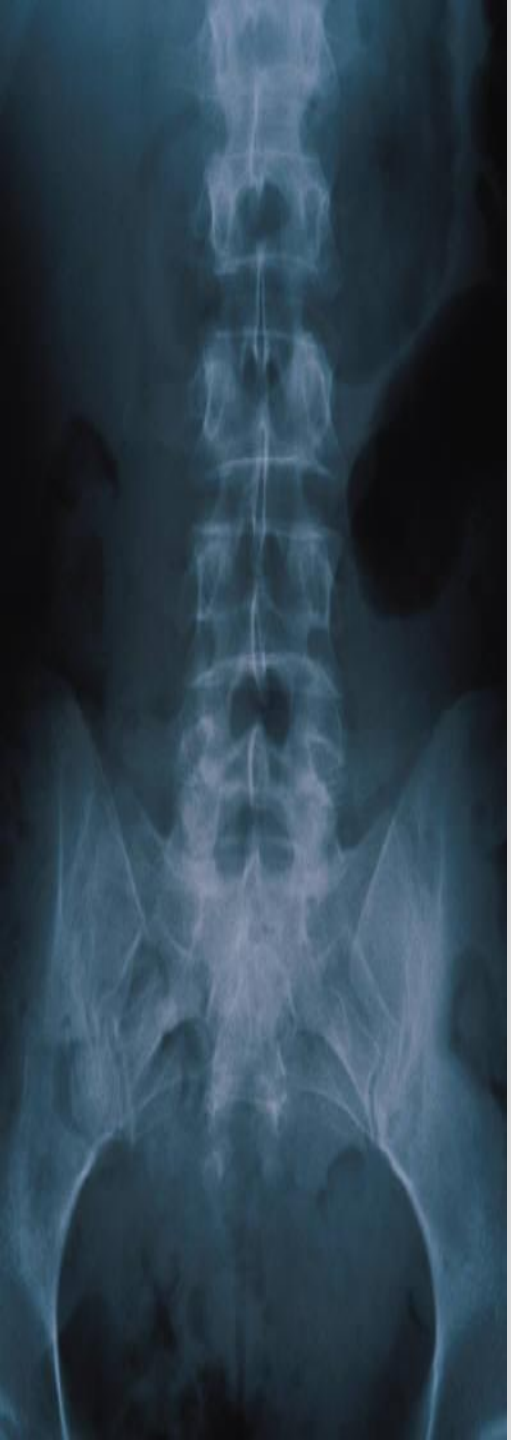
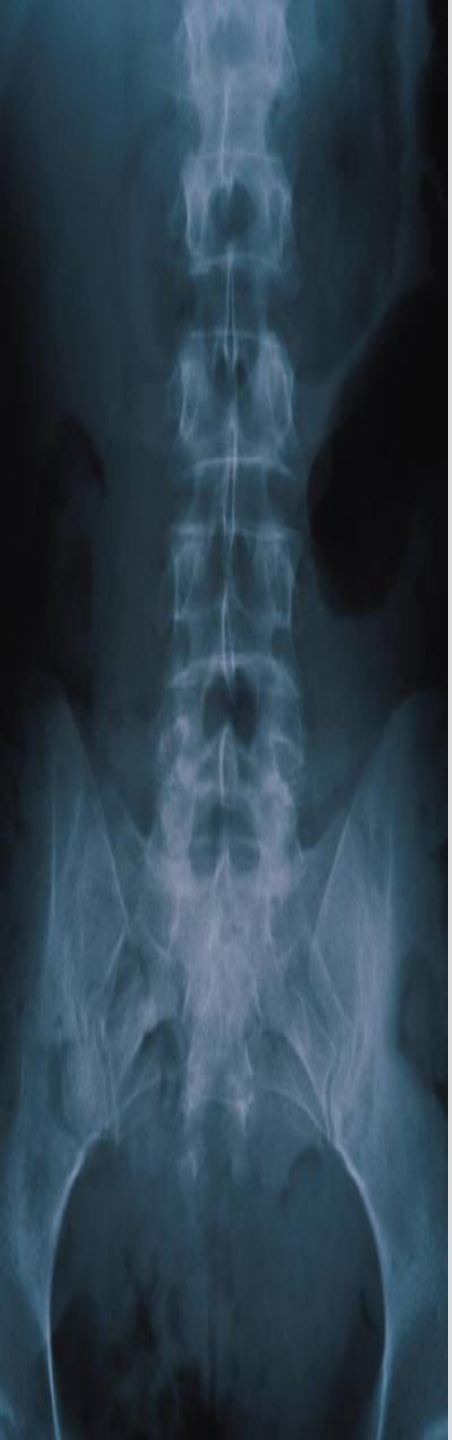
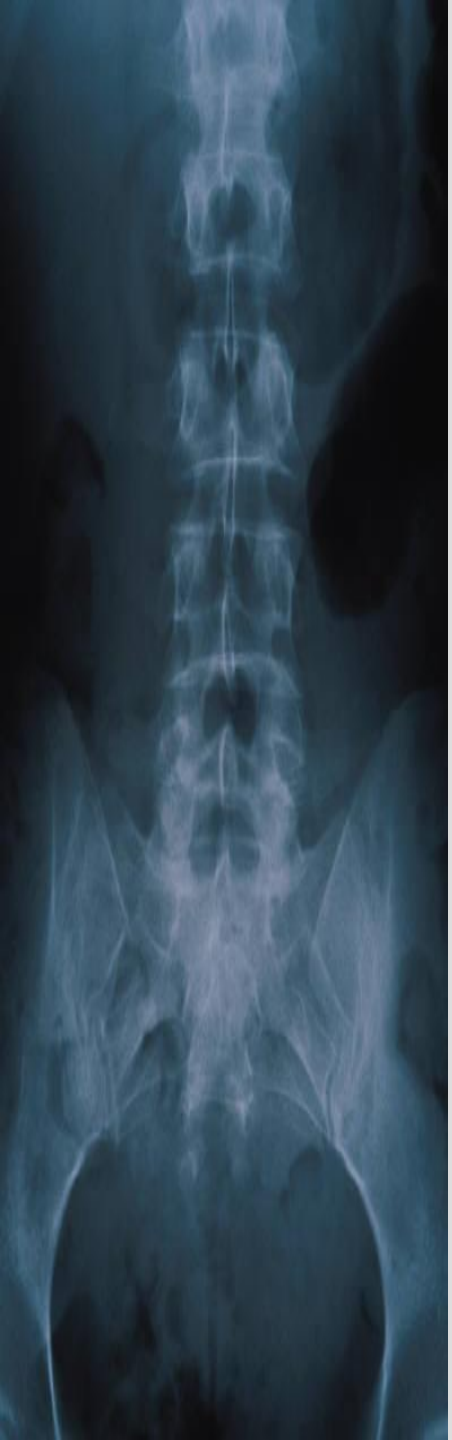


Critical appraisal of RCTs

Bad trials



What are the top three causes of death in the Western world?



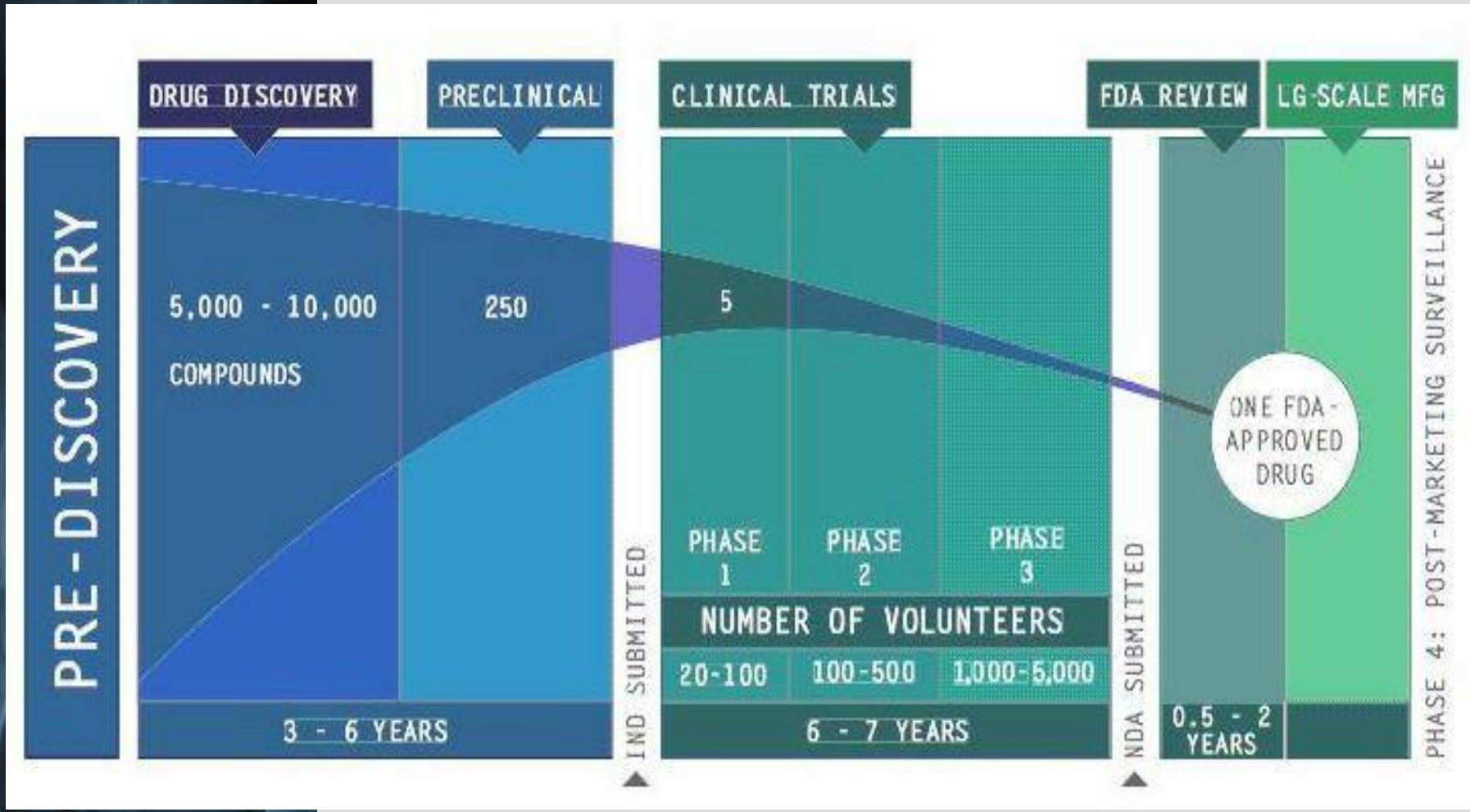
Top three causes of death:

