Randomized Controlled Clinical Trials for Surgical Operations – Square Peg--Round Hole?
ARE SURGEONS TOO CREATIVE?

New operations don’t face the same scrutiny as new drugs—and critics are increasingly worried about risks to patients.
Increasing call for “evidence based medicine”

- New, expensive technology
- Pressure from payors
- Hospital budget restraints
- Patients
Trial of a New Drug

- Drug doesn’t change over time
- Variable biological response
- Unforeseen, late side effects, toxicity
Surgical research or comic opera: questions, but few answers

“Surgical Scientist” oxymoron?
Limitations of RCTs in Surgery

- Long time frame – for design, training, data collection, follow-up and analysis
- Cannot be blinded/double blinded
- Costly – hundreds of thousands to millions of dollars
- Lack of infrastructure and experience for data collection
- Lack of education in clinical epidemiology
Limitations of RCTs in Surgery

- Often not generalizable (strict inclusion/exclusion criteria)
- Learning curve for procedure may be steep
- Evolution in technical modifications, risk, selection criteria, post-op care
- Not reversible (drug effects often are)
- Difficult to standardize. Variations common – may influence success rates
Limitations of RCTs in Surgery

• Skill of surgeon
“When a basic scientist is informed that another investigator cannot reproduce his work, it has a chilling effect...”
“... for the surgeon, however, it’s a source of pride.”

Dr. Judah Folkman
Limitations of RCTs in Surgery

- Surgery (for symptomatic relief) has a large placebo effect
- Pre-selection bias (lack of equipoise)
- Commercial competition, personal prestige
- Surgical versus non-surgical treatment: potential for financial loss or loss of independence
- Less than 7% of published surgical trials are randomized and of these, quality is very low
Limitations of RCTs in Surgery

- Timing of trial (too soon or too late?)
Limitations of RCTs for Evaluating Emerging Operations

“Emerging heart operations through RCTs could have resulted in unreliable and misleading conclusions.

The list of discarded operations might have included heart transplantation, mechanical circulatory assist devices, cardiac valvular procedures, coronary artery bypass grafting, and repair of congenital lesions.”

Berger et al.
Randomized Clinical Trial

Pro – Considered Authoritative
Randomized Clinical Trial

Con – Considered Authoritative
Randomized Clinical Trials

When flawed, propagate misleading information considered “authoritative”
Critical Review of Literature
Lung Cancer Screening
The Mayo Trial

- Underpowered (could only detect 50% reduction in mortality)
- Compliance only 75% in intervention group
- Annual chest radiography in 50% of controls
- 50% of deaths due to ischemic cardiac disease
Transmyocardial laser revascularisation in patients with refractory angina: a randomised controlled trial

P M Schofield, L D Sharples, N Caine, S Burns, S Tait, T Wistow, M Buxton, J Wallwork

Methods 188 patients with refractory angina were randomly assigned TMLR plus normal medication or medical management alone. At 3 months, 6 months, and 12 months after surgery (TMLR) or initial assessment (medical management) we assessed exercise capacity with the treadmill test and the 12 min walk.

Case: Transmyocardial Revascularization

TRANSMYOCARDIAL REVASCULARIZATION FOR END-STAGE CORONARY ARTERY DISEASE

TRANSMYOCARDIAL REVASCULARIZATION WITH A CARBON DIOXIDE LASER IN PATIENTS WITH END-STAGE CORONARY ARTERY DISEASE

O.H. Frazier, M.D., Robert J. March, M.D., and Keith A. Horvath, M.D., for the Transmyocardial Carbon Dioxide Laser Revascularization Study Group*

Frazier et al. NEJM, 341:1021-8;1999
Case: Transmyocardial Revascularization

Presumably, this benefit would be due to TMLR, as nobody would be so foolish as to propose that a mere thoracotomy, which was done in the treatment arm but not in the control group, could account for the improvement.
Evaluation of Internal Mammary Artery Ligation and Sham Procedure in Angina Pectoris

