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Clinical trial data for all drugs in current use

Must be made available for independent scrutiny

Fiona Godlee editor in chief, *BMJ*, London WC1H 9JR, UK
fgodlee@bmj.com

The drug industry does many good things. It produces medicines that can improve health and save lives. It creates jobs and stimulates economic growth. Sadly it does bad things too. Persistently and systematically over decades it has withheld and misreported data from clinical trials.[1] As a result, a whole range of widely used drugs across all fields of medicine have been represented as safer and more effective than they are, endangering people's lives and wasting public money. Such wilful distortion is scientific misconduct.[2] It is not something we can forgive because of the good things drug companies do. As Ben Goldacre says in the introduction to his new book *Bad Pharma*, "Drug companies around the world have produced some of the most amazing innovations of the past fifty years, saving lives on an epic scale. But that does not allow them to hide data, mislead doctors, and harm patients."[3]

Hats off then to GlaxoSmithKline, which announced last month that it would allow access to anonymised patient level data from its clinical trials.[4] An independent panel will assess all requests, and the company's chief executive officer, Andrew Witty, says access will be granted on the basis of a reasonable scientific question, a protocol, and a commitment from the researchers to publish their results. Trial data collected since 2007 will be placed on a password protected website. Earlier data, not yet available in standard digitised formats, will be made available on "an ad hoc basis."

Whether researchers will find it as easy to get past the panel as Witty suggests we will have to wait and see. It will be particularly important to know how many requests are turned down and for what reasons.

And amid the plaudits, a moment of doubt. Surely what this apparently brave and benevolent action really serves to highlight is the rank absurdity of the current situation. Why aren't all clinical trial data routinely available for independent scrutiny once a regulatory decision has been made? How have commercial companies been allowed to evaluate their own products and then to keep large and unknown amounts of the data secret even from the regulators? Why should it be up to the companies to decide who looks at the data and for what purpose? Why should it take legal action (as in the case of GlaxoSmithKline's paroxetine and rosiglitazone),[5 6] strong arm tactics by national licensing bodies (Pfizer's reboxetine),[7] and the exceptional tenacity of individual researchers and investigative journalists (Roche's oseltamivir)[8] to try to piece together the evidence on individual drugs?

Goldacre's book makes it clear that the reasons are complex and there are no simple solutions. But there is no doubt that medical journals could do more. Rather than no longer publishing industry funded trials, as some have suggested, they could leverage their power and publish only where there is a commitment to make the relevant anonymised patient level data available on reasonable request. The International Committee of Medical Journal Editors has so far declined to take such a step. The *BMJ* will require this commitment for all clinical trials of drugs and devices—whether industry funded or not—from January 2013.

The *BMJ* will require authors to commit to supplying anonymised patient level data on reasonable request from 2013

The *BMJ* is also intensifying its efforts to help resolve a three year battle to gain access to the full data on oseltamivir (Tamiflu). In 2009 the Cochrane respiratory group, led by Tom Jefferson, was commissioned by the UK government to update its systematic review of neuraminidase inhibitors. Despite a public promise to release "full study reports" (internal company reports) for each trial, each of which can run to thousands of pages,[8] Roche has stonewalled, variously pleading patient or commercial confidentiality, or claiming that sufficient data have already been provided.[9]

In fact the Cochrane group has told the *BMJ* that about 60% of Roche's data from phase III trials of oseltamivir have never been published. And although the European Medicines Agency (EMA) could have requested these data from Roche, it did not do so. This means that tax payers in the United Kingdom and around the world have spent billions of dollars stockpiling a drug for which no one except the manufacturer has seen the complete evidence base. Indeed the EMA's unprecedented infringement proceedings launched against Roche last month suggest that even the manufacturer has never fully evaluated evidence it has collected on the drug's adverse effects.[10] What has Roche got to hide?

Two weeks ago in an attempt to break the deadlock, the *BMJ* wrote to one of the UK's leading academics, John Bell, regius professor of medicine at Oxford University, who is a member of Roche's board of directors. The letter is published this week.[11] In a response not for publication, Bell said he has referred the matter to Roche and is awaiting a response.