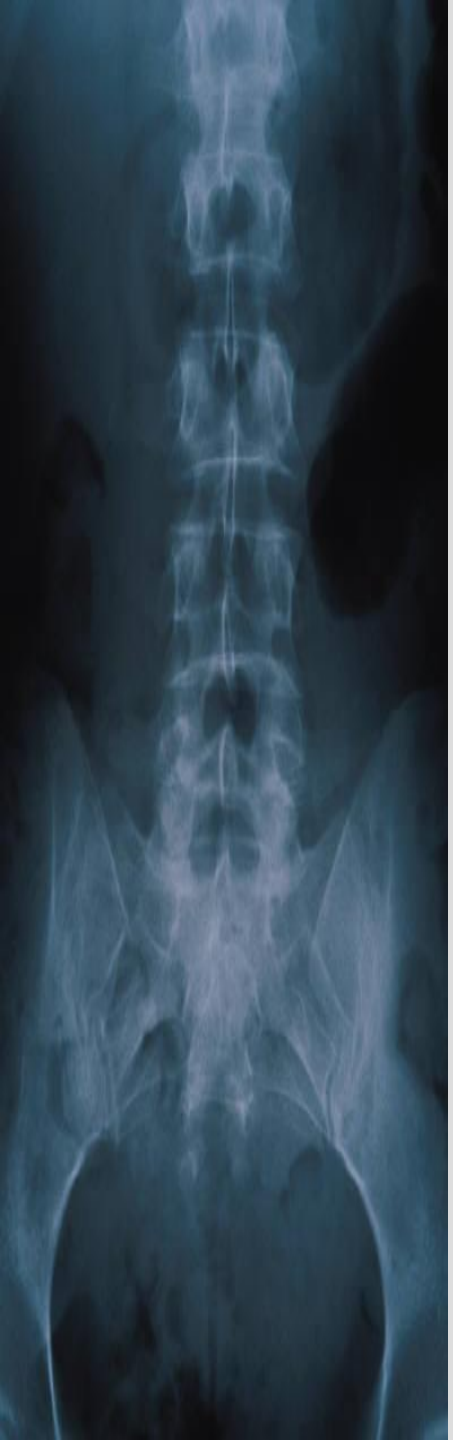
1 Heart disease

2 Cancer

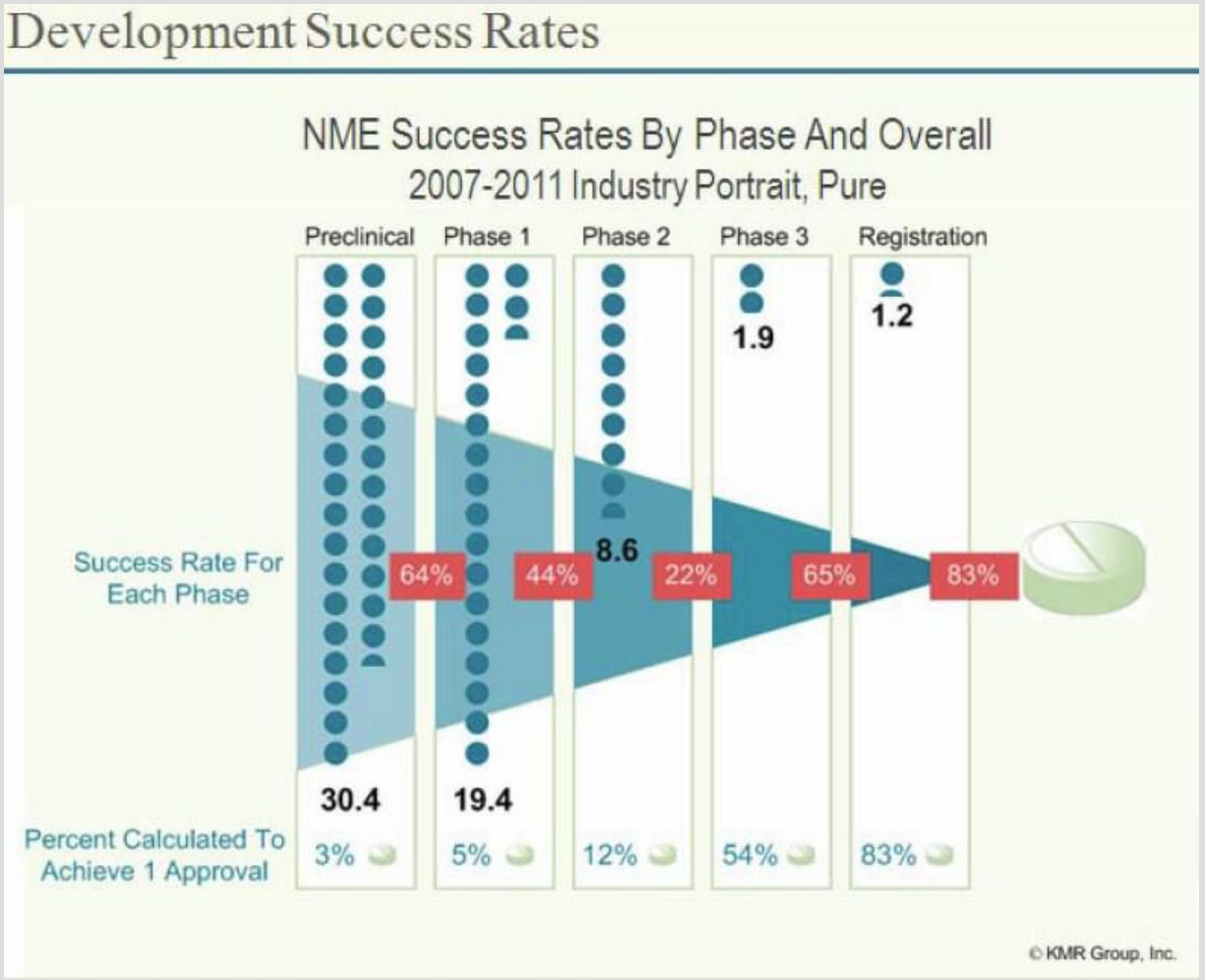
3 Therapeutic drugs

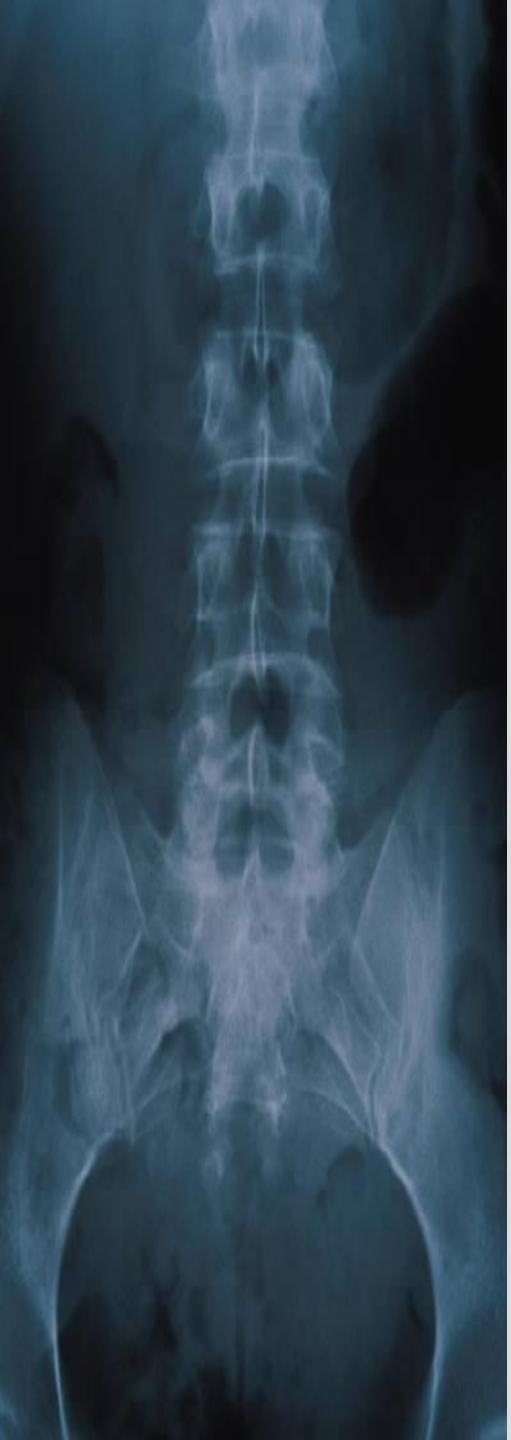
The drug development cycle





"KMR is a global leader in the area of benchmarking, analytics and performance management. Focused exclusively on biopharmaceutical R&D, we offer peerless data on topics ranging from R&D Productivity to enrollment"



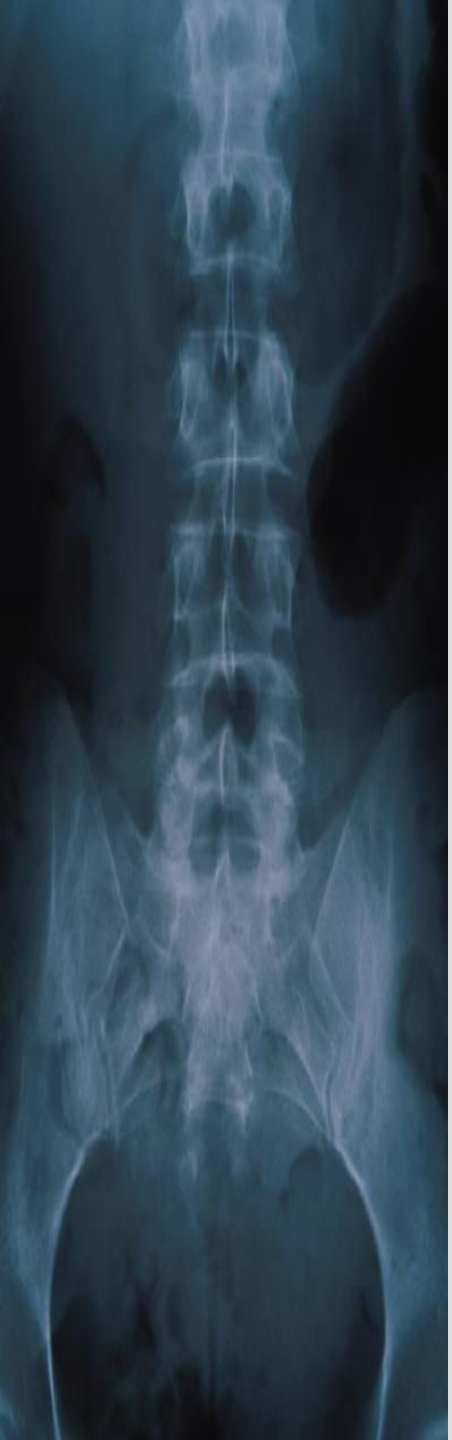


An expensive business

Pharmaceutical industry claims that the mean cost of bring a new drug to market is US $ 800m.

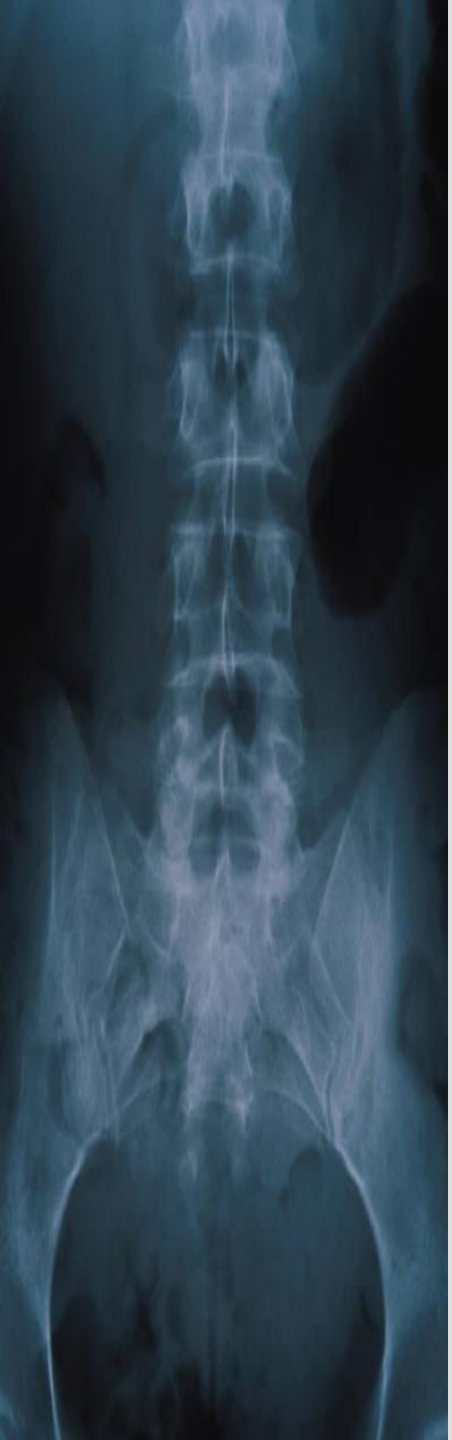
Gotzsche[1] suggests a more reasonable figure is US $ 100m.

[1] *Deadly medicines and organised crime: how big pharma has corrupted healthcare*. 2013. Radcliffe.



Fraud and research misconduct

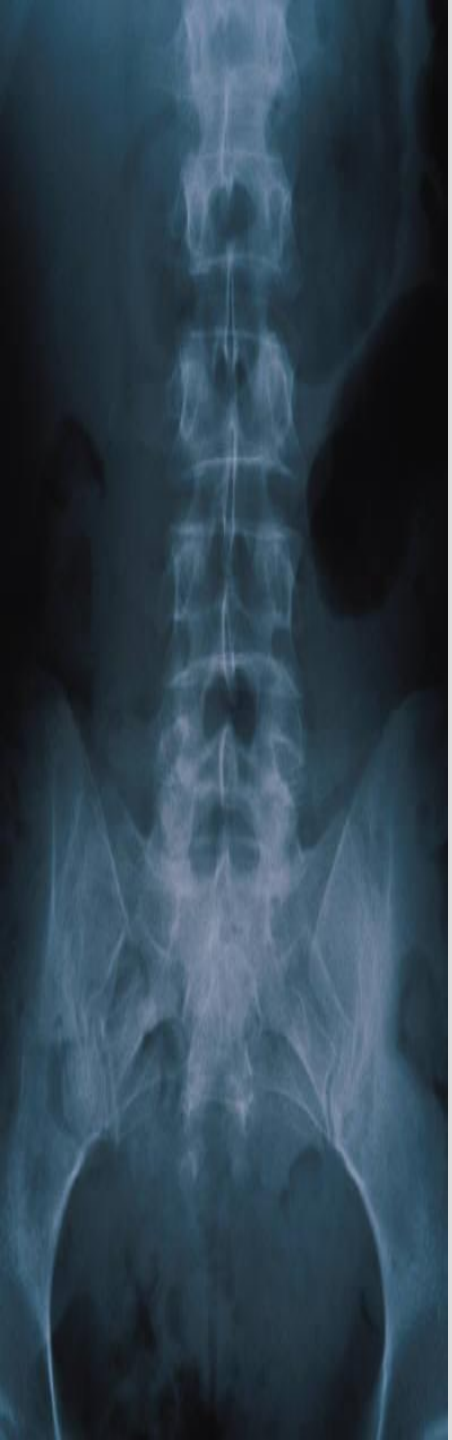
- Fabrication (Yoshitaka Fujii, 172 studies of granisetron for prevention of postoperative nausea)
- Plagiarism
- Tidying up results
- Manipulation of results (aversion therapy)



Fraud and research misconduct

- Scale of the problem [1]: 2% of scientists admitted fabrication, falsification or modification, but 14% knew of colleagues who'd done this
- 33% admitted other questionable practices, and 70% said they knew colleagues who' d performed these

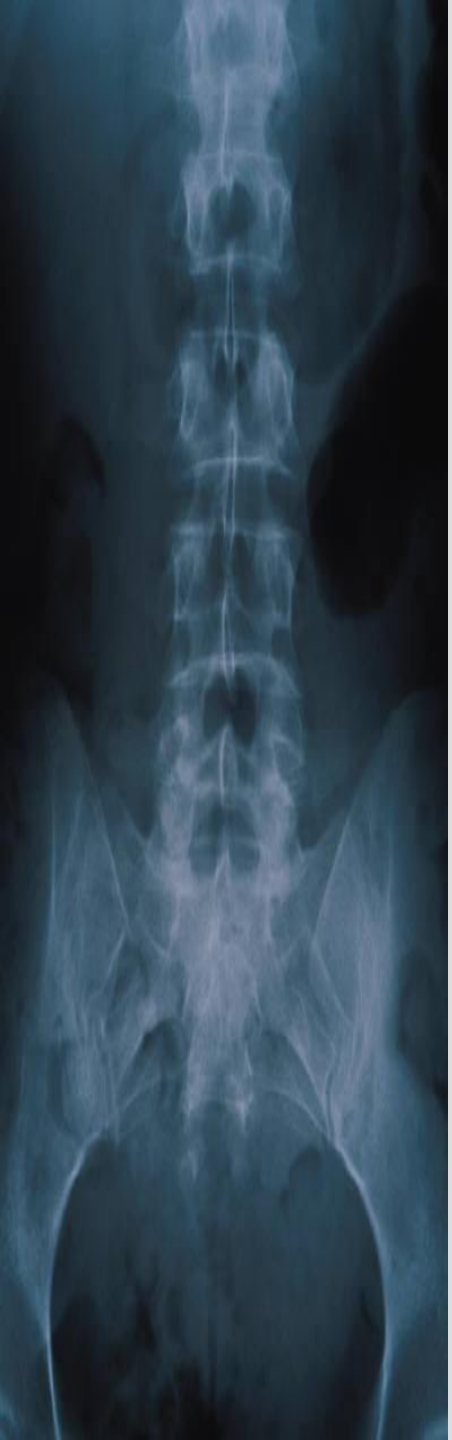
[1] Fanelli D. How many scientists fabricate and falsify research? A systematic review and meta-analysis of survey data. *PLoS One*. 2009; 4(5): e5738



Authorship issues

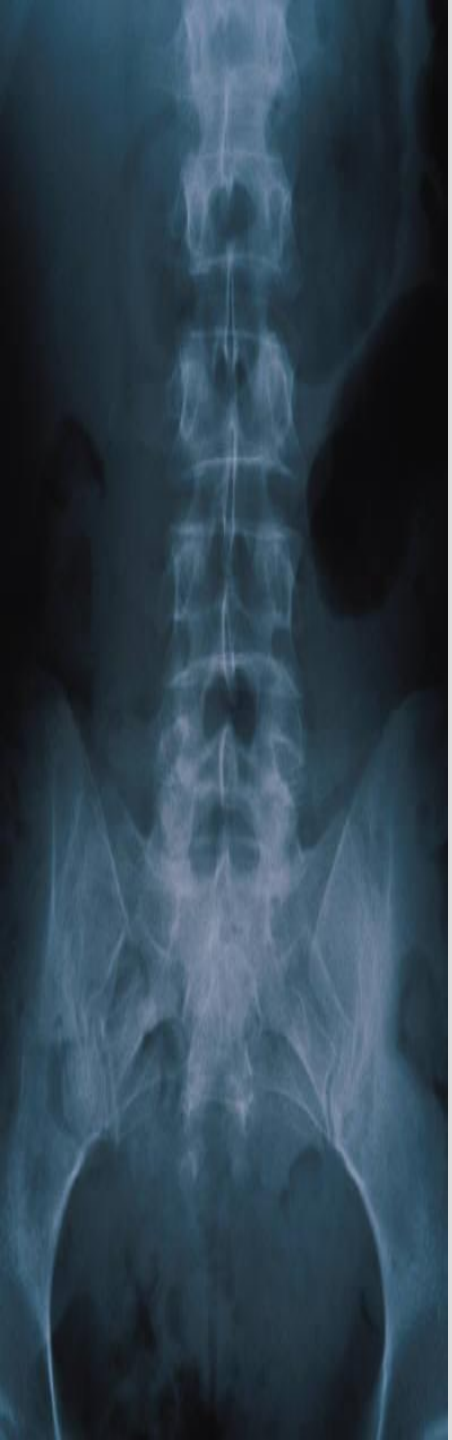
- Honorary authorship
- Fictitious authorship (Matzinger, P. and Mirkwood, G.)
- Ghost authorship. Currently estimated in 505 of clinical trials.

