Vlado Perkovic
George Institute for Global Health
University of Sydney
Disclosures

I am employed by the George Institute and the University of Sydney, and serve on the Board of George Clinical, a wholly owned subsidiary that provides contract research services to academia and industry.

I lead or serve on the Steering Committees of several trials (funders: National Health and Medical Research Council of Australia, Janssen, Abbvie, GSK, Boehringer Ingelheim, Eli Lilly, Canadian Institutes of Health Research, Baxter, Pfizer), am on the Executive of the Australasian Trials Network and Chair the ISN Advancing Clinical Trials initiative.

I have received honoraria for scientific presentations and/or advisory board attendance from Abbvie, Astra Zeneca, BMS, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Merck, Pfizer, Reata, Sanofi and Servier.

I have a policy of honoraria being paid to my employer.
Trials in kidney disease - challenges

- Difficult recruitment
- High drop out (and drop-in)
- Burden on patients and sites
  - Additional visits, data, drugs etc
- Limited site capacity
- Endpoints are difficult and late
- Increased risk of adverse effects
- Variable regulatory approaches
- Growing disengagement from community
Recruitment targets

Slow recruitment and extension periods are common

<table>
<thead>
<tr>
<th>Study</th>
<th>Extension of recruitment time (months)</th>
<th>Recruitment shortfall</th>
<th>Actual recruitment</th>
<th>Recruitment extension (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HONEYPOT</td>
<td>371</td>
<td>7%</td>
<td>6%</td>
<td>24 months</td>
</tr>
<tr>
<td>FAVOURED</td>
<td>568</td>
<td>3%</td>
<td>7%</td>
<td>18 months</td>
</tr>
<tr>
<td>HERO</td>
<td>53</td>
<td>10%</td>
<td>6%</td>
<td>21 months</td>
</tr>
<tr>
<td>BLOCADE*</td>
<td>72</td>
<td>12%</td>
<td>10%</td>
<td>30 months</td>
</tr>
</tbody>
</table>

Australasian Kidney Trials Network Studies

Suetonia Palmer, AKTN
ADVANCE: Recruitment in Diabetes

Proportion of target randomised (%)

- ANZ/SEA (2000)
- Canada (500)
- China (3000)
- India (450)
- Europe - central (2500)
- Europe - northern (2500)
Why is it hard to recruit?  
Example from diabetic kidney disease

Event rate vs population size in ADVANCE

<table>
<thead>
<tr>
<th>Population</th>
<th>Number</th>
<th>(%)</th>
<th>Annual Event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>11,140</td>
<td>(100)</td>
<td>CV    2.6</td>
</tr>
<tr>
<td>eGFR &lt; 60</td>
<td></td>
<td></td>
<td>3.9</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td></td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>eGFR&lt;60 and macro</td>
<td></td>
<td></td>
<td>7.3</td>
</tr>
</tbody>
</table>
Albuminurinuia and eGFR are highly variable

- Repeating measurements as entry criteria leads to screen failure rates of ~50% or more- ? rationale