18 patients with angina

<table>
<thead>
<tr>
<th></th>
<th>IMA ligation</th>
<th>Sham</th>
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<tr>
<td>Marked Improvement in angina</td>
<td>10</td>
<td>5</td>
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<tr>
<td>Significant increase in exercise tolerance</td>
<td>10</td>
<td>5</td>
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</tbody>
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Overall decrease in ntg use

AN EVALUATION OF INTERNAL-MAMMARY-ARTERY LIGATION BY A DOUBLE-BLIND TECHNIC*

LEONARD A. COBB, M.D.,† GEORGE I. THOMAS, M.D.,‡ DAVID H. DILLARD, M.D.,§
K. ALVIN MERENDINO, M.D.,‖ AND ROBERT A. BRUCE, M.D.‖

SEATTLE, WASHINGTON

Cobb et al. NEJM, 260:1115-1118;1959
Evaluation of Internal Mammary Artery Ligation and Sham Procedure in Angina Pectoris

“It is concluded that if the internal mammary artery procedure has any merit whatsoever, attempts to evaluate it in terms of increased exercise tolerance or decreased need for nitroglycerin ignore the psychogenic component of angina”

“It is better to know nothing that to know what ain’t so.”

Josh Billings
Randomized Clinical Trials

- “the paucity of properly conducted clinical trials (in surgery) serves as a testament to their difficulty to perform in practice.”

Cook, Alscher, Hsiang
American Journal of Surgery 185:2003
Randomized Controlled Trials

Reporting Standards (n = 158)
  • overall inadequate

Quality of Trials (n = 69)
  • low in large proportion
  • worse in surgical journals

Quality of Evidence – RCT vs. observational
  • generally the results from observational studies correlate with those of RCT

Robin McLeod
Annals of Surgery 2006
The Clinical Trial: Deceitful, Disputable, Unbelievable, Unhelpful, and Shameful—What Next?

Richard Horton, MD
*The Lancet, London, United Kingdom*

“A survey of 442 medical statisticians, completed in 1998, obtained a 37% response rate. * Despite this poor return, half of all respondents knew of at least one fraudulent project done in the previous 10 years. Forty-three (26%) statisticians reported fabrication and falsification; 32 (20%) described deceptive reporting of data; 31 (19%) knew of data suppression; and 16 (10%) were aware of instances of deceptive design and analysis. Worse still, 30% of this sample had engaged in a fraudulent project.”


YEP, SON,
WE HAVE MET
THE ENEMY
AND HE IS US.
“The weakness of randomised controlled trials (RCTs) is that they are conducted on a set of patients who cannot be regarded as a random sample from the population that will be treated outside the trial. Observational data collected in a prospective clinical database may provide more realistic estimates.”

Institute of Medical Statistics and Biometrics.
Milan, Italy

Marubini et al.
The Lancet: 347. 1996
The New England
Journal of Medicine

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Volume 314 JANUARY 2, 1986 Number 1

INFLUENCE OF THE INTERNAL-MAMMARY-ARTERY GRAFT ON 10-YEAR SURVIVAL AND OTHER CARDIAC EVENTS

FLOYD D. LOOP, M.D., BRUCE W. LYTLE, M.D., DELOS M. COSGROVE, M.D., ROBERT W. STEWART, M.D., MARLENE GOORMASTIC, M.P.H., GEORGE W. WILLIAMS, Ph.D., LEONARD A.R. GOLDING, M.D., CARL C. GILL, M.D., PAUL C. TAYLOR, M.D., WILLIAM C. SHELDON, M.D., AND WILLIAM L. PROUDFIT, M.D.
vein graft only vs. IMA plus vein graft(s)

- 1.4 x risk of late M.I.
- 2.0 x risk of cardiac reoperation
- 1.6 x risk of death in 10 years

*Loop et al. NEJM 1986*
The Medical Breakthrough
Every Physician
And Every
Emphysema
Patient Must
Know About...

