Building up a Successful Career in Clinical Trial Research

Marc A. Pfeffer MD, PhD
Dzau Professor of Medicine, Harvard Medical School
Cardiovascular Division, Brigham & Women’s Hospital
Boston, Massachusetts

Consultant to Amgen, AstraZeneca, Bayer, DalCor Pharma UK, Genzyme, Lilly, Medicines Company, MedImmune, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Salix, Sanderling, Sanofi, Takeda, Teva, Thrasos and Vericel and having received research grant support from Amgen, Celladon, Novartis, Sanofi. The Brigham and Women’s Hospital has patents for the use of inhibitors of the renin-angiotensin system in selected survivors of MI with Novartis Pharmaceuticals. Co-inventor with share of the licensing agreement irrevocably transferred to charity.
NIH definition of Clinical Research

- Research with human subjects that is:
- Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects.

- It includes:
  - mechanisms of human disease
  - therapeutic interventions
  - clinical trials
  - development of new technologies

- Epidemiological and behavioral studies.
- Outcomes research and health services research.

Mortality in relation to smoking: 50 years’ observations on male British doctors
Richard Doll, Richard Peto, Jillian Boreham, Isabelle Sutherland
*BMJ* 2004;328:1519
Medical Science: Generation of Data to develop/test hypothesis, quantify relationships

- Case reports (experiences)
- Administrative data bases
- Epidemiologic organizations
- Animal
- Mechanistic
- Surrogate or Biomarker
- RCT (range of outcomes)

What is done with information?
Should Clinical care be influenced?
Legal Levels of Evidence

- Hearsay
- Allegation

---------------- Legal------
- Probable Cause (initiate search warrant)
- Fair preponderance of the evidence (51% civil)
- Clear and convincing (higher burden some preconviction matters)
- Beyond a Reasonable Doubt (presumption of innocence- guilt)
NIH Clinical Trial Definition

- A research study in which human subjects are prospectively assigned to interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical.

- Randomization is specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

- An intervention is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.

Clinical Investigation

- Objective – to use scientific processes to generate new information to better understand disease mechanisms and therapies

- Randomized placebo controlled trial (RCT) is our most definitive method to quantify benefits as well as risks - critical data to better inform patient/physician decision making

- Clinical Trialist – Uses the RCT to provide the evidence to advance medical practice - is striving to improve current best practice - to change
Clinical Investigators

We are agents of change—for the most part challenging status quo – attempting to provide data evidence to better:

- understand health and disease processes
- improve medical practice
  - diagnostics
  - therapeutics
  - implementation
- education

Highest bar – to generate data (evidence) which leads to improved clinical care
RCT Progress
New “to do’ s”
Not “to do’ s” (undo’ s)
Changes in Practice (Education)

- ASA
- Lytic, PCI
- ACE I
- BB
- Statin
- ICD /CRT
- MRA

“to do’ s” (I)

“undo’ s” (III)
(false comfort zone)

- anti-arrhythmics
- Inotropic agents
- CCB high risk MI
- HRT
- ESA
The Cardiac Arrhythmia Suppression Trial
Death or RSD

Days After Randomization

Patients Without Event (%)

Placebo (n = 743)

Encainide or Flecainide (n = 755)

P = 0.001

Beta Blockers Decrease Mortality in Mild to Advanced Symptomatic HF

**MERIT-HF**
- Placebo vs. ER Metoprolol Succinate
- Follow-up (months)
- Cumulative mortality (%)
  - Placebo: 0, 3, 6, 9, 12, 15, 18, 21
  - ER Metoprolol Succinate: 0, 3, 6, 9, 12, 15, 18, 21
- Mortality: 34%

**CIBIS-II**
- Placebo vs. Bisoprolol
- Time (days)
- Probability of survival
- Log rank $P = .00006$
- Survival (%)
  - Placebo: 97, 95, 93, 91, 89, 87, 85, 83
  - Bisoprolol: 99, 98, 97, 96, 95, 94, 93, 92
- Mortality: 34%

**COPERNICUS**
- Placebo vs. Carvedilol
- Months
- Survival (%)
  - Placebo: 100, 98, 96, 94, 92, 90, 88, 86
  - Carvedilol: 102, 100, 98, 96, 94, 92, 90, 88
- Mortality: 35%

Prior Knowledge

Past experiences

Colleagues (mentor/trainees)

Environment

Discovery
ORGAN WORK AND ORGAN WEIGHT

BY FLORENCE WALTER AND T. ADDIS, M.D.

