Challenges in the Conduct of Clinical Trials:
Lessons from the CORAL Trial

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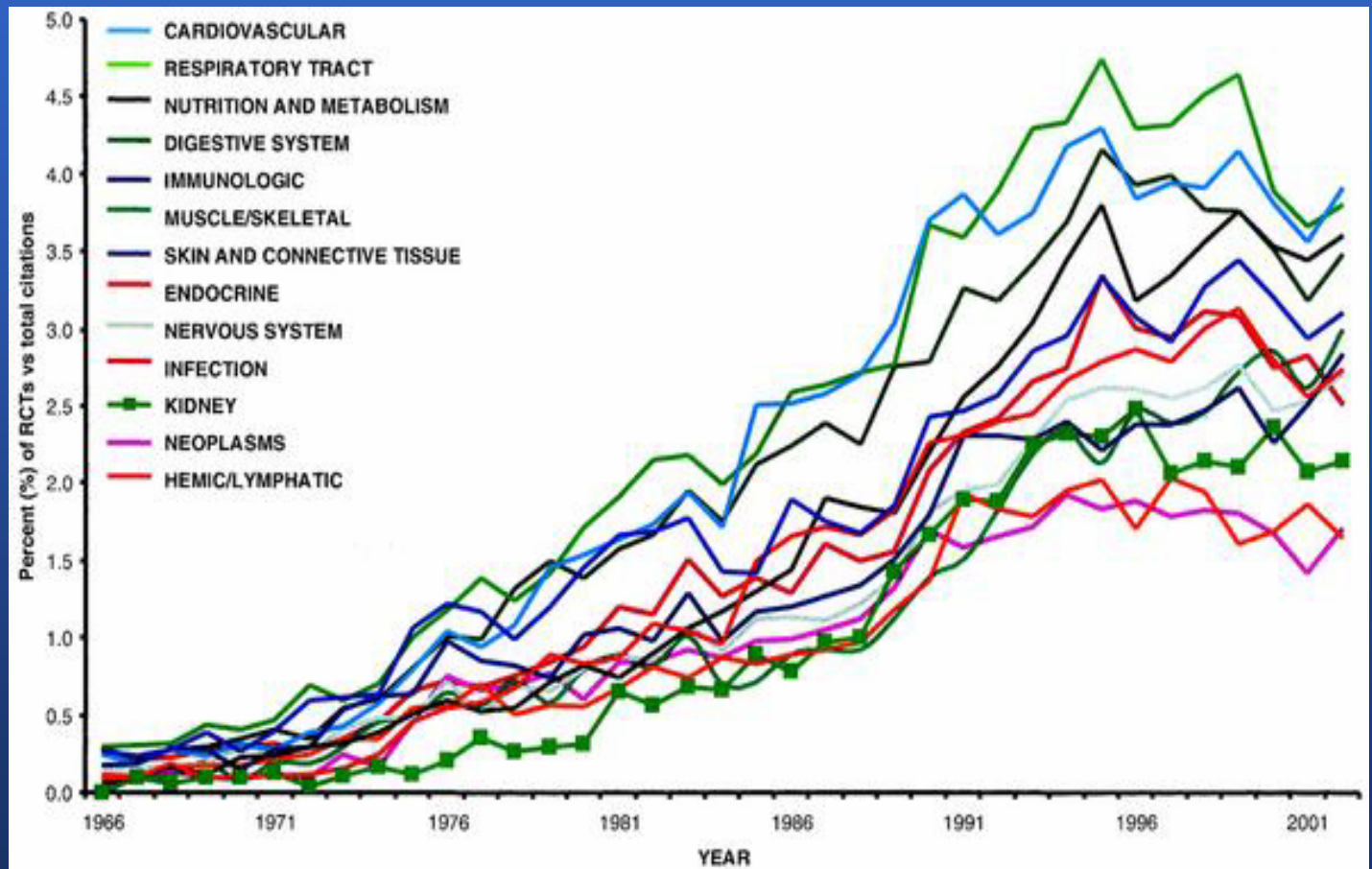
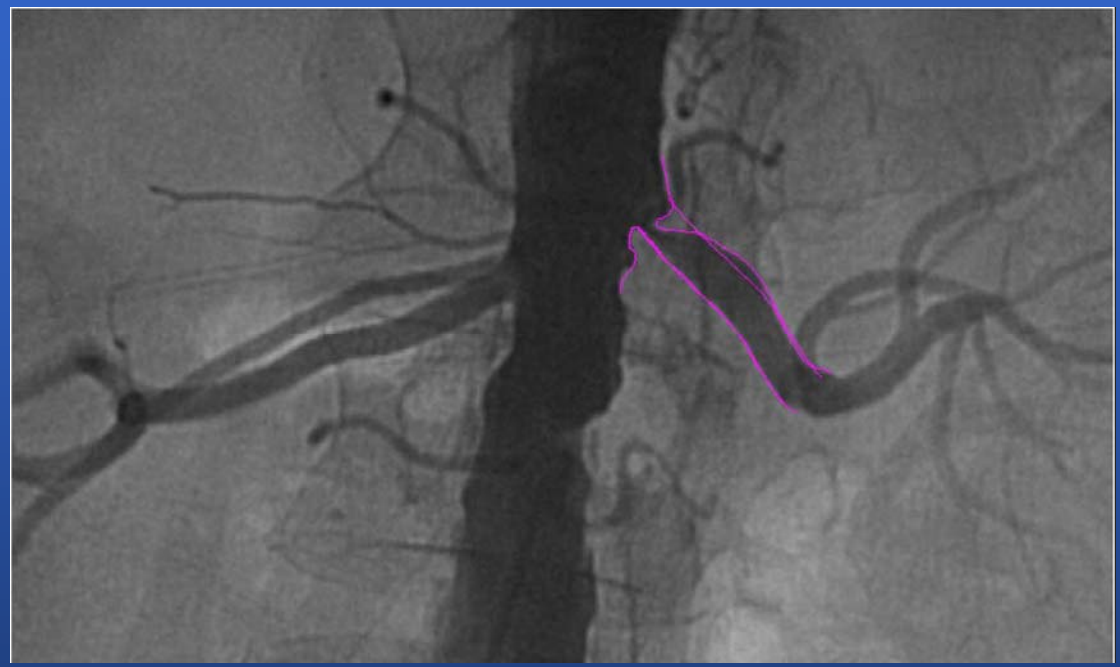
A Paucity of Randomized Trials: Percentage of RCT versus *total citations in specialties of internal medicine from 1966 to 2002*



