)

I: Insulin (multiple daily injections or pump) and target HbA1c ~6% (someone without diabetes)

C: No more than 2 injections of insulin daily

O: Complications

Results: over mean follow-up of 6.5 years, reduced risk of microvascular complications by over half

Epidemiology of Diabetes Interventions and Complications (EDIC)

P: willing participants from DCCT (>90%)

E: previously randomised to intensive glycaemic control

C: previously randomised to less tight glycaemic control (conventional)

O: complications

Diabetes Control and Complications Trial
Epidemiology of Diabetes Interventions + Complications

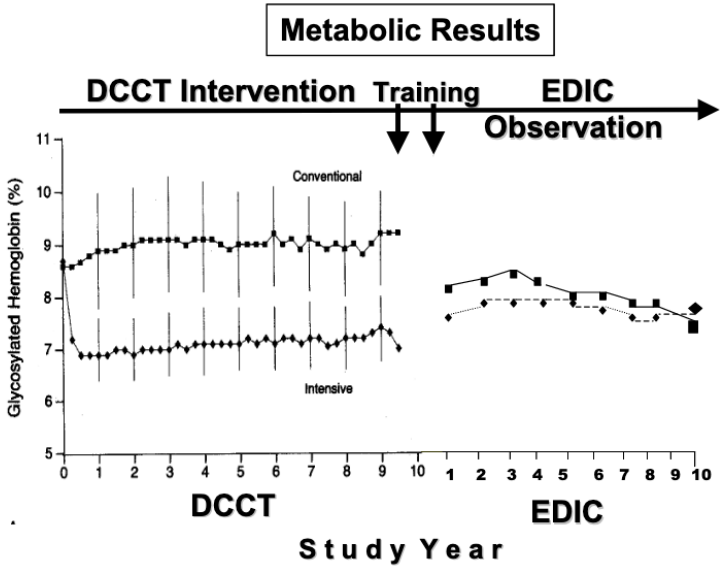


Figure 1.1: Glycemic Levels during DCCT/EDIC as measured by glycosylated hemoglobin (HbA1c). Medians with 25th to 75th percentiles shown.

Table 1.1
Reduction in Risk for Microvascular Complications with Intensive Therapy, Compared with Conventional Therapy, during DCCT and EDIC (Combined Primary Prevention and Secondary Intervention Cohorts)

Complication	Percent Reduction During DCCT	Percent Reduction During EDIC
Retinopathy		
3-step change	63	72
Proliferative	47	76
Macular edema	26*	77
Laser therapy	51	77
Nephropathy		
Microalbuminuria (> 28mg/min)	39	53
Clinical albuminuria (> 208mg/min)	54	82
Neuropathy+	60	

*P< 0.001 for all reductions, except for macular edema during DCCT, which was ns.
+EDIC assessment of neuropathy different than DCCT assessment, precluding comparison of DCCT and EDIC results

https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetPdf.cgi?id=phd000390

UGDP

Goal: To measure “the efficacy of hypoglycaemic treatments in the prevention of vascular complications in type 2 diabetes”

P: People (mostly women) with ‘type 2 diabetes’
I/C: Randomised to 6 treatments
Fixed dose insulin or variable dose insulin
Phenformin or placebo
Tolbutamide or placebo
O: Cardiovascular disease

What happened:
Because of an apparent increase in mortality both the tolbutamide and phenformin arms stopped
Placebo arms compared to insulin arms
Results:
Fewer hospitalisations for heart disease in the insulin groups, not ‘statistically significant’
Blood glucose control better in insulin group, not ‘statistically significant’
Insulin did not decrease, but did not increase, cardiovascular disease

Enormous controversy flared in wake of study

- "The Achilles Heel of the UGDP study"
- Results analysed by "advanced, elaborate and novel statistical techniques"
- "The storm of controversy aroused by these results is probably without parallel in modern medicine. Every aspect of the design, execution, analysis, and interpretation of the trial have been minutely criticised by clinicians and statisticians, while the supporters of the trial have defended it with equal vigour"

Kilo C et al. JAMA 243:450-7. 1980
Lancet, Sept 13, 1975

Avoiding the Pitfalls of Long-Term Therapeutic Trials: Lessons Learned from the UGDP Study

HOLBROOKE S. SELTZER, M.D. Dallas, Tex.

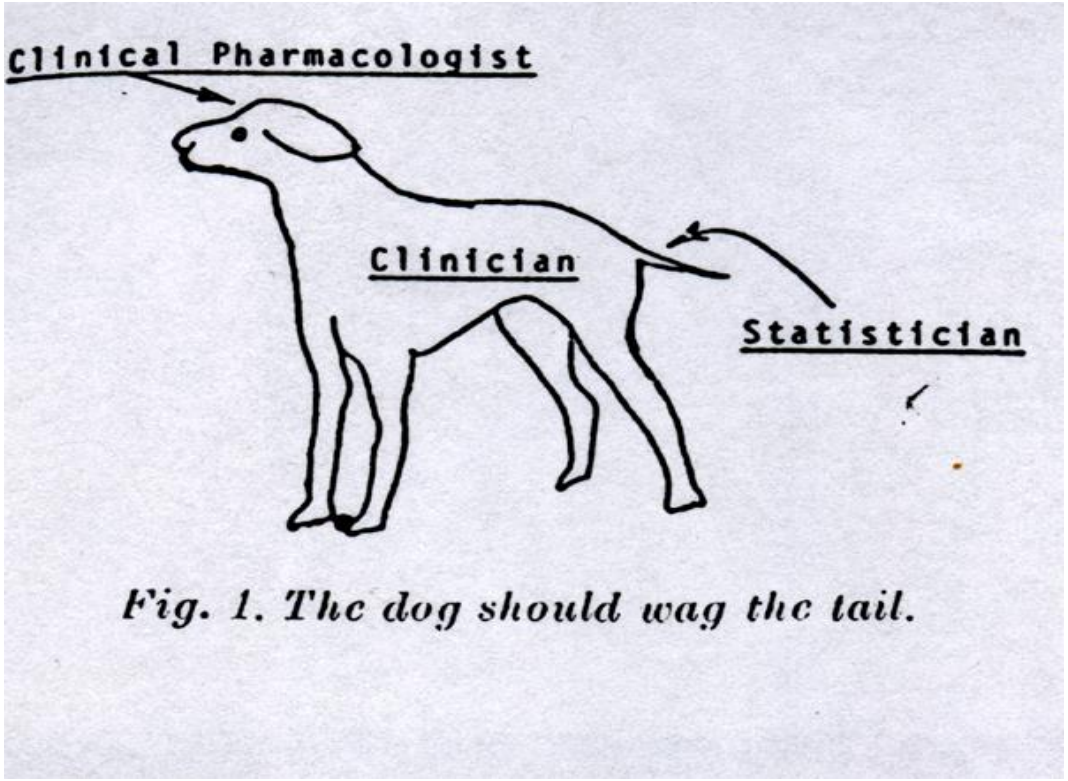
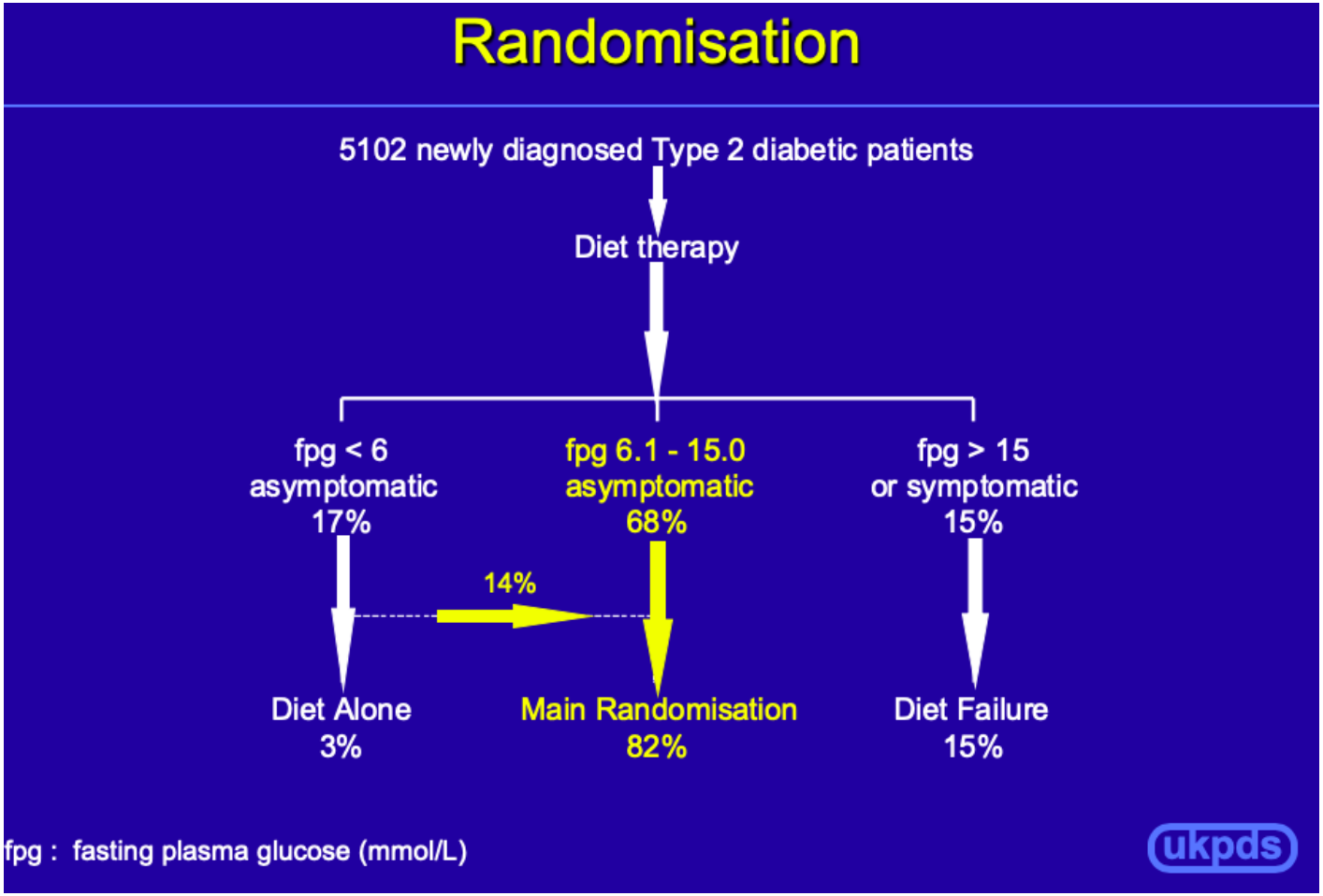


