Promoting Effective Drug Development Programs: Opportunities and Priorities for FDA's Office of New Drugs

Master protocols: One solution for CKD drug development

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Disclosures

• Fellowship
  • Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship

• Research funding
  • Gambro, Baxter, CSL, Amgen, Eli Lilly, and Merck

• Scientific presentations/Advisory boards
  • Akebia, Baxter, Boehringer Ingelheim, CSL, Vifor, Janssen, Amgen, Roche

• CREDENCE Trial
  • Global Scientific Lead, Steering Committee member

• Any consultancy, honoraria, or travel support are paid to my institution
Insufficient evidence in kidney disease

Number of RCTs published in 13 internal medicine specialities: 1966-2010

... but our ambition is big

Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy

International Society of Nephrology summit report

“At least 30% of people with CKD globally should be involved in a clinical trial”

A Levin, Lancet 2017; 390: 1888–917
Master protocol trials for chronic kidney disease

- Ongoing trial
- Common endpoint
- Shared infrastructure
- Multiple agents
- Shared control arm
- Adaptive randomization
- Potential Bayesian statistics
Ongoing trial

- Common endpoint
- Shared infrastructure
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Prostate cancer
- 2005 – ongoing
- Over 10,000 participants

Neoadjuvant treatment for locally advanced breast cancer
- 2010 - ongoing

REMAP-CAP
- Community-acquired pneumonia in critical care
- 2016 – Ongoing

...and others
Ongoing trial

Common endpoint

Shared infrastructure

Multiple agents

Shared control arm

Adaptive randomization

Potential Bayesian statistics

Woodcock *NEJM* 2017; 377:62-70
Trials of ‘Glomerular diseases’: snapshot from clinicaltrials.gov, Oct 18, 2019

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<th>Glomerular Disease</th>
<th>Albuminuria</th>
<th>Proteinuria</th>
<th>eGFR</th>
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Proteinuria in remission definitions: International Clinical Trials Research Platform (ICTRP) 2001 - July 20th 2019
Master protocol trials shared infrastructure

- Endpoint assessment, Endpoint evaluation
- Monitoring, DSMB, Oversight
- Contracting, Site staffing
Indication: newly diagnosed advanced prostate cancer

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http://www.stampedetrial.org/
Ongoing trial
Common endpoint
Shared infrastructure
Multiple agents
Shared control arm
Adaptive randomization
Potential Bayesian statistics

https://www.ispytrials.org/results/past-agents
• Reduces sample size
• Participants have increased likelihood of receiving an active agent

Incidence of primary glomerulonephritis (GN)

**Adults**

- Membrano-proliferative GN 0.2/year
- Mesangio-proliferative GN 0.2/year
- Minimal change disease 0.6/year
- Focal segmental glomerulosclerosis 0.8/year
- Membranous nephropathy 1.2/year
- IgA nephropathy 2.5/year

**Children**

- In general ~ 0.1/year
- Minimal change disease 2.0 – 15.6/year

McGrogan *NDT* 26(2), 2011; 414–430
Finding participants is challenging
Focal Sclerosing Glomerulosclerosis trials

- All trials
  - n=2168 participants

- Active trials
  - n=1404 participants (65% total recruitment target ever)

- Completed /terminated trials
  - Targeted n=764
  - Actual n=605 (79%)

Source: International Clinical Trial Registry Platform (ICTRP)
Search criteria: condition FSGS, Trial Phase 2-4, Interventional trials
Search interval: 2001 to July 20th, 2019

T Bradbury, draft
Finding participants is challenging even for ‘common’ conditions

Diabetic Kidney Disease trials
- **CREDENCE**
  - 6.4 pt/site
- **SONAR**
  - 6.8 pt/site
- **EVOLVE**
  - ~7.8 pt/site

Cardiovascular trials
- **EMPA-REG**
  - 11.9 pt/site
- **CANVAS**
  - 15.2 pt/site
- **DECLARE**
  - 19.5 pt/site
Potential for adaptive randomisation

- Increases efficiency for identifying effective agents

**Diagram:**

- Fixed phase
- Response Adaptive Randomisation Phase

**Legend:**

- Control arm continues

**Agents:**

- Agent 1
- Agent 2
- Agent 3
- Capacity to include external knowledge
- Particularly useful for multiple rare but similar conditions

Bayesian hierarchial modelling in which there is “partial borrowing” of results in subtypes (pathologies)

Berry, Molecular Oncology 9(5) 2015, 951-959
Master protocol trials in Nephrology

• Allow patients greater access to research agents
• More efficient for evidence generation
  • Test more agents and more research questions
  • Allow rare conditions to be tested together as ‘subtypes’
  • Lower costs
  • Reduce time
• Can incorporate external learnings

Turn competition into collaboration