Strippoli, JASN 15:411, 2004

How to conduct of a successful clinical trial: I

- Pick a common clinical problem



Atherosclerotic Renal Artery Stenosis

≈1-4 million patients in the US

14-42% with PVD Greco 1997	*11-40% with CAD* Conlon 2001	*1-5% of hypertensives*	***7% of the elderly*** Hansen 2002

Clinical Trials: II

- Pick a disease for which the best treatment is not known
- 2006 AHRQ sponsored review

Effectiveness of Management Strategies for Renal Artery Stenosis: A Systematic Review

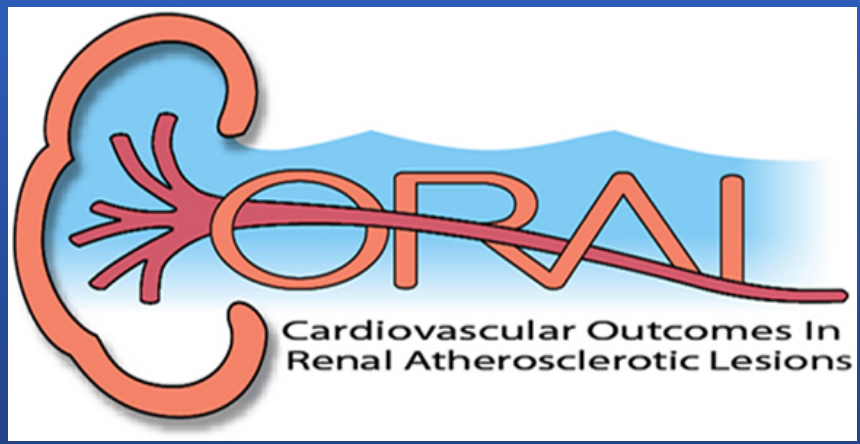
Ethan Balk, MD, MPH; Gowri Raman, MD; Mei Chung, MPH; Stanley Ip, MD; Athina Tatsioni, MD; Alvaro Alonso, MD; Priscilla Chew, MPH; Scott J. Gilbert, MD; and Joseph Lau, MD

Conclusion: "Available evidence does not clearly support one treatment approach over another for atherosclerotic renal artery stenosis."