Fig. 1. The dog should wag the tail.

"Clinical pharmacologists can do without the statisticians, but not without clinicians"

Seltzer, 1972 The Journal of Clinical Pharmacology and New Drugs, 1972

UKPDS


Randomisation
5102 newly diagnosed Type 2 diabetic patients
Diet therapy
fpg < 6
asymptomatic
17%
fpg 6.1 - 15.0
asymptomatic
68%
fpg > 15
or symptomatic
15%
14%
Diet Alone
3%
Main Randomisation
82%
Diet Failure
15%
fpg : fasting plasma glucose (mmol/L)
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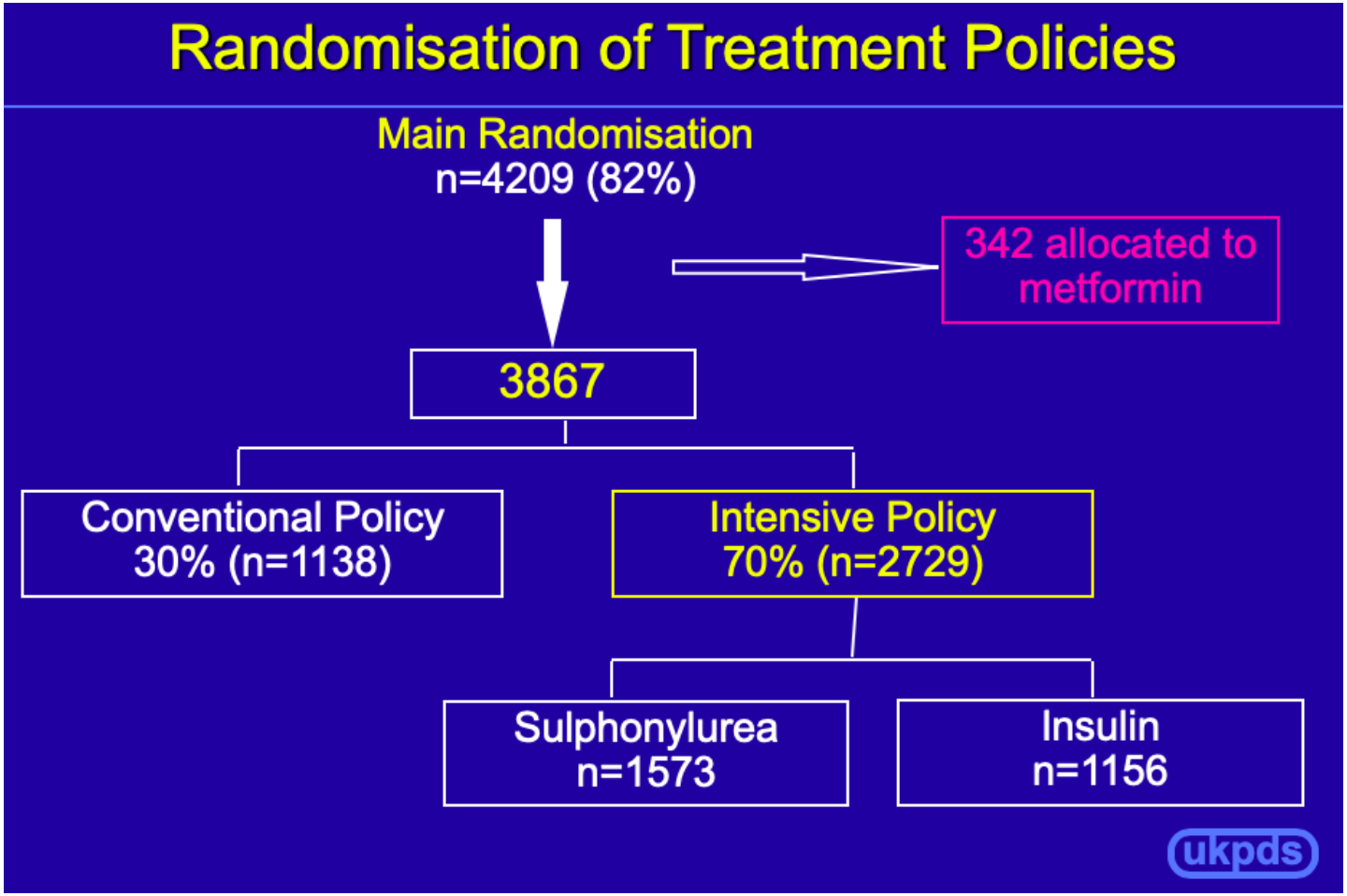
Secondary randomisation



Results

Glucose Control Study Summary

The intensive glucose control policy maintained a lower HbA_{1c} by mean 0.9 % over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of:

12%	for any diabetes related endpoint	p=0.029
25%	for microvascular endpoints	p=0.0099
16%	for myocardial infarction	p=0.052
24%	for cataract extraction	p=0.046
21%	for retinopathy at twelve years	p=0.015
33%	for albuminuria at twelve years	p=0.000054

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Results metformin

Metformin in Overweight Patients

- compared with conventional policy

32% risk reduction in any diabetes-related endpoints	p=0.0023
42% risk reduction in diabetes-related deaths	p=0.017
36% risk reduction in all cause mortality	p=0.011
39% risk reduction in myocardial infarction	p=0.01

