Statistical Analysis Plan
Mira Trainee Grant Writing Workshop

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Outline

• Grant text and organization
• Statistical analysis section
• Appendix
• Additional considerations
Do you know statistics?

- A good / bad statistical section can make or break a grant application
- Consult a statistician if possible
- A statistician as co-investigator in your grant is a huge plus
- When describing the roles of applicants note who will be supporting statistical analysis and interpretation of findings
Guidelines and reviewer guidelines
Analysis plan

• It is not just about writing a good statistical section

• INTEGRATION and considerations across the proposal

• Organization is key (flow)
General considerations of flow

• Introduction/gaps aligned with objectives
• Methods and outcome measures using same order
• If an outcome measure will be used for aim 2 then mention it while explaining the outcome
  o (e.g., HRQL will be used for cost effectiveness)
Outcome measures

• Always provide the level of measurement
  o Nominal and Ordinal (provide categories)
  o Continuous (provide range of scores)

• Psychometric properties as possible
Analysis plan - Example

WHICH EXERCISE FOR LOW BACK PAIN? Predicting response to exercise treatments for patients with low back pain

The trial will answer the following questions:

**Aim 1:** Does the Lumbar Spinal Instability Questionnaire (LSIQ) modify the response of patients with chronic non-specific LBP to motor control exercise or graded activity at 12 months follow up?

*Hypotheses:* Patients with chronic non-specific LBP and low scores on the LSIQ will respond best to graded activity, and patients with high scores on the LSIQ will respond best to motor control exercises.

**Aim 2:** Is there a difference in cost-effectiveness between patients that received the “matched” intervention compared to those that did not received their “matched” exercise at 12 months follow up?

*Hypotheses:* Matched exercise therapy will be more cost-effective than non-matched exercises at 12 months follow up.

**Aim 3 (exploratory):** Does a group of baseline characteristics (central sensitization, nociceptive pain, coping strategies, fear of movement and the OREBRO questionnaire) modify the response of patients with chronic non-specific LBP to motor control exercise or graded activity at 12 months follow up?

*Hypotheses:* Patients with chronic non-specific LBP will respond best to graded activity if they have low scores on LSIQ, have central sensitization, poor coping strategies, fear of moment or high scores on the OREBRO back pain screening questionnaire. Patients will respond best to motor control if they have high score on the LSIQ, do not have neuropathic pain or predominant central sensitization and have good coping strategies.
Analysis plan - Example

The primary analyses will be by intention-to-treat. For the primary and secondary outcome, a P-value of <0.05 will be considered statistically significant. Group allocation will remain masked until analyses and interpretation are finalized.

**Treatment effectiveness analysis (Aim 1 & Aim 3)** (See section 2.18 for subgroup analysis)

The effect modification analysis will be conducted for the primary outcome and secondary outcomes separately. Linear mixed models with terms for patients (fixed), treatment group, predictor (potential effect modifier such as LSIQ), physiotherapists, treatment group x physiotherapists, treatment group x predictor (potential effect modifier) and baseline score for the dependent variable will be constructed. Treatment effect modification will be evaluated using a group x predictor interaction. A pre-specified threshold of 1.5 units, ~1.0 standard deviation will be used for a clinically important interaction effect. For aim 3 we will also attempt to build multivariate models using a backwards selection procedure.

**Cost-effectiveness analysis (Aim 2)**

Interventions for LBP have an impact on the utilization of health care services and can affect the burden to patients. As such, we will conduct two economic evaluations along with the RCT: one cost-effectiveness analysis (CEA) and one cost-utility analysis (CUA) following the methodology outlined in Drummond. The CEA will use the primary outcome, i.e. changes in the score on PFSF, as the effect and the CUA will use changes in health-related quality of life, as measured with the EQ-5D-5L. We will estimate costs from the Ontario health care system perspective but also consider the societal perspective, as well as the patient perspective. The societal perspective includes health care system costs as well as indirect costs from loss of productivity. The patient’s perspective includes costs for the patient.
Data analysis section

• Number analysis as per objectives (keep the same order)
• Give names to the analysis
• Provide as much detail as possible about the analysis to demonstrate that you know what you are doing
• Provide variables that will be included in the analysis
  o E.g, one way ANOVA for disability by age groups
  o E.g, regression analysis with x as dependent variable and Q A C D will be included as independent variables
• Provide methods for interpretation of results (e.g., cut offs, MCIDs)
• Provide level of significance and corrections (Bonferroni etc)
Analysis plan - Example

The primary analyses will be by intention-to-treat. For the primary and secondary outcome, the level of significance will be set at 0.05. Group allocation will remain masked until analyses and interpretation are finalized.