<table>
<thead>
<tr>
<th></th>
<th>No / % of events</th>
<th>Favors RAASI</th>
<th>Favors Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAASI</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BENEDICT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 urine collection</td>
<td>74/14.5</td>
<td>49/21.0</td>
<td>0.66 (0.46 - 0.94)</td>
<td></td>
</tr>
<tr>
<td>2 urine collections</td>
<td>63/12.4</td>
<td>44/18.9</td>
<td>0.61 (0.42 - 0.90)</td>
<td></td>
</tr>
<tr>
<td>3 urine collections</td>
<td>57/11.2</td>
<td>41/17.6</td>
<td>0.60 (0.40 - 0.89)</td>
<td></td>
</tr>
<tr>
<td>DIRECT Type 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 urine collection</td>
<td>217/14.1</td>
<td>224/14.4</td>
<td>0.96 (0.80 - 1.16)</td>
<td></td>
</tr>
<tr>
<td>2 urine collections</td>
<td>165/10.7</td>
<td>179/11.5</td>
<td>0.92 (0.74 - 1.13)</td>
<td></td>
</tr>
<tr>
<td>DIRECT Type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 urine collection</td>
<td>197/22.3</td>
<td>234/26.7</td>
<td>0.79 (0.66 - 0.96)</td>
<td></td>
</tr>
<tr>
<td>2 urine collections</td>
<td>174/19.7</td>
<td>206/23.5</td>
<td>0.80 (0.65 - 0.98)</td>
<td></td>
</tr>
<tr>
<td>ALTITUDE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 urine collection</td>
<td>850/46.4</td>
<td>1011/54.6</td>
<td>0.79 (0.72 - 0.86)</td>
<td></td>
</tr>
<tr>
<td>2 urine collections</td>
<td>789/43.0</td>
<td>949/52.1</td>
<td>0.80 (0.73 - 0.88)</td>
<td></td>
</tr>
<tr>
<td>3 urine collections</td>
<td>776/42.3</td>
<td>941/50.6</td>
<td>0.78 (0.71 - 0.86)</td>
<td></td>
</tr>
</tbody>
</table>
Some options:

- Use broad inclusion criteria to maximise eligible participants.
- Do not ‘fail’ potential participants unless there is good data supporting this.
- Consider expanding populations-capacity challenges.
Global Population—~7 Billion

Asia total = 3.6 B

- CHINA
- INDIA
- OTHER ASIA

Half of the planet lives in Asia

Australia ~0.3%
Potential numbers of participants

RELATIVITIES BY POPULATION SIZE

Potential patients

- Australia: 100
- UK: 300
- US: 1500
KDIGO Controversies Conference on Challenges in the Conduct of Clinical Trials in Nephrology
September 8-11, 2016 | Paris, France

Liyanage, Lancet 2015

Estimated number of patients receiving RRT

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated number of patients receiving RRT (x million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>2.62</td>
</tr>
<tr>
<td>2015</td>
<td>3.13</td>
</tr>
<tr>
<td>2020</td>
<td>3.78</td>
</tr>
<tr>
<td>2025</td>
<td>4.53</td>
</tr>
<tr>
<td>2030</td>
<td>5.44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated number of patients receiving RRT (x million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>(0.97→2.16)</td>
</tr>
<tr>
<td>North America</td>
<td>(0.64→1.26)</td>
</tr>
<tr>
<td>Latin America</td>
<td>(0.37→0.90)</td>
</tr>
<tr>
<td>Europe</td>
<td>(0.53→0.83)</td>
</tr>
<tr>
<td>Africa</td>
<td>(0.08→0.24)</td>
</tr>
<tr>
<td>Oceania</td>
<td>(0.03→0.05)</td>
</tr>
</tbody>
</table>
Growing Capacity

- Increasing collaboration
- Training programs
- Regular conferences on kidney trials
- Leveraging experienced organisations

NB. ISN Advancing Clinical Trials Initiative
Adherence: the EVOLVE trial
The impact of drop-in and drop-out

1948 Were assigned to receive cinacalcet

- Patients on cinacalcet at end of the study:
  - 870 (45%)
  - 2.4% PTx
  - 45% Total

1935 Were assigned to receive placebo

- 440 (23%)
- 7.6% PTx
- ~30% Total

of consent
- 2 Were determined to be ineligible
- 222 Started commercial cinacalcet 11.4%

loss to follow-up and withdrawal of consent
- 5 Were determined to be ineligible
- 440 Started commercial cinacalcet 22.7%