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Many, many trials like this

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

US Food and Drug Administration 2008

Guidance for Industry

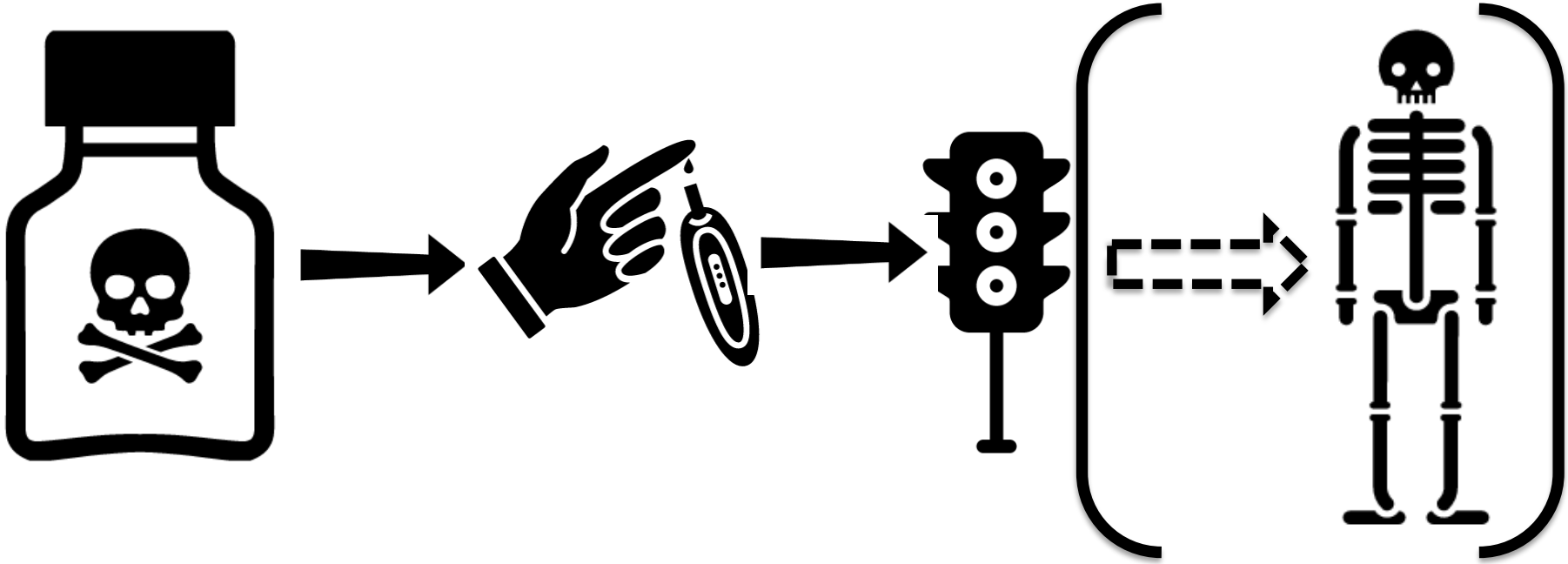
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf

Why the regulators?
Because drug safety is the remit of the regulators

https://blogs.shu.edu/ghg/2014/06/16/drug-safety-and-corporate-governance/

Potential problems with approving diabetes drugs on basis of blood glucose lowering



Delwar Hossain, Lahymik, Sebastian Langer Noun Project

Trials then and now

	What regulators previously got	What FDA now wants
Population	Type 2 diabetes healthy – no CVD	Type 2 diabetes high CVD risk
Intervention	New drug	New drug
Comparison	Placebo	Placebo
Outcome	HbA1c	'**Major Adverse Cardiac Events' (MACE)** CVD events and death
Duration	6 months	Years
Type	Superiority	"Non-inferiority"
Question	In healthy people, is the new drug better than placebo with respect to glucose lowering?	In people with or at high risk for CVD, is new drug not worse than placebo with respect to safety?

Non-inferiority trials and why safety trials in diabetes have placebo comparators

- Non-inferiority trials determine whether a new treatment is not worse than a reference treatment by **more than an acceptable amount**

- Traditionally against **active** drug with **well established effectiveness**
- But, current diabetes trials are **safety trials**
- "A placebo comparator is necessary ..because the CV impact of other oral AHAs (such as sulfonylureas or thiazolidinediones) is not sufficiently well-established to serve as a benchmark ..."

TECOS protocol section 1.3 Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232-42.
Noun project: Radhakrishnan, GK Lay, Luis Prado

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Recruiting to safety studies

So, that must mean it's safe?

Well, hmmm, probably… but they're not entirely sure, which is why they're doing this study.

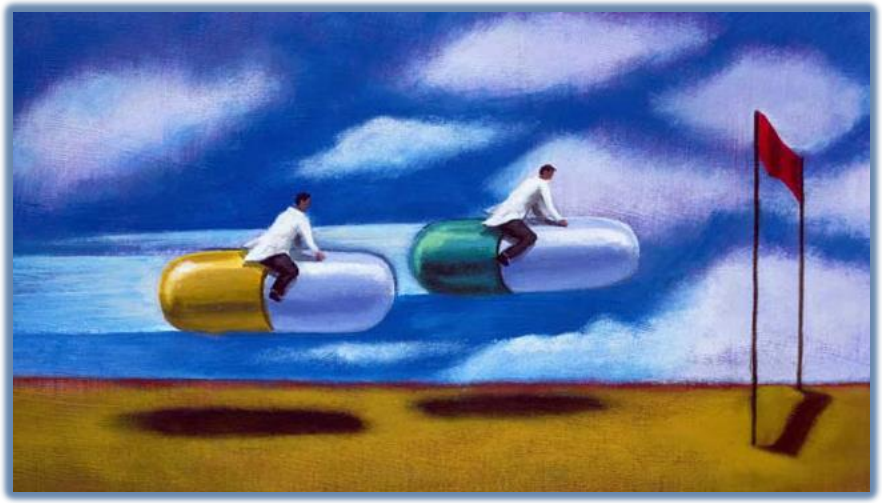
Well, it's 'newish' – it's been on the market for a few years.

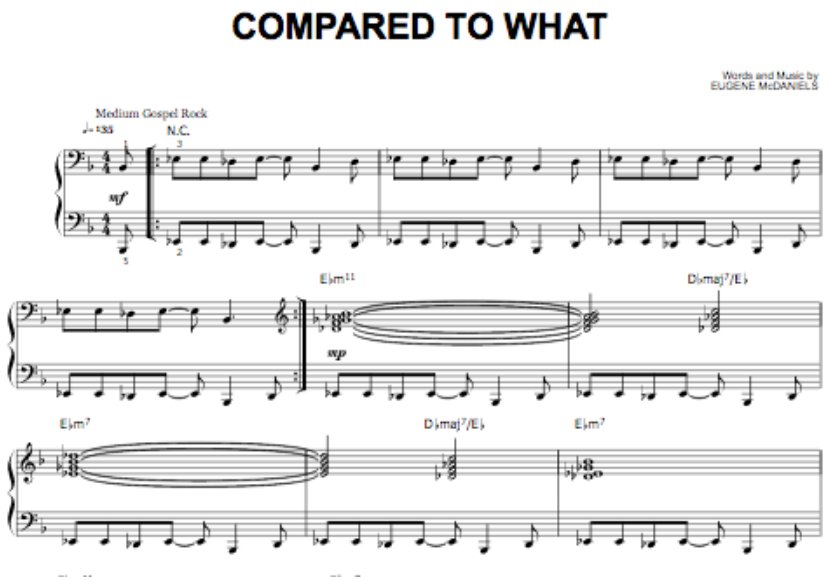
Tell me about the trial you want me to join; is this drug new?

Actually, there's no reason to think that it **would** cause a heart attack, but they still want to check….

No thank you!