Ann Intern Med. 2006;145:901-912.

Clinical Trial: III

- Ask a clinically relevant question
  - *Don't rely on surrogate endpoints*



Does angioplasty and stenting, combined with optimal medical therapy, improve patient and/or kidney survival, cardiovascular outcomes, or quality of life in patients with atherosclerotic RAS, as compared to optimal medical therapy alone?

IV: Design a valid trial

Randomized trial

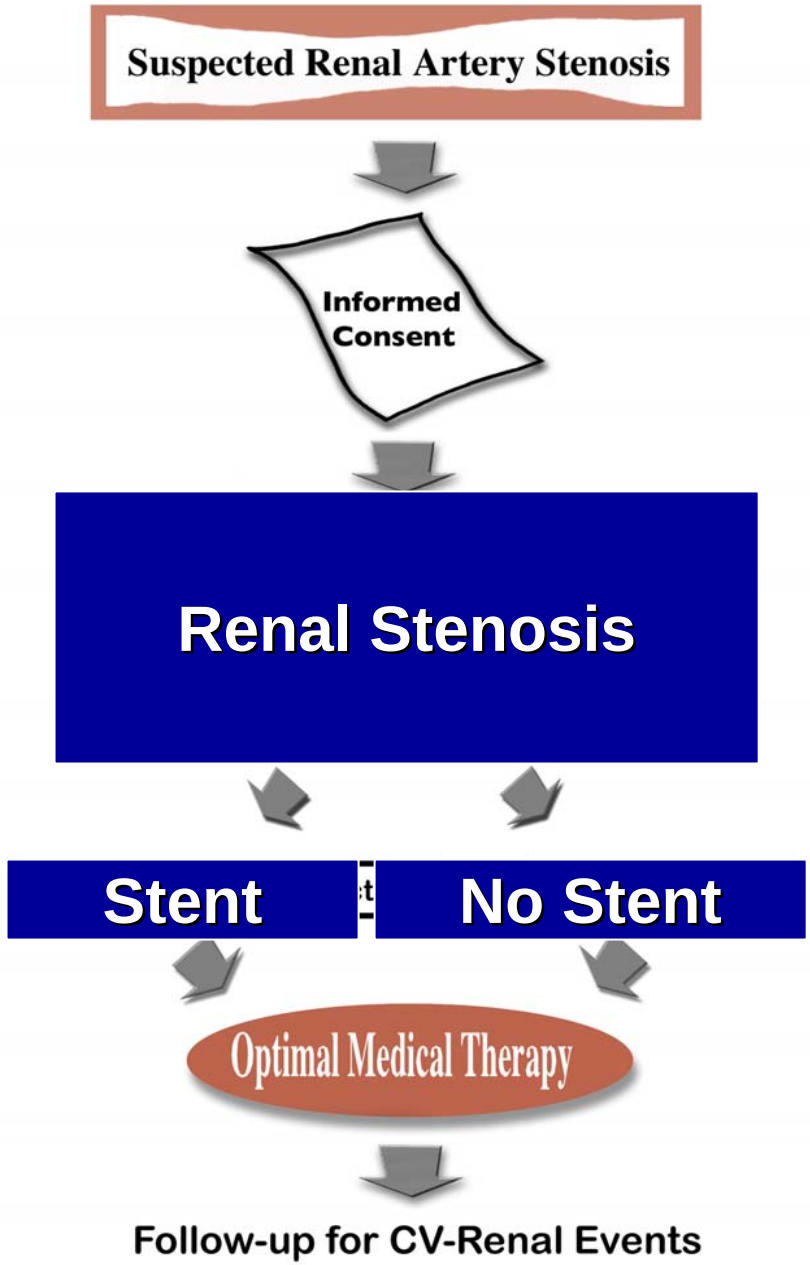
Target Enrollment 1,080 patients

5.5 year follow-up study

Primary Endpoint Composite

- –Cardiovascular or Renal Death
- –Stroke
- –Myocardial Infarction
- –Hospitalization from CHF
- –Progressive Renal Insufficiency
- –Renal Replacement Therapy

