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

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The CALERIE Study

- **Multi-center, randomized, controlled clinical trial.**
- **<u>Hypothesis</u>: 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.**
- **<u>Problem</u>: Most CALERIE participants failed to main-tain adherence at 25% CR during the study.**
- **How do we deal with this in the analyses?**

Different Statistical Analyses in RCTs

Hernán MA, Hernández-Díaz S, *Clin Trials* 2012;9:48-55.

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.**

<u>Primary References</u>:

- **Robins JM, *et al*. *Epidemiology* 2000;11:550-60.**
- **Hernán MA, *et al*. *Epidemiology* 2000;11:561-70.**

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:**

$$g(\mu_{it}) = \alpha + \tau_t + \beta_1 x_i + \beta_2 \%CR_{it} \qquad (1)$$

- **Advantage:**
  - **Uses all the data**
  - **Includes covariates to increase precision.**

$$g(\mu_{it}) = \alpha + \tau_t + \beta_1 x_i + \beta_2 \%CR_{it} \qquad (1)$$

- **We are primarily interested in the $\{\tau_t\}$ terms.**
- **But, we need to "adjust" for the $\%CR_{it}$ observed.**
- **<u>Problem</u>: $\%CR_{it}$ is a function of a number of influences – especially previous values of the outcome measure.**

$$g(\mu_{it}) = \alpha + \tau_t + \beta_1 x_i + \beta_2 \%CR_{it} \qquad (1)$$

- **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 β_2 so that it reflects the "causal effect" of $\%CR_{it}$.**
- **How: Use a weighted GEE model to derive consis-tent 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:

$$g(\%CR_{it}) = \lambda + \psi_t + \delta_1 v_i + \delta_2 L_{it} + \delta_3 L_{i,t-1} + \ldots \qquad (2)$$

- 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.**

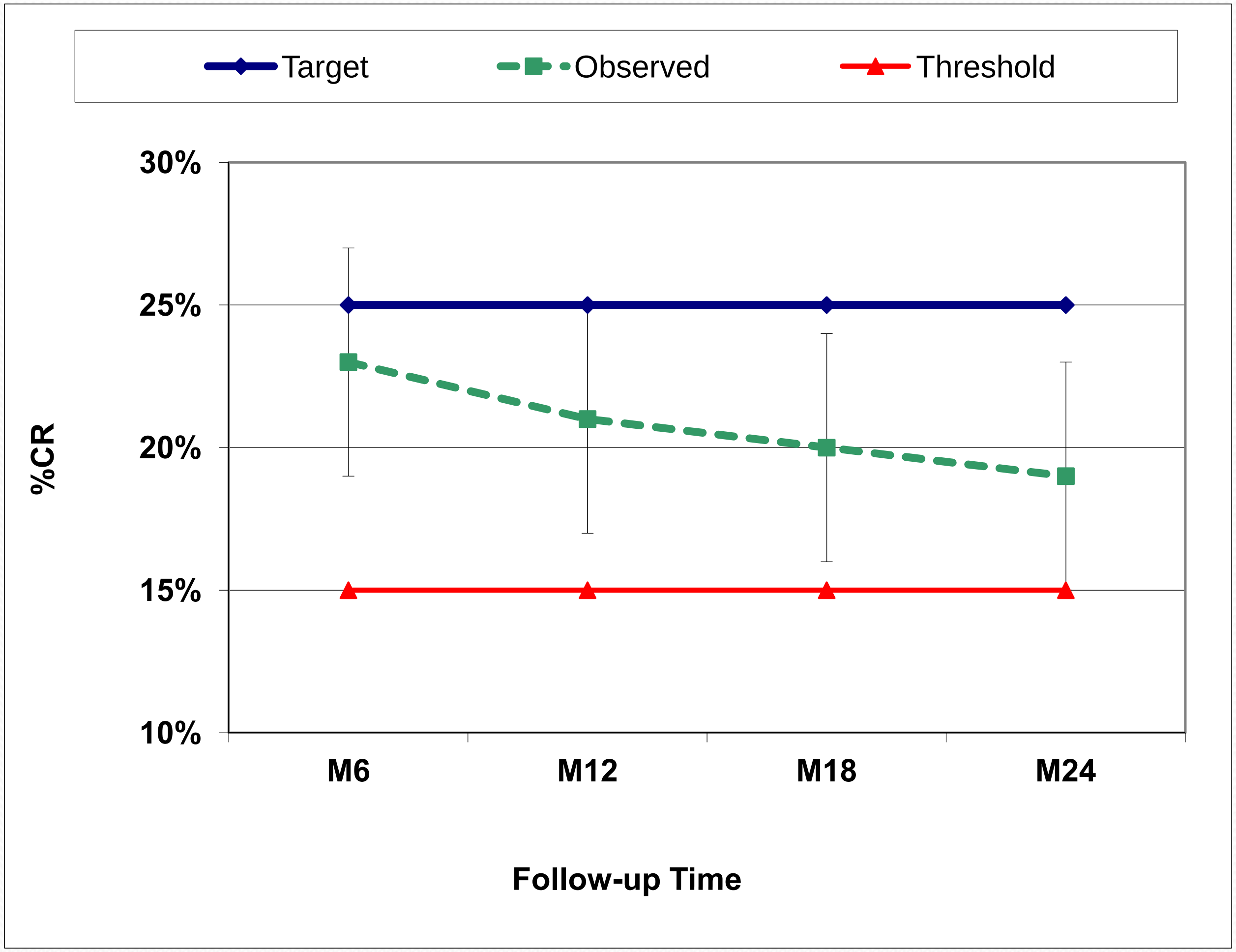
Design of the Simulation Study

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:



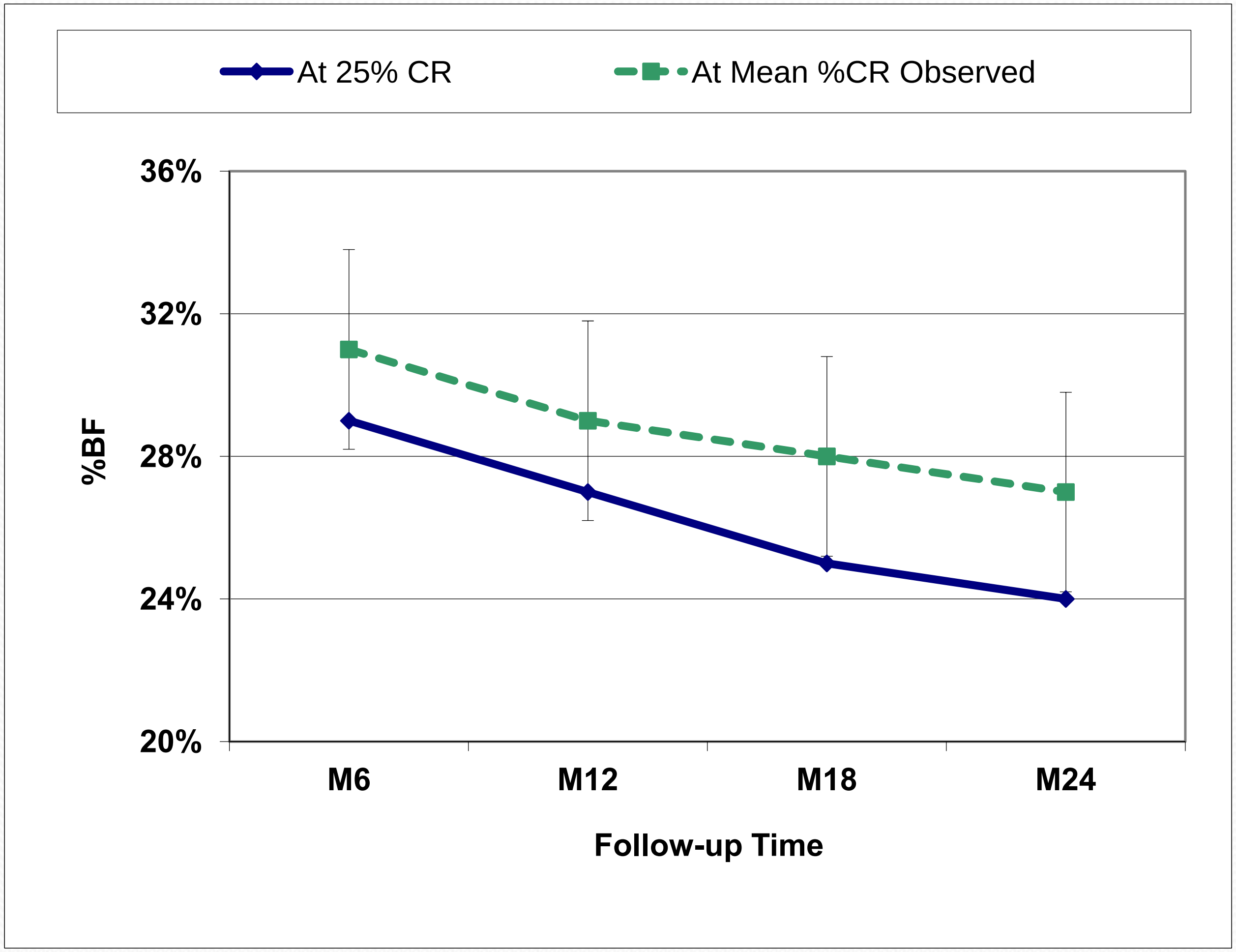
Giving flight to research

%CR Probability Distribution:

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

Month:	M6	M12	M18	M24
Prob (%CR ≥ 25%)	0.31	0.16	0.11	0.07
Prob (%CR < 15%)	0.02	0.07	0.11	0.16

Outcome Measure: %BF



%BF Probability Distribution:

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

Month:	M6	M12	M18	M24
Average Bias Induced	+2	+2	+3	+3
Prob (%BF > Target*)	0.67	0.76	0.83	0.86