LOGARITHM OF ORGAN WEIGHT

LOGARITHM OF BODY WEIGHT.
A

LV

RV

- Cattle
- Horse
- Swine
- Sheep
- Man
- Seal
- Goat
- Dog
- Rabbit
- Rat

Stroke Work (gm-m)

$SW_L = 0.59 \text{ BW}^{1.15}$

$SW_R = 0.12 \text{ BW}^{1.14}$

Body Weight (kg)

B

$SW_L = 0.45 \text{ VW}^{1.00}$

$SW_R = 0.26 \text{ VW}^{0.99}$

Ventricle Weight (gm)
EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY II. RELATIONSHIP OF LEFT VENTRICULAR HYPERTROPHY, THE WIDTH OF THE CARDIAC MUSCLE FIBER AND HYPERTENSION IN THE RAT

ALFRED CHANUTIN, Ph.D. AND EDWIN E. BARKSDALE, M.D.
Heart Failure from the Point of View of Quantitative Anatomy

A. J. Linzbach, M.D.

1960

Infant  Adult  Athlete  Concentric hypertrophy  Eccentric hypertrophy
Contractile State of Cardiac Muscle Obtained from Cats with Experimentally Produced Ventricular Hypertrophy and Heart Failure

By James F. Spann, Jr., M.D., Robert A. Buccino, M.D., Edmund H. Sonnenblick, M.D., and Eugene Braunwald, M.D.
Population Implications of Electrocardiographic Left Ventricular Hypertrophy

WILLIAM B. KANNEL, MD, MPH, ANDREW L. DANNENBERG, MD, MPH, and DANIEL LEVY, MD

Risk of Developing CHF

Age-Adjusted Annual Rate/1,000

- None
- Voltage only
- Voltage + S-T+T

35-64 yrs 65-94 yrs
Men

35-64 yrs 65-94 yrs
Women
Development of a Strain of Spontaneously Hypertensive Rats*

KOZO OKAMOTO and KYUZO AOKI

Department of Pathology, Kyoto University School of Medicine, Kyoto.
(Director: Prof. K. Okamoto)

(Received for Publication, January, 11, 1963)

JPN Circulation Journal 27: 282-293, 1963
Hemodynamics of spontaneously hypertensive rats.
I. Effects of pressure elevation

MARC A. PFEFFER AND EDWARD D. FROHLICH (With the Technical Assistance of Janice M. Pfeffer)
Departments of Physiology and Biophysics and of Medicine, University of Oklahoma Health Sciences Center,
College of Medicine, Oklahoma City, Oklahoma 73190
Pumping ability of the hypertrophying left ventricle of the spontaneously hypertensive rat.
M A Pfeffer, J M Pfeffer and E D Frohlich

Circ Res. 1976;38:423-429
Felix Z. Meerson

Cardiac function and morphology with aging in the spontaneously hypertensive rat

1973

JANICE M. PFEFFER, MARC A. PFEFFER, MICHAEL C. FISHBEIN, AND EDWARD D. FROHLICH
Regression of cardiac hypertrophies of various origin

MARGARET BEZNAK, B. KORECKY, AND GWYNNETH THOMAS
Angiotensin Converting Enzyme Inhibition and Ventricular Remodeling in Heart Failure

JANICE M. PFEFFER, Ph.D.
MARC A. PFEFFER, M.D., Ph.D.

