

Closing the Gaps: Moving Closer to a Collaborative Culture

Comments on Disclosure Timing: Balancing increased transparency and competitive advantage

Submission to WHO International Clinical Trials Registry Platform March 2006

Introduction

Public confidence in health care has been continually eroded^{1,2} by revelations of fraud³, unanticipated adverse events⁴, data suppression⁵, inappropriate involvement of sponsors and publication bias^{6,7,8}, and corruption of the evidence base of medical practice^{9,10,11,12} with consequent ethical implications¹³. These developments add cogency and urgency to the position of the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP) in promoting both transparency and accountability in clinical research. Both the rationale and support for that position have been described in a previous submission¹⁴.

Transparency or competitive advantage?

Conflicting values

When this question is posed in this way, there is a danger that it may be inferred that these two values are mutually exclusive alternatives. The underlying assumption could be construed as stating that competition is normative in science as well as in commerce. In the previous submission it was argued that science is *not* intrinsically competitive¹⁵ but that a progressive blurring of the boundaries between science and commerce^{16,17} has generated a destructive climate of secrecy¹⁸ which is contrary to the public interest and common good^{19,20,21}. These issues in turn have generated considerable public concern,^{22,23,24,25,26,27,28} that must be addressed²⁹.

The nature and effect of competition

Unlike commerce, competition in science may be seen as potentially ruinous. Idealistically the beneficent objective of improving the health of mankind is incompatible with profit driven commercialism, threatening the common purpose of the generation, dissemination and utilisation of knowledge. None of this negates the role which the biopharmaceutical and bioengineering industry has played in innovation, nor of the increasing costs of bringing a product to the market, nor the fundamental right for a fair return on investments. However broader issues around competition in health care raise concern about the directions such competition takes, leading to potentially misdirected effort in duplication, cost to society, expansion into inappropriate markets³⁰ and ultimately concealment^{31,32}. In particular, excessive competition in limited markets diverts resources into promotion, and increases the costs of products and devices, for marginal gain. As noted by many authors, including those cited above, competitiveness leads to conflict of interest³³, and corrosion of trust^{34,35}.

Alternatives

The common good is best served in an environment of collaboration, and shared ideas, and health care systems work best when industry and providers share development and delivery with clear guidelines. Only a shift from a culture of competition to one of openness is likely to address all these issues and restore the confidence of the public, health care providers and government. With regards to claims that transparency leads to abuse of proprietary information it is troubling that industry ethics has failed to provide adequate mechanisms for the prevention of abuse of information to date.

The issues

Priorities in registration

The ICTRP position on clinical trial registration needs to be understood in its broadest context of a fundamental reshaping of the research culture to one of open access^{36,37}. Key components of this are access to research protocols³⁸, and to the data generated by them^{39,40}. A number of submissions have downplayed trial registration preferring to shift the emphasis to results databases⁴¹. On the contrary clinical trial registration is pivotal, because it provides a portal to information, and a common identifier that will make information retrieval and synthesis much simpler and easier. Ultimately it provides the potential for automatic prospective gathering of clinical research information as a dynamic process, easily converted to guidelines for health care providers and consumers. The current round of consultations and discussions focuses on Disclosure Timing Policy, that is, what information will be disclosed and when.

Claims for exemption

WHO's position is clear in its call for submissions⁴² that the norm will be total disclosure. Therefore discussion revolves around the claims for exceptions to these, which to date have involved questions of; (a) which trials should be covered; (b) what specific items might be excluded; (c) for how long; and (d) the criteria and mechanisms for making such exemptions. As stated in the previous submission the burden of proof rests with those who seek exemption. To date, as stated in the announcement of the consultation⁴³, two distinct groups of parties, industry and academics, have been identified who might be potentially adversely affected by the full implementation of the proposed policy.

Issues related to academics

Normal mechanisms of scientific ethics and integrity, which would be enhanced by a collaborative culture, should be sufficient protection for the academic sector. In actuality the registry concept enhances protection by providing proof of concepts and original ideas, and this has received public support⁴⁴. Only those who seek to conceal their research should have cause to fear. Since we are unaware of any submissions of concern from academics, this will not be dealt with further in this submission.

Issues related to industry

(a) Which trials?

