Pragmatic Trials for Uncommon Conditions?

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Model for 1st wave of Collaboratory demonstration projects

Pragmatic trials conducted within a small number of health systems, each with a large total number of patients

- Model works for conditions that are common (need sufficient number of potential trial participants within the health system practices)
- Model also works well if the health system is very large (e.g., Veterans Administration)
- Major focus is on implementing the intervention and obtaining high quality data from EMRs

Question for today's presentation

How can we use pragmatic trial approaches to evaluate interventions for diseases or conditions that are not common and not sufficiently represented in a small number of health care systems?

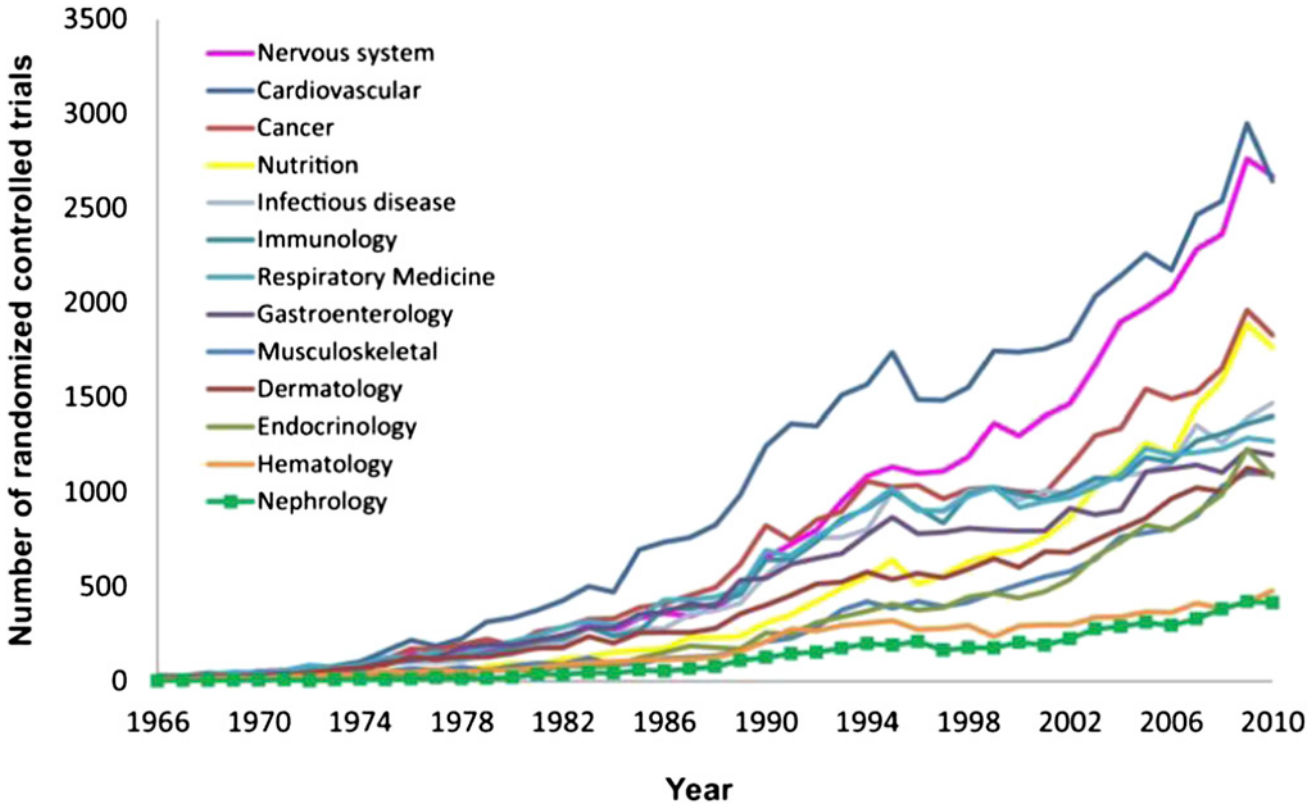
Why is this important?

- Many (most?) diseases and conditions are not sufficiently represented in a small number of health systems to allow large pragmatic trials
- To maximize knowledge generation, a learning health system should accommodate not only common diseases but also uncommon diseases.

Caveats

- I have only recently started thinking about this issue
- I have a few ideas, many questions and few answers

Randomized controlled trials in nephrology



Palmer S et al. Amer J Kidney Dis 2011; 58:335-337

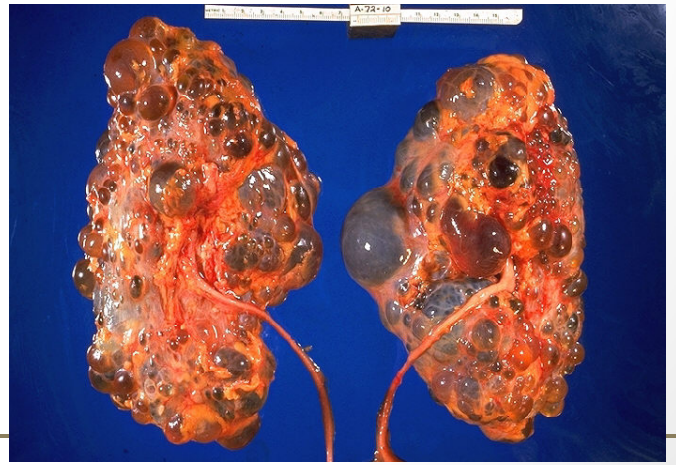
Between 2002 and 2012 only 7 drugs were approved by FDA to treat kidney diseases*

Year	Drug	Condition
2002	Losartan	Diabetic nephropathy (Type 2)
2002	Irbesartan	Diabetic nephropathy (Type 2)
2011	Rituximab	Granulomatosis with polyangiitis
2012	Eculizumab	Atypical hemolytic uremic syndrome

*5 additional drugs that treat complications of kidney disease (anemia, hyperphosphatemia, secondary hyperparathyroidism, transplant rejection) were approved during this period.

