Adjusting for Sub-Optimal Adherence in the CALERIE Study: Application of the Marginal Structural Model

James Rochon, PhD¹
Carl Pieper, DrPH², and Manjushri Bhapkar, MS²
for the CALERIE Study Group

¹Rho Federal Systems, Chapel Hill, NC
²Duke University Medical Center, Durham, NC
Adjusting for Sub-Optimal Adherence in the CALERIE Study: Application of the Marginal Structural Model

1. Overview of the CALERIE Study
2. Problems with ITT and Per-Protocol Analysis
3. Marginal Structural Model
4. Design of the Simulation Study
5. Results
6. Application of the MSM in CALERIE
The CALERIE Study

- Multi-center, randomized, controlled clinical trial.
- **Hypothesis**: two years of significant caloric restriction (25% CR) will have a beneficial effect on markers of the aging process.
- Laboratory methods provide an objective measure of adherence at the scheduled time points.
- **Problem**: Most CALERIE participants failed to maintain adherence at 25% CR during the study.
- How do we deal with this in the analyses?
Different Statistical Analyses in RCTs


**Intention-to-Treat Analysis:**

- Include all participants and all observations in the analysis irrespective of the %CR actually observed.
- Reflects “real world” application of an intervention – efficacy will be undermined by poor adherence.
- Makes sense from a public health perspective.
Per-Protocol (PP) Analysis:

- Attempts to address mechanistic questions by focusing on that subset “adherent” to the intervention.
- Restrict the analysis to those participants adherent at 25% all the way through the study.
- Include only those observations while %CR is at least 15%.
- Arbitrary and inefficient.
- Selection bias of an unknown magnitude and in an unknown direction.
Fundamental Problem:

- %CR is a time-dependent process that interacts dynamically with the primary outcome over time.
- Poor adherence may lead to a smaller than expected reduction in, for example, percent body fat (%BF).
- This may demoralize the participant which in turn leads to a greater drop in adherence.
- Or, indeed, it may motivate the participant to redouble his/her efforts to adhere.
- Standard analytic approaches are not appropriate in this setting.
Marginal Structural Model

- Inverse probability weighting (IPW) class of models.
- Goal is to derive the “causal effect” of a time-dependent process.

Primary References:


593 citations in ISI Web of Knowledge since 2000.
GEE Model:

- Consider the caloric restriction intervention arm.
- Start with a GEE model for the outcome measure:
  \[ g(\mu_{it}) = \alpha + \tau_t + \beta_1 x_i + \beta_2 \%CR_{it} \]  
  (1)

- Advantage:
  - Uses all the data
  - Includes covariates to increase precision.
\[ g(\mu_{it}) = \alpha + \tau_t + \beta_1 x_i + \beta_2 \%CR_{it} \] 

1. We are primarily interested in the \( \{\tau_t\} \) terms.
2. But, we need to “adjust” for the \( \%CR_{it} \) observed.
3. **Problem**: \( \%CR_{it} \) is a function of a number of influences – especially previous values of the outcome measure.
\[ g(\mu_{it}) = \alpha + \tau_t + \beta_1 x_i + \beta_2 \%CR_{it} \]  

(1)

- Robins et al. (2000) demonstrated that when there are time-dependent confounders, the estimates of the regression parameters in (1) are not consistent for causal associations.

- **Approach**: Estimate \( \beta_2 \) so that it reflects the “causal effect” of \%CR_{it}.

- **How**: Use a weighted GEE model to derive consistent estimators.
Weights:

- The weights, $w_{it}$, are inversely proportional to the probability of observed %CR profile through visit $t$, given current and past covariate history.

- Can be derived empirically by a second GEE model:
  \[
g(\%CR_{it}) = \lambda + \psi_t + \delta_1 v_i + \delta_2 L_{it} + \delta_3 L_{i,t-1} + \ldots \quad (2)
  \]

- Important assumption: no unmeasured confounders.

- Weights are used in the GEE model (1) using the WEIGHT statement in PROC GENMOD.
Why Does this Work?