Chertow et al, NEJM 2012
# Primary Composite Endpoint: Sensitivity Analyses

<table>
<thead>
<tr>
<th>Analysis Type</th>
<th>Placebo (N=1935)</th>
<th>Cinacalcet (N=1948)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>952 (49.2)</td>
<td>938 (48.2)</td>
<td>0.93 (0.85, 1.02)</td>
<td>0.112</td>
</tr>
<tr>
<td>Lag Censoring (6 mos)</td>
<td>658 (34.0)</td>
<td>638 (32.8)</td>
<td>0.85 (0.76, 0.95)</td>
<td>0.003</td>
</tr>
<tr>
<td>Censor at PTX</td>
<td>911 (47.1)</td>
<td>916 (47.0)</td>
<td>0.90 (0.82, 0.99)</td>
<td>0.031</td>
</tr>
<tr>
<td>Censor at KTX</td>
<td>907 (46.9)</td>
<td>891 (45.7)</td>
<td>0.90 (0.82, 0.99)</td>
<td>0.029</td>
</tr>
<tr>
<td>Censor at Commercial Cinacalcet Use</td>
<td>818 (42.3)</td>
<td>870 (44.7)</td>
<td>0.90 (0.82, 0.99)</td>
<td>0.032</td>
</tr>
<tr>
<td>Censor at PTX or Commercial Cinacalcet Use</td>
<td>786 (40.6)</td>
<td>854 (43.8)</td>
<td>0.87 (0.79, 0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Censor at PTX, Commercial Cinacalcet, or KTX</td>
<td>748 (38.7)</td>
<td>812 (41.7)</td>
<td>0.84 (0.76, 0.93)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
ADVANCE: End-stage kidney disease

Cumulative incidence (%)

In-trial

- Hazard Ratio: 0.35 (95% CI: 0.15-0.83)
- Event no.: (7 vs 20)

Follow-up (years)

0 2 4 6 8 10

0 1 2

Standard
Intensive

KDIGO Controversies Conference on Challenges in the Conduct of Clinical Trials in Nephrology
September 8-11, 2016 | Paris, France
Adherence in the ADVANCE trial:

![Graph showing adherence rate over time for different regions: Australia and New Zealand, Asia, North America, and Europe.](image)

- **Australia and New Zealand**: High adherence initially, but drops significantly over time.
- **Asia**: High adherence initially, drops more gradually than Australia and New Zealand, but remains consistently above other regions.
- **North America**: Moderate adherence throughout, stable and not as high as Asia.
- **Europe**: Lowest adherence, consistently below 20% from the start.

**Months**

- 0
- 3
- 4
- 6
- 12
- 18
- 24
- 30
- 36
- 48
- 54

**adherence rate**

- 0.0%
- 20.0%
- 40.0%
- 60.0%
- 80.0%
- 100.0%
- 120.0%
Some potential strategies:

• Simplify protocol to minimise burden
• Consider run-in periods:
  • Placebo vs active? (NB. Safety, baseline measures)
  • Optimal duration?
• Shorter duration studies (trade off vs long term data)
**ADVANCE endpoint adjudication**

Conclusion: ‘no discernable impact’

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Adjudication</th>
<th>Number of events</th>
<th>Favours active</th>
<th>Favours placebo</th>
<th>Relative risk reduction (%; 95% CI)</th>
<th>P homog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined macro + micro</td>
<td>Invest.</td>
<td>1018</td>
<td>1087</td>
<td></td>
<td>8 (-1 to 15)</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>EPAC</td>
<td>861</td>
<td>938</td>
<td></td>
<td>9 (0 to 17)</td>
<td></td>
</tr>
<tr>
<td>Major macro-vascular</td>
<td>Invest.</td>
<td>557</td>
<td>586</td>
<td></td>
<td>6 (-6 to 16)</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>EPAC</td>
<td>480</td>
<td>520</td>
<td></td>
<td>8 (-4 to 19)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>Invest.</td>
<td>177</td>
<td>172</td>
<td></td>
<td>-2 (-26 to 17)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>EPAC</td>
<td>136</td>
<td>135</td>
<td></td>
<td>0 (-27 to 21)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>Invest.</td>
<td>258</td>
<td>250</td>
<td></td>
<td>-2 (-22 to 14)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>EPAC</td>
<td>193</td>
<td>184</td>
<td></td>
<td>-4 (-28 to 15)</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>Invest.</td>
<td>188</td>
<td>236</td>
<td></td>
<td>21 (4 to 35)</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>EPAC</td>
<td>211</td>
<td>257</td>
<td></td>
<td>18 (2 to 32)</td>
<td></td>
</tr>
</tbody>
</table>