Healy et al. The interface between authorship, industry and science in the domain of therapeutics. Br J Psychiatry. 2003; 182: 22-7



Recruitment

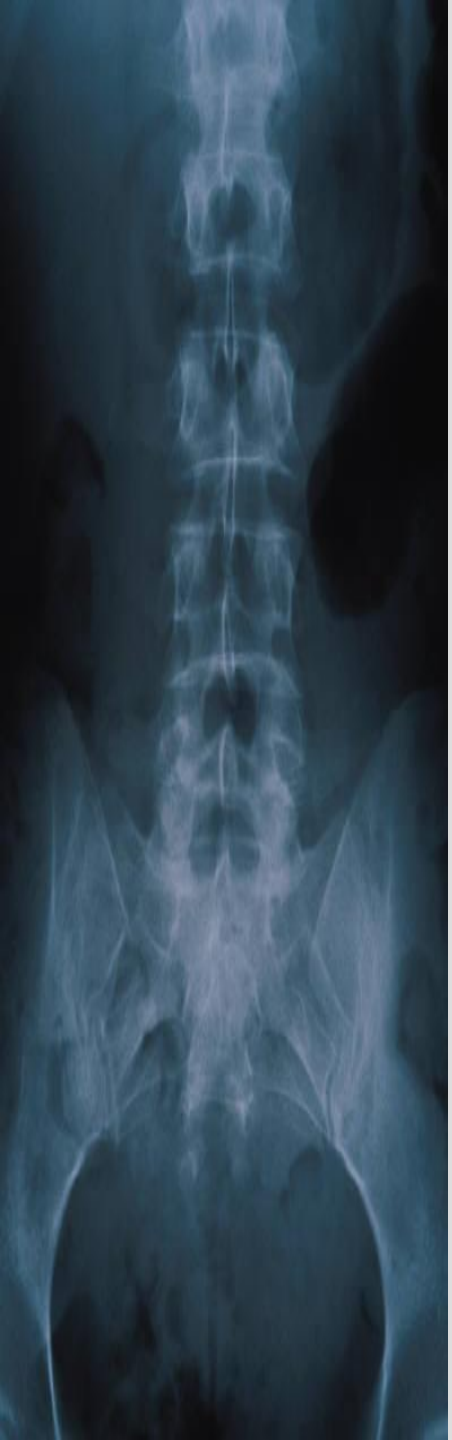
- Freakishly perfect “ideal” patients
- High number of exclusion categories
- Danone



Hickson M et al. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial *BMJ* 2007; 335: 80

Exclusion categories:

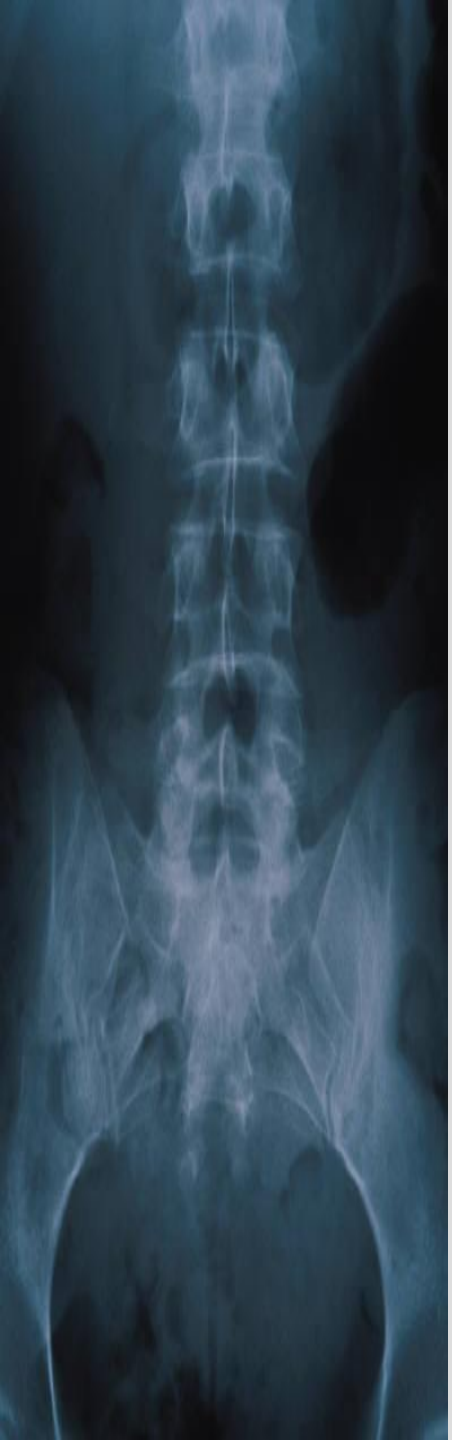
- diarrhoea on admission or within the preceding week
- reported recurrent diarrhoea
- bowel pathology that could result in diarrhoea
- intake of high risk antibiotics (clindamycin, cephalosporins, aminopenicillins)
- more than two courses of other antibiotics in the past four weeks
- severe life threatening illness
- immunosuppression
- bowel surgery
- artificial heart valve
- history of rheumatic heart disease
- history of infective endocarditis
- regular probiotic treatment before admission
- lactose intolerance or intolerance to dairy products



Subsequent letter to the BMJ observed:

"It took over two years to recruit 135 patients out of 1760 screened individuals, and only 113 of these were followed up for evidence of diarrhoea. Put simply, how can data pertaining to less than 7% of a potential target population be extrapolated to routine use?"

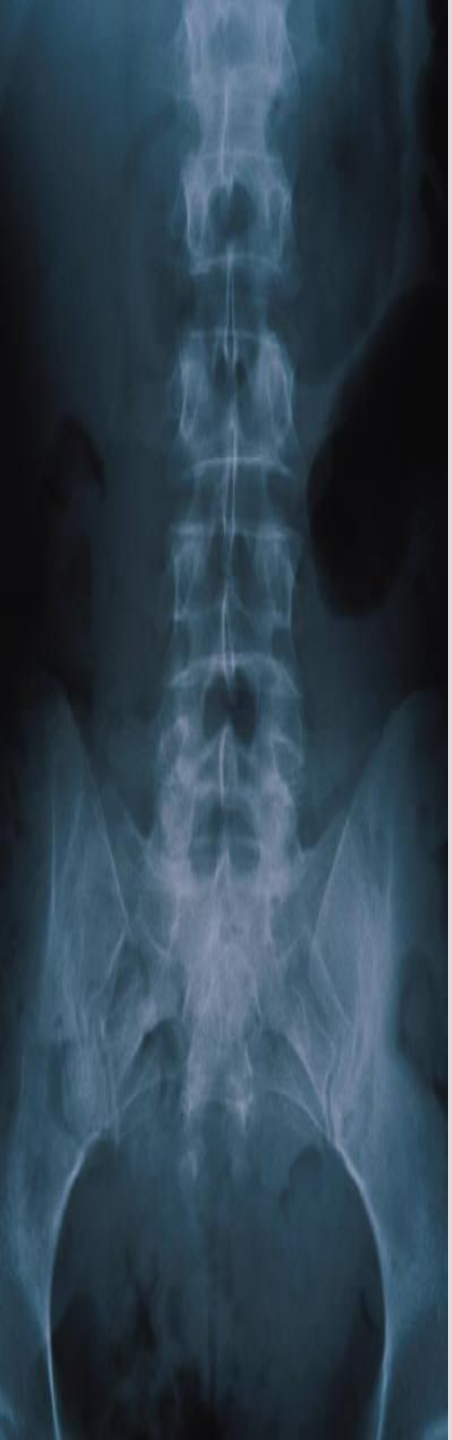
BMJ 2007; 335: 171.1



Comparative trials where the control group is misprescribed

- Paroxetine versus amitryptyline for depression. Amitryptiline makes you drowsy: best only to take it at night
- New antipsychotic drugs versus 20 mg a day haloperidol (high dosage/high risk side effects)
- Fluconazole (anti-fungal agent for cancer) compared with amphotericin B delivered orally rather than intravenously

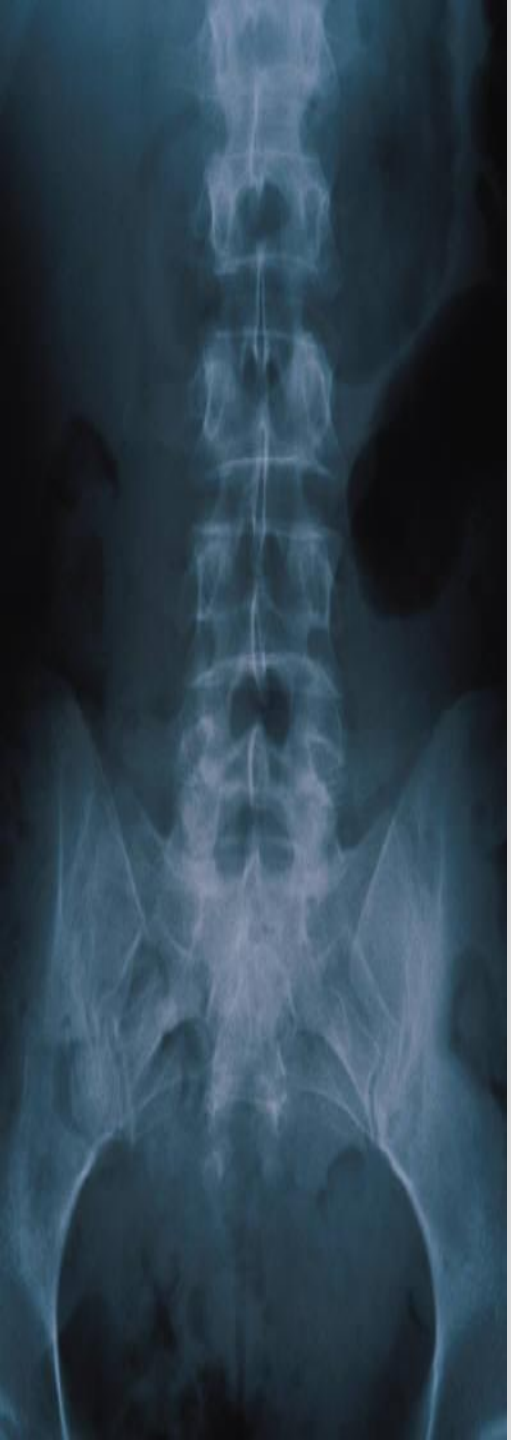
Reported in Safer DJ. Design and reporting modifications in industry-sponsored comparative psychopharmacology trials. *Journal of nervous and mental disease*. 2002; 190(9): 583-92



Trials that are too short

- Fenphen: short term trials show immediate weight loss, but do not capture heart valve defects that appear over longer periods[1]
- Benzodiazapines alleviate anxiety in the short term but long term use reduces benefits and leads to addiction
- But, long-term trials not always best: Roche upset when nine week use of Herceptin appeared as beneficial as twelve month long-term use

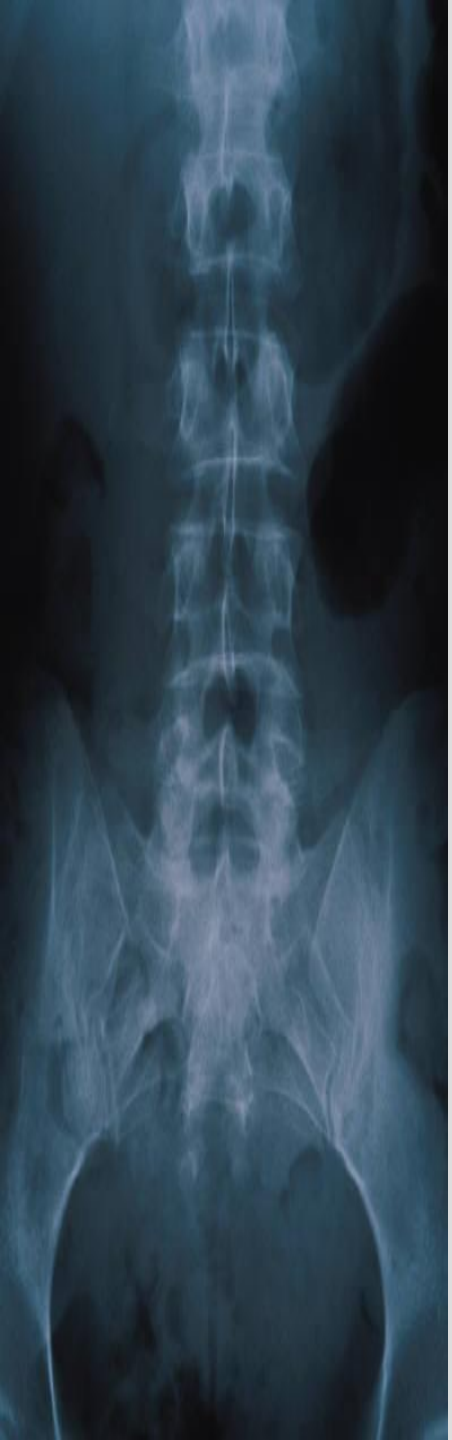
[1] Califf RM et al. Principles from clinical trials relevant to clinical practice: part 1. *Circulation*. 2002; 106(8): 1015-21



Trials that stop early

"If you stop a trial early, or late, because you were peeking at the results as it went along, you increase the chances of getting a favourable result. This is because you were exploiting the random variation that exist in the data. It is a sophisticated version of the way someone can increase their chances of winning in a coin toss by using this strategy: 'Damn! OK, best of three…Damn! Best of five! OK, best of seven"

Goldacre B. *Bad pharma: how drug companies mislead doctors and harm patients* 2012 London. Fourth Estate



CLASS trial: celecoxib versus NSAIDs for pain relief without GI complications

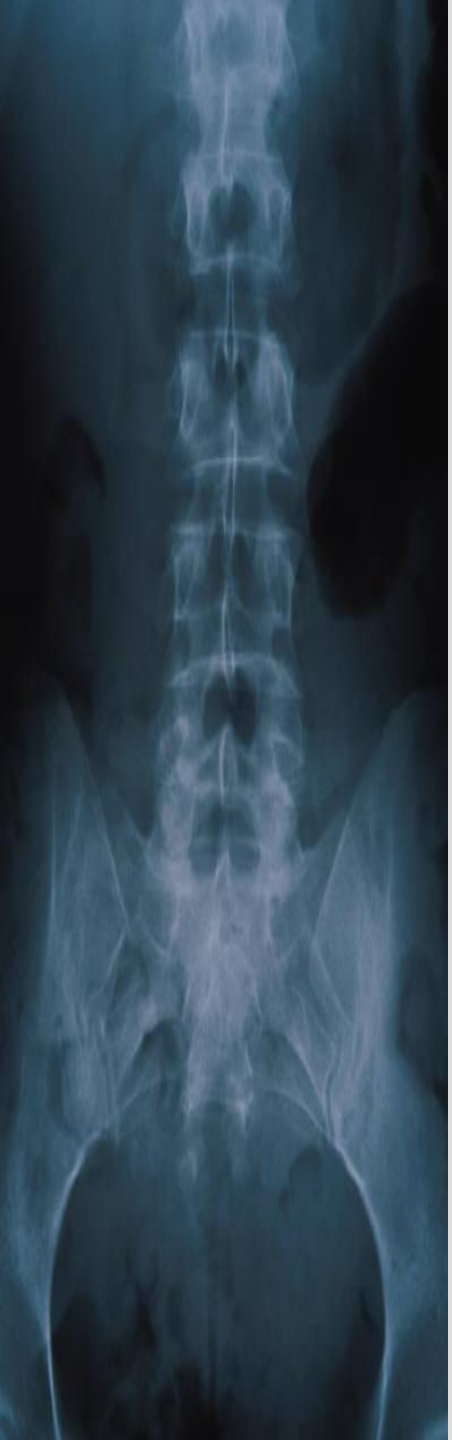
A six month trial showing that patients experienced fewer adverse GI side-effects, but…

Original intention: follow up for one year

Twelve month outcomes showed no benefit for celecoxib…

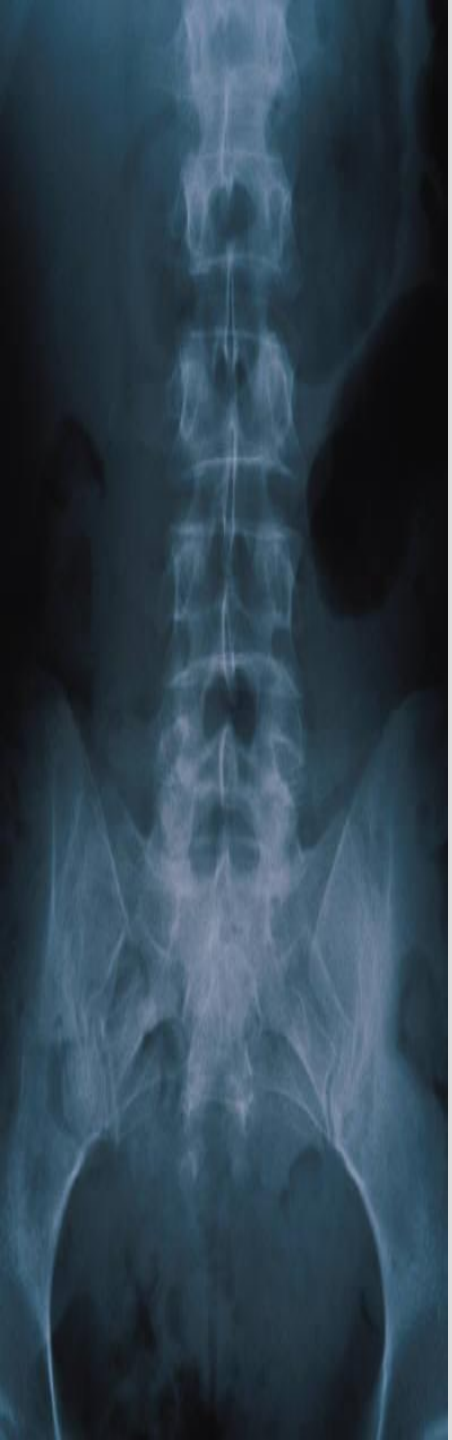
Truncated trials usually report benefits that are exaggerated by an average of 25%[1]

