Randomized trials that changed medical practice

May, 2000

The following list includes those trials that according to the opinion of the members of the Evidence-Based Discussion Group satisfy the following criteria:

   a. demonstrated reversal of the treatment effect (in comparison with previous non-randomized trials)
   b. showed that potentially harmful, very toxic, complicated or expensive treatments were not superior to less harmful and less complicated treatments
   c. resulted in dramatic beneficial effect (e.g. having relative-risk reduction >30%)
   d. provided "an example of the danger of applying pathophysiologic reasoning to therapeutic actions without first testing the hypothesis by means of adequately designed trials".

Although suggested by some members of the group, at this time systematic reviews or meta-analyses are not included in the list.

This is a work in progress and of potentially great importance (it can help us learn about effectiveness of our therapeutic innovative efforts). Please send your comments or information about trials (djulbebm@moffitt.usf.edu) that are not included in the list and that according to your opinion should have been included. In addition, we would welcome inclusion of any new trials that are deemed to meet above criteria.

A similar list was compiled by Fineberg in 1987 (in part cited here) who reviewed 28 "landmark" studies, and found that only 2 had an immediate (1-2 year) impact on practice. (M Ebell):Clinical evaluation: how does it influence medical practice? Fineberg HV Bull Cancer 1987 74:3 333-46

Please note that the listed articles have NOT been reviewed; references are included as they were submitted to B. Djulbegovic, who then compiled a list. Therefore, it is possible that some of the papers included do not meet above stated criteria for a "trial that changed our practice."
The following individuals have contributed to the list:

Bardri Badrinath, Brian Budenholzer, Mike Campbell, David L. Doggett, Mark Ebell, Peter Ellis, Bruce Guthrie, Janet E. Hiller, Gary Jackson, Richard W Morris, Roy Poses, Steve Simon, Daniel L. Sontheimer, Donald Stanley, Jeffrey A. Tice, Nico van Duijn, Julius Weinberg, Samuel Wiebe, Kenneth S. Yew

**Cardiology and Thrombosis**

Teo KK, Yusuf S, Fuberg CD. Effects of prophylactic anti-arrhythmic drug therapy in acute myocardial infarction. JAMA 1993;270:1589-95

(e.g. prophylactic use of lidocaine (and other anti-arrhythmic drugs?) during myocardial infarction was shown to be more harmful than placebo


Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH,


("A cardiology professor in 1980 told my fellow students and me that the RCTs I will cite would be unethical because those assigned to the placebo group would be denied "life saving treatment." Thank God (or whoever) that not everyone shared his opinion") (B. Budenholzer)


("My favorite example is the CAST study showing that treatment of ventricular ectopy with type I anti-arrhythmic based on the assumption that this would prevent life-threatening arrhythmias actually lead to a higher death rate") (R. Poses)

("showed that class I antiarrhythmics suppressed ventricular extrasystoles but lead to increased total mortality" ) (P. Ellis)


(HERS is still controversial but current, and instructive in counterpoint to the overwhelming observational evidence in favor of HRT for CHD prevention.) (J. Tice)


"Comment: This is another trial that contradicted earlier observational and laboratory studies about favorable effects of estrogen alone or in combination with medroxyprogesterone on coronary artery disease. The authors concluded that "women with heart disease should not use conjugated estrogen, alone or in combination with medroxyprogesterone". Note that data on primary prevention are still not available".


("Until 4S I was deeply sceptical about drug treatment for cholesterol. 4S changed that to cautious belief. Equally importantly, for me WOSCOPS reinforced 4S by showing very similar sized effects in a different population. For me, WOSCOPS was more important in making me trust 4S for secondary prevention than in radically changing my practice for primary prevention of heart disease. And then there's been all the rest with a cumulative impact.") (B. Guthrie)

Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2.


Ligation of int. mammary artery as a treatment for coronary artery disease


(ligation was no better than sham surgery, with small incision in the chest)


A truly historic trial that established efficacy of heparin in the treatment of thrombotic disease. In recent years, the treatment of pulmonary embolism/deep vein thrombosis has been further refined in RCTs (some cited above) demonstrating further benefit of low-molecular weight heparin over unfractionated heparin in several clinical situations. This field has tremendously advanced thanks to RCTs.


**Endocrinology**

**Infectious Diseases**


(The use of steroids in these circumstances was supported by theoretical work, animal studies and case reports. Some might have claimed that the evidence for the use of steroids was "overwhelming" and that the study was unethical! The results showed that steroids were in fact harmful.) (J. Weinberg)


This trial not only established superiority of streptomycin over bed rest (standard treatment at the time), but was **first truly randomized trial** to be reported. This "1948 watershed" signifies the introduction of randomized controlled trials as one of the most important forms of scientific inquiry ever designed in clinical medicine. (Note that the first trial which allocated patients randomly was one designed to test the efficacy of immunisation against whooping cough, but it was reported three years later in BMJ 1951; i: 1463-1471).


