Getting started: The 1-page protocol synopsis

Richard A. Preston, M.D., M.S.P.H., M.B.A.
Professor of Clinical Medicine,
Chief, Division of Clinical Pharmacology
Miller School of Medicine
University of Miami
Components of a Clinical Research protocol

Introduction
Research objectives
Primary and secondary endpoints
Background and rationale
Methods
  • Study design
  • Selection of subjects. Case definition. Inclusion/exclusion criteria
  • Detailed procedures for patient entry. Randomization.
  • Detailed study evaluations and procedures visit by visit
  • Flow chart of study events
  • Stopping criteria and safety
  • Statistical Methods
    – Sample size calculation
    – Statistical analysis
Administrative aspects. Humans subjects research. HIPPA
1- Page Protocol Synopsis

Introduction/Background: 5-10 sentences.

Research objectives
• The objective(s) of this study is/are… (List 1-3)
• Primary and secondary endpoints (1-3)

Methods
• Study design and overview (4-5 sentences)
• Study participants and entry (4-5 sentences)
  – Inclusion criteria (5-10)
  – Exclusion criteria (5-10)
• Participant safety/risks (4-5 sentences)
• Statistical Methods (3-4 sentences)
  – Sample size calculation
  – Statistical analysis
1- Page Protocol Synopsis

1. Concise overview to share with potential collaborators, research unit directors, clinic faculty

2. Detailed enough to allow determination of merit and feasibility

3. Less time consuming than attempting an entire protocol from scratch

4. Promotes moving ahead with an idea

5. Flexible: Can be modified easily

6. Key elements are there: Can be expanded to full protocol when ready
Case Example

Mechanisms of impaired potassium handling with dual RAAS blockade in patients with CKD
1- Page Protocol Synopsis

Introduction/Background: 5-10 sentences.

Research objectives
• The objective(s) of this study is/are...
• Primary and secondary endpoints

Methods
• Study design and overview
• Study participants and entry
  – Inclusion criteria
  – Exclusion criteria
• Participant safety/risks
• Statistical Methods
  – Sample size calculation
  – Statistical analysis
Chronic kidney disease (CKD) in US

20 million in US with stage III chronic kidney disease (GFR<60 ml/min)

10-fold increase in risk for CVD.
Leading cause of CKD is Diabetes Mellitus
Highest prevalence of CKD is among the elderly

292,000 patients with ESRD requiring renal replacement
5-year survival is 32%. Estimated 2.2 million with ESRD by 2030

Effective treatment options to delay progression to ESRD are limited
1. BP control <130/80 (125/75 if proteinuria > 1 gram)
2. **Single agent** RAAS blockade with either ACE inhibitor or AII blocker
3. **Dual agent** RAAS blockade with ACE inhibitor or ARB plus Aldosterone antagonist

The main adverse effect that limits the use of RAAS blockade is hyperkalemia
1- Page Protocol Synopsis

Introduction/Background: 5-10 sentences.

Research objectives

- The objective(s) of this study is/are...
- Primary and secondary endpoints

Methods

- Study design and overview

- Study participants and entry
  - Inclusion criteria
  - Exclusion criteria

- Participant safety/risks

- Statistical Methods
  - Sample size calculation
  - Statistical analysis
Participant safety/risks

The study participants will be monitored closely in the Division of Clinical Pharmacology inpatient research center. The study coordinators and the study PI will assess all adverse events (AE) immediately. In the event of an AE, the PI and the study team will carefully assess the nature, severity, and possibility of study medication relatedness. If, in the opinion of the PI, there is a likely possibility of a clinically important drug-related AE, the study medication will be discontinued. This will be handled under the care of the PI on a case by case basis.
Increase in serum potassium

1. Study participants will be required to have a serum potassium of less than 5.0 mmol/L prior to entry into the study.
2. Serum potassium will be determined at each outpatient visit and on admission to the research unit.
3. Calcium Chloride for IV injection as well as 50% glucose and insulin injection will be readily available during the entire potassium handling study.
4. Participants will be discontinued from the study for K>5.5 at any point in the study except during acute K-loading study.
5. ECG changes suggestive of changes of hyperkalemia from baseline ECG (peaked T waves, shortened PR interval) will be followed immediately with a STAT sample for potassium and appropriate intervention as determined by the study PI.
**Statistical Methods**

1. Sample size is calculated to be 15 to allow detection of 1 mmol/hour reduction of UkV at hour 2-3 with alpha 0.05 and power 0.80. 20 subjects is conservative enrollment.