**Hazard ratio (95% CI)**

0.6 0.8 1.0 1.2 1.4
Endpoint adjudication in kidney disease

- What is the impact of endpoint adjudication on renal outcomes?
- Is there value in adjudicating biochemical measures?
- Is confirmation important?
- Can we streamline the process?
Safety issues in diabetes and CKD trials

- Dual RAS blockade: Hyperkalaemia, AKI
- Bardoxolone: Heart failure
- Avosentan: Heart failure
- Thiazolidinediones: Heart failure/MI
- DPP 4 inhibitors: ? Heart failure
- Steroids: Infection

How do we define and collect these optimally?
Monitoring

Aims:

• Detect fraud - consent, data etc
• Assess adherence to protocol
• Check that data is complete and correct (especially safety, endpoints)
• Etc.

Much of this can be done more effectively and efficiently using central monitoring methods, with targeted site activities based on risk.
Dutch neurologist found guilty of fraud after falsifying 438 case records

A Dutch court has found a neurologist guilty of serious scientific fraud after he falsified reports for medical research and concealed earnings from the tax authorities.

Between 1989 and 1993, Dr H J Gelmers made 438 false case record forms as part of the second European stroke prevention study for the German pharmaceutical company Boehringer Ingelheim. The study was investigating whether dipyridamol reduced the chances of patients having a second stroke.

Reports showed falsely that patients had participated. Patient visits and research were reported that had not taken place. None of the patients later interviewed by investigators had been informed of the research by Dr Gelmers; nor were their GPs. Most of the 600 000 guilders (£171 000; $266 000; €272 000) earned from the research was not disclosed to the tax authorities.

» Not detected on routine site monitoring
» Picked up via central monitoring of drug levels
The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators’ training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.
Overview: FDA Monitoring Draft Guidance

• Intends to assist sponsors in developing risk-based monitoring strategies and plans
  – Tailored to the specific human subject protection and data integrity risks of the trial
  – Focuses on critical study parameters
  – Encourages use of a combination of monitoring activities
  – Encourages greater reliance on centralized monitoring practices, where appropriate
Challenges with risk-based monitoring

- Requires a lot of work to get right - few centres have strong experience in the area
- Experience very important
- Estimating risk accurately is crucial
- Buzzword vs meaningful approach
IDMC role in context of regulators

Challenges to Data Monitoring Committees When Regulatory Authorities Intervene

Karl Swedberg, M.D., Ph.D., Jeffrey S. Borer, M.D., Bertram Pitt, M.D., Stuart Pocock, Ph.D.,

Regulatory Reply to the ATMOSPHERE Data Monitoring Committee

TO THE EDITOR: We agree with Swedberg et al., whose Sounding Board article is now published in the Journal, regarding the role and responsibilities of the data monitoring committee. We also agree that the benefit-risk balance of medicinal products containing aliskiren in light of the results of the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular Endpoints (ALTITUDE). The CHMP

Novartis Reply to the ATMOSPHERE Data Monitoring Committee

TO THE EDITOR: The Sounding Board article by Swedberg and colleagues, now published in the Journal, describes the experience of the data monitoring committee of the Aliskiren Trial to working group of the Heads of Medicines Agencies network in the European Economic Area that includes representatives of the European Medicines Agency and the European Commission,
All patients with STEMI in Sweden and Iceland undergoing primary or rescue PCI. N=11 709 *)

Enrolled in TASTE N=7259
N=3621 assigned to thrombus aspiration
N=3399 underwent thrombus aspiration
N=222 underwent conventional PCI
N=3445 underwent conventional PCI
N=1162 underwent thrombus aspiration
N=3535 underwent conventional PCI
N=3621 were followed up
N=3623 were followed up
N=1162 were followed up
N=3535 were followed up

Enrolled in Denmark N=247

Randomized in TASTE N=7244
N=3621 assigned to thrombus aspiration
N=3623 assigned to conventional PCI

Erroneous enrollments N=15
Not enrolled N=4697

KDIGO
Routinely collected data
Registries, administrative data, electronic health records, etc

Potential roles:
• Identify patients
• Randomize
• Collect baseline and procedure characteristics (CRF)
• Assist with and collect consent forms
• Identify endpoints
• Longer term follow up
HD- the ultimate registry?