Industry concerns about registration have been proportional to the stage of development of a novel agent or device. There has been general agreement on registration of pivotal (phase III) trials, but less on early (Phase I, II) trials. However the duty of care to subjects

is a fundamental one, irrespective of trial design, purpose, or phase of development. Knowledge is cumulative, and access to information concerning prior trials is crucial to the development, access to and execution of subsequent trials. The recent tragic events in a phase I trial at Northwick Park Hospital in London, and the subsequent lack of available information⁴⁵, highlight the necessity of registration of the details of *all* trials. The Alzheimer's Society poses the question – “could these catastrophic outcomes have been averted?” if prior registration had been in place, a question also argued in a recent editorial⁴⁶. Consequently the position of WHO, the International Committee of Medical Journal Editors (see below), the World Association of Medical Editors, consumer groups⁴⁷ and some industry spokespersons⁴⁸ that all trials should be registered is compelling.

(b) What items?

There seems to be an emerging consensus from industry that withholding of information would occur under exceptional circumstances only^{49,50,51}. However registration of Intervention Names and Primary Outcomes remains far from satisfactory⁵². As pointed out by Abbott Laboratories⁵³, industry concerns have also focussed on three other items (Scientific Title, Secondary Outcome, and Sample Size), omission of which has been argued would make registration meaningless. As Abbott imply, this is not a question of intellectual property, but rather of competitive advantage. However Drazen and Wood point out that commercial sensitivity is no defence, since these data are routinely provided to ethics committees, investigators, subjects and regulators⁵⁴, a position supported by consumer groups such as the Alzheimer's Society and European Cancer Patient Coalition. On the other hand Abbott's position that this information is protected under U.S. (*Trade Secrets Act, Food, Drug and Cosmetics Act*), U.K (*Freedom of Information Act*) and E.U. law does not have relevance, since these laws deal with unauthorised disclosure of information provided in confidence, not with the voluntary disclosure as proposed. Furthermore the provision of this information by some sponsors and not by others undermines any coherent argument for withholding it. Abbott also argues that U.S. state law provides penalties for abuse of commercial information under unfair trade practices, but it is this very protection from abuse that is the reason why industry should not fear full registration, because protective laws are already in place.

(c) How long?

As stated by Abbott, any such withholding of information should be brief, but such a stipulation requires a more rigorous definition. Arguments about ‘commercial sensitivity’ are too vague, and open to abuse. Any proposal for withholding would require detailed demonstration of the amount of time required and be subject to periodic review.

(d) Criteria and mechanisms

Contrary to Abbott's position (option 2), WHO and ICMJE have already stipulated that withholding information from registries is unacceptable, therefore any argument devolves to the degree of public access. The issues at stake are far too important to leave to the sponsor alone and if considered necessary, approval of withholding and for how long should be decided by an independent body.

Response

Response to selected industry submissions

Interpretation of WHO position

AdvaMed⁵⁵ appears to misrepresent or at least overstate the position taken by WHO in calling for submissions addressing balance. AdvaMed states that it strongly agrees with the proposition on the ICTRP website, whereas ICTRP merely acknowledge that the commercial sector has expressed concerns about potential adverse effects of complete and early disclosure in some circumstances. To that end ICTRP has called for submission of concrete examples.

Devices

AdvaMed's contentions that disclosure will lead to loss of innovation and increased costs is speculative, and while the incentive of competition is acknowledged, there are considerable countervailing forces. Collaboration is more likely to decrease costs, improve patient safety and improve the uptake of new ideas into health care practice.

AdvaMed appears to use the Institute of Medicine (IOM) to support its claims, so this requires a more careful reading. In June 2005, the IOM convened a workshop of diverse entities including industry, and subsequently appointed a joint committee that undertook further discussions before releasing its report in January 2006⁵⁶. This reflects the diverse inputs and notes considerable areas of agreement and disagreement. The final report therefore reflects the range of inputs, and failure to reach agreement. While the report does not deal with devices explicitly, it would be a mistake to infer from AdvaMed's submission that device trials were in any way explicitly exempted from the need for registration.