Autosomal dominant polycystic kidney disease (ADPKD)

- Affects 1/400 – 1/1000 individuals in U.S. (600,000 people)
- Slowly progressive, most reach ESRD between ages of 50 and 60 years.
- Fifth most frequent cause of end-stage renal disease in U.S.
- There has been substantial progress in understanding pathogenesis, identifying targets for interventions and establishing intermediate outcomes for clinical trials



TEMPO trial: tolvaptan for ADPKD

- Vasopressin V_2-receptor antagonist vs placebo (2:1 randomization) for early stage ADPKD (eGFR>60)
- Primary outcome: annual rate of change in total kidney volume by MRI
- Enrollment: 1445 patients over 24 months
- 129 sites, 15 countries
- Follow-up: 3 years
- Sponsor: Otsuka Pharmaceuticals

Torres V et al. N Engl J Med 2012; 367:2407-2418

HALT PKD trials: intensive RAAS inhibition for ADPKD

- Study A: early disease (eGFR>60 ml/min/1.73 m^2)
  - ACEi plus ARB vs ACEi alone
  - 2 blood pressure targets
- Study B: later disease (eGFR 25-60 ml/min/1.73 m^2)
  - ACEi plus ARB vs ACEi alone; single blood pressure target
- Primary outcome
  - Study A: change in kidney volume by MRI
  - Study B: composite of time to 50% reduction in eGFR, ESRD or death
- Enrollment: 548 patients in Study A and 470 patients in Study B over 3 years
- Follow-up
  - Study A: 4 years
  - Study B: at least 5 years (average 6.5 years)
- 7 centers of excellence (major referral centers for ADPKD)
- Sponsor: NIH

Chapman AB et al; CJASN 2010; 5:102-109

TEMPO vs HALT PKD

	TEMPO	HALT PKD
Sponsor	Industry	NIH
Budget	Massive	Not massive
Intervention	Novel agent	Medications used frequently in this population
Centers	Large number of centers, most without particular ADPKD expertise	Small number of centers of excellence
Participants per center	11	About 70
Enrollment period	2 years	3 years
Trial duration	5 years	8 years

Most patients with ADPKD are treated by community nephrologists

Question for today's presentation

How can we use pragmatic trial approaches to evaluate interventions for diseases or conditions that are not common and not sufficiently represented in a small number of health care systems?

What do we need to be able to do?

Recruit patients, consent patients, implement the intervention, collect data, and assess safety at a large number of sites….

- without on-site research teams
- without relying on site-specific electronic communication systems or tracking systems
- without relying on site-specific EMRs

Consider a patient-driven rather than investigator-driven approach

Investigator-driven versus patient-driven trial implementation

- Investigator-Driven: investigator seeks out patients for enrollment into trial, implements intervention and collects data during follow-up
  - Requires substantial effort by investigators
  - Limits the sites for enrollment and the accessibility of trial to patients
- Patient-Driven: patient approaches treating physician and provides physician with information about the trial. The physician implements the intervention and the physician and/or the patient provides data during follow-up
  - Requires highly informed and motivated patients, willing physicians, and mechanism for data capture and transmission
  - Can evaluate only those interventions for which there is high level of physician experience and comfort

Components

- Recruitment
- Consent
- Eligibility determination
- Randomization
- Implementation of intervention
- Data collection
- Outcome ascertainment
- Adverse event reporting

Recruitment sources for patient-driven trial implementation

- Patient contact registries
- Social networking websites
- Patient advocacy groups
- Wikipedia
- Study website using search engine preferencing strategies

Consent, eligibility determination, adherence, and adverse events

- Patient provides consent and demonstration of understanding via internet
- Treating physician verifies eligibility and submits documentation via internet
- Patient completes adherence assessments via internet
- Patient performs web-based adverse event reporting with selected supplementation by physician

Outcome ascertainment

- Patient completes PROs
- Patient requests data from treating physician and submits via internet
- Patient downloads data directly from the EMR and submits via internet

Could the ADPKD trials have been conducted using patient-driven implementation?

	TEMPO	HALT PKD
Highly informed patients?	Yes	Yes
Highly motivated patients?	Yes	Yes
Treating clinician comfort implementing intervention?	No	Yes
Mechanism for data capture and transmission?	Probably not	Probably
Outcomes that can be obtained from clinical care?	Not easily (MRI)	Study A: Not easily (MRI) Study B: Yes (eGFR)

How would a patient-driven HALT PKD trial differ from an investigator-driven trial?

- More rapid enrollment, larger N, shorter follow-up
- Less expensive
- Less tightly-controlled implementation of intervention
- Fewer data elements
- Would safety be monitored adequately?

Summary

- Health system-centered pragmatic trials work well for diseases or conditions that are highly prevalent but not for diseases that are not highly prevalent.
- Patient-driven pragmatic trials require highly motivated patients and interventions for which there is a high level of physician comfort. However, because they are not dependent on the health system's infrastructure or IT systems, patient-driven trials can be implemented across a limitless number of settings allowing evaluation of interventions for diseases with lower prevalence.