The Last Chance You've Prayed For

Now There Is A Cure

Unless you are a victim of emphysema, or a loved one who has lived with a victim, you may not understand what a new medical breakthrough really means. Just a few years ago, life for emphysema victims was an end in the quality of life that many looked forward to in their retirement years. Now thanks to a medical breakthrough, there is a cure. It's an operation that is so minimally invasive that emphysema patients can return to work as soon as 70% of their lung capacity most patients go home within a week.

We are sure you will want to know more about this new procedure. Read this informative brochure and then contact us for help.

1-800-US LUNGS (1-800-875-8647)
GENERAL THORACIC SURGERY

THORACOSCOPIC LASER BULLECTOMY: A PROSPECTIVE STUDY WITH THREE-MONTH RESULTS

Stephen Hazelrigg, MD\textsuperscript{a}, Theresa Boley, RN, MS\textsuperscript{a}, Joseph Henkle, MD\textsuperscript{a}, Carl Lawyer, MD\textsuperscript{a}, David Johnstone, MD\textsuperscript{b}, Keith Naunheim, MD\textsuperscript{c}, Cesar Keller, MD\textsuperscript{c}, Robert Keenan, MD\textsuperscript{d}, Rodney Landreneau, MD\textsuperscript{d}, Frank Sciurba, MD\textsuperscript{d}, Richard Feins, MD\textsuperscript{b}, Paul Levy, MD\textsuperscript{b}, Mitchell Magee, MD\textsuperscript{a}
“… our statisticians encourage clinical investigators to design trials that may make their lives a little too easy by making our lives more difficult. Rather than constraining human choices to meet the needs of statisticians, I think we should encourage the statisticians to devise methods of evaluating the sorts of choices that free and intelligent citizens make all the time.”

*Lantos J. The MacLean Center for Clinical Medical Ethics. The University of Chicago. 1994.*
Introduction of New Procedures

1) Health Care Providers should restrict the application of promising new procedures to a limited number of centers of excellence, having appropriate resources and experience.

2) Centers should be required to document and report specified information regarding morbidity, mortality and objective measures of outcome.

3) This data should be periodically reviewed and evaluated by an independent scientific panel.
Introduction of New Procedures

By this means the procedure can be offered to appropriate patients, insurers and patients can be protected against abuse, and the necessary data be acquired for objective analysis.
“Evidence-based medicine: what it is and what it isn’t...”
Sackett DL et al. BMJ 1996;312:71-72

- “Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”.
- Evidence-based medicine is not “cookbook” medicine....External clinical evidence can inform, but can never replace, individual expertise (judgment), and it is this expertise that decides whether the external evidence applies to the individual patient at all....”
“Evidence-based medicine perpetuates a myth current in the medical profession that treatments not demonstrated to be successful in double-blind, placebo-controlled trials are not effective.”

“The randomised, controlled trial is a powerful tool if used correctly, but it is no holy grail and its limitations should be more widely appreciated.”
RCTs in Surgery

• Not the solution

• Part of the problem
REBUTTAL – PRO position

Randomized Controlled Clinical Trials are Necessary to Evaluate New Surgical Operations

Timothy J. Gardner MD
AATS 2010
Toronto, May 5 2010
Required reading for all Thoracic Surgeons over the age of 50 and for a few selected younger ones (*You know who!*)
Health Care is Front and Center…

“Homes have been lost, jobs shed, businesses shuttered. Our health care is too costly, our schools fail too many… The question we ask today is not whether our government is too big or too small, but whether it works, whether it helps families find jobs at a decent wage, care they can afford, a retirement that is dignified.”
Why are Costs Excessive & Variable?

“Only a limited amount of evidence is available about which treatments work best for which patients and whether the added benefits of more-effective but more-expensive services are sufficient to warrant their added costs—yet current practice tends to adopt more-expensive treatments even in the absence of rigorous assessments of their impacts....”

