

Premature termination of clinical trials: do the benefits outweigh the risks?

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A recent article in the BMJ reports on an increasing trend for premature completion of clinical trials. Clinical trials are conducted in order to collect safety and efficacy data for new drugs or devices. There are two main reasons for clinical trials to be stopped early: excessive harm caused by the intervention or the early finding of outstanding benefits. Significant health benefits have brought several trials to a premature end in life-threatening conditions, at the expense of obtaining long-term data. A recent systematic review identified 143 clinical trials up to 2004, which were stopped early due to beneficial findings, with a significant increase in this practice between 1990-1994 (0.5%) and 2000-2004 (1.2%)¹. Can the premature termination of these trials really be justified and does this mean that crucial information about the long-term implications of such drugs and devices is lost? Here we consider the possible advantages and disadvantages of early trial completion.

Benefits

All clinical trials are subject to scrutiny by a data and safety-monitoring committee, which evaluates whether participants are receiving ethically acceptable care. Where it becomes apparent that the experimental (or

control) intervention is causing harm to participants, continuation of the trial is unethical and the trial will be ended. This will result in the discontinuation of a potentially harmful or ineffective drug or device¹. Conversely, it may be considered unethical to continue a clinical trial where superior benefits of the active intervention are demonstrated from an early stage, thereby disadvantaging individuals in the control group. The longer a clinical trial continues, the longer until the drug is licensed for use outside of the clinical trial population and the longer a potentially life-saving treatment is withheld from terminally ill patients. Ending a clinical trial early can mean early identification, approval and distribution of new treatments.

Risks

Not following a clinical trial to completion means that the long-term effects of the intervention remain unknown, with uncertainty about its full impact. For example, although a trial may find in year one that an intervention is potentially harmful in one endpoint, year two data may demonstrate significant benefits in other outcomes such as mortality rates.

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HAPPY 60TH BIRTHDAY



On 5th of July 1948, a new 'free at the point of access' health service was launched, as part of a policy that revolutionised healthcare in the UK. Sixty years later, despite the many challenges it faces, it retains a world-class reputation. On 5 February 2009, *The Lancet* plans to hold the first annual Health of the Nation Summit to assess the state of the NHS after 60 years, to identify its current weaknesses and investigate its opportunities. In the meantime, we say "Many Happy Returns"!



NO SMOKING
IT IS AGAINST THE
LAW TO SMOKE IN
THESE PREMISES

A “smokefree” year: how do you feel about that?

On July 1st 2007, England followed Ireland, Wales and Scotland in implementing a full smoking ban in virtually all enclosed public places and workplaces. The primary aim of this move was to protect employees and the general public from the effects of second-hand smoke, e.g. lung diseases, lung cancer, ischaemic heart disease. A secondary objective was to support people trying to give up smoking, providing an environment in which there is less social pressure to smoke. You may remember our article last year ([Good Questions, June 2007](#)) that hypothesised the advantages and disadvantages of the smoking ban. One year on, we thought it would be interesting to revisit this issue to see how a smoke-free year has affected attitudes and behaviour in England.



- 165,000 smokers quit around the time of the smoking ban last July; a rise of >25% on the previous year¹. More than 40% of smokers in England have tried to quit since the smoking ban²

- Britain's largest dry-cleaning business has blamed the smoking ban for a slowdown in trade, due to less need to eradicate stale smoke smells⁷



- More than half of hospital trusts report treating fewer heart attacks by up to 41%³
- 80% of people in the UK continue to support the smoke-free legislation. 73% tend to visit the pub as often as they did before (16% go more often). This mimics the Department of Health pre-legislation survey in which 63% of respondents said that the ban would not affect how often they go to the pub, 15% saying they would go more often⁴.
- Research shows that bar/pub workers already feel the health benefits of the smoking ban⁵
- An online survey by the University of Wales (N=149) suggests that before the smoke-free legislation, more than half (53%) respondents experienced symptoms from second-hand smoke, e.g. nausea, breathing problems, sore eyes and coughing. The smoking ban has substantially reduced, but not totally eliminated, the effects of second-hand smoke⁶.
- Cigarette litter has increased in the streets⁸
- Breweries have experienced a fall in sales⁹ resulting in redundancies (possibly confounded by low-price alcohol in supermarkets and fear of recession)
- Some pub-goers still oppose the legislation. The customers of one Lancashire pub have even petitioned Parliament to let them smoke in their local, stating “the smoking ban is having an adverse effect on the social structure and enjoyment within their local pub; they consider it a valuable asset within the local community”¹⁰. Department of Health figures indicate 19 court hearings since the ban
- All this has prompted bookmakers William Hill to offer odds of 33/1 that the UK smoking ban will be overturned by the next General Election.