**Treatment effectiveness analysis (Aim 1 & Aim 3)** (See section 2.18 for subgroup analysis)

The effect modification analysis will be conducted for the primary outcome and secondary outcomes separately. Linear mixed models with terms for patients (fixed), treatment group, predictor (potential effect modifier such as LSIQ), physiotherapists, treatment group x physiotherapists, treatment group x predictor (potential effect modifier) and baseline score for the dependent variable will be constructed. Treatment effect modification will be evaluated using a group x predictor interaction. A pre-specified threshold of 1.5 units, ~1.0 standard deviation will be used for a clinically important interaction effect. For aim 3 we will also attempt to build multivariate models using a backwards selection procedure.
Caution

• Properly name the elements of the analysis
• Use correct analysis for each level of measurement
• Make sure you propose an analysis for all of your objectives as well as collected outcomes
  o why are you collecting outcomes if you are not using it?
Appendix
### Statistical Analysis Table

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hypothesis</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome (Aim 1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMPACT of LBP measured using 9 PROMIS items (score from 8 to 50)</td>
<td>The Back to living well program will be better at improving the <em>personal impact of low back pain</em> as compared to the minimal intervention at all time points.</td>
<td>Repeated-measure linear mixed models will be used to assess the effect of treatment on the primary and secondary outcomes. Linear mixed models with terms for patients (fixed), treatment group, treatment group x time and baseline score for the dependent variable will be constructed.</td>
</tr>
<tr>
<td><strong>Secondary outcomes (Aim 3)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient specific functional scale (score from 0-10)</td>
<td>The Back to living well program will be better at improving function (PSFS scores) as compared to the minimal intervention at all time points.</td>
<td>Repeated-measure linear mixed models will be used to assess the effect of treatment the outcome. Linear mixed models with terms for patients (fixed), treatment group, treatment group x time and baseline score for the dependent variable will be constructed.</td>
</tr>
<tr>
<td>Oswestry Disability index (ODI) (0-100)</td>
<td>The Back to living well program will be better at improving disability (ODI scores) as compared to the minimal intervention at all time points.</td>
<td>Repeated-measure linear mixed models will be used to assess the effect of treatment the outcome. Linear mixed models with terms for patients (fixed), treatment group, treatment group x time and baseline score for the dependent variable will be constructed.</td>
</tr>
</tbody>
</table>
## Statistical Analysis Table (cost)

<table>
<thead>
<tr>
<th>Economic evaluation</th>
<th>Cost-effectiveness analysis (CEA)</th>
<th>Cost-utility analysis (CUA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Difference between the ‘IMPACT of LBP’ scores at baseline and at 12 months</td>
<td>Difference between EQ-5D-5L scores at baseline and at 12 months</td>
</tr>
<tr>
<td>Costs &amp; Perspective: MOHLTC</td>
<td>All health care costs covered by the MOHLTC from ICES</td>
<td>All health care costs covered by the MOHLTC + indirect costs from loss of productivity</td>
</tr>
<tr>
<td>Societal</td>
<td>Direct costs: medical (cost-sharing for health care services) + non-medical (transportation, parking, etc.)</td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>Indirect costs (time, loss of productivity)</td>
<td></td>
</tr>
</tbody>
</table>

**MOHLTC:** Ministry of Health and Long-Term Care

**Societal:** All health care costs covered by the MOHLTC + indirect costs from loss of productivity

**Patient:** Direct costs: medical (cost-sharing for health care services) + non-medical (transportation, parking, etc.)
# Statistical Analysis Table (Pilot)