Ratio of LV Weight to Body Weight (mg/g)

Ratio of RV Weight to Body Weight (mg/g)
Effect of Treatment on Longevity in Spontaneously Hypertensive Rats

Edward D. Freis and Dennis Ragan

Mortality (%)

Age (weeks)

CONTROL (36)

TREATED (48)

HCTZ + Reserpine + Hydralazine
Longitudinal Changes in Cardiac Function and Geometry During the Natural Development of Left Ventricular Hypertrophy in the Spontaneously Hypertensive Rat

A Dissertation For the Degree of DOCTOR OF PHILOSOPHY

Janice M. Pfeffer
The University of Oklahoma
1977

Edward D. Frohlich, MD, Advisor

1944 - 2000
EFFECT OF PRACTOLOL ON THE EXTENT OF MYOCARDIAL ISCHAEMIC INJURY AFTER EXPERIMENTAL CORONARY OCCLUSION AND ITS EFFECTS OF VENTRICULAR FUNCTION IN THE NORMAL AND ISCHAEMIC HEART.

Libby P, Maroko PR, Covell JW, Malloch CI, Ross J Jr, Braunwald E.
Myocardial Infarct Size and Ventricular Function in Rats

Marc A. Pfeffer, Janice M. Pfeffer, Michael C. Fishbein, Peter J. Fletcher, Joel Spadaro, Robert A. Kloner, and Eugene Braunwald

Peak Cardiac Index

LVEDP

*p < 0.05 vs control
**p < 0.01 vs control
Ejection Fraction Index (%) vs. Infarct Size (%)

$r = -0.91$

$EPI = -79 - 1.14 \times (IS\%)$
Left Ventricular Diastolic Pressure-Volume Relations in Rats with Healed Myocardial Infarction

Effects on Systolic Function

Peter J. Fletcher, Janice M. Pfeffer, Marc A. Pfeffer, and Eugene Braunwald
Progressive ventricular remodeling in rat with myocardial infarction

JANICE M. PFEFFER, MARC A. PFEFFER, PETER J. FLETCHER, AND EUGENE BRAUNWALD (With the Technical Assistance of Cynthia R. Steinberg and Peter Finn)
LV REMODELING POST-MI

NORMAL LV

Septum a b c Free wall

EARLY

LVEDP ↑
infarct expansion
mechanical disadvantage

LVEDP ↑
wall thinning + LV dilatation
mechanical advantage

LATE

LVEDP ↑↑
further LV dilatation
mechanical disadvantage
Influence of chronic captopril therapy on the infarcted left ventricle of the rat.

J M Pfeffer, M A Pfeffer and E Braunwald
Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril.

M A Pfeffer; J M Pfeffer; C Steinberg; P Finn
Effect of Captopril on Progressive Ventricular Dilatation After Anterior Myocardial Infarction

Marc A. Pfeffer, M.D., Ph.D., Gervasio A. Lamas, M.D., Douglas E. Vaughan, M.D., Alfred F. Parisi, M.D., and Eugene Braunwald, M.D.

**End-Diastolic Volume**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 25</td>
<td>n = 27</td>
</tr>
</tbody>
</table>

Baseline | 1 Year
---|---

Placebo:
- Baseline: 220 ml
- 1 Year: 260 ml (Δ 20.6 ± 7.6 p < 0.02)

Captopril:
- Baseline: 220 ml
- 1 Year: 230 ml (Δ 9.6 ± 6.2 N.S.)
EFFECT OF CAPTOPRIL ON MORTALITY AND MORBIDITY IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