Meanwhile, frustrated by the lack of progress, Jefferson and colleagues have given the *BMJ* their entire email correspondence with Roche, which is now published at bmj.com/tamiflu, as David Payne explains.[12] They have also shared with us their correspondence with the World Health Organization and US Centers for Disease Control and Prevention. The emails show that none of the Cochrane group's questions have been answered. All future emails to and from the Cochrane group will be added to the site.

The open correspondence on bmj.com aims to hold specific individuals and organisations to account. Their actions are preventing independent scrutiny of the results of clinical trials and putting patients' lives at risk. We also hope it will contribute to a sea change in the public mood. Goldacre's book presents an opportunity to raise awareness of a scandal too long ignored by those in power. We should seize this moment with both hands.

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NEWS, p 2; FEATURE, p 26; OBSERVATIONS, p 35

bmj.com/blogs

- David Payne on hypoxia, Everest-style
- Matiram Pun: Mountain medicine—pilgrims, research, and peace

Acetazolamide for the prophylaxis of acute mountain sickness

Time for a more personalised approach to dosage?

Chris Imray professor and consultant vascular and renal transplant surgeon, Warwick Medical School, University Hospital Coventry and Warwickshire, Coventry, CV2 2DX, UK
christopher.imray@uhcw.nhs.uk

In 2000, a systematic review concluded that when ascending rapidly to above 4000 m, prophylactic dexamethasone 8-16 mg daily or acetazolamide 750 mg daily both reduced acute mountain sickness.[1] However, acetazolamide 500 mg daily was not found be effective. At the time, many doctors who specialise in high altitude sickness thought that this did not reflect their clinical experience.[2 3]

In a linked systematic review and meta-analysis, Low and colleagues look at the important question of the efficacy of acetazolamide at lower doses to prevent acute mountain sickness above 3000 m.[4] They found that acetazolamide 250 mg and 500 mg daily were both effective in reducing the severity of acute mountain sickness. The different altitudes studied (3000 *v* 4000 m) could have led to differences in the incidence and severity of acute mountain sickness and may partly account for the studies' different conclusions.[1 4]

More people are travelling to high altitude for work (soldiers, miners, construction workers, and astronomers) or recreation (skiing, trekking, mountain biking, and mountaineering). On ascent to altitude, several adaptive physiological processes occur (including hyperventilation, erythropoiesis, and increased cardiac output), all of which tend to increase convective oxygen transport to the tissues, a process termed "acclimatisation."[5]

Failure to acclimatise results in acute mountain sickness—a symptom complex consisting of headache and nausea, fatigue, dizziness, or difficulty sleeping. Symptoms appear six to 12 hours after arrival at altitude (usually >2500 m) and normally resolve within one to three days.[5] The risk of acute mountain sickness depends on the person's susceptibility, the rate of ascent, and the absolute altitude achieved (box). Surprisingly, physical fitness does not protect against its development, and ascending slowly and allowing time to acclimatise remains the best approach.[5] People who travel above 3000 m should ascend at less than 300 m a day, with a rest day for every 1000 m climbed.[6]

Risk categorisation of acute mountain sickness and suggested prophylactic approaches[6]

Low risk

People with no history of altitude illness who are ascending to below 2800 m

Those taking more than two days to arrive at 2500-3000 m with subsequent increases in sleeping height of less than 500 m/day

Suggested approach: Gradual ascent should be adequate and prophylactic drugs are not usually necessary

Moderate risk

People with a history of altitude illness who are ascending to above 2500-2800 m in one day

Those with no history of acute mountain sickness but who are ascending to above 2800 m in one day

All people ascending more than 500 m/day (increase in sleeping height) at altitudes above 3000 m

Suggested approach: Gradual ascent, prophylactic acetazolamide (250-750 mg daily) should be considered. Lower doses are likely to be sufficient.

High risk

People with a history of acute mountain sickness who are ascending to above 2800 m in one day

All those with a history of high altitude pulmonary oedema or high altitude cerebral oedema

All those ascending to above 3500 m in one day

All those ascending by more than 500 m/day (increase in sleeping height) above 3500 m

Very rapid ascents (such as Mount Kilimanjaro)

Suggested approach: Prophylactic acetazolamide (250-750 mg daily) should be seriously considered. Consider higher doses

Altitudes are the height at which the person sleeps. Ideally the drug is started a day before exposure to high altitude.