<table>
<thead>
<tr>
<th>Proceed</th>
<th>Proceed with Protocol Amendments</th>
<th>Significant Amendments Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=25 within 4 months</td>
<td>n ≥ 15 within 8 months</td>
<td>n &lt; 10 within 8 months</td>
</tr>
<tr>
<td>50% of eligible participants consent to participate</td>
<td>40% of eligible participants consent to participate</td>
<td>25% of eligible participants consent to participate</td>
</tr>
<tr>
<td>Exercise program</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60% of participants report exercise at least 3 times a week</td>
<td>40% of participants report exercise at least 3 times a week</td>
<td>25% of participants report exercise at least 3 times a week</td>
</tr>
<tr>
<td>Content Acceptability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% found treatment useful (Likert ≥ 4/5)</td>
<td>25% found treatment useful (Likert ≥ 4/5)</td>
<td>&lt; 25% found treatment useful (Likert ≥ 4/5)</td>
</tr>
<tr>
<td>50% found treatment helpful (Likert ≥ 4/5)</td>
<td>25% found treatment helpful (Likert ≥ 4/5)</td>
<td>&lt; 25% found treatment helpful (Likert ≥ 4/5)</td>
</tr>
<tr>
<td>Format Acceptability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% found treatment delivery (in-person and home) acceptable (Likert ≥ 4/5)</td>
<td>25% found treatment delivery acceptable (Likert ≥ 4/5)</td>
<td>&lt; 25% found treatment delivery acceptable (Likert ≥ 4/5)</td>
</tr>
<tr>
<td>50% reported being likely to recommend this treatment</td>
<td>25% reported being likely to recommend this treatment</td>
<td>&lt; 25% reported being likely to recommend this treatment</td>
</tr>
</tbody>
</table>
Sample size calculation

• Always provide a sample size calculation and justification

• Even for pilot studies you need to justify and there are suggested calculation that can be used (Thabane)
Sample size calculation - elements

• Outcome measure used for sample size calculation (usually your primary outcome)
  o You can also mention whether your sample will be enough for other outcomes or secondary objectives
• Statistical analysis proposed for the primary outcome
• Formula used for the sample size calculation (avoid just citing websites)
• All parameters used for calculation (alpha, power, correlations) including mean and standard deviations as appropriate
  o Provide reference for the numbers used or strong justification based on clinical important differences (e.g., MCID)
  o Don’t just say we used a moderate effect size without given exact numbers
• Provide drop out rate calculation with potential justification for the correction
Sample size calculation - example

It has been demonstrated through simulation studies that the sample size of a 2 x 2 interaction (e.g. treatment x effect modifier) in a mixed effects model is fourfold that to detect a main effect of the same magnitude. We argue that interaction effects are usually smaller in validation studies than pilot studies and therefore, we have powered this study for a clinically significant interaction of 15 points. Assuming from previous systematic reviews the main effect of these exercise approaches compared to no treatment is approximately 15 points on a 100-point scale for the ODI at 12 months, an interaction of 15 would mean that the effect would be approximately 22.5 when patients receive the correct targeted intervention and 7.5 when patients do not receive the targeted intervention. This would generate a significant improvement in outcomes that are clearly considered clinically relevant (>10 points). Sample size was calculated for the primary outcome of function using PASS 16 software for mixed models tests for two means based on the methods of Vierron et al. A sample size of 90 achieves 85% power to detect a difference of 15 between the two means (main effect) when the standard deviation of the response variable is 25 and the intraclass correlation (ρ) is 0.10 using a test with a significance level of 0.05. A sample size of 360 (90 x 4) is required to appropriately power the study for the interaction effect. Thus, a total of 414 participants (207 per treatment group) will be included to account for a 15% loss to follow up.
Additional considerations
Sex and Gender Analysis

Analysis plan

• Cite guidelines (e.g., SAGER, CIHR training)
• Integrate with the grant not only within defined sections
  o Background
  o Aims
  o Recruitment strategy
  o Methods
  o Statistical analysis

Heidari S, SAGER Guidelines BMC 2016
Stakeholder and End-User Engagement

**Analysis plan**

- Verify importance of factors and variables
- Ascertain whether there is a good proxy for a specific concept
- Inquire about potential confounding factors

Mullins CD, et al JAMA 2022
Stakeholder and End-User Engagement

**Reviewing and Interpreting Results**

- Assess believability of results
- Suggest alternative explanation or approaches
- Provide input for sensitivity analysis

Mullins CD, et al JAMA 2022
Stakeholder and End-User Engagement

Translation

- Interpret results to be meaningful
- Document which results are easy or difficult to understand
- Indicate which results are counterintuitive

Mullins CD, et al JAMA 2022
Stakeholder and End-User Engagement

How to approach this within a grant?

• Description of the role of stakeholder and end-users
• Ideally integrated within the grant
Summary

• Organize your grant numbering your aims and statistical analysis
• Be as specific as possible with the type of analysis
  o Always report the variables included (with appropriate language per statistical test)
• Provide appendices summarizing the analysis (as appropriate)
• INTEGRATE
• Consider end-user engagement and EDI