Trials important for clinical care should assess relevant clinical comparisons





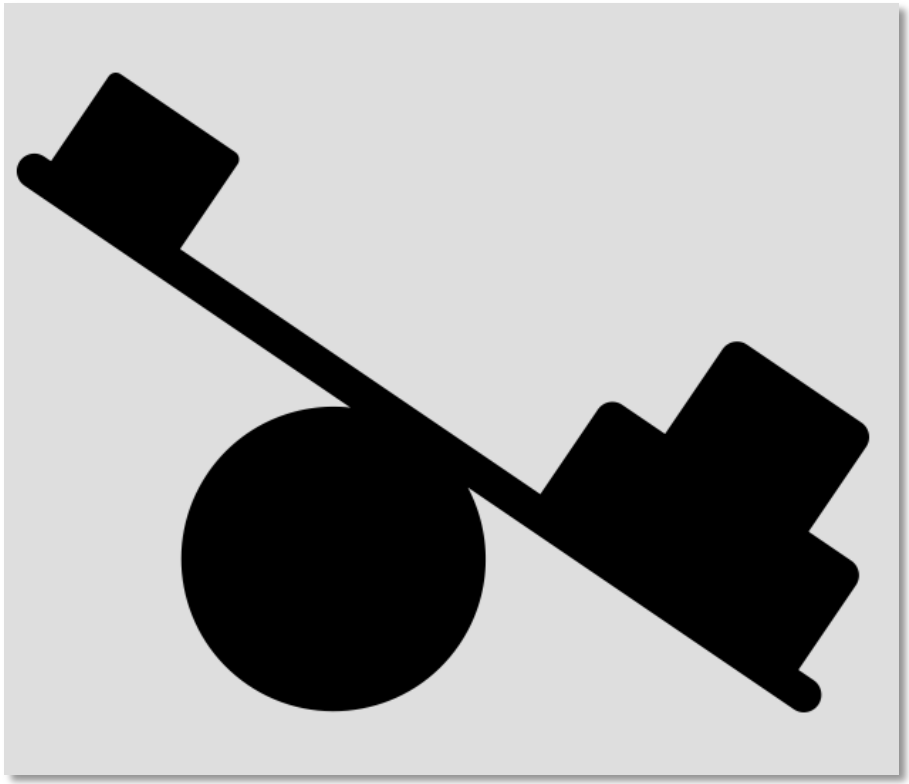
Wrong comparator for clinical practice

"?!?!?!?!"

It seems your metformin and gliclazide aren't controlling your diabetes anymore…let's see…. would you like to use a new diabetes drug… or would you like a placebo?

Not a fair comparison for clinical practice

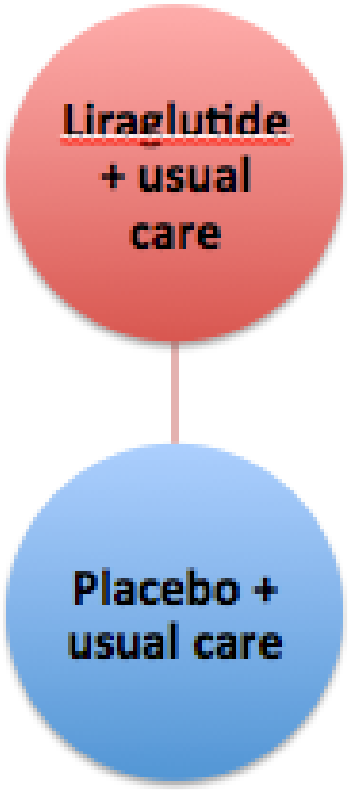
standard care



New drug + standard care

Creative Stall Noun Project

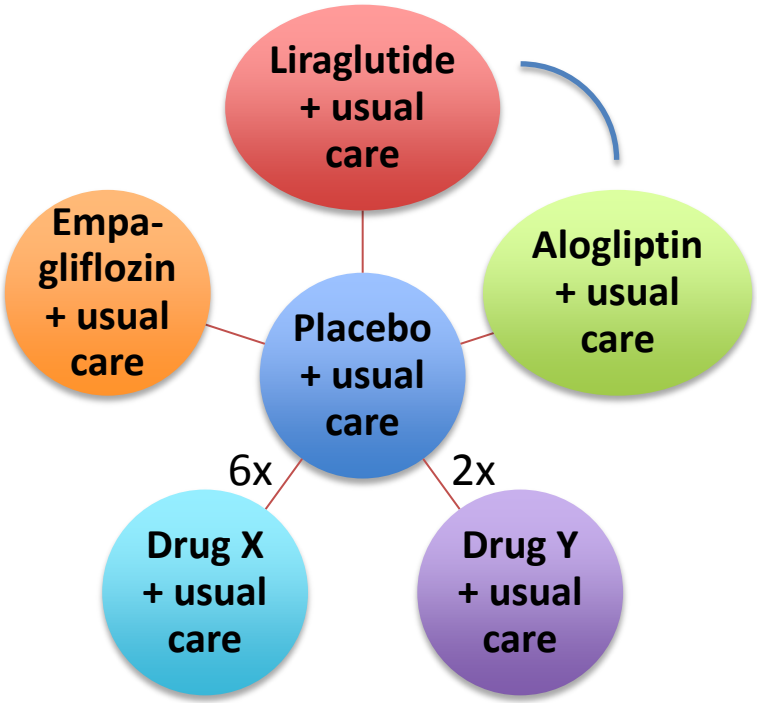
‘Usual care’ is constrained in placebo arm (and, of course, real doctors don’t offer placebos)



- LEADER– aspired to same HbA1c in both group
  - Doctors “free to add or adjust the dose(s) of any glucose-lowering drugs including insulin… but excluding drugs affecting the incretin pathway (e.g., other GLP-1 receptor agonists, DPP-4 inhibitors) or pramlintide.”
- Makes sense in a blinded trial
- But, LEADER cannot answer whether liraglutide is more effective or cost effective than another GLP agonist
- Actual comparison?
  - liraglutide + usual care vs. placebo + ‘unusual’ care
- Not an issue for all trials – DEVOTE (Insulin degludec vs. insulin glargine)

Section 3.1.3 Protocol for Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;374:311-22.

To compare drugs requires indirect comparison



Networks require 'common comparator'

- OK for comparing within-class, not cross-class
- Common comparator not 'common'
  - EMPA-REG OUTCOME no SGLT-2s
  - LEADER no DPP-4s or GLP agonists

'Naïve comparison'

- Different baseline risks for dying
  - LEADER (liraglutide) – high CV risk
  - EXAMINE (alogliptin) - recent MI

'Matched-adjusted indirect comparisons'

- Publications may exclude important covariates

Protocols for: LEADER – liraglutide N Engl J Med 2016;374:311-22. EXAMINE – alogliptin N Engl J Med 2013; 369:1327-1335; EMPA-REG OUTCOME (empagliflozin) N Engl J Med 2015; 373:2117-2128

Data are so immature

Life extending?

EMPA-REG all-cause mortality

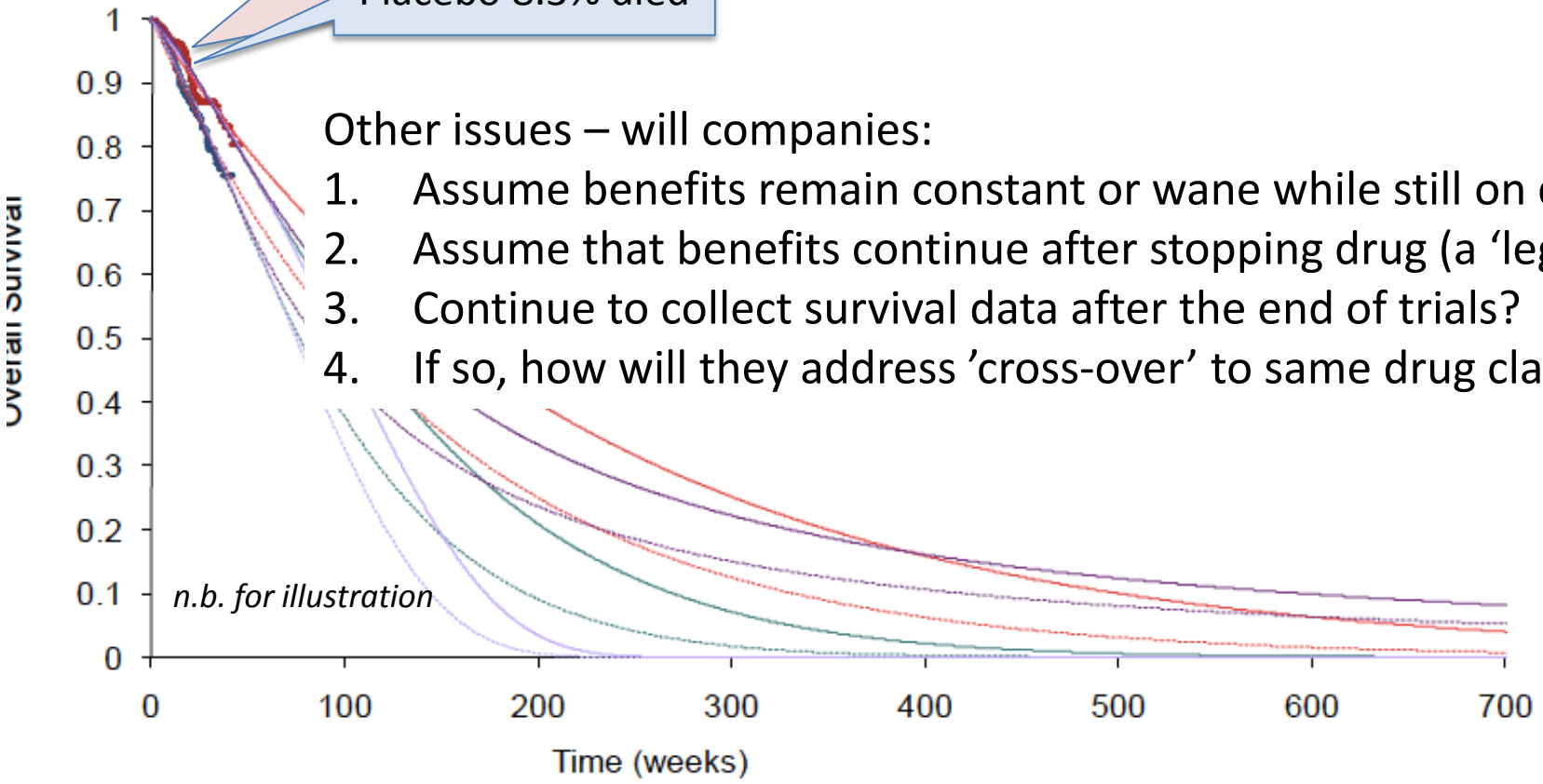
	Placebo (N = 2333)		Empagliflozin (N = 4687)		Hazard Ratio (95% CI)
	no	*%*	*no*	*%*	
Death from any cause	194	8.3%	269	5.7%	0.68 (0.57 – 0.82)