- 90% Power for Primary Endpoint
- 80% Power for all-cause Mortality



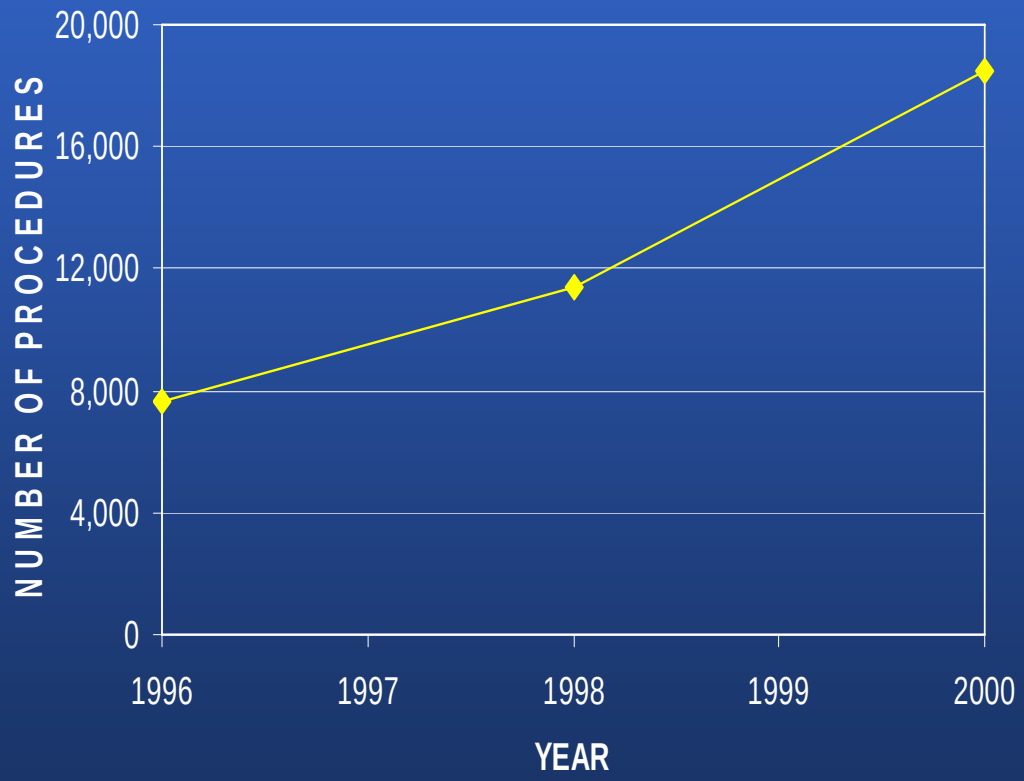
Clinical Trials V: Obtain Funding

- Randomized trials are extremely expensive
  - CORAL (1080 subjects for 3 years) $30 million
- Sources
  - NIH
    - Limited resources
    - Competing priorities: CORAL = 80-120 RO1 grants
  - Industry
    - Product specific
    - Different goals

Enroll the subjects: The Achilles Heel

- CORAL
  - Are enough procedures being done?
  - Find experienced centers
    - 100 enrolling centers worldwide
    - 85 US enrolling centers
  - Recruit committed site investigators