[1] Bassler D et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA*. 2010; 303(12): 1180-7



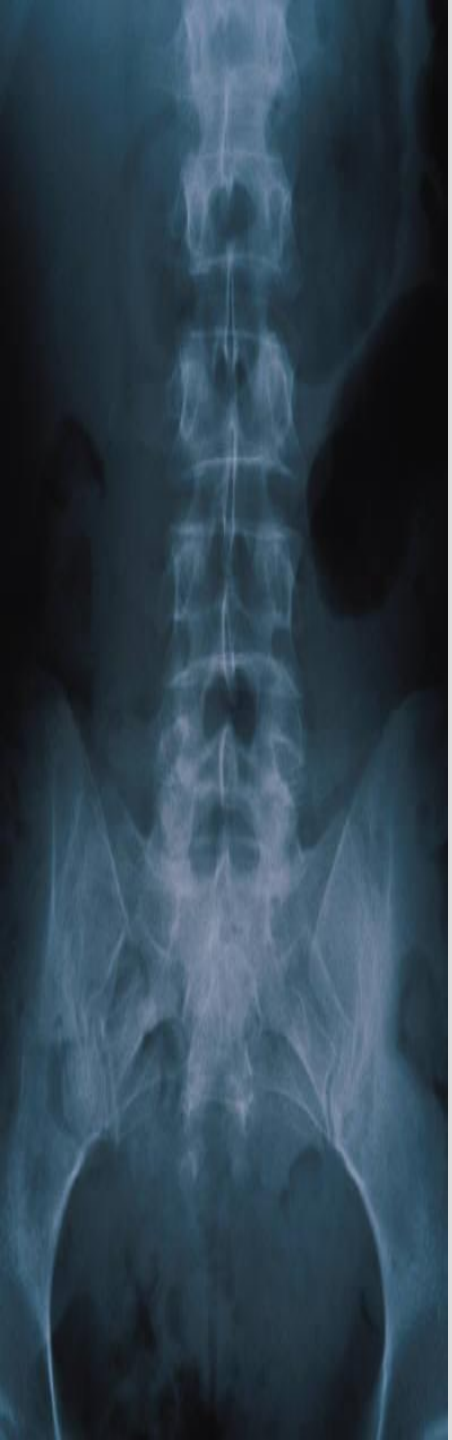
How about obvious massive differences?

Bisoprolol versus placebo during blood vessel surgery. Trial stopped early when 2 deaths in treatment group compared with 18 in placebo group. Result!



Later long term trials found this was just a fluke result which had encountered a clump of deaths. Bisoprolol confers no benefit

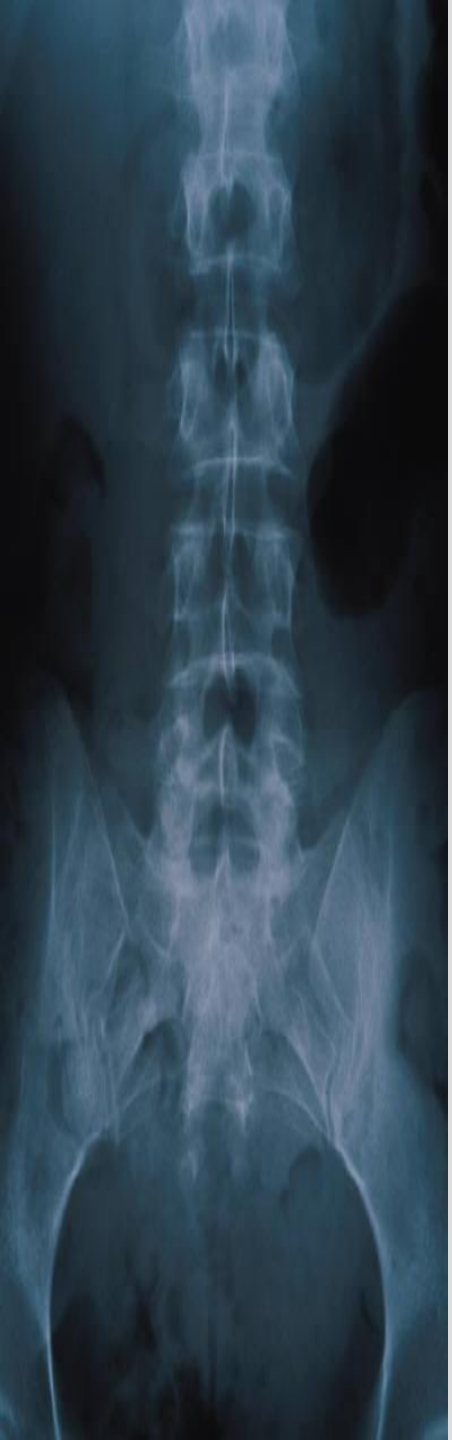
Mueller PS et al. Ethical issues in stopping randomized trials early because of apparent benefit. *Annals of internal medicine*. 2007; 146(12): 878-81



Cochrane's experience

Home versus hospital treatment for varicose veins

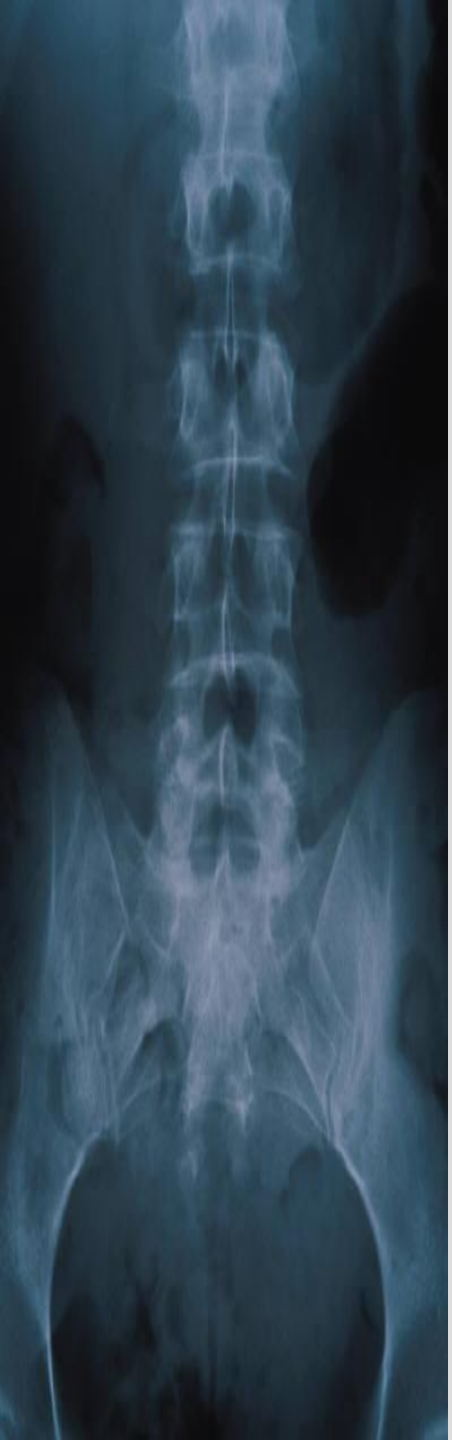
Cochrane, A. (1989) One man's medicine



Trials that stop late

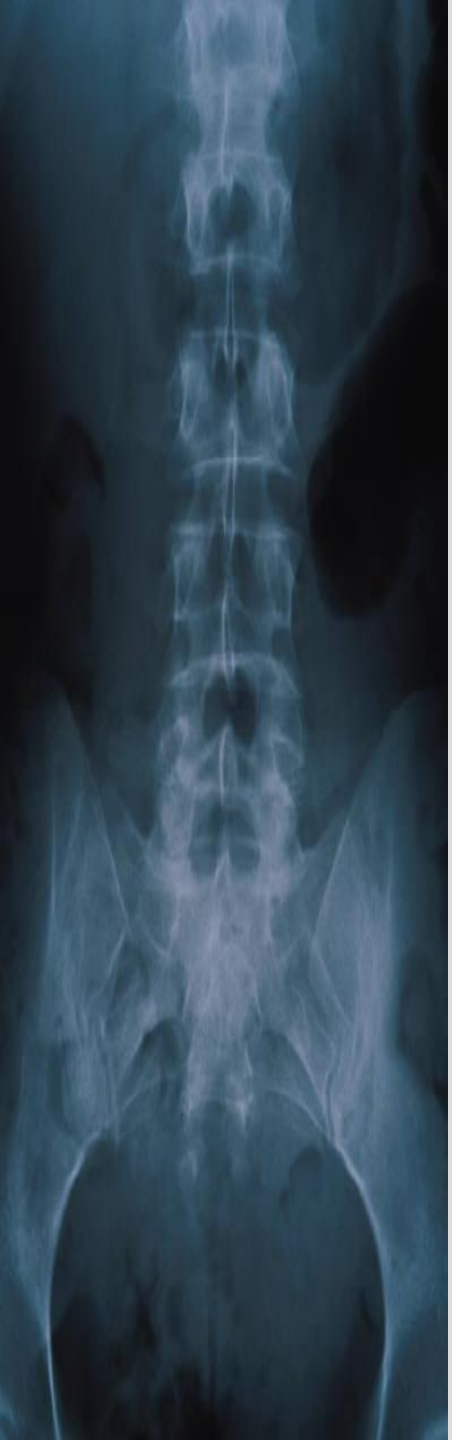
- Salmeterol versus placebo for asthma trial for FDA
- 28 week “active” trial showed relative risk of death as 1.31 (0.83-2.09)
- 28 week “active” plus six month “passive” follow up showed relative risk of death as 1.04 (0.70-1.55)

Lurie P et al. Misleading data analyses in salmeterol (SMART) study. *The Lancet*. 2005; 366(9493): 1261-2



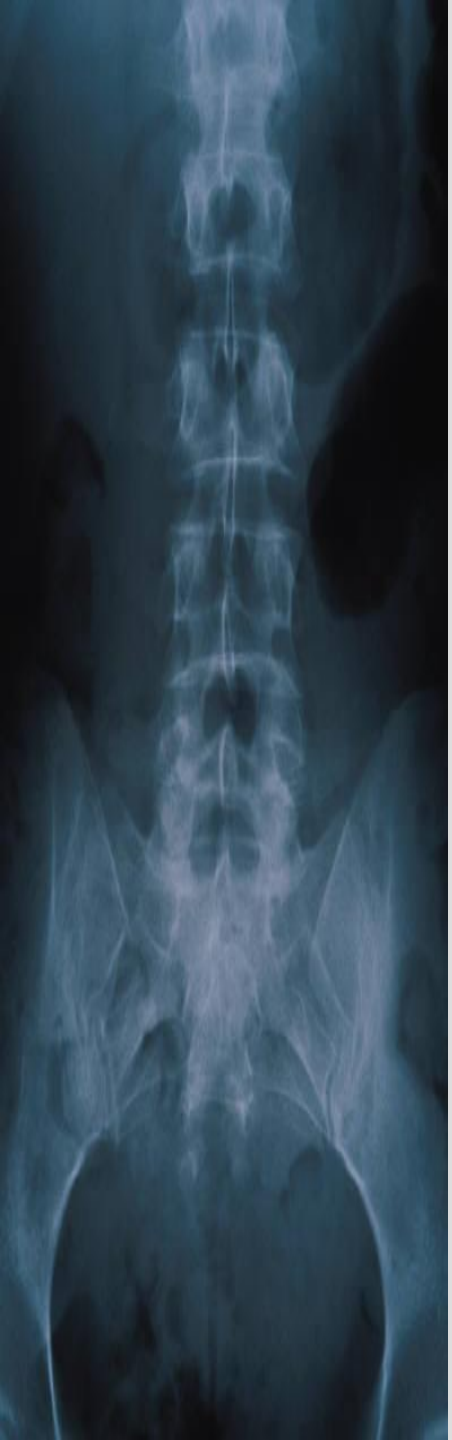
Trials that are too small (1)

Run lots of small scale trials and only publish the few that show your drug works well. The FDA tries to prevent this by requiring that clinical trials are registered on its *ClinicalTrials.gov* website but compliance is poor:



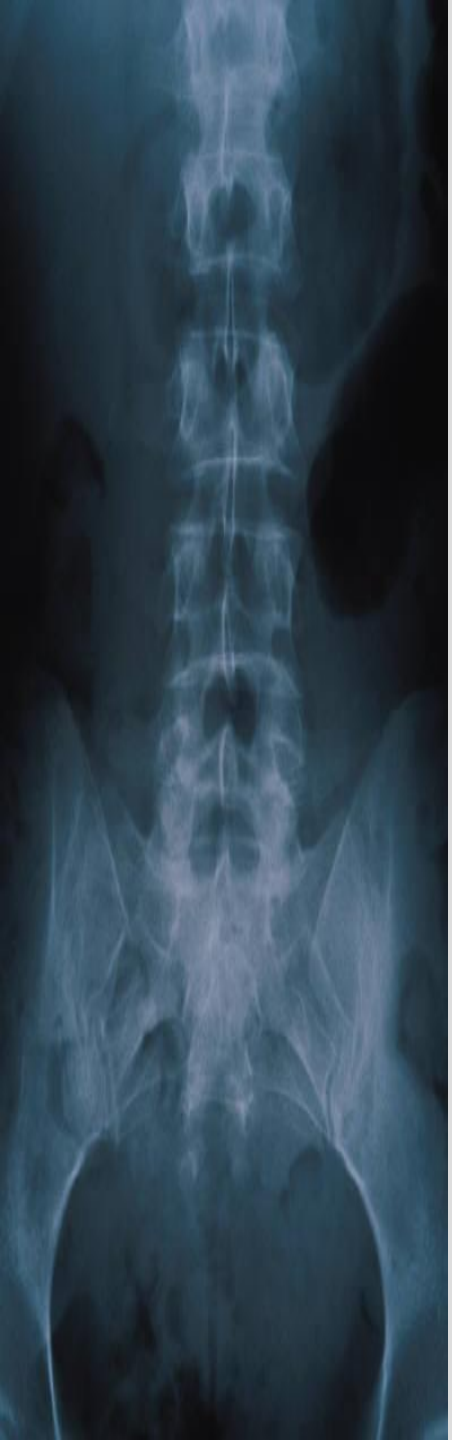
ClinicalTrials.gov

- 40% of protocols registered only after recruitment has begun
- 40% of protocols fail to state the primary outcome measure
- 75% of trials fail to publish the results on thus (the? This?) website
- 25% of trials fail to publish their results anywhere
- Number of companies fined for non-compliance: 0



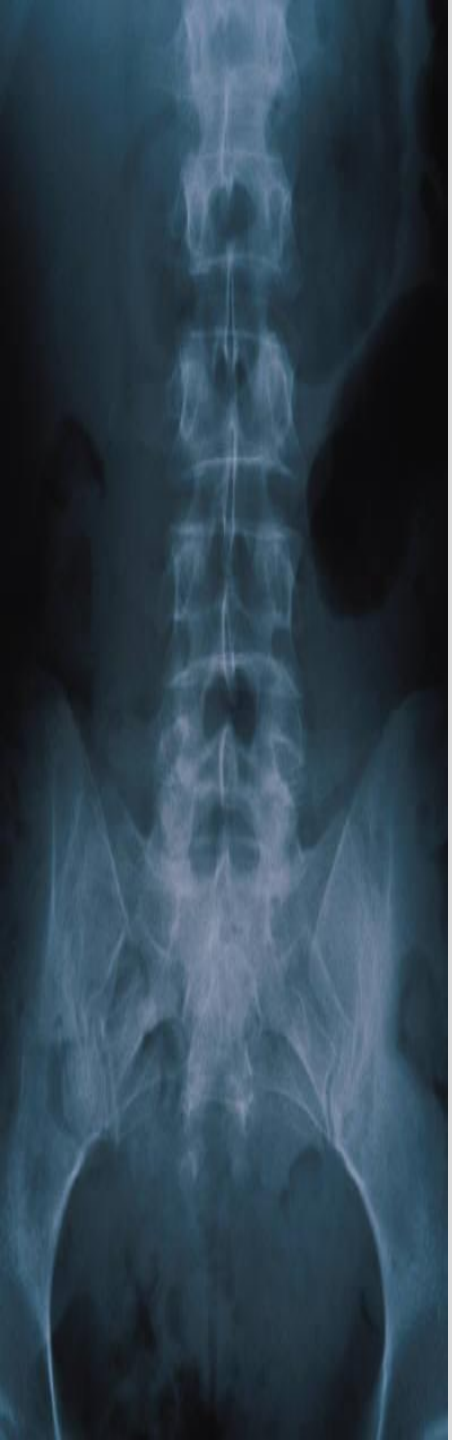
Trials that are too small (2)

Power your studies so that they have enough participants to detect small, statistically significant but clinically insignificant improvements, but not enough to detect small but clinically vital increases in serious adverse effects.