NEJM.org - Boehringer Ingelheim Protocol. N Engl J Med 2015;373:2117-28.

EMPA-REG OUTCOME and data 'maturity' - considerable uncertainty

Empagliflozin 5.7% died so 94.3% alive (or otherwise censored) at trial end

Placebo 8.3% died



Other issues – will companies:

1. Assume benefits remain constant or wane while still on drug?
2. Assume that benefits continue after stopping drug (a 'legacy')?
3. Continue to collect survival data after the end of trials?
4. If so, how will they address 'cross-over' to same drug class?

N.b. Has been tried by manufacture: "Modeling cardiovascular outcomes of treatment with Empagliflozin in type 2 diabetes based on hard outcomes data" by manufacturer. Abstract. 'Value in Health' Vol 19, 2016, Page A203

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Statistical principles
Define the statistical plan and stick to it

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Current *Step 4* version
dated 5 February 1998

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

'When designing a clinical trial the principal features of the eventual statistical analysis of the data should be described '

'Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory '

‘If you give yourself multiple chances of finding a positive results, but use statistical tests that assume you only had one go,
you hugely increase your changes of getting a misleading false positive’

Ben Goldacre. Bad Pharma.

Why I like the New England Journal of Medicine

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ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

September 16, 2016 | DOI: 10.1056/NEJMoa1607141

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Supplementary Material

Protocol (PDF File, 4331KB)

Supplementary Appendix (PDF File, 1610KB)

Disclosure Forms (PDF File, 301KB)

No mention of analysis other than non-inferiority

Protocol

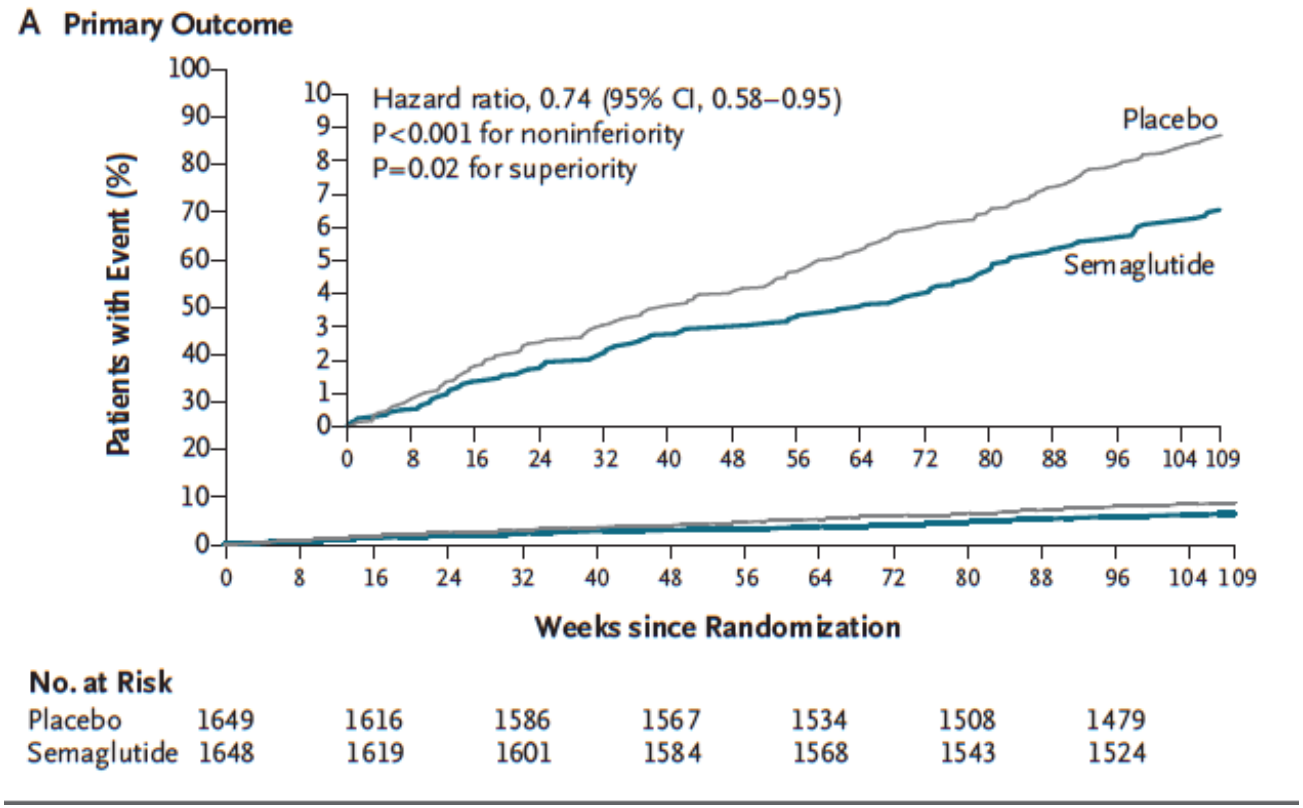
Trial ID: NN9535-3744

SUSTAIN™ 6 – Long term outcomes

A long-term, randomised, double-blind, placebo-controlled, multinational, multi-centre trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes

Trial phase: 3a

Yet, analyses for superiority done



Doing post hoc analyses

'There's nothing wrong in doing them. The problem is believing them'

Professor Sir Rory Collins quoting Professor Sir Richard Peto,
Professor of Medical Statistics and Epidemiology, Oxford University

'Thinking scientifically (not commercially) it makes sense to minimize the risk of type 1 error'

Dr. Harvey Motulsky

'The definition of a medical statistician is one who will not accept that Columbus discovered America because he said he was looking for India in the trial plan.'

