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*

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>2002</td>
<td>Losartan</td>
<td>Diabetic nephropathy (Type 2)</td>
</tr>
<tr>
<td>2002</td>
<td>Irbesartan</td>
<td>Diabetic nephropathy (Type 2)</td>
</tr>
<tr>
<td>2011</td>
<td>Rituximab</td>
<td>Granulomatosis with polyangiitis</td>
</tr>
<tr>
<td>2012</td>
<td>Eculizumab</td>
<td>Atypical hemolytic uremic syndrome</td>
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*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<sub>2</sub>-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

HALT PKD trials: intensive RAAS inhibition for ADPKD

- **Study A**: early disease (eGFR > 60 ml/min/1.73 m²)
  - ACEi plus ARB vs ACEi alone
  - 2 blood pressure targets
- **Study B**: later disease (eGFR 25-60 ml/min/1.73 m²)
  - 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

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

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?

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<tr>
<td>Highly informed patients?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Highly motivated patients?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treating clinician comfort implementing intervention?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mechanism for data capture and transmission?</td>
<td>Probably not</td>
<td>Probably</td>
</tr>
<tr>
<td>Outcomes that can be obtained from clinical care?</td>
<td>Not easily (MRI)</td>
<td>Study A: Not easily (MRI) Study B: Yes (eGFR)</td>
</tr>
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</table>
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.