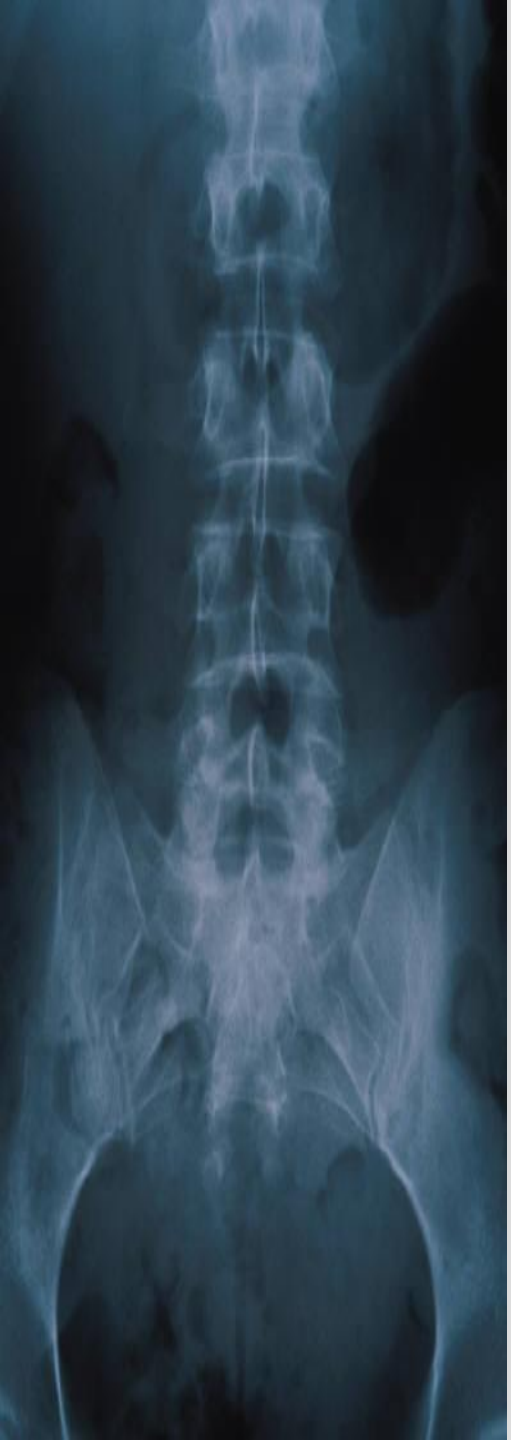
Trials that measure surrogate outcomes

- Statin trials versus placebo use stroke and death as outcomes, and show statins performing quite well
- Inter-statin trials tend to measure cholesterol levels as outcomes, rather than incidence of stroke



Transitivity and surrogate outcomes

- Niacin increases high density lipoproteins (HDLs). Higher HDL is associated with lower risk of cardiovascular events. So taking niacin …
- High oestrogen levels are associated with lower risk of heart disease. HRT raises oestrogen levels. So taking HRT…



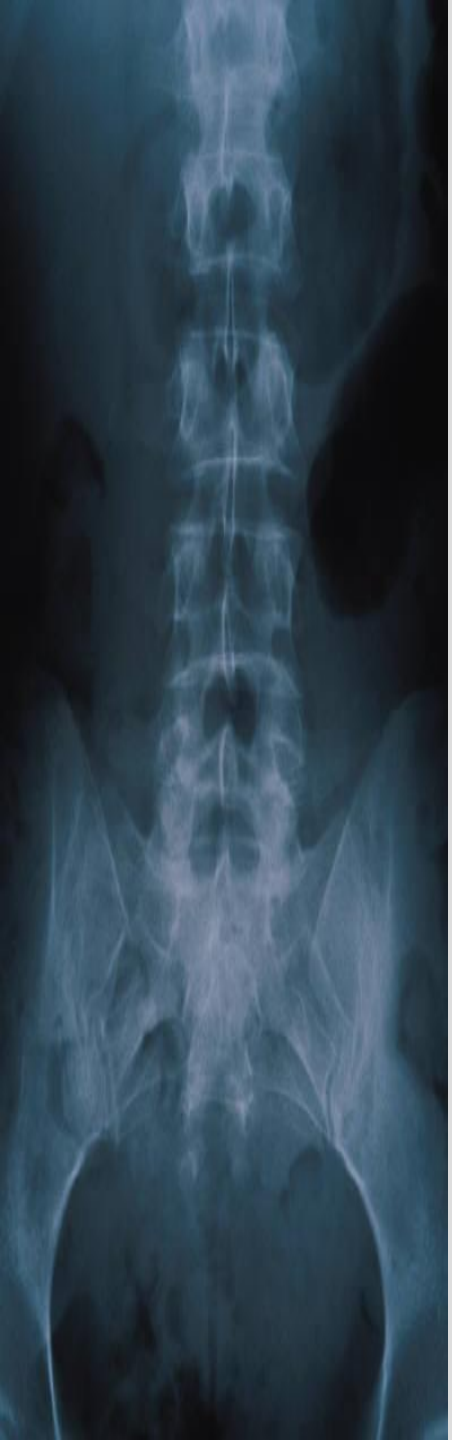
Trials that bundle outcomes together inappropriately

The United Kingdom Prospective Diabetes Study (UKPDS)

Does intensively managing the blood-sugar levels of patients with diabetes improve their real-world outcomes?

Commonly quoted as finding a 12% reduction in adverse outcomes…

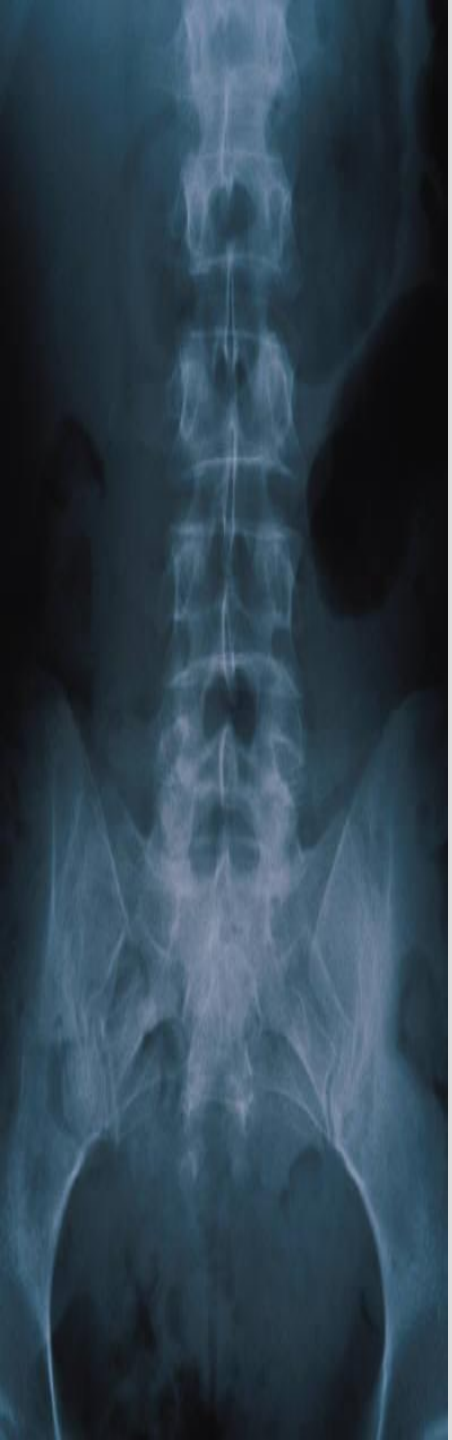
Shaughnessy AF et al. What happened to the valid POEMS? A survey of review articles on the treatment of type 2 diabetes. *BMJ*. 2003; 327(7409): 266.



Composite outcomes:

- Sudden death
- Death from high or low blood sugar
- Fatal heat (heart?) attack
- Non-fatal heart attack
- Angina
- Heart failure
- Stroke
- Renal failure
- Amputation
- Bleeding into the middle chamber of the eye
- Diabetes-related damage to the arteries in the eye requiring laser treatment
- Blindness in one eye
- Cataracts requiring extraction

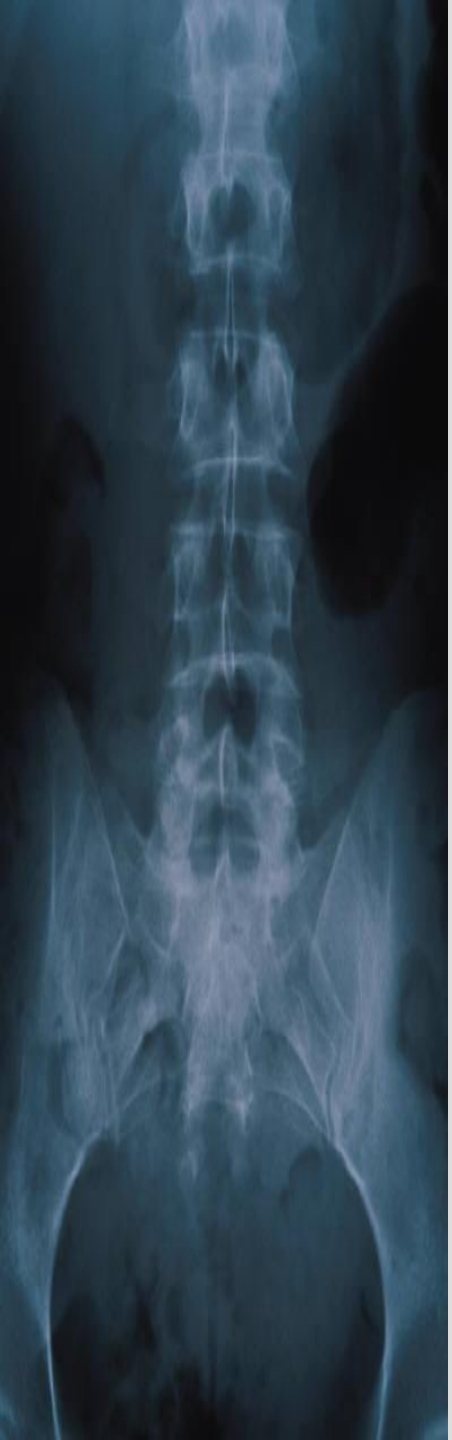
Which one of these is not really a 'patient oriented evidence that matters' (POEM)?



Disguising adverse effects: some dirty tricks and an honest failure

- Bundle SAEs together to hide severity. Emotional lability?
- Include in the analysis only the first adverse effect a patient suffers (e.g. cramp), excluding later more serious adverse effects (e.g. MI)
- Withdraw participants with SAEs from the study and assign them to a non-compliance group
- Dismiss reports of SAEs as false alarms or anecdotal, even though 80% of these turn out to be correct [1]
- Doctors currently report less than 5% of SAEs and online systems allowing patients to self-report are cumbersome and underused.

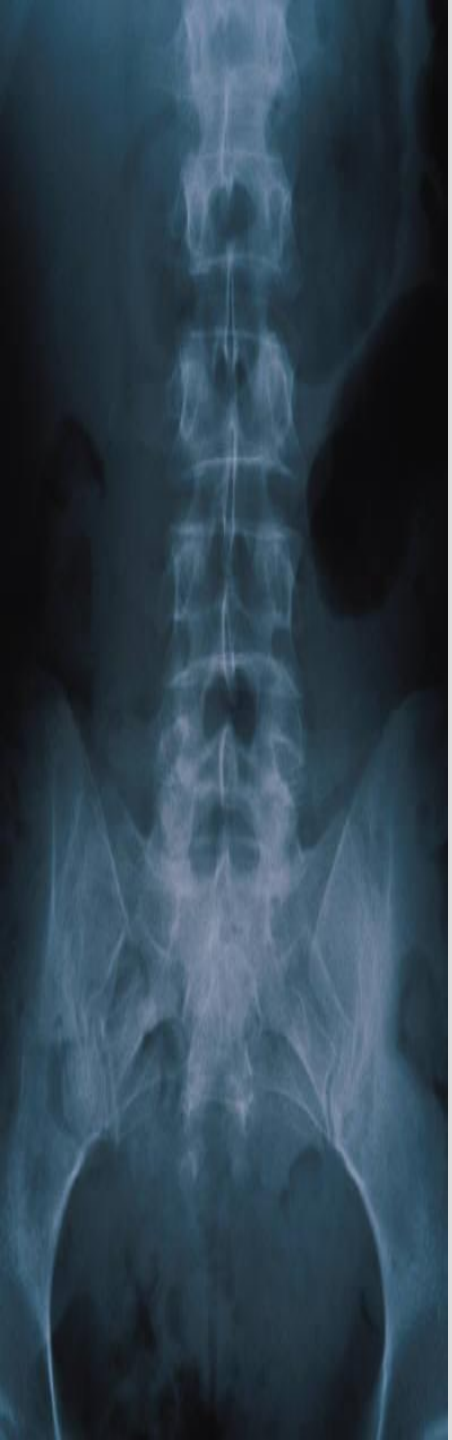
[1] Venting G. Validity of anecdotal reports of suspected adverse drug reactions: the problem of false alarms. 1982. BMJ; 284: 249-53



Trials that ignore drop-outs

- Intention to treat analysis versus
- Per protocol analysis

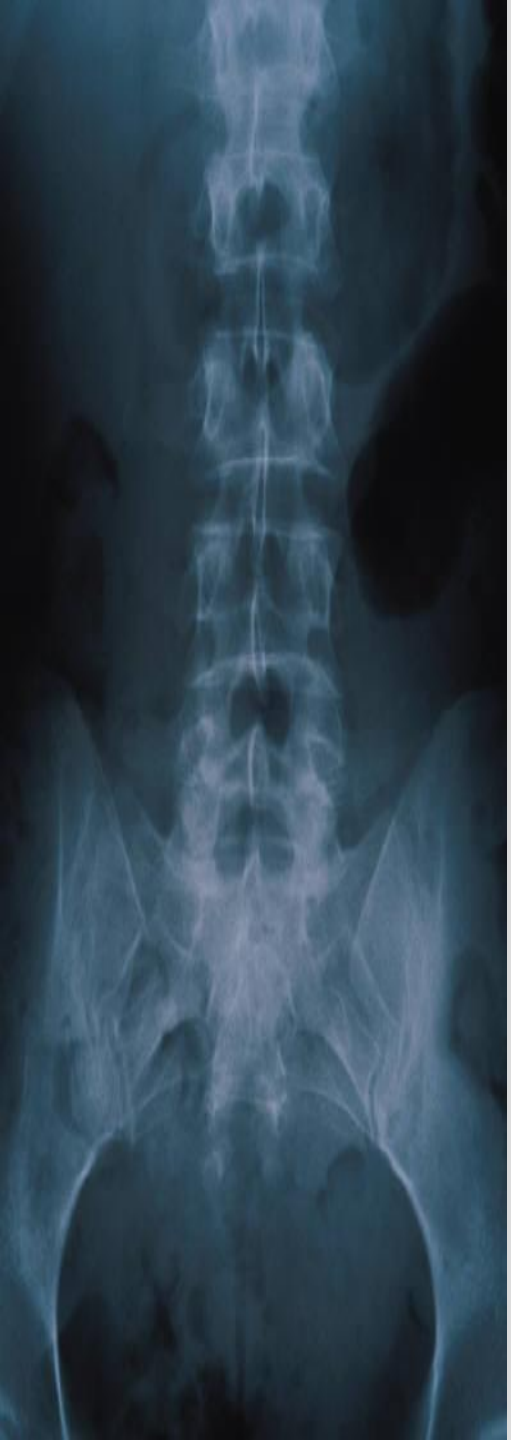
  (The difference between giving someone some tablets and forcing the same tablets down their throat whether they want them or not.)