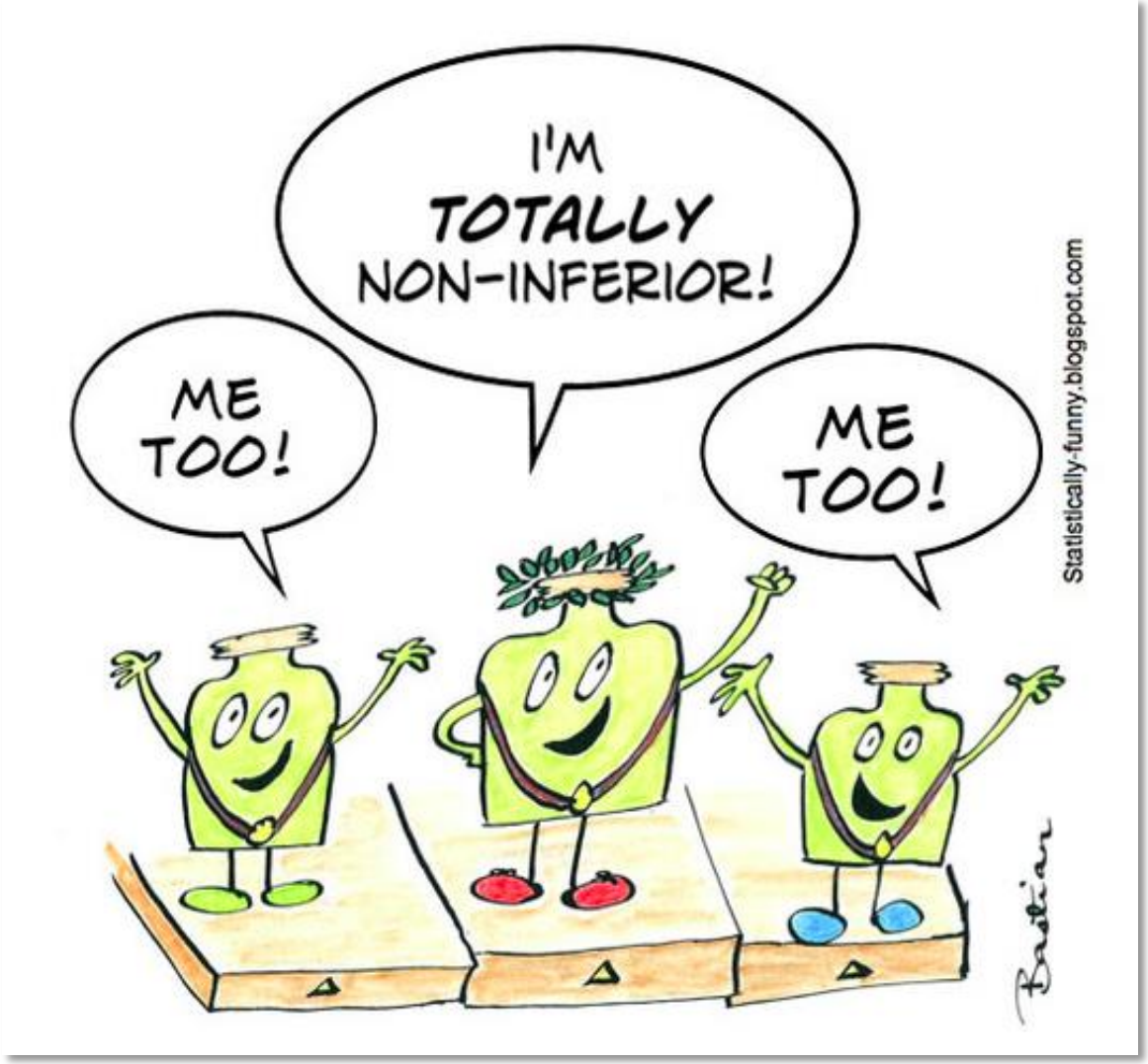
Professor Stephen J Senn

Personal communication 27 May 2017; Intuitive Biostastics, Oxford University Press ***Statistical Issues in Drug Development, Wiley*

Current trials are measuring quality of life
But, results using them not likely to be generalisable

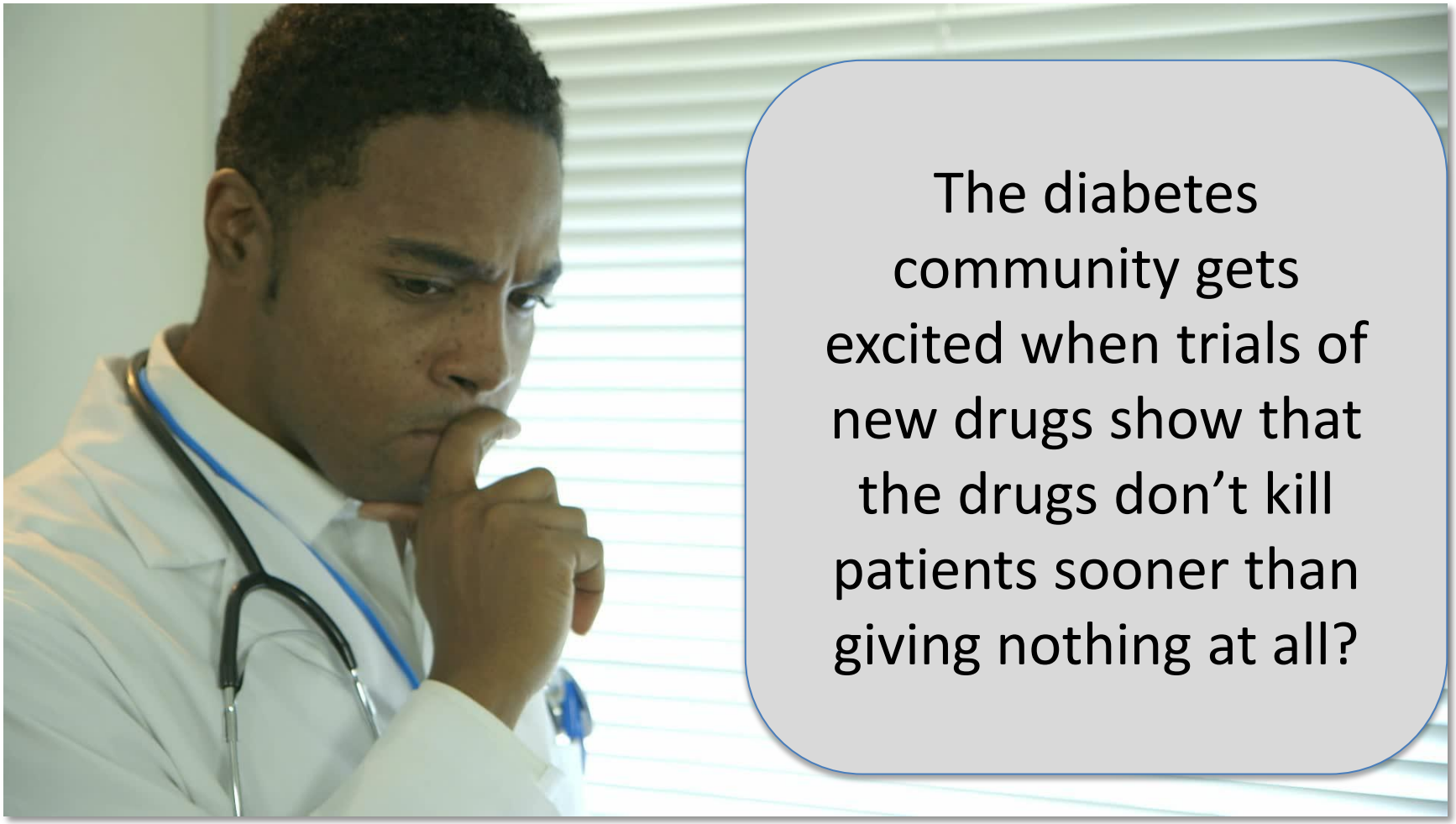
I stock photo

Why are we getting so excited?
Olympics for CVD trials in diabetes



http://sci-med-cartoonery.tumblr.com/post/113617790888/when-drugs-go-head-to-head

In summary, is it time to get worried when…..

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Analysing trials like observational studies
Barca vs. Cambridge United 'friendly'

Score at half-time: 5-1

At half-time: Messi and 5 others swap with Cambridge United players

Score at full-time: 6-4

What would the score have been had the players not 'crossed over'?
How much more effective is Barcelona, really?

Metaphor courtesy of Nick Latimer

Example – cancer, but applies to diabetes

1. Patients take cancer treatments until disease progression
2. Pharma do trials with 1° endpoint of disease progression
   - Because they can; also smaller, shorter, cheaper
3. Patients randomised to old treatment; at progression, then get new treatment
4. NICE wants to know how much longer new drug makes people live
5. Although trial is 'finished', patients followed (a while) to death
6. Pharma analyses patients by treatment to which they are randomised; if new drug lengthens life, this analysis lessens apparent benefit
7. Trial does not answer question: How much longer do people live **on** new treatment compared with people **not** on new treatment? Rather, answers question: How much longer do people live who get new drug **earlier** compared with **later**?
8. Techniques exist today disentangle the treatment effect

Analysing trials like ovservational studies determining the ‘counterfactual’

What would have happened if…?