Results of the Survival and Ventricular Enlargement Trial

MARC A. PFEFFER, M.D., PH.D., EUGENE BRAUNWALD, M.D., LEMUEL A. MOYÉ, M.D., PH.D.,
LOFTEY BASTA, M.D., EDWARD J. BROWN, JR., M.D., THOMAS E. CUDDY, M.D.,
BARRY R. DAVIS, M.D., PH.D., EDWARD M. GELTMAN, M.D., STEVEN GOLDMAN, M.D.,
GREG C. FLAKER, M.D., MARC KLEIN, M.D., GERVASIO A. LAMAS, M.D., MILTON PACKER, M.D.,
JACQUES ROULEAU, M.D., JEAN L. ROULEAU, M.D., JOHN RUTHERFORD, M.D., JOHN H. WERTHEIMER, M.D.,
AND C. MORTON HAWKINS, SC.D., ON BEHALF OF THE SAVE INVESTIGATORS*

![Graph showing mortality rate over years for Placebo and Captopril groups.](image)

- Placebo: 1116, 987, 915, 609, 262
- Captopril: 1115, 1000, 938, 614, 288

Risk reduction = 19%
P = 0.019
Chronology: ACE Inhibition, Acute MI, Clinical Endpoint Trials

<table>
<thead>
<tr>
<th>87</th>
<th>88</th>
<th>89</th>
<th>90</th>
<th>91</th>
<th>92</th>
<th>93</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVE</td>
<td>AIRE</td>
<td>SMILE</td>
<td>CONSEN</td>
<td>TRACE</td>
<td>CHINESE</td>
<td>GISSI 3</td>
</tr>
</tbody>
</table>
ACE Inhibitor
MI Mortality Trials

<table>
<thead>
<tr>
<th>Broad (short term)</th>
<th>Selective (higher risk, long term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS II</td>
<td>SAVE (EF ≤ 40%)</td>
</tr>
<tr>
<td>GISSI-3</td>
<td>AIRE (clinical HF)</td>
</tr>
<tr>
<td>ISIS-4</td>
<td>TRACE (wall motion score, EF ≤ 35%)</td>
</tr>
<tr>
<td>Chinese-Cap</td>
<td>SMILE (anterior MI, no lytic)</td>
</tr>
</tbody>
</table>

5 lives saved/1000 over 6 weeks

60 lives saved/1000 over 3 years
Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril.

M St John Sutton, M A Pfeffer, T Plappert, J L Rouleau, L A Moyé, G R Dagenais, G A Lamas, M Klein, B Sussex and S Goldman

Left Ventricular Enlargement at One Year, cm²

### Diastole

- No CV Events (n = 309)
- Adverse CV Events (n = 111)

**P < 0.001**

### Systole

- No CV Events (n = 309)
- Adverse CV Events (n = 111)

**P < 0.001**
EFFECT OF CAPTOPRIL ON MORTALITY AND MORBIDITY IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

Results of the Survival and Ventricular Enlargement Trial

Marc A. Pfeffer, M.D., Ph.D., Eugene Braunwald, M.D., Lemuel A. Moyé, M.D., Ph.D., Lofty Basta, M.D., Edward J. Brown, Jr., M.D., Thomas E. Cuddy, M.D., Barry R. Davis, M.D., Ph.D., Edward M. Geltman, M.D., Steven Goldman, M.D., Greg C. Flaker, M.D., Marc Klein, M.D., Gervasio A. Lamas, M.D., Milton Packer, M.D., Jacques Rouleau, M.D., Jean L. Rouleau, M.D., John Rutherford, M.D., John H. Wertheimer, M.D., and G. Morton Hawkins, Sc.D., on Behalf of the SAVE Investigators*
LV Dysfunction (Progressive)

- Asymptomatic
- Remodeling
- MI
- Symptomatic CHF
  - Sudden
  - Ischemic
  - Sudden
  - Pump failure

DEATH
Reinfarction

SOLVD

- Placebo
- Enalapril

Events %

Years

Risk reduction (95% CI) = 22% (6-35%)
P < 0.001

SAVE

- Placebo
- Captopril

Events rate

Years

Risk reduction (95% CI) = 25% (5-40%)
P = 0.015

NEJM 1991

NEJM 1992
Primary Outcome – Ramipril vs Placebo

RR = 0.78 (0.70–0.86)  P = 0.000002
ACEi in Vascular Disease
Total Deaths

Study

HOPE
EUROPA
PEACE
Overall (95% CI)