Peter Orszag
Congressional Budget Office 2007
Comparative Effectiveness Research

- Comparative effectiveness research: a rigorous evaluation of the impact of different options that are available for treating a medical condition (CBO)
  - ...may compare similar treatments, such as competing drugs--or analyze different approaches
    - ...may focus on medical risks/benefits, or weigh costs
- The purpose is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels (IOM)
American Recovery and Reinvestment Act

Allocation: $1.1 billion

- NIH: $400 million
- AHRQ: $300 million
- HHS: $400 million

Federal coordinating counsel for CER

- Advise on CER Federal infrastructure needs
- Federal officials including AHRQ, NIH, VA

IOM issued report on priorities June 2009

http://www.opencongress.org/bill/111-h1/text
Coronary Artery Bypass is Superior to Drug-Eluting Stents in Multivessel Coronary Artery Disease*

Robert A. Guyton, MD
Division of Cardiothoracic Surgery, Department of Surgery, Emory University School of Medicine, Atlanta, Georgia

Percutaneous intervention for the treatment of multivessel coronary artery disease continues to displace coronary artery bypass graft surgery. But controlled trials of percutaneous intervention versus coronary bypass, in meta-analysis, have shown a significant survival advantage for coronary bypass. Studies of bare metal stents have not presented any data to prompt reversal of this conclusion for all but the small portion of patients most suited for stenting. Drug-eluting stents have no survival advantage compared with bare metal stents. Data from real-world registries have shown that the current therapy of multivessel disease patients has resulted in a relative excess mortality of as much as 46% in patients with initial stenting compared with patients with initial coronary bypass. Ethical considerations demand that patients with multivessel disease be informed of the documented mortality benefit of coronary bypass graft surgery.

Radial artery patency and clinical outcomes: Five-year interim results of a randomized trial

Brian F. Buxton, MB, BS, FRACS, FRCS, FACS, FRCS(C)
Jai S. Raman, MBBS, MMed, FRACS
Permyos Ruengsakulrach, MD, PhD, FRCST
Ian Gordon, MSc, PhD, AStat
Alex Rosalion, BSc, MB, BS, FRACS
Rinaldo Bellomo, MBBS, MD, FRACP
Mark Horrigan, MB, BS, FRACP
David L. Hare, MB, BS, DPM, FRACP

J Thorac Cardiovasc Surg 2003;125:1363-1371
Left Atrial Radiofrequency Ablation During Mitral Valve Surgery for Continuous Atrial Fibrillation: A Randomized Controlled Trial

George Doukas; Nilesh J. Samani; Christos Alexiou; et al.

Context  Although left atrial radiofrequency ablation (RFA) is increasingly used for the treatment of chronic atrial fibrillation during mitral valve surgery, its efficacy to restore sinus rhythm and any resulting benefits have not been examined in the context of an adequately powered randomized trial.

Objective  To determine whether intraoperative RFA of the left atrium increases the long-term restoration of sinus rhythm and improves exercise capacity.

Design, Setting, and Patients  Randomized, double-blind trial performed in a single UK tertiary referral center with enrollment between December 2001 and November 2003. A total of 101 patients referred for mitral valve surgery with at least 6 months' history of uninterrupted atrial fibrillation were assessed for eligibility; 97 were enrolled. Patients were followed up for 12 months.
Off-Pump vs Conventional Coronary Artery Bypass Grafting: Early and 1-Year Graft Patency, Cost, and Quality-of-Life Outcomes: A Randomized Trial

John D. Puskas, Willis H. Williams, Elizabeth M. Mahoney, et al.

“Conclusion: In this randomized single-surgeon trial among unselected patients with angiographic follow-up, OPCAB achieved similar graft patency in the hospital and at 1 year. Cardiac outcomes and health-related quality of life at 30 days and 1 year were similar and patients incurred a lower cost. OPCAB may provide complete revascularization that is durable and cost-effective.”
On-Pump versus Off-Pump Coronary-Artery Bypass Surgery

A. Laurie Shroyer, Ph.D., Frederick L. Grover, M.D., Brack Hattler, M.D., Joseph F. Collins, Sc.D.,
Gerald O. McDonald, M.D., Elizabeth Kozora, Ph.D., John C. Lucke, M.D., Janet H. Baltz, R.N.,
and Dimitri Novitzky, M.D., Ph.D., for the Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group