**Gastroenterology**

Gastric freezing in the treatment of peptic ulcer


[dramatic results for beneficial effect of gastric surgery in the treatment of peptic ulcers were obtained in uncontrolled studies; RCT demonstrated that surgery was no more successful than less aggressive medical treatments resulting in abandoning this aggressive procedure; cited in: Alman D. What randomized trials and systematic reviews can offer decision makers. Horm Res 1999;51 (suppl 1):36-43]


**Nephrology**


(Showed that plasmapheresis was ineffective (?detrimental) in the treatment of severe lupus nephritis) (P. Ellis)

**Oncology.**


(trials listed above help defined current practice of adjuvant chemotherapy and lumpectomy instead of mastectomy in breast cancer)

(trial that defined the current practice of using ABVD as a combination of choice in Hodgin's disease)


(trials that help defined current practice of adjuvant therapy in rectal and colon cancer)


(the key trial that introduced CHOP chemotherapy in the treatment of malignant lymphomas; over next 20 years numerous phase II trials have been introduced claiming superiority of so called second and third chemotherapy regimens; the issue was finally settled in 1993 with publication of RCT showing that CHOP has remained least toxic and equally effective chemo regimen in the treatment of NHL; see below)


(trials that defined the current practice of using CHOP as a combination of choice in NHL in advanced disease)


(trials that defined the current practice of using CHOP+XRT as a combination of choice in NHL in early stages)

(this and related trials reported in the abstract form at the ASCO 1999 effected practice of referral in the United States by showing no difference in survival between high-dose and standard treatment arm) (see N Engl J Med 2000;342:1138-1139).

**melphalan+prednisone (MP) vs. colchicine in the treatment of amyloidosis**

[reversal of the effect; MP in RCT was shown superior to colchicine (N Engl J Med 1997; 336:1202) that was earlier, in non-RCT trial (Am J Med 1987;87:1182), was claimed to be superior to M+P)]

**surgery vs. surgery+adjuvant chemoRx in treatment of osteosarcoma**

(dramatic beneficial effect of adjuvant chemoRx proving that surgical technique is not sufficient. N Engl J Med 1996;314:1600)

**Obstetrics and Gynecology**


(This trials also "raised severe problems about when to stop a major international trial, where the treatment effect appears opposite to that expected, but when stopping early may reduce the impact of the trial and so make it less likely to change medical practice.) (M.Campbell)


(We thought we were doing such good, now it appears that we may have been increasing the chance of tears rather than decreasing.) (G. Jackson )

**use of DES to prevent miscarriages in pregnant women**

Chalmers TC. The impact of controlled trials on the practice of medicine. Mt Sinai J Med 1974;41:753-759

(outcomes were worse in DES treated group compared to control; this is considered as classic example of the danger of introducing chemotherapy based


("In our study - which was large and had an intention to treat analysis we not only showed no benefit of antenatal TRH but also an indication of adverse effects in the group excluded in prior analyses". (JE Hiller)


"Proved magnesium was superior for prevention of eclampsia, and changed opinions, as witnessed by number of editorials in journals following publication. Magnesium was largely preferred in the US, but phenytoin was preferred in Europe (particularly the U.K.) prior to this study."(D. Sontheimer)

Folate And Neural Tube Defect


**Ophtalmology**

Optic nerve decompressive surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. The Ischemic Optic Neuropathy Decompression Trial Research Group [see comments]. JAMA 1995; 273: 625-632

This is "another RCT that changed medical (surgical) practice. Optic nerve decompression was a favoured and widespread treatment prior to this trial which proved its uselessness and potential harmfulness" (S. Wiebe)

**Neurology**

Extracranial/Intracranial bypass surgery for stroke prevention in symptomatic atherosclerotic stroke. This common surgical procedure was abandoned after the RCT demonstrating no benefit (The EC/IC Bypass Study Group. Failure of Extracranial-Intra cranial Arterial Bypass to Reduce the Risk of Ischemic Stroke. N.Engl.J.Med. 1985; 313: 1191-1200.)
Also of interest:

"A peculiar category is the 'tomato effect', in fact a type 4 error. The example - as far as I can recall it - is the efficacy of gold injections in R.A. based on a infectious theory. When that infectious theory was proven wrong, the gold therapy was abandonned and with that the real efficacy of that therapy, untill the efficacy of gold was rediscovered, and proven in properly designed studies."
(Nico van Duijn)


"The best example I can think of is ECMO. It was so successful and so rapidly adopted that there was a lot of debate about whether a randomized trial would be ethical.

A rather technical discussion of "adaptive randomization" (an approach that tried to overcome some of the ethical problems with studying a therapy like ECMO) appears in Ware JH "Investigating Therapies of Potentially Great Benefit: ECMO" Statistical Science (November 1989) 4(4):298-317" (S. Simon)

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Send all comments regarding this list to:

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