*Sliding Doors, 1998. ‘..*based on the two paths the central character's life could take depending on whether she catches a train, and causing different outcomes in her life.’

https://en.wikipedia.org/wiki/Sliding_Doors

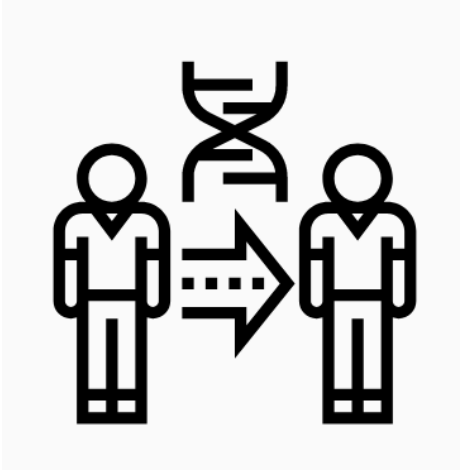
Inverse Probability of Censoring Weighting IPCW

- USA is killing Scotland
- At half, 1/3 the Scottish team defects to the Team USA
- Ref kicks the switching Scottish players out (akin to ‘censoring’)
- Full Scottish team play depleted USA team, and final score does not reflect true difference (akin to ‘informative censoring’)

- Imagine after players get kicked out, coach goes to the bench and replaces switchers with identical subs
- He need match the players only on characteristics that predict success, say, height and agility – if all the players were Glaswegian, he need not choose subs from Glasgow, as this does not predict success (confounders)
- Score would now reflect what would have happened had nobody switched

Observational analysis of trials IPCW

- Inverse probability weighting method does not introduce new participants (say from other trials, like the players on the substitutes' bench), but it does 'clone' non-switchers
- Method finds non-switchers who have same risk of dying (for the same reasons) as switchers, clones them to replace switchers, then ignores any data from switchers from this time onward.
- Being ill increases the risk of switching (in trial) and of dying (in general). Suppose trial randomises 4 ill people to the old drug, 3 of 4 switch, and 1 of 4 does not; statistician weights the ill participant who does not switch by 4, the inverse of 1 in 4. Participant has been cloned 3 times, and there are now 4 of him.
- New drug's true effect on survival, compares survival in people randomised to the new drug versus survival in people in the randomized-to-the-old-drug, repopulated, group - as if switching had never happened.
- PS. The name is wrong!



Analysing observational studies as trials

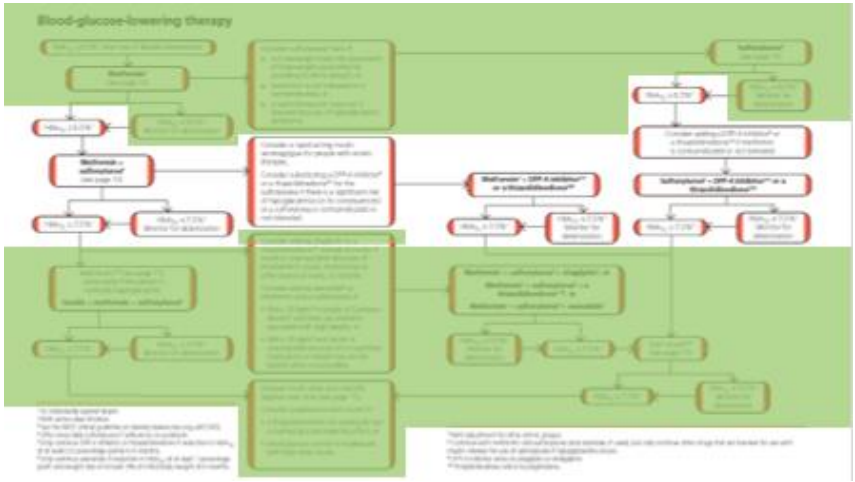
Trials

- Huge advantage of trials is randomization
- Both groups (diabetes drug A vs diabetes drug drug B) equal (at least at baseline)

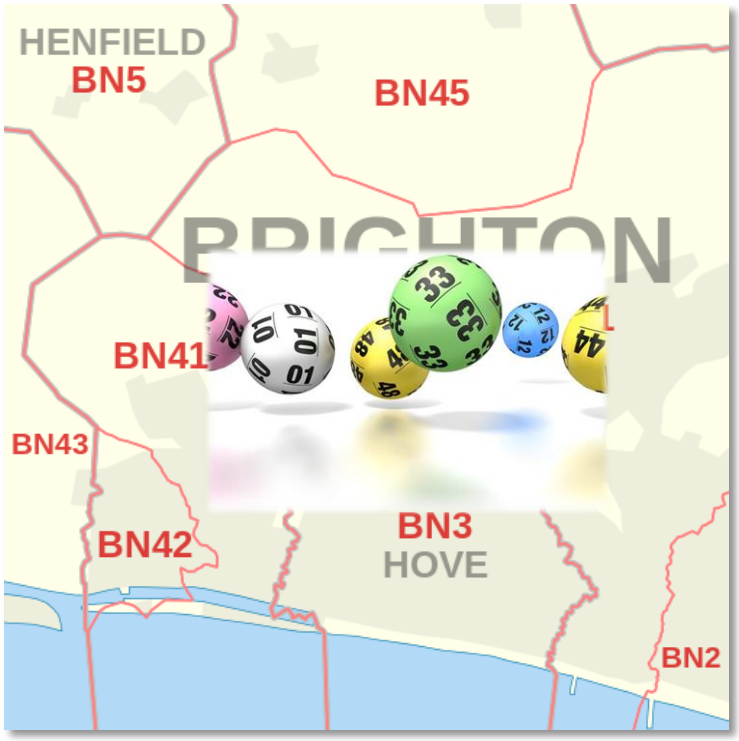
Observational studies

- ‘Instrumental’ variables
- Natural randomizer
- Distinguished people who take diabetes drug A from drug B, but groups are otherwise the same

Analysing observational data as diabetes trials



Which drug in
type 2 diabetes 2nd?



‘Post code lottery’
Exploiting ‘haphazard variation’

New Trial Designs

- “It is ironic that we take the same clinical trial approach toevaluate all manner of potentially amazing transformative experimental therapies and yet we don’t experiment with thedesign of the clinical trial itself.”

  Don Berry, MD Anderson

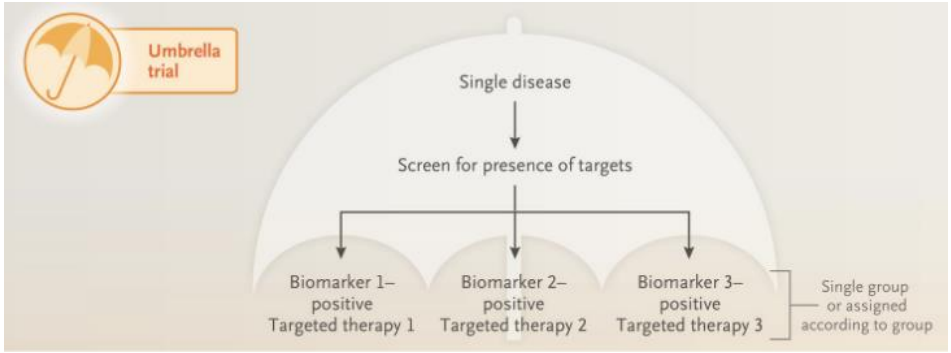
Berry DA. (2015). Brave New World....Mol Oncol 9: 951-959

Basket Trials in Diabetes

- In cancer, groups patients, not by tumour site, but by genetic mutation
- ‘biomarker-based trial design’
- Many cancers, one mutation
- Could be used for diabetes – glucose is a biomarker?
- (Are our trials in type 2 diabetes already basket trials?)