CONCLUSIONS

At 1 year of follow-up, patients in the off-pump group had worse composite outcomes and poorer graft patency than did patients in the on-pump group. No significant differences between the techniques were found in neuropsychological outcomes or use of major resources. (ClinicalTrials.gov number, NCT00032630.)
The National Emphysema Treatment Trial: A Paradigm for Future Surgical Trials
Douglas E. Wood, MD, and Malcolm M. DeCamp, MD
Section of General Thoracic Surgery, University of Washington, Seattle, Washington, and Division of Thoracic and Cardiovascular Surgery, Cleveland Clinic Foundation, Cleveland, Ohio

Paying the Piper: The NETT Strikes a Sour Note
Joel D. Cooper, MD
Division of Cardiothoracic Surgery, Washington University School of Medicine, St. Louis, Missouri
Rebuttal
Advantages of Randomized Clinical Trials

- Elimination of bias
- Balance treatment groups in terms of known or unknown prognostic factors
- Major impact on payors
Endarterectomy for Asymptomatic Carotid Artery Stenosis

Asymptomatic with Stenosis 60% or greater

Aspirin, Medical Management

11% 5yr Stroke Rate

Carotid Endarterectomy

5.1% 5yr Stroke Rate
Randomized Clinical Trial

- Preventative procedure
- Comparison with alternative medical or surgical intervention
- Oncology trials – where outcome relates to long term results (survival, time to recurrence, etc.)
“Parachute use to prevent death and major trauma related to gravitational challenge”.
Smith GCS, Pell J P. BMJ 2003;327:1459-61

Parachutes reduce the risk of injuries after gravitational challenges, but their effectiveness hasn’t been proven with randomized controlled trials
Case Controlled Series

- No alternative therapy
- Natural history of condition well documented, and impact of intervention obvious
- Magnitude of effect measurable, significant, and expected
NETT Surgery vs. Ciccone et al
Heterogeneous Upper Lobe Predominant

90 day Mortality

LVRS  5%
(n=261)

Ciccone et al  4%
(n=250)
Survival following LVRS

Survival

0 1 2 3 4 5
Time in years

Ciccone et al
NETT Heterogeneous Upper Lobe Predominant Surgery
FEV₁ % Predicted

PreOp  6 Mos  1 Year  3 Years  5 Years

Ciccone et al
NETT Heterogeneous Upper Lobe Predominant Surgery
LVRS Reduction in RV

Ciccone et al
NETT Heterogeneous Upper Lobe Predominant Surgery
The notion of equipoise is a sham, forced upon the investigators by Medicare and the NIH in an attempt to justify the denial of LVRS to Medicare beneficiaries.

G. A. Patterson
NETT Surgery vs. Medical Rx

Heterogeneous Upper Lobe Predominant

Survival

0 1 2 3 4 5
Time in years

Med. Therapy (n=250)

Surgery (n=261)

Survival

92% 90% 80% 74% 67% 59%

p = .02

p = .02
TMLR – medicare approved

LVRS – medicare denied
• Statistical difference does not prove clinically important difference
“There are lies, damn lies, and statistics.”

-B. Disraeli
Evidence-based medicine perpetuates a myth current in the medical profession that treatments not demonstrated to be successful in double-blind, placebo-controlled trials are not effective. National newspapers report that only 15% of NHS treatments are of proven value, the unstated implication being that 85% are ineffective, so the health budget could be cut by a commensurate amount without harm to patients. In fact, 82% of primary treatments are evidence based, at least in certain circumstances. Doctors talk of evidence-based medicine and managers wish such concepts to be incorporated into business plans. The obvious response to such nonsense is to ask if one is willing to practise without penicillin or appendicectomy. The randomised, controlled trial is a powerful tool if used correctly, but it is no holy grail and its limitations should be more widely appreciated.
Randomized Control Trials

In situations where one wishes to detect a small but clinically important difference, a randomized controlled trial is mandatory.

Robin McLeod
Annals of Surgery 2006
Preventative Procedure

e.g. Adjuvant therapy for cancer resection (lobectomy, esophagectomy)

e.g. Carotid endarterectomy in asymptomatic patient
What are Clinical Guidelines?