Dexamethasone 8-16 mg daily remains an option in those in whom acetazolamide is not appropriate. Dexamethasone can be combined with acetazolamide if extreme ascent profiles are essential.

Improving oxygenation with the carbonic anhydrase inhibitor, acetazolamide, or attenuating the cytokine and inflammatory responses with the glucocorticoid, dexamethasone, are both effective prevention strategies.[5] However, the potential side effects of glucocorticoids are generally thought to outweigh the benefits and these drugs are not normally used for prophylaxis. Exceptions are if acetazolamide is contraindicated or when a very rapid ascent rate is essential—for example, for unacclimatised rescue workers. The evidence supporting alternative approaches—such as ginkgo biloba, antioxidants,[5 6] and hypoxic preconditioning—is less clear.[7]

Acetazolamide causes a metabolic acidosis that stimulates ventilation. The drug is excreted unmetabolised in the urine. Although early studies showed that acetazolamide is efficacious in preventing acute mountain sickness,[8 9] the optimal dosage is unclear.

Even though the efficacy of acetazolamide for the prevention of acute mountain sickness is more limited when the baseline risk is low, Low and colleagues' study provides clinicians with evidence to support the use of a lower dose of acetazolamide in prevention.[4] This is important because higher doses of acetazolamide may increase the risk of drug side effects. Various drug interactions have been described, but the most common ones are with high dose aspirin, cardiac glycosides, antihypertensive drugs, and lithium. The drug should be avoided in pregnancy, particularly during the first trimester, and should not be prescribed in the presence of hepatic or renal impairment.

Recognised dose dependent side effects of acetazolamide include paraesthesia, diuresis, and altered taste,[10] and less commonly, headache and nausea.[11] A recent meta-analysis assessed efficacy, harm, and dose responsiveness.[12] The study found that the faster the ascent rate (14 m/h (when climbing) *v* 133 m/h (mechanised transport) *v* 4438 m/h (hypobaric chambers)), the greater the risk of acute mountain sickness, but also the greater the efficacy of acetazolamide. The risk of paraesthesia was the same for all doses, whereas the risk of polyuria and taste disturbance increased with 500 mg and 750 mg daily. Caution is needed in people with a known cross sensitivity to sulfonamides, and acetazolamide is contraindicated in those with a history of anaphylaxis with sulfonamides.

In conclusion, the risk of acute mountain sickness depends on the ascent rate, the absolute altitude attained, and the individual's susceptibility. No single preventive strategy will work in every situation, so a personalised approach, which takes into account the cumulative risk factors, is recommended.[6]

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RESEARCH, p 15

On the basis of available evidence is it reasonable to advise people that eating one or two portions of fish a week could reduce the risk of CHD and stroke

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The role of fish oils in the prevention of stroke

Supplements may not be protective in at risk patients who are optimally managed

Janette de Goede postdoctoral researcher
janette.degoede@wur.nl
Johanna M Geleijnse associate professor, Division of Human Nutrition, Wageningen University, 6700 EV Wageningen, Netherlands

Fish consumption once or twice a week is widely recommended for cardiovascular health. Fish is the main dietary source of the long chain omega 3 fatty acids eicosapentaenoic acid and docosahexaenoic acid. Low doses of these fatty acids (about 250 mg/day) have been suggested to protect against death from coronary heart disease (CHD).[1] Fewer data are available on the part that fish intake plays in preventing stroke. In a linked systematic review and meta-analysis of prospective studies and randomised controlled trials, Chowdhury and colleagues evaluate the role of fish and omega 3 fatty acid intake in the primary and secondary prevention of stroke.[2]

Several meta-analyses on fish and incident stroke have been published previously.[3-5] A 2004 meta-analysis of eight population based prospective cohort studies found that eating fish at least once a week was significantly associated with a 13-31% reduction in the risk of stroke when compared with eating fish less than once per month. The association was most pronounced for ischaemic stroke. A recently published update of this meta-analysis, which analysed 16 prospective cohort studies, came to a similar conclusion, although the effect sizes were smaller (9-14% lower risk).[5] Another meta-analysis, published in 2011, which was based on 15 prospective cohort studies, found that eating three extra portions of fish per week was significantly associated with a 6% reduction in the risk of stroke.[4] The authors assumed a dose-response effect, with a linear association between fish intake and reduced risk of stroke.