AdvaMed's arguments for special consideration for devices is based on four grounds; (a) that many countries have a risk based approach to regulation of devices; (b) that several countries have different regulations for drugs and devices; (c) the specifics of the economics of the industry; and (d) the short life cycle. None of these address the issues at hand, namely the need for integrity in the clinical evidence base. While acknowledging heterogeneity of risk, this is not unique to devices, nor is a limited life cycle, and many drugs do not make it to market. This does not mean that we cannot learn from the development of products. Nor does the history or current state of regulations indicate that the status quo is by any means ideal. On the contrary, continuing well publicised problems with Guidant^{57,58} defibrillators and stents⁵⁹ point to the need for a similar degree of regulation and transparency for devices as for drugs, not less.

AdvaMed argue that devices evolve iteratively but it could be argued that all health care evolves iteratively, the journalistic concept of 'breakthrough' being the exception not the norm, and that transparency facilitates iteration. With regards to AdvaMed's position on weak patent protection, this speaks more to the need for reform of patent law than for compromising transparency in health care. They also point to the issue of analogues as an argument for exemption, but this too is not unique to devices. There appears to be some misunderstanding in the submission with respect to the requirements of registration and

intellectual property, since registration does not require disclosure of all of the device's properties, design and characteristics, merely a unique and identifiable name or number, and the purpose of the device.

There is no actual documented evidence of disadvantage despite claims for the disappearance of many companies if registration is implemented as proposed. To state that ICMJE excludes 'early phase' trials is somewhat of a misreading. ICMJE, like the IOM recognise that there is no 'bright line' between 'early' and 'late' phase, an increasingly blurred distinction, and therefore advise;

*"Authors whose trial is unregistered will have to convince the editor that they had a sound rationale when they decided not to register their trial."*⁶⁰

Furthermore the World Association of Medical Editors states;

*"For these reasons, the World Association of Medical Editors supports efforts to register **all** clinical trials at their inception. Because registration is useful only to the extent that it includes **all** trials, it should be required of the research community as a whole and not voluntary according to the source of funding or preferences of the investigators."*⁶¹ (Emphasis added)

With regards to AdvaMed's difficulty understanding how 'early' phase trials "inform health and health care practice" it is important to realise that knowledge is cumulative, that each piece of incremental knowledge must be evaluated in the context of all other relevant knowledge, and no knowledge should be discarded. The position taken by AdvaMed that inclusion of 'early' phase trials can be misleading or confusing is not convincing provided that publishing practice follows accepted guidelines, nor is it clear how their inclusion could make the database unwieldy. Zarin (2006) points out that the database is growing at 250 trials per week. With appropriate search engines and search strategies even the world's largest database (the internet) functions efficiently. Finally it is surprising that AdvaMed complains that device manufacturers were not consulted, since a device manufacturer (Guidant) sits on the Scientific Advisory Board.

Abbott Laboratories

This submission provides a hypothetical example and therefore fails to meet the requirements of WHO's call for documented examples. Surrogate endpoints are unlikely to be incorporated into clinical trials prior to FDA approval, and such approval should properly include public input. If the surrogate endpoint involves new technology, that technology should be protected by patent.

Abbott's second example involves another company using a new trade name for a new indication for an approved drug. This would be unacceptable because registration should involve all synonyms including a unique identifier for the product. As long as the company held the patent on the product, a trial in a new indication should provide no competitive disadvantage.

PhRMA

Four examples are provided where it is claimed that withholding of key elements would be justified, although it is unclear whether they are speculative or real. In the first example they cite trials of inhalational insulin. This is curious since it has been well known in medical circles for many years that insulin manufacturers were testing inhalational delivery. This raises a more general point about industrial intelligence, since it is widely stated that most manufacturers have a very good idea of their competitor's strategies⁶², and that claims for the need for secrecy are only posturing. The second and third examples are discussed above since they also appear in the Abbott submission. The fourth example dealing again with formulation raises the question of the amount of detail on formulation that would be required in the registration process (as in the discussion on devices). The key element is whether the trial can be identified in any literature and evidence synthesis.

One of the tasks of the forthcoming special session will be to explore the degree of consensus raised by PhRMA. As with the 2005 IOM workshop the differences will largely be between industry and the worlds of ethics and evidence based medicine, which are largely in agreement. Hopefully there will be some narrowing of those differences, one area of which may be the concept of "informing" clinical practice which appears to be open to interpretation at present. We agree that considerations of transparency apply equally to public and private sector, consistent with the stated position that *all* subjects involved in research deserve equal respect. Inclusion of clinical trials registration should be incorporated into Good Clinical Practice.