“Clinical Guidelines are systematically developed statements to help practitioners and patients decide on appropriate healthcare for specific clinical conditions and/or circumstances.”

Clinical Practice Guidelines: Directions for a New Program
Institute of Medicine, NAS. 1990
Factors Which Can Distort Conclusions of RCTs

- Statistical analysis
  - Type I Error – treatment inappropriately considered significant when it is not (due to chance) – most studies designed to avoid this
  - Type II Error – failure to detect a significant difference, even though one exists
    - study population at low risk for adverse outcome
    - study population too small
    - follow-up too short

Bonchek
THE CULT OF THE DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

SJ ELLIS MD, RF ADAMS MRCP, Keele University, Stoke-on-Trent, and 'John Radcliffe Hospital, Oxford

SUMMARY The double-blind, placebo-controlled trial is held as the gold standard in medical knowledge, but this tool of investigation has its weaknesses. These include ethical limitations on the types of comparison that can be undertaken, the central conflict between best practice for an individual and trial protocols, problems of applicability to the general population and applicability of work done on one population to another, type II errors, publication bias, misuse and limitations of statistics, fraud, maintenance of blinding, asking the wrong question, and a simplistic, reductionist view of clinical management. The concentration on the randomised, controlled trial devalues information from other sources, such as natural history studies, clinical experience and case reports. The randomised, controlled trial is an important source of information and as physicians we should welcome more well-crafted trials, but they are not the only source of information. (Br J Clin Pract 1997; 51(1): 36-39)
Agency for Healthcare Policy and Research (AHCPR)

Quality of scientific evidence

- Randomized clinical trials
- Well designed clinical studies
- Expert panel consensus
Reflections on randomised controlled trials in surgery

Michael Baum

Guidelines

A synthesis of evidence, science, judgment, experience, caring and accountability.
“The purpose of this paper is to highlight the role of randomised controlled trials in the development of surgery. However, randomised comparisons are unnecessary when the natural history of the disease is well established and the effect of the operation is spectacular.”

*Baum M. The Lancet. 1999.*
“The infrastructure required for a randomised controlled trial is generally expensive to set up and this rigour of design is not always necessary; the effects of some surgical procedures may be large and unlikely to be confused with sources of bias or confounding.”

“...there is evidence that non-randomised designs can provide valid estimates of effectiveness if standard epidemiological principles are applied to the design of studies and analyses of data.”

“The importance of the case series in surgical research is beyond doubt. Therefore, it seems reasonable to ask whether we can trust this study method to yield a valid result. According to conventional epidemiological wisdom, the answer is no.”

“To retain their academic reputation surgeons must find imaginative ways to collaborate with epidemiologists to improve the design of the case series and to plan randomised trials.”

“In 1923, the medical statistician, Major Greenwood wrote that ‘. . . I should like to shame (surgeons) out of the comic opera performances which they suppose are statistics of operations’. Only when the quality of publications in the surgical literature has improved will surgeons reasonably be able to rebut the charge that as much as half of the research they undertake is misconceived.”

Does absence of a trial mean a treatment cannot be recommended? In surgery that would leave us with very little to offer.

Tom Treasure
Volume Reduction Surgery

SAN DIEGO UNION TRIBUNE  
July 11, 1993

EMPHYSEMA

Now There’s a Cure

Call About Successful

New Laser Procedure

1-800-XXX-XXXX
Are there effective, alternative treatments?

- Yes
  - Radiotherapy/Chemotherapy vs. Surgery
    - Ca prostate
    - ENT tumors
    - Small cell carcinoma

- No
  - Transplantation
  - LVRS
“The impetus for proliferation of early, randomized, surgical studies has come from the financial support offered by the government. Once such studies begin, they generate their own central bureaucracy and peripheral constituency, and changing their course is like turning a battleship around. Abandonment of a flawed or obsolete randomized study involves an admission of error and a loss of financial support – a form of academic suicide.”