The present meta-analysis by Chowdhury and colleagues included data from 12 randomised controlled trials (RCTs) that tested the effect of an increased intake of long chain omega 3 fatty acids, as well as 26 prospective studies, 21 of which had data on fish intake, 10 on long chain omega 3 fatty acid intake, and four on circulating concentrations of omega 3 fatty acids.[2] The analysis examined data from 794 000 participants, among whom there were 34 817 stroke events. On the basis of the cohort studies, consumption of fish two to four times a week compared with once a week or less was significantly associated with a 6% reduction in the risk of stroke. When the top third of baseline long chain omega 3 fatty acid consumption (as measured by self reported dietary exposure) was compared with the bottom third, the relative risk of stroke was 0.90 (95% confidence interval 0.80 to 1.01). Similar results were seen for the top compared with bottom third of baseline fish consumption (0.91, 0.86 to 0.97). Results for ischaemic and haemorrhagic stroke were broadly similar.

Analysis of observational data showed that biomarkers of omega 3 fatty acids in blood were not associated with the risk of stroke. In addition, meta-analysis of data from the RCTs—in which those in treatment groups consumed on average 1.8 g of long chain omega 3 fatty acids a day (about 10-20 times the dietary dose in Western countries) over three years—showed that supplementation did not reduce stroke. Overall, the pooled relative risk for supplementation was 1.03 (0.94 to 1.12). Ten of the 12 randomised controlled trials included patients with previous cardiovascular disease. In these secondary prevention trials, the risk of stroke was increased by 17% in the group supplemented with long chain omega 3 fatty acids, although this finding was not statistically significant, and possibly merits further study.

Chowdhury and colleagues conclude that the potential beneficial effect of fish intake on stroke probably results from the interplay of a wide range of nutrients in fish and cannot primarily be attributed to long chain omega 3 fatty acids. Although this hypothesis seems reasonable, the effects of fish and long chain omega 3 fatty acids cannot be separated in cohort studies because the two are highly correlated. The effect sizes for fish and for long chain omega 3 fatty acid intakes were similar in the current meta-analysis. However, for long chain omega 3 fatty acids, the 95% confidence interval around the estimate was wider—probably because of the smaller number of stroke events—and statistical significance was not reached.

Fish consumption is low in most European countries and the United States. For example, in the Netherlands about 40% of the population eat fish less than once a month.[6] There is strong evidence that fish consumption only once a week compared with less than once a month or none at all protects against fatal CHD.[7] In the present meta-analysis of stroke, however, people who ate fish once a week were included in the reference group. Beneficial associations within the very low range of intake, as is common in Western countries,[5] were not captured in this analysis.

In nutritional cohort studies, residual confounding from other dietary or lifestyle habits is always a concern. Such confounding can be avoided in RCTs, but inverse associations between long chain omega 3 fatty acid intake and incident stroke have not been supported by RCTs.[8 9] However, trials included in the present meta-analysis were not primarily designed to detect an effect on stroke. Furthermore, most participants in RCTs have been patients with CHD, who would have received gold standard medical treatment (particularly those in later trials). In well treated patients, the absolute risk of stroke is reduced and beneficial effects of omega 3 fatty acids on top of treatment will be difficult to detect. The current findings are in line with disappointing results from RCTs of supplementation with long chain omega 3 fatty acids for the prevention of CHD.[10 11] It seems that the additional benefit of supplementation in patients who are optimally managed may be small.[12]

On the basis of available evidence is it reasonable to advise people that eating one or two portions of fish a week could reduce the risk of CHD and stroke. Any benefit of long chain omega 3 fatty acid supplementation for the secondary prevention of CHD and stroke is likely to be small. However, it is possible that patients who are less than optimally medically treated or who have additional risk factors (for example, as a result of comorbidities such as diabetes) may benefit.[13 14]

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RESEARCH, p 14

Many of the new indicators that the government has decided to implement are simply unworkable