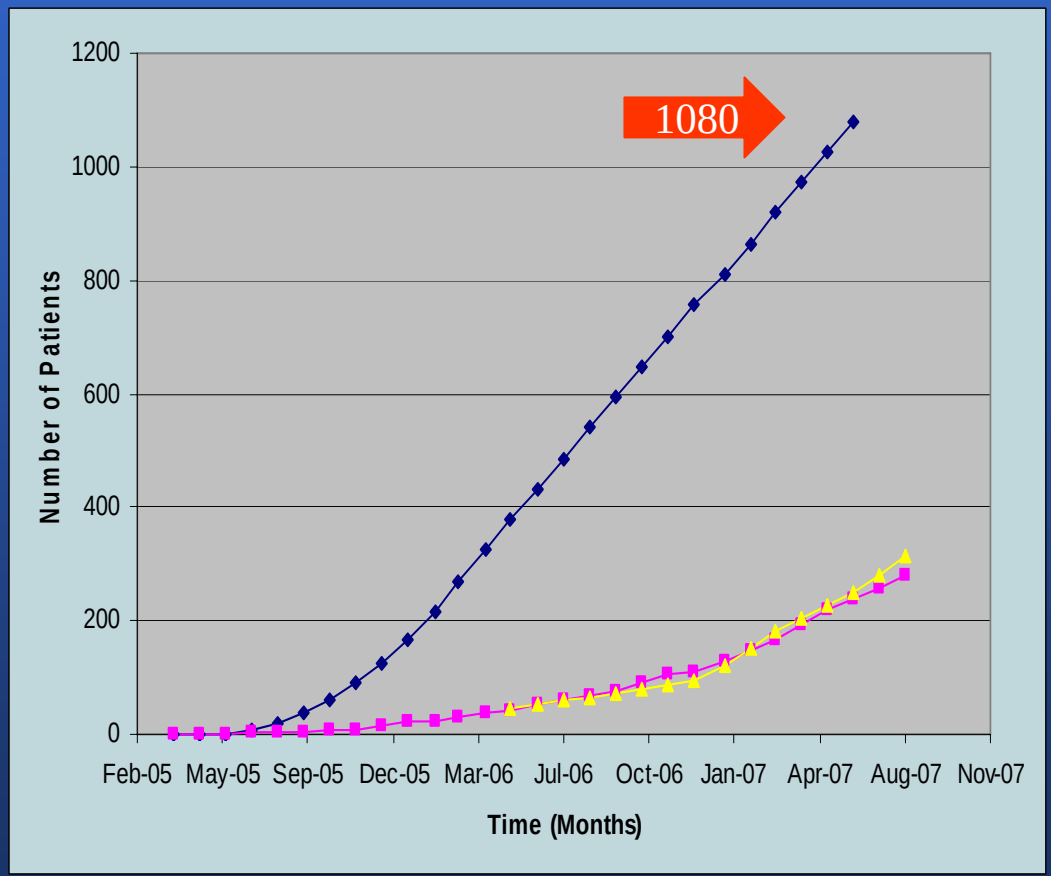
Renal Artery Interventions in the USA



- Current estimate 35,000 total procedures annually 2005 & 2006
- Financial cost

  ~ $2,000 -$6,000 per procedure

Enrollment in the CORAL Trial: 290



- **180 patients enrolled from June 2006 to June 2007**
- **180/35,000 ≅ 0.5% or 1/200 all procedures**
- **456 reported screen failures due to patient or physician preference**
- **Number of such screen failures if stenting not covered outside of the study = ?**

How to Stimulate Enrollment?

- Remove barriers to enrollment
  - Protocol revised and simplified
  - Exclusion criteria eliminated
- Create incentives for patients & investigators
  - Patients receive 4 free medications for blood pressure and lipids
  - Per patient reimbursement increased
- Procedures outside of study: Recent MEDCAC Meeting on RAS, State of the Evidence and the impact of coverage policies on clinical trials such as CORAL
  - Only cover procedures for patients entered into approved clinical trials
  - Problem: Case Series and Registries may qualify as approved clinical trials

Registries vs. Randomized Trials

- Registries collect information on patients undergoing a procedure or therapy
- All patients receive the procedure being examined
- Registries provide no useful information on the relative utility of the procedure versus no procedure
- Registries may be useful after a randomized trial has demonstrated benefit, to refine clinical practice

Registries can undermine enrollment in Randomized trials

- All patients get the intervention, No untreated group
  - If you and/or patient believe in the procedure, entry into registry may be preferred over randomization
- Financial incentives
  - Procedure fees: 100% vs 50% if randomized
  - Industry supported registries typically very well funded per patient enrolled
- Amount of Data collected in a registry typically much less than a randomized trial
  - Registry much easier for center to perform

Registries in RAS

- FDA is currently mandating registries for companies seeking approval for a stent to be deployed in the renal artery
- Typical Endpoint – restenosis rate
- Positive study – lower restenosis rate than historical controls, acceptable complication rate
- WHY DO WE CARE ABOUT RESTENOSIS IF OPENING THE RENAL ARTERY PROVIDES NO BENEFIT OR IS HARMFUL?