“While smoking behaviour seems to have changed, it is currently unclear whether attitudes have really changed”

While smoking behaviour seems to have changed, it is currently unclear whether attitudes have really changed. There was significant opposition pre-implementation and that opposition remains, with fears from pub landlords, regular pub-goers and other businesses supported by emerging evidence. However, there are plans to extend the ban further in some parts of the UK to those wanting to adopt children under the age of five or who wish to receive IVF treatment on the NHS. Countries around the world continue to implement smoking bans, although opposition is evident everywhere. Indeed the recent ban on smoking in public places on the Isle of Man resulted in 16 of 32 prisoners in a prison wing launching a hunger strike in protest!

References

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2. Huntly, K (2008). British Lung Foundation. Public smoking ban encourages smokers to quit. Available at <http://www.lunguk.org/media-and-campaigning/media-centre/latestpressreleases/Publicsmokingban.htm>
3. Pavia, W (2008). Heart attack admissions fall by up to 40% since smoking ban. *The Times*, Sunday 15 June 2008.
4. Office of National Statistics (ONS) (2008). News Release: Widespread Support for Smoking Ban. Available at <http://www.statistics.gov.uk/pdfdir/smoke0608.pdf>
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7. Allen, K (2008). Dry-cleaners say smoking ban stinks. *The Guardian*, Wednesday January 30 2008
8. DEFRA (2008). News Release: No room for let up in the battle against litter says Minister. <http://www.defra.gov.uk/news/2008/080304b.htm>
9. Yuk, PK (2008). Enterprise Inns hit by smoking ban. *Financial Times*, Tuesday 13 May 2008
10. Harrington, J (2008). Locals petition Parliament for smoke ban exemption. *Morning Advertiser*, Friday 1 February 2008

Health Awareness - dates for your diary

Sickle Cell Awareness Month

Hemochromatosis Awareness Month

Dementia Awareness Week (6-12 July)

World Population Day (11 July)

The Samaritans Awareness Day (24 July)

National Transplant Week (6-13 July)



Premature termination of clinical trials...

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For example, early trial results found atenolol to be harmful in certain respects, but in following the trial through to completion, atenolol was found to reduce mortality in acute myocardial infarction by 15%².

Statistically significant findings, which demonstrate benefit, may be due to type I or type II errors (chance findings) resulting from analysing the data at a "random high". Therefore, caution should always be exercised in interpreting any findings from trials, which are finished early. Some authors have suggested that the traditional level for statistical significance (5% chance of error) should be abolished in trials that are terminated early due to beneficial findings, in favour of more robust significance ($p < 0.001$), allowing for a 0.01% chance of error³.

Conclusions

It is important to acknowledge that the decision to stop a trial before completion is rarely based on treatment findings alone, with other relevant variables (such as previous research findings, systematic literature reviews) contributing to the pool of evidence for the intervention.

Valid arguments may be made for both completing some clinical trials early (where

the treatment on offer has the proven potential to save lives) and for ensuring trial completion and subsequent long-term data related to the intervention. It is clear however, that every clinical trial is distinctive in nature and therefore the decision about whether to finish a trial early will always depend on the relative issues associated with each trial, including its hypotheses, comparator arm, marketplace, and trial participants.

References

1. Montori VM, Devereaux PJ, Adhikari NKJ (2005). Randomised trials stopped early for benefit: A systematic review. *JAMA*, 294(17): 2203-2209
2. ISIS-1 Collaborative group (1986). Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet*, ii: 57-66
3. Pocock SJ (2005). When (not) to stop a clinical trial for benefit. *JAMA*, 294(17): 2228-2230

In the news...