- Analogous to sample surveys when we differentially select more participants from certain age, race or SES strata.
- Apply weighting inversely proportional to the probability of selection to correct for the over/under-sampling.
- Creates a “pseudopopulation” with $w_{it}$ copies of subject $i$ at time $t$.
- In this pseudopopulation, the confounding is removed.
Design of the Simulation Study

**Goal:** Compare ITT, PP and MSM in their abilities to predict the physiologic effect at 25% CR.

**Hypotheses:**

- ITT is biased for mechanistic questions
- PP mitigates some of the bias
- MSM mitigates much more.
%CR Profile:

![Graph showing %CR profile over follow-up time with target, observed, and threshold lines.](image)
%CR Probability Distribution:

- Std. Dev. = 4%; autocorrelation = 0.7.

<table>
<thead>
<tr>
<th>Month:</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prob (%CR ≥ 25%)</td>
<td>0.31</td>
<td>0.16</td>
<td>0.11</td>
<td>0.07</td>
</tr>
<tr>
<td>Prob (%CR &lt; 15%)</td>
<td>0.02</td>
<td>0.07</td>
<td>0.11</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Outcome Measure: %BF

At 25% CR

At Mean %CR Observed

Follow-up Time

M6  M12  M18  M24

%BF

20%  24%  28%  32%  36%
%BF Probability Distribution:

- \( \%BF = \alpha + \beta \%CR + \varepsilon_{it} \)
- Std. Dev. \((\varepsilon_{it}) = 2; \) autocorrelation = 0.7.

<table>
<thead>
<tr>
<th>Month:</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Bias Induced</td>
<td>+2</td>
<td>+2</td>
<td>+3</td>
<td>+3</td>
</tr>
<tr>
<td>Prob (%BF &gt; Target*)</td>
<td>0.67</td>
<td>0.76</td>
<td>0.83</td>
<td>0.86</td>
</tr>
</tbody>
</table>

* the value specified at the target of 25% CR.
Procedures:

- Use a random number generator to simulate the %CR profile for each participant.
- Generate %BF; add random error and autocorrelation.
- Repeat for each of $N=150$ participants in a CALERIE “study.”
- For each study, estimate the %BF using three models:
  - ITT
  - Per-protocol
  - MSM.
• Quantify the **bias** from the target %BF profile specified at 25% CR.

• Repeat this process for 1,000 CALERIE studies.

• Derive average bias over the 1,000 studies.
### Results: Average Bias in %BF According to Statistical Method Applied

<table>
<thead>
<tr>
<th>Month:</th>
<th>M6</th>
<th>M12</th>
<th>M18</th>
<th>M24</th>
</tr>
</thead>
<tbody>
<tr>
<td>As Designed:</td>
<td>+2</td>
<td>+2</td>
<td>+3</td>
<td>+3</td>
</tr>
<tr>
<td>ITT</td>
<td>2.0047</td>
<td>1.9925</td>
<td>2.9938</td>
<td>2.9898</td>
</tr>
<tr>
<td>Per-Protocol</td>
<td>1.7901</td>
<td>1.7886</td>
<td>2.5737</td>
<td>2.4881</td>
</tr>
<tr>
<td>MSM Model</td>
<td>0.7301</td>
<td>-0.6257</td>
<td>-0.2741</td>
<td>-0.9310</td>
</tr>
</tbody>
</table>
ITT Analysis
Per Protocol Analysis
Statistical Model
At 25% CR

Follow-up Time

%BF

M6 M12 M18 M24

A Full-Service CRO
Application of the MSM in CALERIE

- Model for the outcome variable:
  \[ g(\mu_{it}) = \alpha + \tau_t + \beta_1 x_i + \beta_2 (%CR_{it} - 25) + \beta_3 (%CR_{it} - 25)^2 \]  (1)

- Model for %CR_{it}:
  \[ g(%CR_{it}) = \lambda + \psi_t + \delta_1 v_i + \delta_2 L_{it} + \delta_3 L_{i,t-1} + \ldots \]  (2)
• Predictors:
  o Demographics
  o Nutritional markers
  o Phys. activity markers
  o BDI, hemoglobin, MAEDS
  o Attendance
  o Lagged outcome variable
  o Interactions with age, sex and BMI.

• Stepwise procedures to select best predictors.

• Contrast MSM results against the ITT results.
Funding Support:

CALERIE is supported by the following grants from the National Institute on Aging: U01AG022132, U01AG020478, U01AG020487, and U01AG020480.