Practices vary

- Swedish study found that submissions to regulators featured both types of analyses, whereas
- Submissions to journals as academic papers featured only per protocol analysis

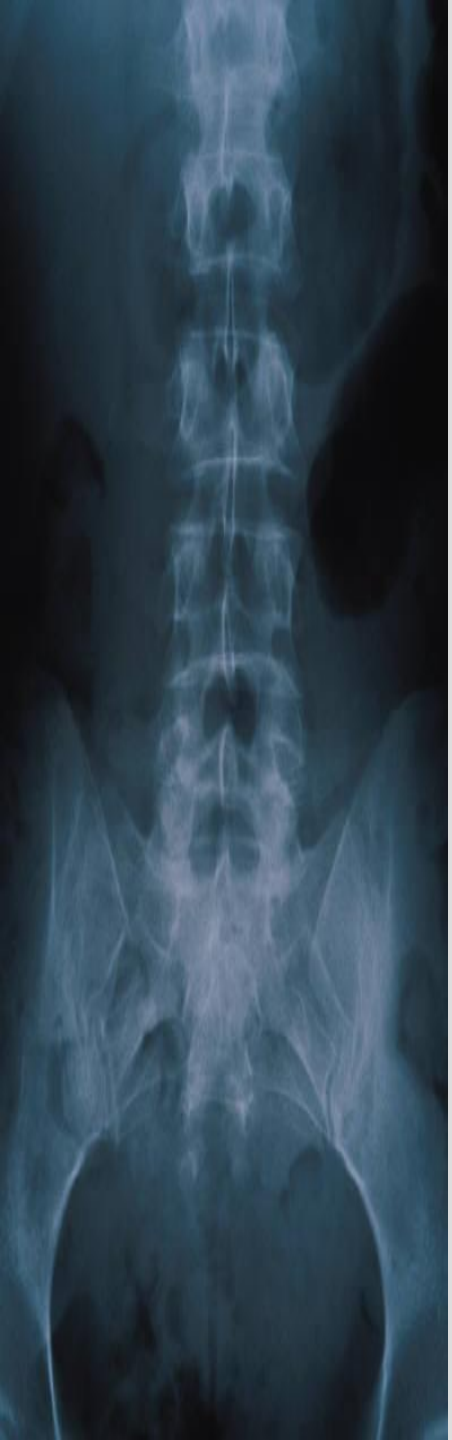
Melander H et al. Evidence b(i)ased medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ*. 2003; 326: 1171-3



Trials that change their main outcome after they've finished

Phenomenon of multiplicity means that if you measure lots of different outcomes some of them may flukily appear significant even when they aren't

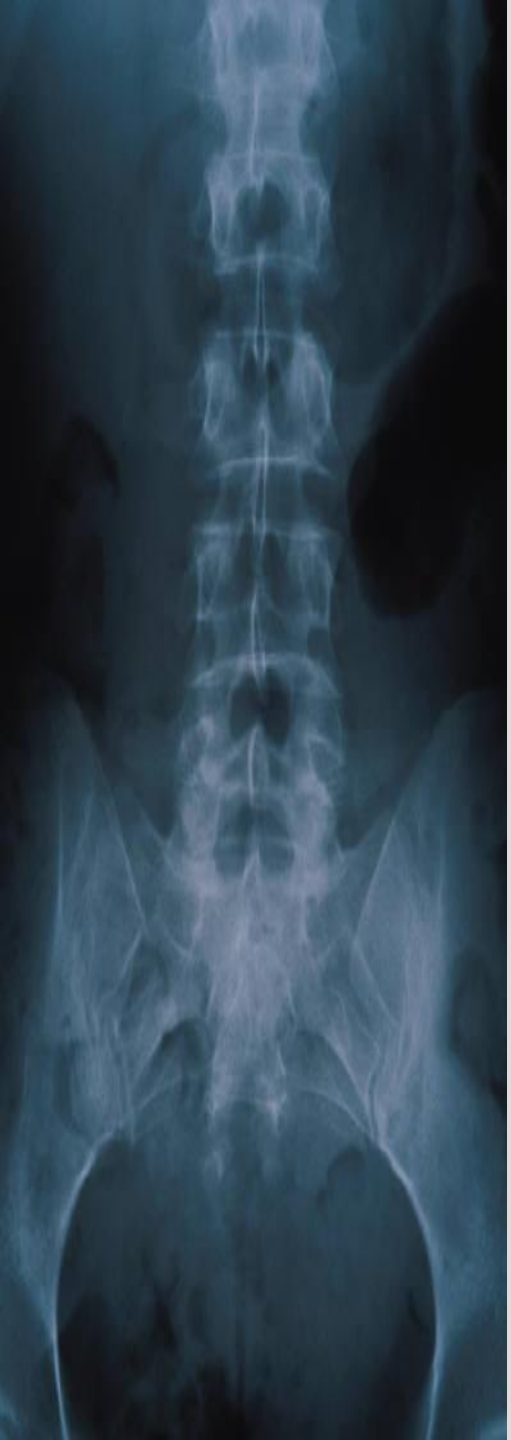
Researchers should declare a primary outcome and that is the result in which you should be interested



Vedula[1] examined protocols of gabapentin trials with the finished papers

- Of 21 primary outcomes listed in the protocols only 11 eventually appeared as primary outcomes in the published papers. Of the other 10…
- 6 weren't reported in any form, and…
- 4 were reported as if they were secondary outcomes

[1] Vedula SS et al. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *New England journal of medicine*. 2009; 361(20): 1963-71



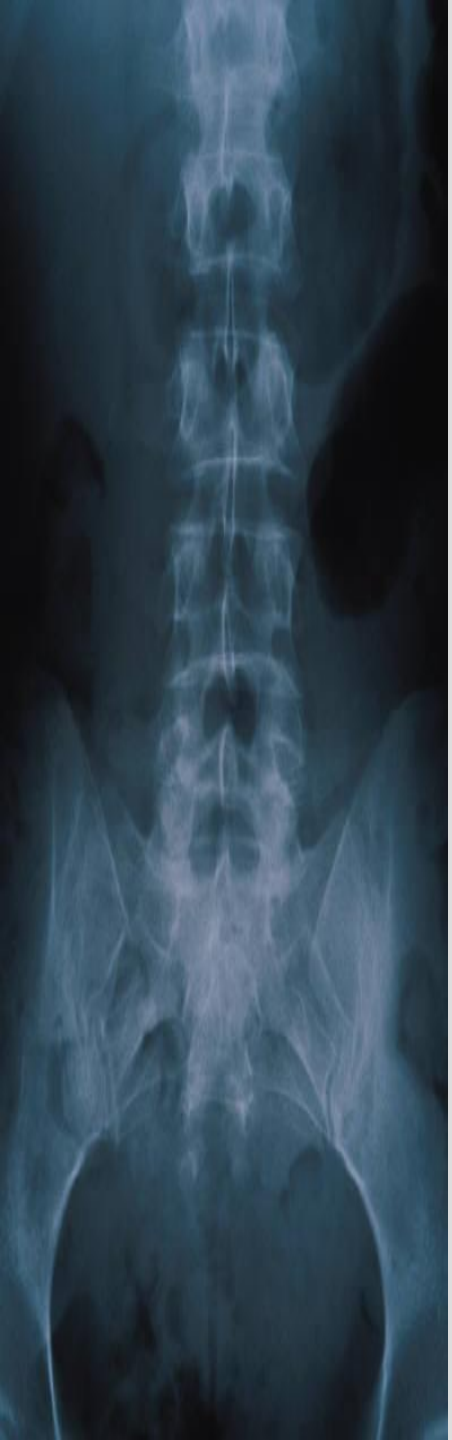
Trials with dodgy subgroup analysis

Recruited 1073 patients with coronary artery disease

Randomly allocated to receive either Treatment 1 or Treatment 2. Both were inert.

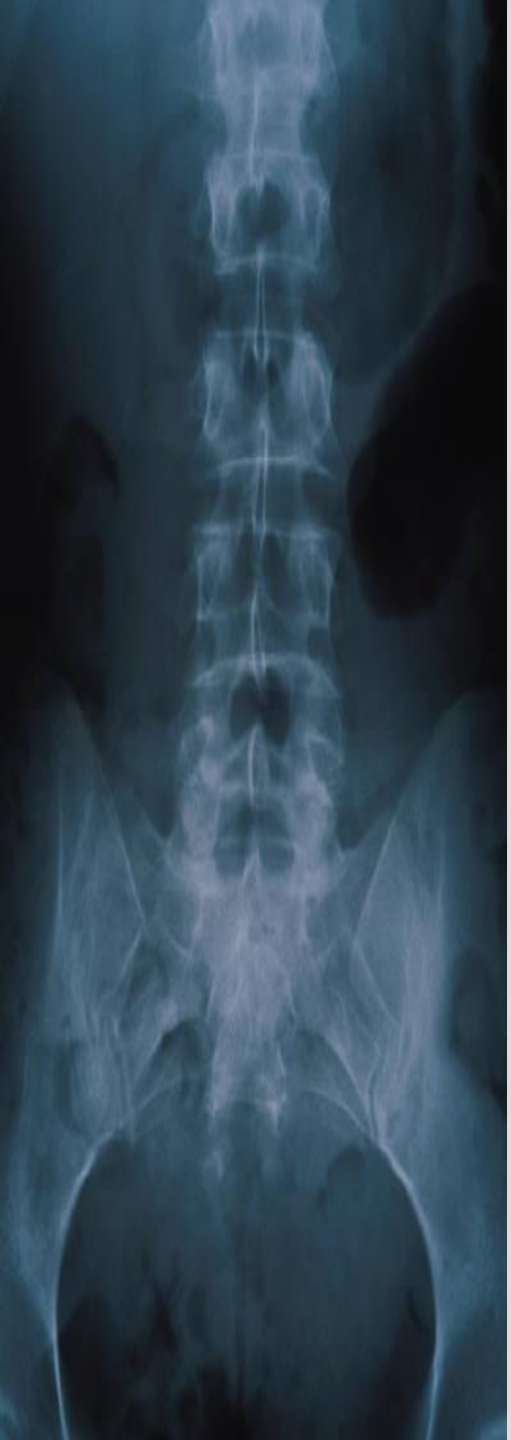
Even so subgroup analysis of a subgroup of 397 patients with three vessel disease and abnormal left ventricular contraction showed survival of Treatment 1 patients to be significantly better than Treatment 2 patients

Lee KL et al. Clinical judgement and statistics. Lessons from a simulated randomized trial in coronary artery disease. *Circulation*. 1980; 61(3): 508-15



Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group.
***Lancet* 1988. 332 (8607): 349-60**

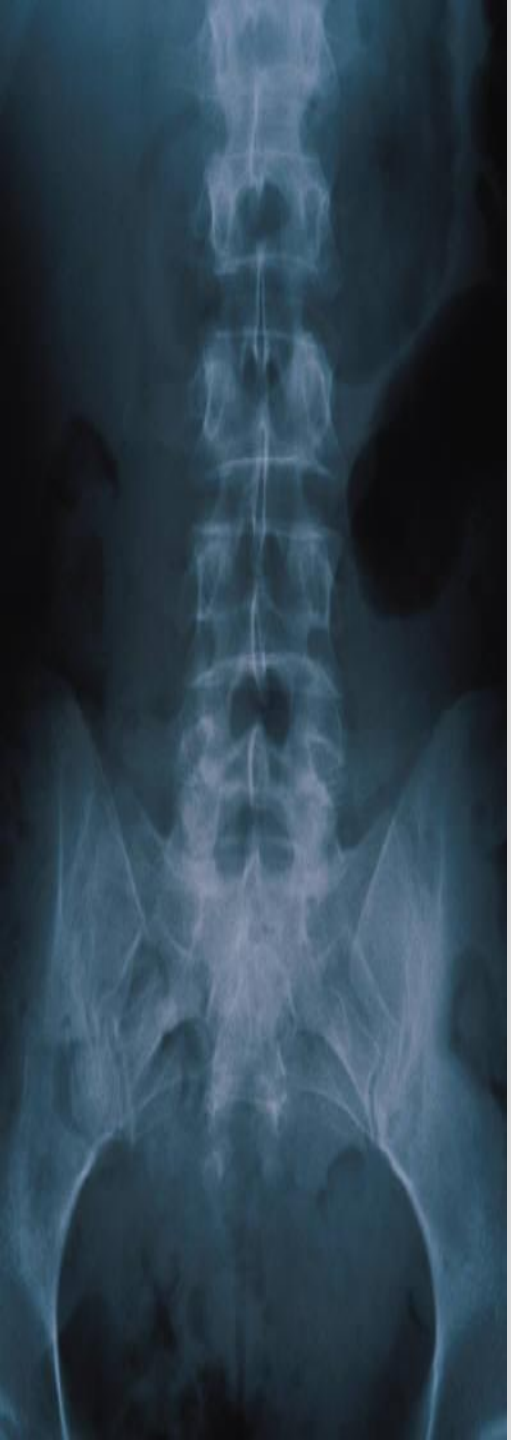
"subdivision of the patients in ISIS-2 with respect to their astrological birth sign appears to indicate that for persons born under Gemini or Libra, there was a slightly adverse effect of aspirin on mortality (9% increase, SD 13; NS), while for patients born under all other astrological signs, there was a striking beneficial effect (28% reduction, SD 5; 2p <0.00001.)"



Seeding trials: vanity authorship with ulterior motives

Vioxx ADVANTAGE trial. Recruited >5000 patients, involving 600 doctors! Idea not to discover whether Vioxx worked, but to get doctors prescribing it and discussing it with their colleagues.