2. Paired t-tests used to detect differences in hour 2-3 UkV and K during K-handling study between drug and placebo.

3. Mixed models to investigate the predictive relationship between dynamic K-handling variables (K, UkV) and ambulatory K

   \[
   \text{Ambulatory K} = F(\text{UkV}, K, \text{eGFR}, \text{drug}, \text{demographic})
   \]
Sample size $N$ required to demonstrate a Difference in UkV (mmol/hr) between Group A and Group B (t-test)

\[ N \quad \text{--} \quad \text{Power, Alpha, SD}^2 \]

\[ \text{Difference}^2 \]

Greater SD \quad \text{Larger N}
Greater Power \quad \text{Larger N}
Smaller alpha \quad \text{Larger N}
Smaller Difference \quad \text{Larger N}
Find Sample Size N for K-handling study: Endpoint UkV (mmol/hr) with the following assumptions

- Set the difference we want to detect to 1 mmol/hr
- Set the SD of the variable to 1 mmol/hr
- Set the desired power to 0.8
- Set alpha to 0.05
Statistical test: t-test
Difference = 1 mmol/hr
Standard deviation = 1 mmol/hr
Power = 0.80
Alpha = 0.05
Statistical test: t-test
Difference = 1 mmol/hr
Standard deviation = 0.5 mmol/hr
Power = 0.80
Alpha = 0.05
Statistical test: t-test
Difference = 1 mmol/hr
Standard deviation = 2 mmol/hr
Power = 0.80
Alpha = 0.05
Statistical test: t-test
Difference = 0.5 mmol/hr
Standard deviation = 2 mmol/hr
Power = 0.80
Alpha = 0.05
Summary: 1- Page Protocol Synopsis

Introduction/Background: 5-10 sentences.

Research objectives
  • The objective(s) of this study is/are…
  • Primary and secondary endpoints

Methods
  • Study design and overview (4-5 sentences)
  • Study participants and entry
    – Inclusion criteria
    – Exclusion criteria
  • Participant safety/risks
  • Statistical Methods
    – Sample size calculation
    – Statistical analysis
Results
## Results: Baseline and Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CKD (N=18)</th>
<th>Control (N=18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.5 (6.84)</td>
<td>39.05 (7.68)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>14/4</td>
<td>14/4</td>
<td>1.0</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic Caucasian</td>
<td>13</td>
<td>16</td>
<td>.40</td>
</tr>
<tr>
<td>Hispanic Black</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>American Caucasian</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.83 (4.26)</td>
<td>28.95 (2.56)</td>
<td>.46</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>141.44 (16.20)</td>
<td>117.22 (9.17)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>81.55 (10.17)</td>
<td>74.16 (7.13)</td>
<td>.017</td>
</tr>
<tr>
<td>GFR (MDRD, ml/min)</td>
<td>45.15 (14.44)</td>
<td>112.10 (13.04)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Serum K (mmol/L)</td>
<td>4.48 (.47)</td>
<td>4.39 (.42)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Hypertensive renal disease: 10/18

Diabetes Mellitus: 8/18

DM nephropathy: 5/8

Insulin-requiring: 3/8
Phase 1. UKV in CKD versus control

Figure 1a
Hourly SEK in control versus CKD

Figure 1c
Ambulatory serum K Lisinopril/spironolactone versus placebo in CKD patients (N=18)
UkV Lisinopril/spironolactone versus placebo

![Graph showing comparison of Lisinopril/Spironolactone and Placebo over different hours post oral potassium load. The graph indicates that there is a significant difference at p = 0.03 and a trend at p = 0.09.]
Serum K

Lisinopril/Spironolactone

Placebo

$\text{p} < .001$

5.5

5.0

4.5

Hours post oral potassium load

Figure 3e
Dynamic delta serum K predicts ambulatory serum K

$r = .57$ (p=.01)
Mixed effect model for ambulatory K as a function of baseline and K-handling variables

\[ Y_{ijk} = (\gamma_{10} + \gamma_{11}\text{Drug}_k + \gamma_{12}\text{Drug}_k \times \text{delta.SEK} + \gamma_{13}\text{Drug}_k \times d.UKV + \gamma_{14}\text{Drug}_k \times \text{MDRD} + u_{1ik}) \\
+ (\gamma_{20} + \gamma_{21}\text{Drug}_k + \gamma_{22}\text{delta.UKV} + \gamma_{23}\text{Drug}_k \times \text{delta.UKV} + u_{2ik})t_{ij} \\
+ \gamma_{30}\text{delta.SEK} + \gamma_{40}\text{delta.UKV} + \gamma_{50}\text{MDRD} + \varepsilon_{ij}, \quad (1) \]
Prediction model for increase in K with dual blockade
Summary

1. **Hypothesis**: CKD patients have a markedly reduced ability to excrete an acute K load but can maintain serum K in an acceptable range by increased cellular translocation

2. **Hypothesis**: Dual RAAS blockade reduces K excretion and the ability to translocate K. Role of aldosterone in translocation of K

3. **Hypothesis**: Steady-state ambulatory K is achieved in most patients within one week of starting dual RAAS blockade. Best time to check K is 1-2 weeks after starting dual RAAS blockade

4. **Hypothesis**: In principle K-handling data (UkV, K) following an oral K load can predict the rise in ambulatory K with dual RAAS blockade. This suggests a simple and inexpensive office test to predict the K response to dual RAAS blockade