Risk ratio
(95% CI)

0.85 (0.73 - 0.95) 43.1
0.89 (0.77 - 1.02) 31.9
0.89 (0.76 - 1.04) 25.0
0.87 (0.79 - 0.94) 100

% Weight

P=0.0004

Lancet 2006
Renin-Angiotensin Aldosterone System

Angiotensinogen → renin → Angiotensin I → Angiotensin II

Non-ACE Pathways (e.g., chymase)

• Vasoconstriction
• Cell growth
• Na/H₂O retention
• Sympathetic activation

Angiotensin II

ACE

Aldosterone

AT₁

AT₂

Bradykinin

Inactive Fragments

Cough, Angioedema

Benefits?

• Vasodilation
• Antiproliferation (kinins)
Acute MI (0.5–10 days)—SAVE, AIRE or TRACE eligible
(either clinical/radiologic signs of HF or LV systolic dysfunction)

Major Exclusion Criteria:
- BP < 100 mm Hg
- Serum creatinine > 2.5 mg/dL
- Prior intolerance of an ARB or ACE-I
- Nonconsent

double-blind active-controlled

Captopril 50 mg tid (n = 4909)
Valsartan 160 mg bid (n = 4909)
Captopril 50 mg tid + Valsartan 80 mg bid (n = 4885)

median duration: 24.7 months
event-driven

Primary Endpoint: All-Cause Mortality
Secondary Endpoints: CV Death, MI, or HF
Other Endpoints: Safety and Tolerability
Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both

Marc A. Pfeffer, M.D., Ph.D., John J.V. McMurray, M.D., Eric J. Velazquez, M.D., Jean-Lucien Rouleau, M.D., Lars Kober, M.D., Aldo P. Maggioni, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., Frans Van de Werf, M.D., Ph.D., Harvey White, D.Sc., Jeffrey D. Leimberger, Ph.D., Marc Henis, M.D., Susan Edwards, M.S., Steven Zelenkofske, D.O., Mary Ann Sellers, M.S.N., and Robert M. Califf, M.D.,

for the Valsartan in Acute Myocardial Infarction Trial Investigators

2003

Valsartan vs. Captopril: HR = 1.00; P = 0.982
Valsartan + Captopril vs. Captopril: HR = 0.98; P = 0.726

Probability of Event

Valsartan
Valsartan + Captopril
Captopril

Months
0 6 12 18 24 30 36

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>4909</td>
<td>4428</td>
<td>4241</td>
<td>4018</td>
<td>2635</td>
<td>1432</td>
<td>364</td>
</tr>
<tr>
<td>Valsartan</td>
<td>4909</td>
<td>4464</td>
<td>4272</td>
<td>4007</td>
<td>2648</td>
<td>1437</td>
<td>357</td>
</tr>
<tr>
<td>Valsartan + Cap</td>
<td>4885</td>
<td>4414</td>
<td>4265</td>
<td>3994</td>
<td>2648</td>
<td>1435</td>
<td>382</td>
</tr>
</tbody>
</table>
Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both

Cardiovascular Mortality and Morbidity: Valsartan vs. Captopril

Hazard Ratio (97.5% CI)

- CV Death (1657 events) Hazard Ratio: 0.8
- CV Death or MI (2234 events) Hazard Ratio: 1.0
- CV Death or HF (2661 events) Hazard Ratio: 1.13
- CV Death, MI, or HF (3096 events) Hazard Ratio: 1.2

P-value (non-inferiority)
- CV Death: 0.001
- CV Death or MI: 0.00001
- CV Death or HF: 0.0001
- CV Death, MI, or HF: 0.000001