If Studies are not available, can we rely on Clinical Practice Guidelines

- There is a natural desire among physicians and payers to have clinical decisions based on evidence
- This has led to robust efforts to write Clinical Practice Guidelines even in settings where there is a lack of convincing evidence from randomized clinical trials

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ACC/AHA PRACTICE GUIDELINES

ACC/AHA 2005 Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): Executive Summary

A Collaborative Report From the American Association for Vascular Surgery/Society for Vascular Surgery,* Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease)

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation

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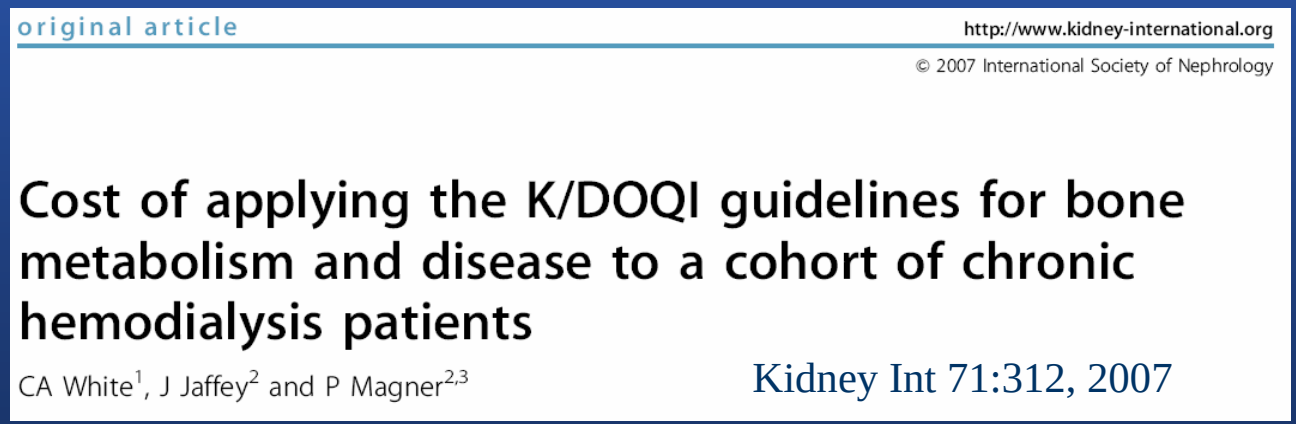
Clinical Practice Guidelines in RAS: Methodology

- Classification of Recommendations
  - "Class I: Conditions for which there is evidence for *and/or general agreement* that a given procedure or treatment is beneficial, useful, and effective."
  - *How does one reach general agreement and what does it mean in the absence of evidence?*

Deleterious Consequences of Clinical Practice Guidelines Based on Observational Data

- Contributes to a sense of complacency in the care of patients.
- May increase cost without improving patient outcomes



original article http://www.kidney-international.org

Cost of applying the K/DOQI guidelines for bone metabolism and disease to a cohort of chronic hemodialysis patients

CA White[1], J Jaffey[2] and P Magner[2,3]

Kidney Int 71:312, 2007

  - One Center, 470 dialysis patients = $500K/year

Deleterious Consequences of Basing Clinical Practice Guidelines on Observational Data

- Serves as an impediment to performing randomized clinical trials
  - Why prove something that is already an accepted part of clinical practice?
  - Clinicians and IRBs reluctant to randomize patients to a control group not treated according to practice guidelines
- Turmoil when subsequent randomized trials don't support the guidelines
  - Upheaval in nephrology regarding anemia management following publication of the CHOIR & CREATE trials.

Himmelfarb JAMA 297:2630, 2007

Conclusions

- Randomized Clinical trials are expensive, difficult to perform and relatively uncommon; enrollment is a major barrier
- Coverage policies may affect enrollment by altering the chances that an unproven therapy will be provided outside of a study
- Registries cannot substitute for well-designed randomized trials and may hinder enrollment in those trials
- Clinical Practice Guidelines based on observational data may increase cost without improving patient outcomes and discourage enrollment in randomized trials
- NIH, CMS, and the FDA should work collaboratively to encourage the performance of randomized clinical trials of unproven therapies.