- [Drug approval for NHS to speed up](#)
- [NHS overhaul plans to be laid out](#)
- [Anti-inflammatory for Alzheimer's](#)
- [Controversial diet drug approved](#)
- [Allergic rhinitis: common, costly, and neglected](#)
- [A cost-effective way to save the world?](#)
- [Emerging theory on chronic fatigue syndrome](#)
- [Media doctor admits to plagiarism](#)

In Brief

■ [Collaborative effort by FDA and EMEA to consider additional test results](#)

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have combined for the first time to produce a framework, which allows submission of a single application to the two agencies. Pharmaceutical companies can submit the results of seven new safety tests that evaluate kidney damage during animal studies of new drugs. These biomarkers were developed and tested by the Predictive Safety Testing Consortium (PSTC), whose members include scientists from 16 pharmaceutical companies. This project is also the first in which a group of drug companies has worked together to propose new safety tests.

■ [The NIHR Public Health Research \(PHR\) programme](#)

Autumn 2008 sees the launch of the National Institute for Health Research (NIHR) Public Health Research programme, designed to evaluate a wide range of public health interventions. The programme aims to provide new knowledge on the benefits, costs, acceptability and wider effect of non-NHS interventions intended to improve public health and reduce health inequalities. The programme will be funded up to 2011. The first call for proposals will be mid-November 2008. Further details of the programme are available [here](#).

■ [FDA requests boxed warnings on antipsychotic medication](#)

The US Food and Drug Administration (FDA) has requested that manufacturers of "conventional" antipsychotic drugs make safety-related changes to prescribing information. The text needs to warn about an increased risk of death when used by elderly patients treated for dementia-related psychosis. In 2005, the FDA announced similar uniform language changes for "atypical" antipsychotics. Neither class of antipsychotic is currently FDA-approved for use in the treatment of dementia-related symptoms, but they are often prescribed off-label. Further information is available [here](#).

■ [Boost for healthy lifestyles in Scotland](#)

Scotland has made significant progress in recent years in reducing the number of deaths from chronic disease. However, there is concern that the impact of rising levels of overweight and obese people will reverse that progress; the cost of obesity to the NHS in Scotland is more than £171m (data from 2003). In response, the Scottish government has launched an action plan targeting diet and exercise. Over the next three years the government will spend over £56m, of which £40m is new money, on promoting physical activity, healthy diets and healthy weight.



The Journal of the American Medical Association

In the Journals

Patient-Important Outcomes in Registered Diabetes Trials

1	The safety and efficacy of many diabetes interventions remains a concern. Few RCTs assess the effects of interventions on patient-important outcomes (PIOs), i.e. death, and quality of life*. The objective of this review was to determine the extent to which ongoing and future RCTs in diabetes assess PIOs.
2	Of 2019 phase II-IV RCTs identified in primary RCT registries, 1054 were eligible for inclusion. 50% were sampled and the 436 registered since 2004 (when registration became mandatory) were included. Pairs of reviewers extracted and categorised data.
3	Primary endpoints were PIOs in 78 (18%) RCTs; surrogate outcomes in 268 (61%), including HbA1c, cholesterol; physiological and laboratory outcomes in 69 (16%), including C-peptide levels). PIOs were primary or secondary endpoints in 201 (46%) RCTs.
4	PIOs were more likely to be assessed in multivariate analyses, large trials and trials of longer duration. They were less likely in parallel design RCTs and trials of Type 2 diabetes.
5	The authors recommend that a consensus is needed on a standard set of important outcomes to patients in diabetes trials, similar to OMERACT in rheumatology.

* **Comment:** Quality of life (QoL) is defined by the authors as "major morbid events such as stroke, MI, amputation, loss of vision, and end-stage renal disease; minor morbid events such as hypoglycemic events, delayed wound healing, infection, and visual disturbances; and pain and functional status" (p2544). We suggest that these are classified more accurately as morbidity or health status. While these factors undoubtedly impact upon QoL, they cannot be considered to fully encompass QoL, which is a patient-reported outcome.

Gandhi GY et al. JAMA, 2008, 299(21): 2543-2549.

Forthcoming events

14-15 July 2008

BREATHE Workshop:
UCL, London

7-11 September 2008

EASD 44th Annual Meeting:

Rome, Italy

9-12 September 2008

Health Psychology Annual Conference:

University of Bath, UK

22-25 October 2008

ISOQOL 15th Scientific Meeting:

Montevideo, Uruguay

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