- Frequent visits
- Large amount of data already collected
- High event rates

But
- Inconsistent approaches and systems, across and within countries
- Heavy burden of treatment and medical care
Compare randomly selected with non-selected participants vs

Needs:
- Randomised selection
- Full follow up of participants
- Good quality data, especially relevant safety measures
- High uptake of randomised therapy
Cluster randomised trials?

- Ideal for strategy approaches
- Need large numbers of clusters and usually larger numbers of participants
- Intracluster variability can be a challenge
- Well suited to pragmatic approaches, implementation trials (esp stepped wedge), trials of techniques etc
• Pragmatic, cluster-randomised, open-label trial
• Dialysis units randomised- dialysate sodium 137 vs 140 mmol/L
• Outcomes assessed on individual patients
  – Waiver of consent or opt-out consent
• Real-world conditions

…. Randomised allocation rather than random allocation
Data collection and endpoints

• Simple data collection
  – Using routine clinical data systems wherever possible

• Common efficacy and safety endpoints
  – No separate SAE reporting

• Primary endpoint
  – Composite of major cardiovascular events & all cause mortality
    • hospitalised myocardial infarction, hospitalised stroke, coronary artery or cerebrovascular revascularisation, all cause mortality

• Secondary endpoints
  – Composite of primary endpoint plus hospitalized heart failure
  – Individual components of the composites
Enrichment

**Screening Period (up to 14 Days)**
- Run-In Period 2 weeks if receiving max tolerated labeled dose of RAS
- Run-In Period up to 12 weeks if not receiving max tolerated labeled dose of RAS

**Enrichment Period**
- Atrasentan 0.75 mg QD
- > 30% UACR reduction
- < 30% UACR reduction

**Double Blind Treatment Period (425 Events)**
- Atrasentan 0.75 mg QD (1574 subjects)
- Placebo QD (1574 subjects)
- Atrasentan 0.75 mg QD (500 subjects)
- Placebo QD (500 subjects)

**Follow-Up Period (45 Days)**
Collaborative approaches: eg. PEXIVAS

- Core & international
  - Core Funding: National Institute of Health Research (NIHR) UK
  - FDA Office of Orphan Disease Products, USA
  - Canadian Institutes of Health Research, Canada
  - National Health Medical Research Council, Australia/New Zealand
  - Caridian BCT, international disposables
  - Gambro
  - Fresenius Medical Care

- Regional (ANZ)
  - National Institute for Health Research (NIHR) UK
  - FDA Office of Orphan Disease Products, USA
  - Canadian Institutes of Health Research, Canada
  - National Health Medical Research Council, Australia/New Zealand
  - Caridian BCT, international disposables
  - Gambro
  - Fresenius Medical Care
Sample size

• Target recruitment 700 patients- on track

• 17 trials in AAV since 1985
  – None demonstrated a reduction in a death or ESRD
  – Sample Size
    • Median 67 (20 to 174)
Many potential partners
Networks of networks:
Networks of networks:
Networks of networks:
Networks of networks:

Facilitative Infrastructure

Trial Lead

Network

Network

Network

Network

Network

Network

Network

Network
Networks of networks:
Regulators
Pharma
Sites
Populations
Academia
Contract Research Organisations
Compete?
Support?
Partner?
Other?
KDIGO
Trials in kidney disease - some challenges

- Difficult recruitment
- High drop out (and drop-in)
- Burden on patients and sites
  - Additional visits, data, drugs etc
- Limited site capacity
- Endpoints are difficult and late
- Increased risk of adverse effects
- Variable regulatory approaches
- Growing disengagement from community