Monitoring and compliance

There is an obligation to both commitment and collaboration by all parties involved in the design and execution of clinical trials to ensure openness and compliance. Similar considerations apply to those charged with oversight such as ethics committees⁶³, journal editors, registries and reviewers and regulatory authorities. Call for building registration requirements into clinical trials legislation should be supported. In addition to initiatives in the United States, Israel⁶⁴ is to be commended for having already implemented this. The European Union (EudraCT)⁶⁵ has also moved in this direction.

In the mean time continuous monitoring and publicising compliance data appears to be having a beneficial effect with increasing compliance⁶⁶. This provides subjects, investigators and institutions with information that can be used in influencing sponsor policies. There is a moral argument for not collaborating with sponsors which are non-compliant⁶⁷.

Summary

The progress made so far in achieving agreement between involved partners, and in making transparency a reality is encouraging. However a convincing case has not been made either for the exclusion of some trials, nor for that of specific trial registration elements.

Respectfully submitted,

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References

- ¹ Krleza-Jeric K. Clinical trials registration. *PLoS Med.* 200 Mar;3(3):e167
- ² Porter J Foreword: Developing a National Registry of Pharmacologic and Biologic Clinical Trials: Workshop Report. Institute of Medicine, National Academies Press Washington DC 2006 xi-xiii
- ³ [Sox HC, Rennie D.](#) Research Misconduct, Retraction, and Cleansing the Medical Literature: Lessons from the Poehlman Case. *Ann Intern Med.* 2006 Mar 6; [Epub ahead of print]
- ⁴ [Goodyear M.](#) Learning from the TGN1412 trial. *BMJ.* 2006 Mar 25;332(7543):677-8.
- ⁵ [Curfman GD, Morrissey S, Drazen JM.](#) Expression of concern reaffirmed. *N Engl J Med.* 2006 Mar 16;354(11):1193.
- ⁶ [Pildal J, Chan AW, Hrobjartsson A, Forfang E, Altman DG, Gotzsche PC.](#) Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. *BMJ.* 2005 May 7;330(7499):1049.
- ⁷ [Chan AW, Altman DG.](#) Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet.* 2005 Mar 26-Apr 1;365(9465):1159-62
- ⁸ [Chan AW, Altman DG.](#) Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *BMJ.* 2005 Apr 2;330(7494):753.
- ⁹ [Young C, Horton R.](#) Putting clinical trials into context. *Lancet.* 2005 Jul 9-15;366(9480):107-8
- ¹⁰ [Healy D, Cattell D.](#) Interface between authorship, industry and science in the domain of therapeutics. *Br J Psychiatry.* 2003 Jul;183:22-7
- ¹¹ [De Vries R, Lemmens T.](#) The social and cultural shaping of medical evidence: Case studies from pharmaceutical research and obstetric science. *Soc Sci Med.* 2005 Dec 22;
- ¹² [Goodman SN.](#) Ethics and evidence in clinical trials. *Clin Trials.* 2005;2(3):195-6.
- ¹³ [Savulescu J, Chalmers I, Blunt J.](#) Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *BMJ.* 1996 Nov 30;313(7069):1390-3.
- ¹⁴ Goodyear M, Golec L Comments on disclosure timing: Submission to WHO International Clinical Trials Registry Platform January 2006 (http://www.who.int/ictcp/3009_Michael_Goodyear_Lisa_Golec_25Jan06.pdf)
- ¹⁵ Rao AK Regulating scientific research: intellectual property rights and the norms of science *Northwestern University Law Rev* 1999 94(1): 77-152
- ¹⁶ Downie J The power of money: commercialization of research conducted in public institutions *Otago Law Rev* 2006 11(2): 305-325