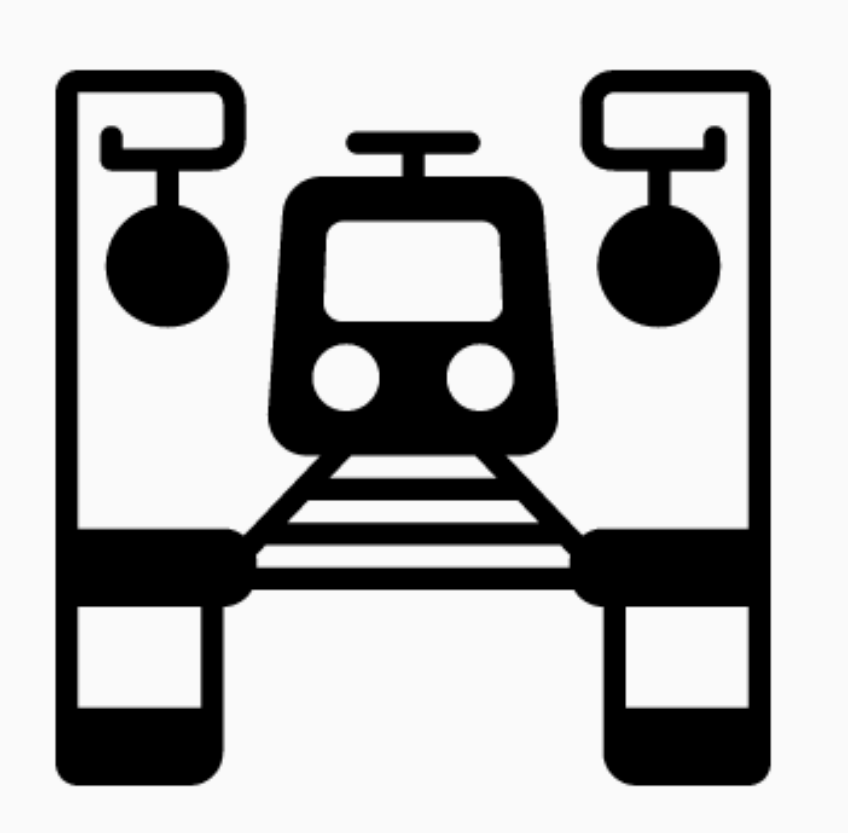
Umbrella Trials in Diabetes

- Also bio-marker based
- 1 cancer, but many mutations
- Upside down basket?
- Trial has many arms - use different drugs for different mutations
- CF-related diabetes?



Woodcock and LaVange. NEJM 2017;377:62-70

Platform Trials in Diabetes



- A "**platform trial**" is a clinical **trial** with a single master protocol in which multiple treatments are evaluated simultaneously
- Obvious applicability to diabetes

MRC Clinical Trials Unit

CANCER RESEARCH UK

NCRI National Cancer Research Institute

NHS National Institute for Health Research Clinical Research Network

STAMPEDE

Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy

A multi-arm multi-stage randomised controlled trial

Version:	**14.10**
Date:	**08-Mar-2016**
MRC CTU ID:	**PR08**
ISRCTN #:	**ISRCTN78818544**
NCT #:	**NCT00268476**
EUDRACT #:	**2004-000193-31**
CTA #:	**00316/0026/001-0001**
MREC #:	**04/MRE07/35**

‘MAMS’
multi-arm, multi-stage adaptive design

Multi-arm, multi-stage adaptive design

- Assesses several agents or combinations of agents
- Each simultaneously against a single control group
- Primary endpoint
- Intermediate endpoint - whether arm continues or not
  - Accumulating data reviewed by data safety monitoring committee ‘guided by lack-of-benefit stopping rule’
  - intermediate outcome must be on causal path (to primary endpoint), but does not have to be a true “surrogate”
  - high negative predictive value but not necessarily a high positive predictive value
- Better than factorial design trials which interaction weakens
- Quicker, smaller, cost-efficient, fewer research approvals

STAMPEDE

started in 2006, >6200 men as of 2017

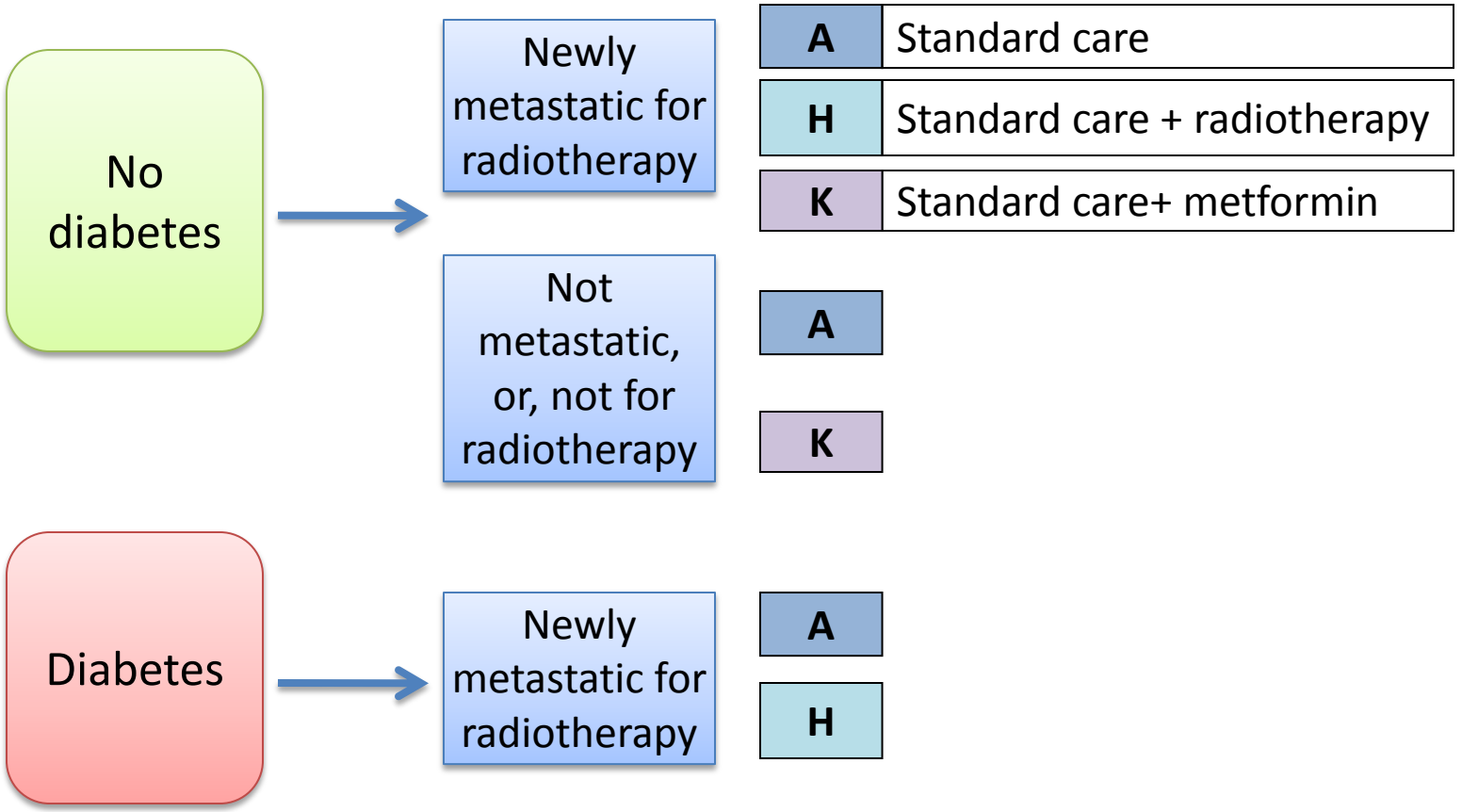
A	ADT alone + standard of care (M0) radiotherapy, or ACT +/- docetaxel +/- (M0) radiotherapy	Recruitment
B	ADT + Zolindronic acid	
C	ADT + Docetaxel	
D	ACT+ Celecoxib	
E	ADT + Docetaxel + Zolindronic acid	
F	ADT + Celecoxib + Zolindronic acid	
G	ADT + Abiraterone	
H	ADT + radiotherapy (M1 patients only)	Recruiting
J	ADT + abiraterone + prednisolone + enzalutamide	
K	**ACT + metformin**	Recruiting

Androgen deprivation therapy = ADT

Radiotherapy is mandated for men with node negative non-metastatic disease.

STAMPEDE metformin comparison

1st determine if for docetaxel as part of standard of care



Treatment would continue for life in metastatic and for 5 years in non-metastatic patients. Overall survival is both intermediate and final endpoint - 1800 patients to be recruited over 3 years

What about ‘pragmatic’ head-to-head trials?

http://www.physiciansweekly.com/aspirin-cartoon/; http://michael.schwanzer.info/random/
http://www.gponline.com/exclusive-five-fold-variation-patients-65-per-full-time-gp-across-england/article/1398534
Ben Goldacre ‘Bad Pharma’