Hill KP et al. The ADVANTAGE seeding trial: a review of internal documents. *Annals of internal medicine*. 2008; 149(4): 252-8

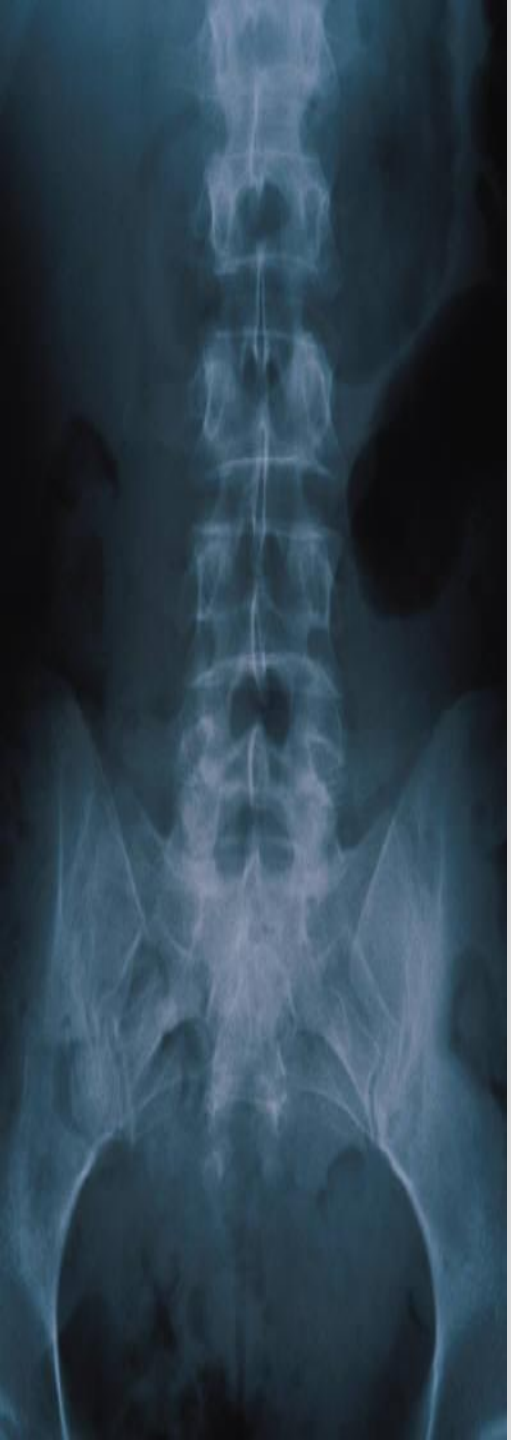


Another seeding trial: STEPS

Involved giving neurontin to epilepsy patients in community neurology clinics

Note: out of 2579 patients there were 73 adverse events, 997 patients reported side effects, and 11 patients died

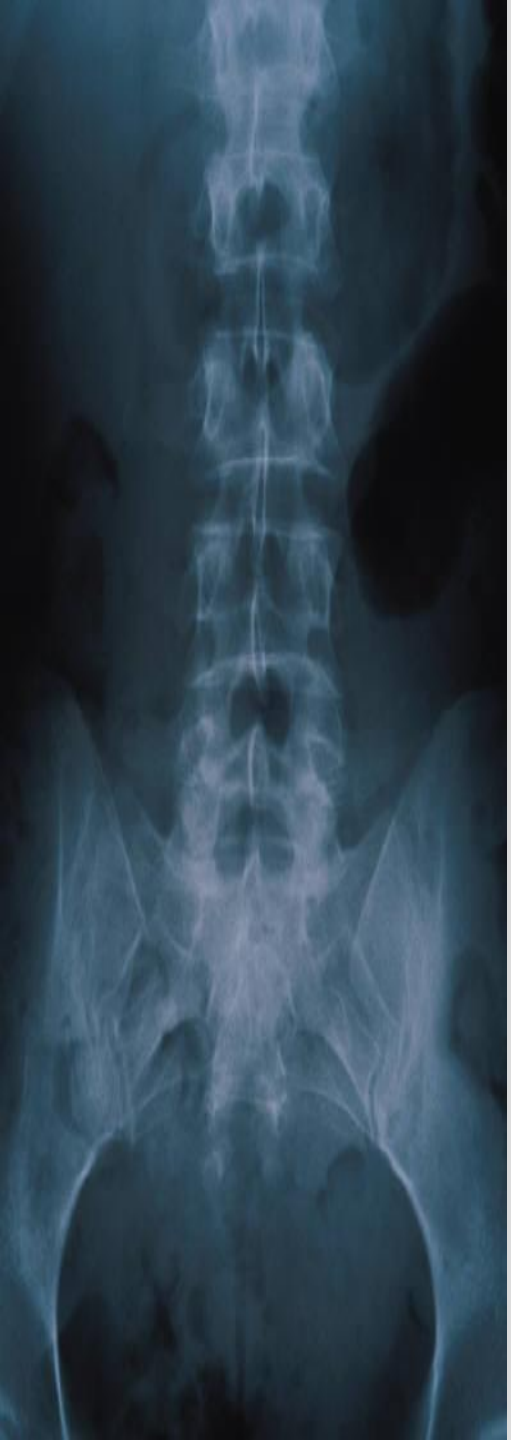
Krumholz SD et al. Study of neurontin: titrate to effect, profile of safety (STEPS) trial: a narrative account of a gabapentin seeding trial. *Archives of internal medicine*. 2011; 171(12): 1100-7.



Present results in the most flattering light

Use Relative Risk rather than Absolute Risk

Reducing risk of MI from 4% to 2% improves Absolute Risk by 2%, but Relative Risk by 50%!



When all else fails…

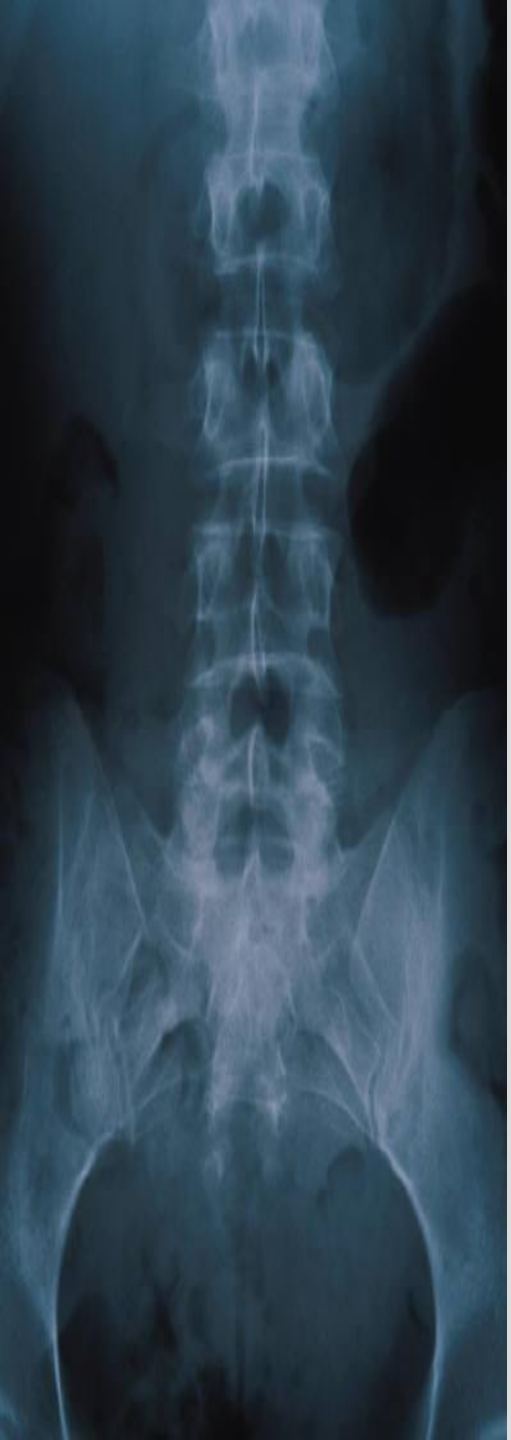
misrepresent the findings

Review[1] examined papers reporting trials on prostaglandin eyedrops as a treatment for glaucoma

Found 39 trials, 29 of which were industry funded

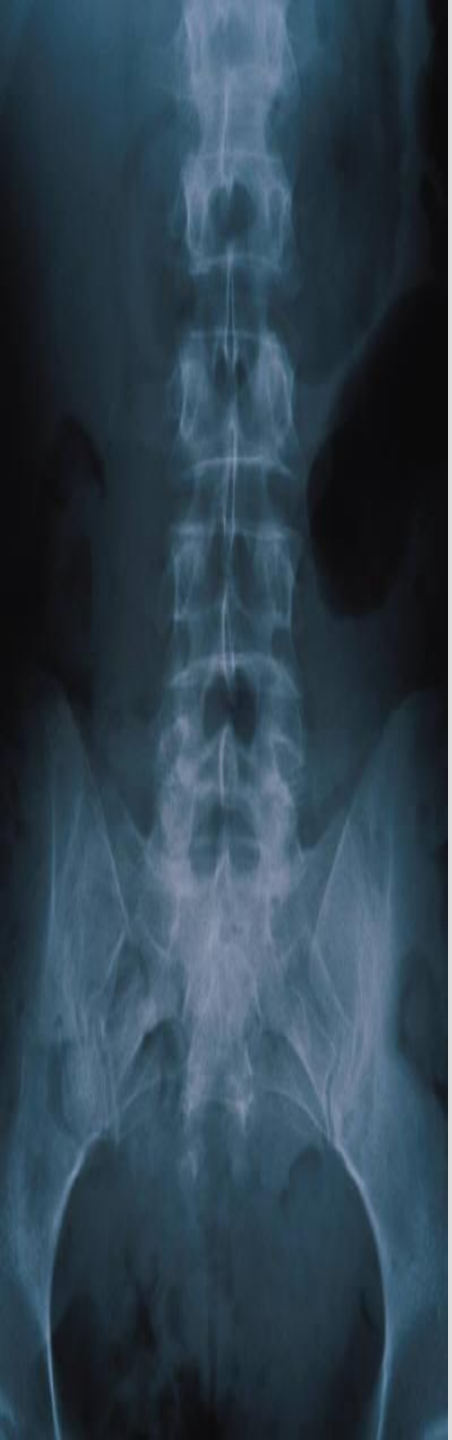
18 of the industry-funded trials presented a conclusion in the abstract that misrepresented the main outcome measure

[1] Alasbali T et al. Discrepancy between results and abstract conclusions in industry – vs nonindustry-funded studies comparing topical prostaglandins. *American journal of ophthalmology*. 2009; 147(1): 33-8. e2

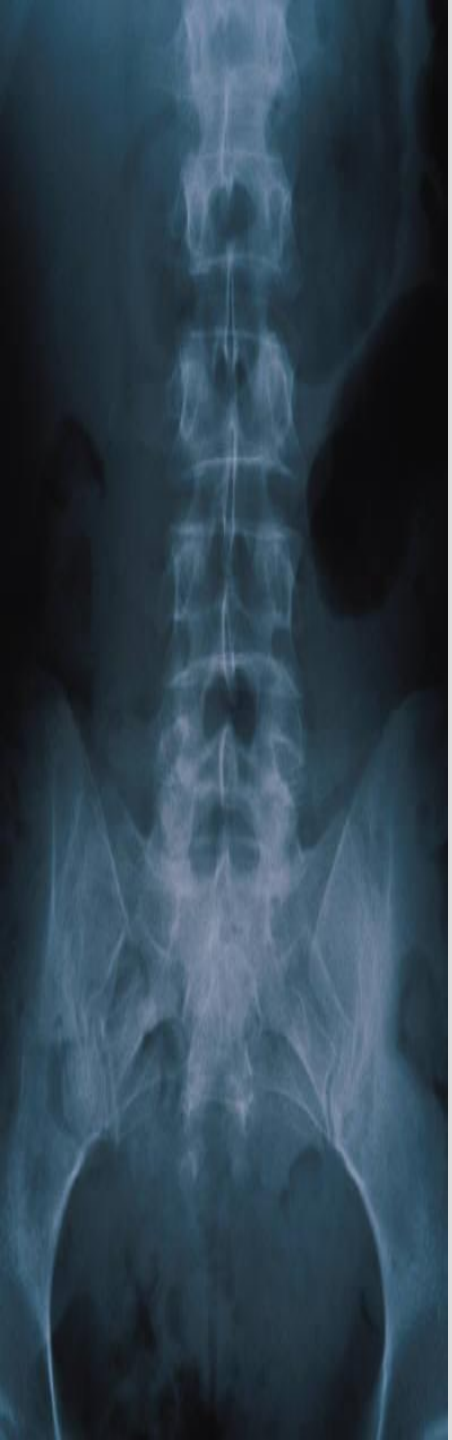


Fugh-Berman A, Ahari S Following the script: How drug reps make friends and influence doctors *PLOS Med* 2007; 4(4): e150

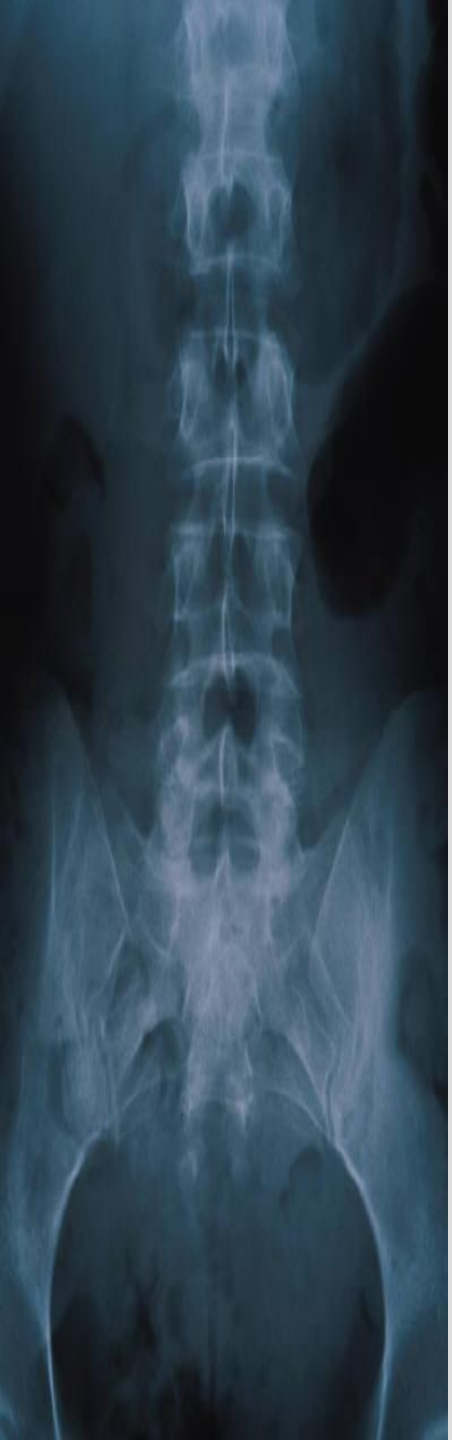
"It's my job to figure out what a physician's price is. For some it's dinner at the finest restaurants, for others it's enough convincing data to let them prescribe confidently and for others it's my attention and friendship...but at the most basic level, everything is for sale and everything is an exchange."



“During training, I was told, when you're out to dinner with a doctor, “The physician is eating with a friend. You are eating with a client.””



“An official job description for a pharmaceutical sales rep would read: Provide health-care professionals with product information, answer their questions on the use of products, and deliver product samples. An unofficial, and more accurate, description would have been: Change the prescribing habits of physicians.”



“While it's the doctors' job to treat patients and not to justify their actions, it's my job to constantly sway the doctors. It's a job I'm paid and trained to do. Doctors are neither trained nor paid to negotiate. Most of the time they don't even realize that's what they're doing…”

» Table 1. Tactics for Manipulating Physicians (1)

Physician Category	Technique	How It Sells Drugs	Comments
Friendly and outgoing	I frame everything as a gesture of friendship. I give them free samples not because it's my job, but because I like them so much. I provide office lunches because visiting them is such a pleasant relief from all the other docs. My drugs rarely get mentioned by me during our dinners.	Just being friends with most of my docs seemed to have some natural basic effect on their prescribing habits. When the time is ripe, I lean on my "friendship" to leverage more patients to my drugs...say, because it'll help me meet quota or it will impress my manager, or it's crucial for my career.	Outgoing, friendly physicians are every rep's favorite because cultivating friendship is a mutual aim. While this may be genuine behavior on the doctor's side, it is usually calculated on the part of the rep.
Aloof and skeptical	I visit the office with journal articles that specifically counter the doctor's perceptions of the shortcoming of my drug. Armed with the articles and having hopefully scheduled a 20 minute appointment (so the doc can't escape), I play dumb and have the doc explain to me the significance of my article.	The only thing that remains is for me to be just aggressive enough to ask the doc to try my drug in situations that wouldn't have been considered before, based on the physician's own explanation.	Humility is a common approach to physicians who pride themselves on practicing evidence-based medicine. These docs are tough to persuade but not impossible. Typically, attempts at geniality are only marginally effective.
Mercenary	The best mercenary docs are typically found further down the prescribing power scale. There are plenty of 6's, 7's, and 8's [lower prescribing doctors] who are eagerly mercenary but simply don't have the attention they desire fawned on them. I pick a handful out and make them feel special enough with an eye towards the projected demand on my limited resources in mind. Basically, the common motif to docs whom you want to "buy out" is to closely associate your resource expenditure with an expectation—e.g., "So, doc, you'll choose Drug X for the next 5 patients who are depressed and with low energy? Oh, and don't forget dinner at Nobu next month. I'd love to meet your wife."	This is the closest drug-repping comes to a commercial exchange. Delivering such closely associated messages crudely would be deemed insulting for most docs so a rep really has to feel comfortable about their mercenary nature and have a natural tone when making such suggestions.	Drug reps usually feel more camaraderie with competing reps than they do with their clients. Thus, when a doctor fails to fulfill their end of the prescriptions-for-dinners bargain, news gets around and other reps are less likely to invest resources in them.