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- ¹⁷ [Lemmens T](#). Leopards in the temple: restoring scientific integrity to the commercialized research scene. *J Law Med Ethics*. 2004 Winter;32(4):641-57.
- 18 Open Comments Of Cancer Patients To WHO On Delayed Public Disclosure Of Clinical Trials Information European Cancer Patient Coalition January 2006 (http://www.who.int/ictrp/3003_ECPC_25Jan06.pdf)
- ¹⁹ [Mirowski P, Van Horn R](#). The contract research organization and the commercialization of scientific research. *Soc Stud Sci*. 2005 Aug;35(4):503-48.
- ²⁰ House of Commons Health Committee. The influence of the pharmaceutical industry. Fourth report of session 2004-05. London: Stationery Office, 2005
- ²¹ Delaney B. Is society losing control of the medical research agenda? *BMJ*, doi: 10.1136/bmj.38771.471563.80 (published 17 March 2006)
- ²² Elliott C Pharma goes to the laundry: public relations and the business of medical education Hasting Centre Report 2004 September-October 18-23
- ²³ [Elliott C](#). Should journals publish industry-funded bioethics articles? *Lancet*. 2005 Jul 30-Aug 5;366(9483):422-
- ²⁴ [Henry D, Doran E, Kerridge I, Hill S, McNeill PM, Day R](#). Ties that bind: multiple relationships between clinical researchers and the pharmaceutical industry. *Arch Intern Med*. 2005 Nov 28;165(21):2493-6
- ²⁵ [Gotzsche PC](#). Research integrity and pharmaceutical industry sponsorship. Trial registration, transparency and less reliance on industry trials are essential. *Med J Aust*. 2005 Jun 6;182(11):549-50.
- ²⁶ [Mathews AW](#). Ghost story: at medical journals, writers paid by industry play big role; articles appear under name of academic researchers, but they often get help; J & J receives a positive "spin". *Wall St J (East Ed)*. 2005 Dec 13;:A1, A8
- ²⁷ Altman DG, Furberg CD, Grimshaw JM, Rothwell P. Lead editorial: Trials - using the opportunities of electronic publishing to improve the reporting of randomised trials. *Trials*. 2006 Mar 23;7(1):6
- ²⁸ Angell M. The truth about drug companies: how they deceive us and what to do about it. New York: Random House, 2004.
- ²⁹ Tumber MB, Dickersin K. Publication of clinical trials: accountability and accessibility. *J Intern Med*. 2004 Oct;256(4):271-83.
- ³⁰ [Healy D](#). Shaping the intimate: influences on the experience of everyday nerves. *Soc Stud Sci*. 2004 Apr;34(2):219-45.
- ³¹ Woolf SH Unhealthy Medicine: All Breakthrough, No Follow-Through *The Washington Post* Sunday, January 8, 2006; B03
- ³² [Woolf SH, Johnson RE](#). The break-even point: when medical advances are less important than improving the fidelity with which they are delivered. *Ann Fam Med*. 2005 Nov-Dec;3(6):545-52.
- ³³ [Barden J, Derry S, McQuay HJ, Moore RA](#). Bias from industry trial funding? A framework, a suggested approach, and a negative result. *Pain*. 2006 Apr;121(3):207-18.
- ³⁴ [Downie J, Baird P, Thompson J](#). Industry and the academy: conflicts of interest in contemporary health research. *Health Law J*. 2002;10:103-22.
- ³⁵ Quick J Maintaining the integrity of the clinical evidence base. *Bull World Health Organ*. 2001;79(12):1093.
- ³⁶ [Haug C, Gotzsche PC, Schroeder TV](#). Clinical trials report card. *N Engl J Med*. 2006 Mar 30;354(13):1429
- ³⁷ [Gøtzsche P](#) Disclosures should not be delayed March 31st 2006 (http://www.who.int/ictrp/006-Peter_Gotzsche_31March06.pdf)
- ³⁸ Johnson K, Lassere M. Clinical trials report card. *N Engl J Med*. 2006 Mar 30;354(13):1427
- ³⁹ [Haug C, Gotzsche PC, Schroeder TV](#). Registries and registration of clinical trials. *N Engl J Med*. 2005 Dec 29;353(26):2811-2
- ⁴⁰ WHO ICTRP Results Reporting (<http://www.who.int/ictrp/results/en/>)
- ⁴¹ PhRMA Second Round Comments on International Clinical Trials Registry Platform (ICTRP) Disclosure Timing March 29 2006 (http://www.who.int/ictrp/002-PhRMA_29March06.pdf)
- ⁴² WHO ICTRP Open Comments Disclosure Timing (<http://www.who.int/ictrp/comments4/en/index.html>)
- ⁴³ WHO ICTRP Formal Consultation on Disclosure Timing Policy (April 26, 2006) (<http://www.who.int/ictrp/consultation/en/index.html>)