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

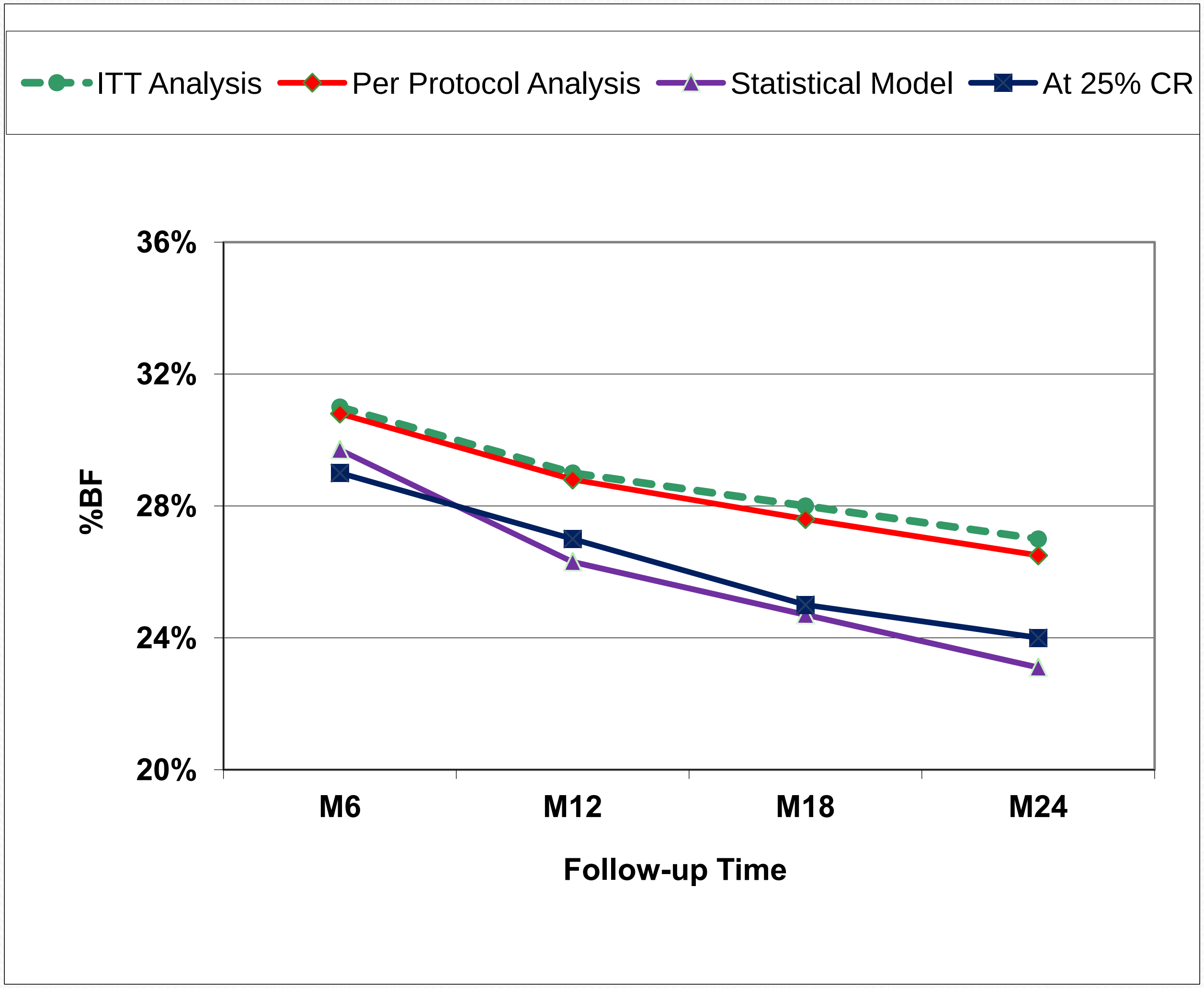
Procedures:

- **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

Month:	M6	M12	M18	M24
As Designed:	+2	+2	+3	+3
ITT	2.0047	1.9925	2.9938	2.9898
Per-Protocol	1.7901	1.7886	2.5737	2.4881
MSM Model	0.7301	-0.6257	-0.2741	-0.9310



ITT Analysis
Per Protocol Analysis
Statistical Model
At 25% CR
36%
32%
28%
24%
20%
%BF
M6
M12
M18
M24
Follow-up Time

Application of the MSM in CALERIE

- **Model for the outcome variable:**

$$g(\mu_{it}) = \alpha + \tau_t + \beta_1 x_i + \beta_2(\%CR_{it}-25) + \beta_3(\%CR_{it}-25)^2 \qquad (1)$$

- **Model for $\%CR_{it}$:**

$$g(\%CR_{it}) = \lambda + \psi_t + \delta_1 v_i + \delta_2 L_{it} + \delta_3 L_{i,t-1} + \ldots \qquad (2)$$

- **Predictors:**
  - **Demographics**
  - **Nutritional markers**
  - **Phys. activity markers**
  - **BDI, hemoglobin, MAEDS**
  - **Attendance**
  - **Lagged outcome variable**
  - **Interactions with age, sex and BMI.**
- **Stepwise procedures to select best predictors.**
- **Contrast MSM results against the ITT results.**

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