» Table 1. Tactics for Manipulating Physicians (2)

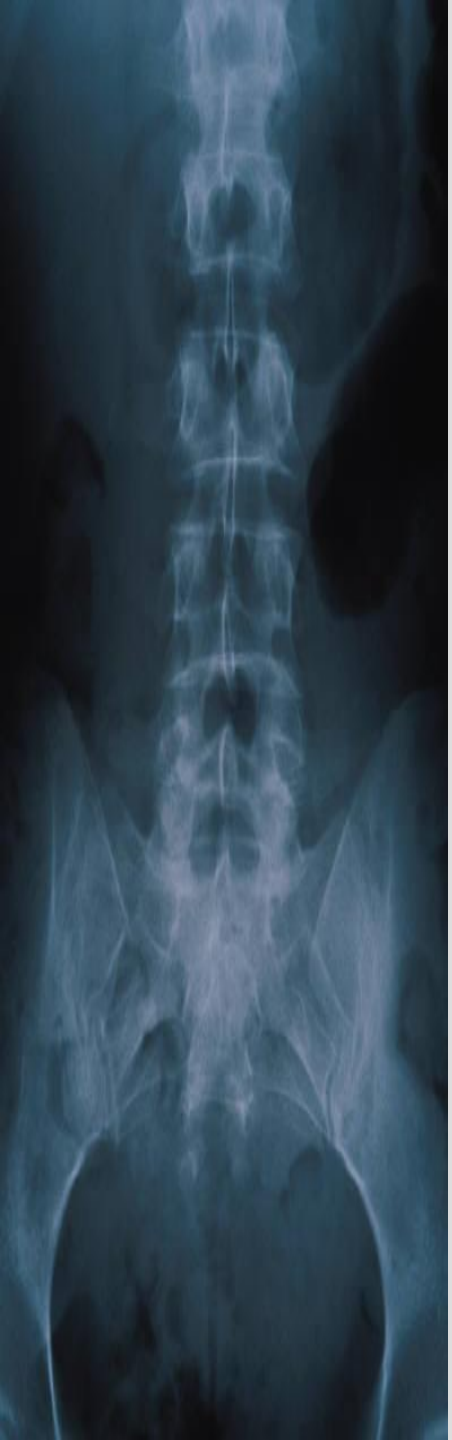
Physician Category	Technique	How It Sells Drugs	Comments
High-prescribers	I rely on making a strong personal connection to those docs, something to make me stand out from the crowd.	Friendship sells. The highest prescribers (9's and 10's) are every reps sugar mommies and daddies. It's the equivalent of spitting in the ocean to try to buy these docs out because, chances are, every other rep is falling head over heels to do so.	The highest prescribers receive better presents. Some reps said their 10's might receive unrestricted "educational" grants so loosely restricted that they were the equivalent of a cash gift, although I did not personally provide any grants.
Prefers a competing drug	The first thing I want to understand is why they're using another drug as opposed to mine. If it's a question of attention, then I commit myself to lavishing them with it until they're bought. If they are convinced that the competitor drug works better in some patient populations, I frame my drug to either capture another market niche or, if I feel my drug would fare well in a comparison, I hammer its superiority over the competing drug.	If, during the course of conversations, the doctors say something that may contradict their limited usage of our products, then the reps will badger them to justify that contradiction. This quickly transforms the rep from a welcomed reprieve to a nuisance, which can be useful in limited circumstances. We force the doctors to constantly explain their prescribing rationale, which is tiresome. Our intent is to engage in discourse but also to wear down the doc until he or she simply agrees to try the product for specific instances (we almost always argue for a specific patient profile for our drugs).	For reps this is a core function of our job. We're trained to do this in as benign a way as possible. No doc likes to be told their judgment is wrong so the latter method typically requires some discretion.
Acquiescent docs	Most docs think that if they simply agree with what the rep says, they'll outsmart the rep by avoiding any conflict or commitment, getting the samples and gifts they want, and finishing the encounter quickly. Nothing could be further from the truth. The old adage is true, especially in pharmaceutical sales: there is no such thing as a free lunch.	From the outset of my training, I've been taught to frame every conversation to ultimately derive commitments from my clients. With every acquiescent nod to statements of my drug's superiority I build the case for them to increase their usage of my product. They may offer me false promises but I'll know when they're lying: the prescribing data is sufficiently detailed in my computer to confirm their behavior. Doctors who fail to honor their commitments, no matter how casually made, convert the rep into a badgering nuisance. The docs are often corralled into a conversational corner where they have to justify their previous acquiescence.	Gifts are used to enhance guilt and social pressure. Reps know that gifts create a subconscious obligation to reciprocate. New reps who doubt this phenomenon need only see their doctors' prescribing data trending upwards to be convinced. Of course, most of these doctors think themselves immune to such influence. This is an illusion reps try to maintain.

» Table 1. Tactics for Manipulating Physicians (3)

Physician Category	Technique	How It Sells Drugs	Comments
No-see/ No-time (hard-to-see docs)	Occasionally docs refuse to see reps. Some do it for ethical reasons, but most simply lack the time. Even when I don't manage to see the doctor, I can still make a successful call by detailing the staff. Although they're on the doc's side for the most part, it's amazing how much trouble one can rile up when the staff are lavished with food and gifts during a credible sounding presentation and then asked to discuss the usage of a drug on their patients.	It's a victory for me just to learn from the staff about which drugs are preferred, and why. That info provides powerful ammunition to debate the docs with on the rare occasions that I might see them. However, it's a greater success when the staff discusses my meds with the doc after I leave. Because while a message delivered by a rep gets discounted, a detail delivered by a co-worker slips undetected and unfiltered under the guise of a conversation. And the response is usually better then what I might accomplish.	One's marketing success in a particular office can be strongly correlated to one's success in providing good food for the staff. Goodwill from the staff provides me with critical information, access, and an advocate for me and my drug when I'm not there.
Thought leaders	As a rep, I was always in pursuit of friendly "thought leaders" to groom for the speaking circuit. Once selected, a physician would give lectures around the district. I would carefully watch for tell-tale signs of their allegiance. This includes how they handled questions that criticized our product, how their prescribing habits fluctuated, or simply how eager they were to give their next lecture.	The main target of these gatherings is the speaker, whose appreciation may be reflected in increased prescribing of a company's products. Local speaking gigs are also auditions. Speakers with charisma, credentials, and an aura of integrity were elevated to the national circuit and, occasionally, given satellite telecast programs that offered CMEs.	Subtle and tactful spokespersons were the ideal candidates. I politely dismissed doctors who would play cheerleader for any drug…at the right price, of course.

These descriptions are based on SA's experience working for Eli Lilly and testimony in IMS Heath Inc. v. Ayotte, US District Court, New Hampshire. Actual tactics may vary.

doi:10.1371/journal.pmed.0040150.t001

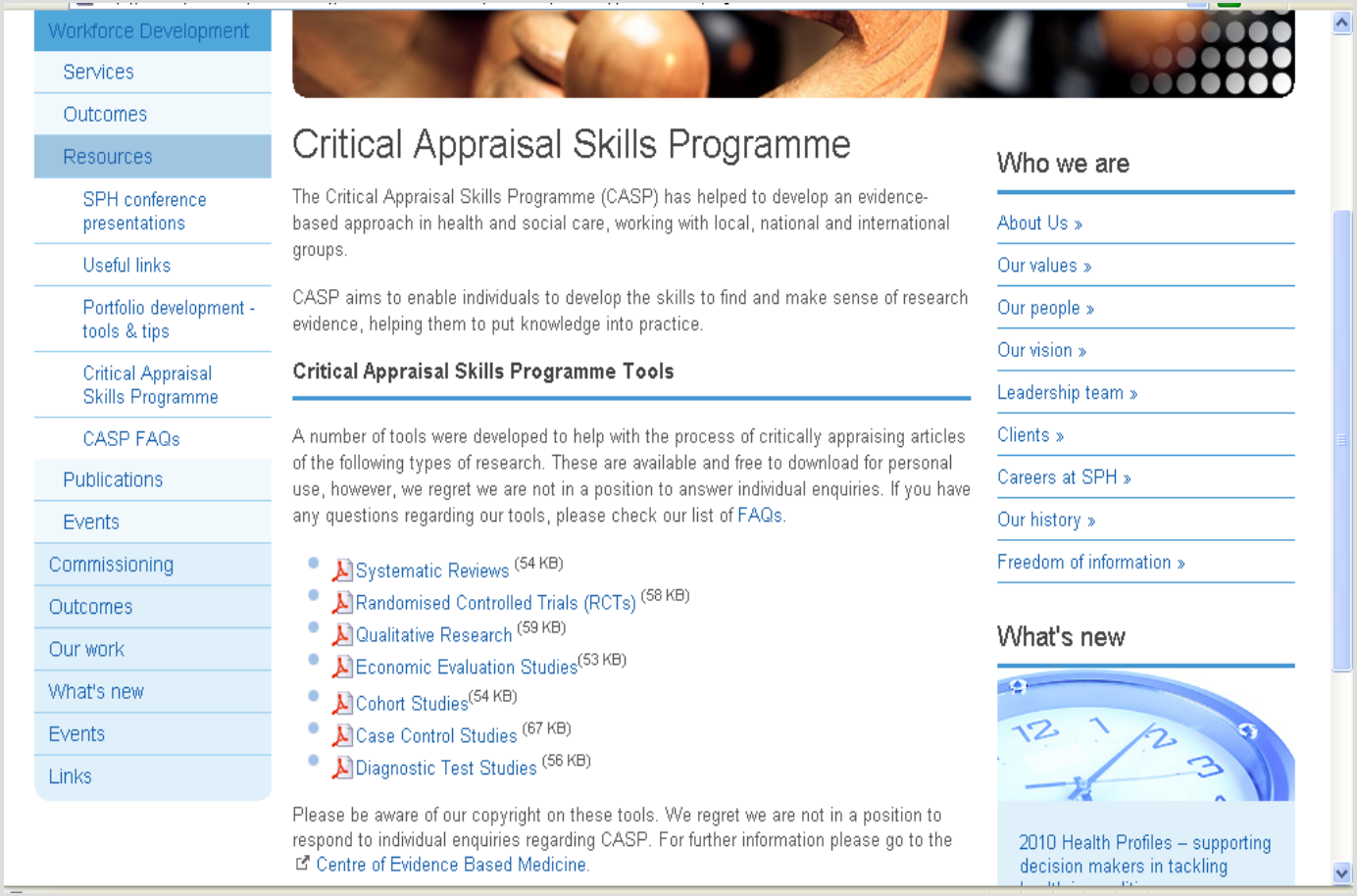


A drug rep's tale

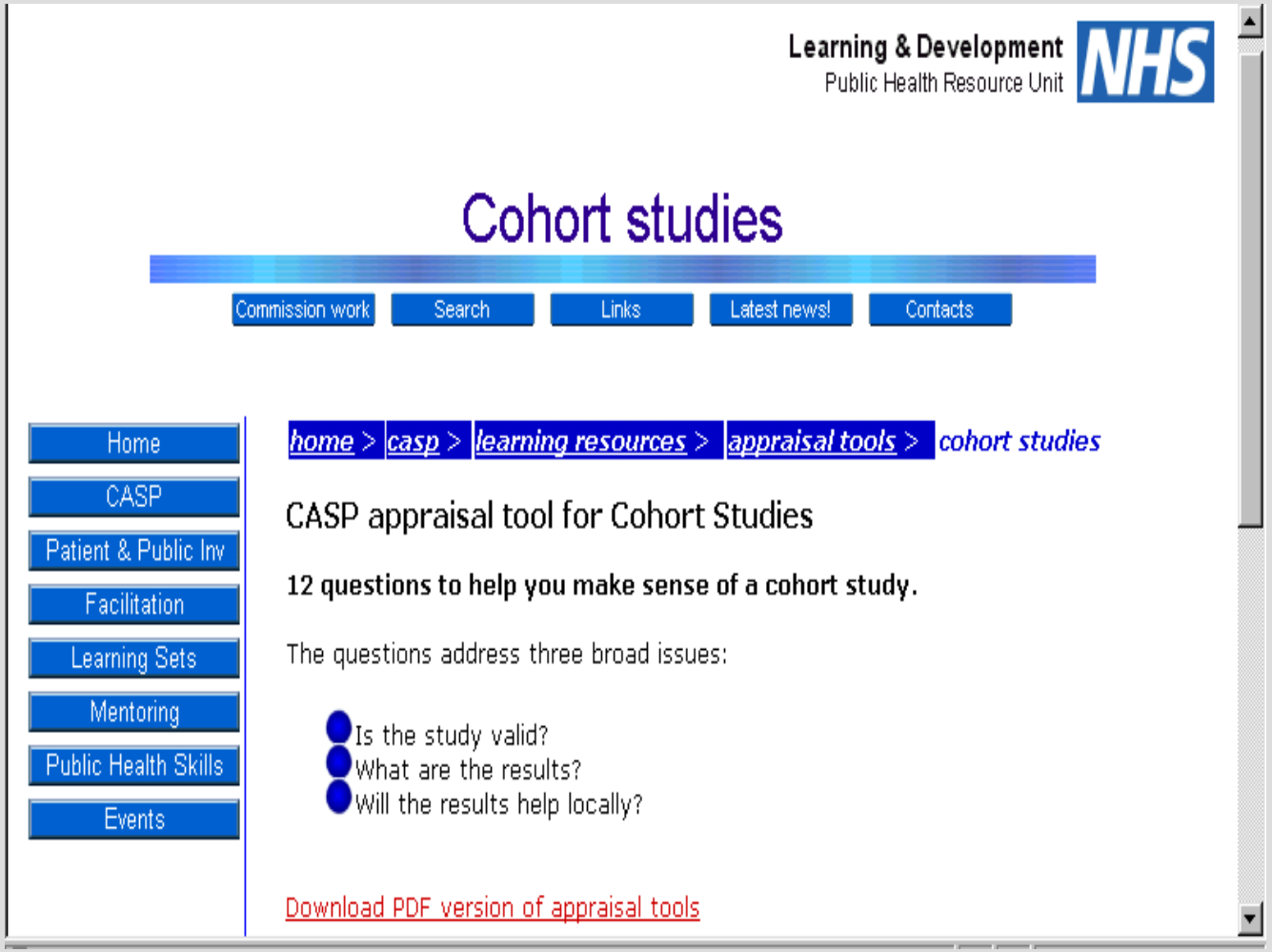
I decided to use coffee as my gift of choice and targeted a hospital where I had established good rapport (i.e. I could walk the halls without being kicked out). I made arrangements to have coffee cards made, giving 10 free cups to any person presenting them at the coffee cart at my teaching institution. They were identified with an Antibiotic S sticker on the back. Within a month, I was clearly in demand for my coffee cards. I was receiving phone calls from residents and staff doctors for cards. I began handing them out to anyone who could write a prescription of Antibiotic S. Several weeks into the program, I received a call from the hospital pharmacy doctor, who was friendly to my company (a paid speaker), but quite upset about not receiving a coffee card. I realise now that if I was giving them to surgeons and infectious disease doctors, my pharmacy doctor was probably offended that I left her out of the loop. With the pharmacy neutralised through coffee, sales far exceeded my expectations and I achieved my quota.

A useful website for resources for critical appraisal. http://www.sph.nhs.uk/

It contains a variety of tools for appraising different types of research design…



…which can be downloaded or printed off for everyday use…



…in a variety of helpful formats.