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- ⁴⁴ Quality Research in Dementia Consumer Network, Alzheimer's Society UK WHO Consultation On Transparency In Clinical Trials March 26, 2006 (http://www.who.int/ictrp/001-Alzheimers_Society_UK_26March06.pdf)
- ⁴⁵ SuperMAB on trial. Lancet. 2006 Mar 25;367(9515):960.
- ⁴⁶ [Goodyear M.](#) 2006 op cit.
- ⁴⁷ European Cancer Patient Coalition January 2006 op cit
- ⁴⁸ Krall RL, Rockhold F. Clinical trials report card. N Engl J Med. 2006 Mar 30;354(13):1427
- ⁴⁹ Feczko J Clinical trials report card. N Engl J Med. 2006 Mar 30;354(13):1426-7
- ⁵⁰ Rockhold FW, Krall RL Clinical trials registration PLoS Med 2006 3(3): e157
- ⁵¹ PhRMA March 29 2006 op cit
- ⁵² [Zarin DA, Tse T, Ide NC.](#) Clinical trials report card. N Engl J Med. 2006 Mar 30;354(13):1428
- ⁵³ Abbott Response to World Health Organization International Clinical Trials Registry Platform (ICTRP) Request for Open Comments on Disclosure Timing January 24, 2006 (http://www.who.int/ictrp/3001_Abbott_USA_25Jan06.pdf)
- ⁵⁴ [Drazen JM, Wood AJ.](#) Clinical trials report card. N Engl J Med. 2006 Mar 30;354(13):1428-9
- ⁵⁵ AdvaMed Response to the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Request for Comments on Delayed Disclosure March 31, 2006 (http://www.who.int/ictrp/003-AdvaMed_31March06.pdf)
- ⁵⁶ Institute of Medicine Developing a National Registry of Pharmacologic and Biologic Clinical Trials: Workshop Report National Academies Press Washington DC 2006
- ⁵⁷ [Eggertson L.](#) Physicians want transparency as Guidant lawsuits grow. CMAJ. 2005 Oct 11;173(8):855-6.
- ⁵⁸ Editorial Anatomy of a Flawed Company New York Times April 1 2006
- ⁵⁹ Feder BJ, Meier B Guidant Withdraws Stents After Discovering Defects New York Times March 30 2006
- ⁶⁰ [De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusic A, Overbeke AJ, Schroeder TV, Sox HC, Van Der Weyden MB; International Committee of Medical Journal Editors.](#) Is This Clinical Trial Fully Registered?: A Statement from the International Committee of Medical Journal Editors (http://www.icmje.org/clin_trialup.htm)
- ⁶¹ The Registration of Clinical Trials WAME Policy Statements July 22, 2005 (<http://www.wame.org/wamestmt.htm#trialreg>)
- ⁶² Open Comments Of Cancer Patients To WHO On Delayed Public Disclosure Of Clinical Trials Information European Cancer Patient Coalition March 2006 (http://www.who.int/ictrp/004-ECPC_31March06.pdf)
- ⁶³ Reidenberg MM. Conflict of interest and medical publication. Sci Eng Ethics. 2002 Jul;8(3): 455-7.
- ⁶⁴ Tamir O, Lipschitz Y, Shemer J. Clinical trials report card. N Engl J Med. 2006 Mar 30;354(13):1427-8
- ⁶⁵ Directive 2001/20/Ec Of The European Parliament And Of The Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use Official Journal of the European Union L121, May 1st 2001 34-44 (http://eudract.emea.eu.int/docs/Dir2001-20_en.pdf)
- ⁶⁶ [Zarin DA, Tse T, Ide NC.](#) Trial Registration at ClinicalTrials.gov between May and October 2005. N Engl J Med. 2005 Dec 29;353(26):2779-87
- ⁶⁷ [Drazen JM, Wood AJ.](#) Trial registration report card. N Engl J Med. 2005 Dec 29;353(26):2809-11