“Randomized controlled trials raise a number of ethical issues. Physicians who participate in such trials must be in a state of “equipoise”, or genuine uncertainty about the relative merits of the two arms of the trial. Otherwise, they would be ethically compelled to recommend the treatment they preferred.”
Introduction of New Procedures

Coverage vs. Validation
What do you want to know?

• Impact on long term survival
• “Value” of procedure (how much better than control group)
• Comparison with acceptable alternative

Need RCT
What do you want to know?

- Magnitude of benefit
- Duration of benefit
- Risk
- Appropriate candidates (indication)

RCT not essential
Retrospective Case Series

If we know the natural history of a disease, and a series of cases are operated on and a much better clinical course ensues, this has been regarded as evidence on which to base a change in practice.

Tom Treasure
Coverage

- Theoretical justification
- Preliminary evidence of efficacy
- Presumption of benefit
- Absence of alternative
- Ongoing reassessment
Validation

- Scientific analysis
- Long term results
- Well controlled case series
- Randomized clinical trials
“Your saying it’s so doesn’t make it so.”

Tom Sawyer
Enfisema ora si può curare
Study questions need for lung reduction surgery

By ROGER SCHLUETER
rschlueter@bmd.com

EMPHYSEMA SUFFERERS

Controversial surgery carries high risk

The new numbers further underline those who survived showed little benefit from the procedure. As a result, one colleague, who owned a surgery, says that the procedure is no longer performed. It appears that the staff of the hospital might be able to walk around a room but cannot walk around a half of a room. Almost all needed supplemental oxygen.

Ninety-six of the 140 patients were listed for surgery. Such severe illness means a patient might be able to walk around a room but cannot walk half a room. Almost all needed supplemental oxygen.

HEALTH

Study Casts Doubt On Surgery Used Against Emphysema

BY LAURA JOHANNES
Staff Reporter of The Wall Street Journal

An increasingly used surgery to remove large chunks of the lung to treat emphysema actually did more harm than good in a group of patients with very severe disease, according to interim findings of a large national study.

Due to their importance, the findings were released well ahead of their original Oct. 11 publication date in the New England Jour-
SPECIAL ARTICLE

EQUIPOISE AND THE ETHICS OF CLINICAL RESEARCH

(Benjamin Freeman, Ph.D.)

Abstract: The ethics of clinical research requires equipoise — a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. Should the investigator discover that one treatment is of superior therapeutic merit, he or she is ethically obliged to offer that treatment. The current understanding of this requirement, which entails that the investigator have no "treatment preference" throughout the course of the trial, presents nearly insuperable obstacles to the ethical commencement or completion of a controlled trial and may also contribute to the termination of trials because of the failure to enroll enough patients.

I suggest an alternative concept of equipoise, which would be based on present or imminent controversy in the clinical community over the preferred treatment. According to this concept of "clinical equipoise," the requirement is satisfied if there is genuine uncertainty within the expert medical community — not necessarily on the part of the individual investigator — about the preferred treatment. (N Engl J Med 1987; 317: 141-5.)
COMMENTARY

The classics: a tribute to the fiftieth anniversary of the randomized clinical trial

Flávio D. Fuchs\textsuperscript{a,*,1}, Michael J. Klag\textsuperscript{b}, Paul K. Whelton\textsuperscript{c}

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\textsuperscript{b}Welch Center for Prevention, Epidemiology and Clinical Research, The Johns Hopkins University, Baltimore, MD
\textsuperscript{c}School of Public Health and Tropical Medicine, Tulane University Medical Center, New Orleans, LA

Received 29 April 1998; revised 9 September 1999; accepted 10 September 1999

In 1998 we celebrated the fiftieth anniversary of the first randomized clinical trial (RCT) [1]. Describing the plan and conduct of a controlled study on the effects of streptomycin in patients with tuberculosis (see below) the authors stated: “determination of whether a patient would be treated by streptomycin and bed rest or by bed rest alone was made by reference to a statistical series based on random sampling numbers drawn up for each sex and each centre by Professor Bradford Hill.” This and other randomized controlled clinical trials, some of them presented in this essay, gave origin to a revolutionary transformation in the standards of medical practice. This essay aims to honor the scientists who pioneered the development of methods for randomized clinical trials and the refinement of their application in practice.
Summary

1. The randomized controlled study design is seldom appropriate for surgical trials due to difficulty in standardizing treatments and the presence of excess bias.