Changes to the GP contract threaten general practice in the UK

Because of government's failure to grasp the funding and capacity problems facing the NHS

Laurence Buckman chairman general practitioners committee, BMA, London WC1H 9JP, UK
l.buckman@ntlworld.com

Last week, the UK government disregarded five months of painstaking negotiations between the BMA and NHS employers to announce a series of wide ranging changes to the general practitioner contract that could potentially damage general practice in the United Kingdom. Some of the changes had never been mentioned before. Extensive and detailed discussions, which had almost led to agreement on a potential package of changes to the GP contract that recognised the need to do as much as possible for patients despite financially austere times, were ignored. The government had been fully informed about negotiations all along, so what happened last week was surprising and distressing.

There is considerable anger among GPs and within the BMA at how this decision was promulgated. Many other sectors of the medical profession are equally taken aback by the government's autocratic approach. Furthermore, many of the new indicators that the government has decided to implement are simply unworkable.

GPs are under substantial pressure both financially and as a result of high workload. GP practice incomes have been frozen for several years, and this has led to real net incomes dropping by more than 20% since the introduction of the GP contract in 2004. At the same time expenses related to keeping GP surgeries functioning have steadily risen. This financial straitjacket has been slowly and relentlessly tightening to the point where most practices have little or no room for expanding their services without the injection of extra funds. Adding additional workload demands to an already stretched primary care service will simply force a reduction in patient access as practices struggle to cope. Like all healthcare professionals, GPs are seeing rising requests for treatment. Whether from an ageing population with complex health needs or the impact of improved treatments that benefit patients, this increase in patient demand means extra pressure on finite resources.

Tied to the intertwined problems of funding and workload are the government's controversial health reforms in England. Whatever their merits, the effect is that GPs are now coping with the impact of another huge NHS reorganisation and the rush towards the implementation of clinical commissioning groups. These groups have brought with them an avalanche of paperwork and legal requirements.

The government has taken an autocratic approach

Despite this backdrop of financial, workload, and organisational pressure, the BMA went into negotiations on behalf of GPs in June 2012 prepared to make further evidence based changes to the contract. Over the years, general practice has built up a strong track record of efficient working, especially since the signing of the 2004 contract, which introduced the quality and outcomes framework, a system whereby practices are set various targets that partly determine their practice funding. GPs have collectively worked hard to drive up testing and treatment of a range of conditions, such as diabetes and hypertension, despite reducing resources. Doctors' representatives were confident that, as government ministers requested, changes could be made that delivered more for patients, while at the same time not tipping practices into crisis.

This was a false hope. The government has decided to implement a large set of indicators, some of which may be unachievable. One indicator rewards GPs for referring patients to certain education programmes, even though these schemes are not available in all areas. Another asks GPs to undertake tougher targets when monitoring patients with hypertension. GPs would be willing to do this, yet the resources needed to make this proposal workable are not being provided. Such indicators leave most GPs in the perverse position of being unable to meet difficult targets without resources and then being penalised further for failing to achieve them.

Alongside this wilful "indicator chaos" is an overall intention to raise the achievement thresholds for all indicators within the framework. Practices will now be expected to treat more patients across the 120 plus clinical indicators. This is based on a simplistic assumption that GPs will treat more patients if they are incentivised to do so. However, there is no evidence to show that practices stop treating patients when they reach a certain target, and those that come up short on some targets, despite their best efforts, do so because their patient population often faces more challenging circumstances than others.[1] The total cost to practices of these threshold changes alone could amount to £126m (€156m; $202m) (personal communication, Department of Health, 2012).

Coupled with numerous other badly thought out changes, this imposition almost seems designed to exacerbate the underlying problems that are already damaging general practice. More work will be piled on while funding will be stripped away. This kind of conduct by the government should worry the wider medical profession. The threat to the GP contract is a politically driven exercise, unsupported by sound clinical knowledge, and deeply flawed because of the basic failure of its drivers to grasp the funding and capacity problems facing our NHS.

In the months ahead, the BMA will be examining the specific details of this complicated imposition, so as to inform the public and patients about its likely impact. The government still has time to rethink its proposals as it embarks on a "consultation" on these changes shortly. It must see sense, otherwise patients, GPs, and the country will suffer.

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