Non-inferiority margin

Non-inferiority not Demonstrated
### Table 3. Adverse Events Leading to a Dose Reduction or a Discontinuation of Study Treatment.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Resulting in Dose Reduction</th>
<th>Resulting in Permanent Discontinuation of Study Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td>number (percent)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>739 (15.1)*</td>
<td>884 (18.2)*</td>
</tr>
<tr>
<td>Renal causes</td>
<td>239 (4.9)*</td>
<td>232 (4.8)*</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>62 (1.3)</td>
<td>57 (1.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>85 (1.7)*</td>
<td>225 (4.6)</td>
</tr>
<tr>
<td>Rash</td>
<td>32 (0.7)*</td>
<td>53 (1.1)</td>
</tr>
<tr>
<td>Taste disturbance</td>
<td>13 (0.3)*</td>
<td>38 (0.8)</td>
</tr>
<tr>
<td>Angioedema</td>
<td>12 (0.2)</td>
<td>22 (0.5)</td>
</tr>
<tr>
<td>Any of the above events†</td>
<td>1112 (22.8)</td>
<td>1404 (28.9)*</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>1437 (29.4)</td>
<td>1690 (34.8)*</td>
</tr>
<tr>
<td>Any reason</td>
<td>2103 (43.1)</td>
<td>2342 (48.2)*</td>
</tr>
</tbody>
</table>
In patients with MI complicated by heart failure, left ventricular dysfunction or both:

- **Valsartan is as effective as a proven dose of captopril in reducing the risk of:**
  - Death
  - CV death or nonfatal MI or heart failure admission

- **Combining valsartan with a proven dose of captopril produced no further reduction in mortality—and more adverse drug events.**
Post-Myocardial Infarction Ventricular Remodeling: Animal and Human Studies  Douglas E. Vaughan and Marc A. Pfeffer
A Symposium: Ventricular Remodeling and Unloading Following Myocardial Infarction

GUEST EDITORS:
Marc A. Pfeffer, MD, PhD
Associate Professor of Medicine
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

Eugene Braunwald, MD
Hersey Professor of the Theory and Practice of Medicine
Harvard Medical School
Chairman, Department of Medicine
Brigham and Women's Hospital
Boston, Massachusetts

This symposium was held on April 5-6, 1991, in Barbados, and was sponsored by an educational grant from Bristol-Myers Squibb.
Concepts

- Growth/Plasticity
- Hypertrophy/adaptive, maladaptive
- Remodeling
- Renewal
- Regeneration

Understanding Harnessing Biology for Therapeutics
Prospective ARNI versus ACEI trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction

Leave Comfort zone of ACEI in MI to test effectiveness and safety of entresto (valsartan/sacubitril) in pts with high risk AMI
Prior Knowledge

Discovery

Environment

Colleagues (mentor/trainees)

Past experiences

Prior Knowledge
Prior Knowledge

Past experiences

Environment

Discovery

Colleagues (mentor/trainees)
Edward Frohlich, M.D.

Janice Pfeffer, Ph.D.

Eugene Braunwald, M.D.
REMARKS ON ANGINA PECTORIS.

BY JOHN WARREN, M. D.

In our inquiries into any particular subject of Medicine, our labours will generally be shortened and directed to their proper objects, by a knowledge of preceding discoveries.
Clinical (Outcomes) Trials, Why do them?

To provide the foundation for evidence-based medicine (safety as well as efficacy)

To continue to improve the practice of medicine

What are the alternatives?
Scientific Knowledge Generated From RCT

“an answer”

+ 

New Insights
Subgroups
Hypothesis Generation
Pathophysiology
Mechanisms
Ancillary Studies
Blood Markers
DNA

“Training”
The Cycle of Clinical Therapeutics

Concept → RCT → Guidelines → Performance

Outcomes

Gold standard for EBM

Education and Feedback

Guidelines

Performance Indicators

Improving Public Health

Califf R et al JACC 2002
"We shall have no better conditions in the future if we are satisfied with all those which we have at present."

*Thomas Edison*