2. The results of surgical RCT’s cannot be generalized and may not be applicable to any individual surgeon’s practice.

3. Not many surgical RCT’s are being done, and those that are being conducted are often of poor quality.
Factors Which Can Distort Conclusions of RCTs

- Selection bias – patients may be diverted from entering trial – because one arm perceived better than the other

Bonchek
Factors Which Can Distort Conclusions of RCTs

- Bias in allocation of patients to treatment groups – refusal of patients to accept assigned arm (especially medical vs. surgical trial)
- Inability to complete treatment

Bonchek
In the 1990s....

New impetus in the movement of Evidence-Based Medicine (First conceptualized by AL Cochrane in 1972)

The Clinical Trial becomes the gold standard of evidence-based medicine

Clinical Guidelines are a synthesis of available evidence (Clinical trials)
In the 2000s...

- The concept and use of Clinical Guidelines are well established.
- Many government agencies and voluntary organizations support the development of guidelines:
  - National Institute for Health and Clinical Excellence (NI CE)
  - Agency for Healthcare Research and Quality (AHRQ)
  - Grades of Recommendation Assessment, Development and Evaluation (GRADE Working Group)
  - Guidelines International Network (enGI Ne)
  - Sub-committee on the Use of Research Evidence (SURE) of the WHO Advisory Committee on Health Research (ACHR)
“Should informed patients decline to participate because they have chosen a specific clinician and trust his or her judgment - over and above the consensus in the professional community - that is no more than the patients right. We do not conscript patients to serve as subjects in clinical trials.”

Preventative Procedure

e.g. Adjuvant therapy for cancer resection (lobectomy, esophagectomy)

e.g. Carotid endarterectomy in asymptomatic patient
“However, our statisticians encourage clinical investigators to design trials that may make their lives a little too easy by making our lives more difficult. Rather than constraining human choices to meet the needs of statisticians, I think we should encourage the statisticians to devise methods of evaluating the sorts of choices that free and intelligent citizens make all the time.”

Lantos J. The MacLean Center for Clinical Medical Ethics. The University of Chicago. 1994.
New Surgical Procedures

- Intervention changes over time
  - Technique / experience evolve
  - Refinements in
    - patient selection
    - pre / post-op management
- Risk changes over time
- Requires subjective assessment of risk / benefit for each patient
- Skill, experience, facilities vary from one center to another
“What mitigating arguments might explain this preoccupation with the case series? Perhaps many surgeons do not see randomised trials as feasible strategy to resolve questions about surgical management. Cynics might even claim that the personal attributes that go to make a successful surgeon differ from those needed for collaborative multicentre research.”

“The possibility that some surgeons may have better outcomes with one procedure and other surgeons with an alternative procedure – i.e., there is an interaction between surgeon and technique – creates a particular difficulty.”

“What makes a surgical technique new is not always easy to define because surgical procedures generally evolve in small steps, which makes it difficult to decide when a procedure has changed sufficiently to justify formal evaluation.”

Absence of Proof of Effectiveness $\neq$ Proof of Absence of Effectiveness
RCT’s in Surgery

Results from well designed observational studies have been shown to correlate very well with those from much more expensive and impractical RCT’s for a wide variety of interventions.
Evaluation of Internal Mammary Artery Ligation and Sham Procedure in Angina Pectoris

18 patients with angina

<table>
<thead>
<tr>
<th></th>
<th>IMA ligation</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked Improvement in</td>
<td>(13)</td>
<td>(5)</td>
</tr>
<tr>
<td>angina</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Significant increase in</td>
<td>10</td>
<td>5</td>
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<tr>
<td>exercise tolerance</td>
<td>10</td>
<td>5</td>
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</tbody>
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Overall decrease in ntg use
