A Novel Approach for Developing Whole System Herbal Therapies

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Outline

1. Multi-factor Herbal Therapies
2. Multi-phase Optimization Strategy
3. A Smoking Cessation Study
4. Discussion
An Idealized Example

Many thanks to Dr. Suzanna Zick for this example ...

- Treatment of moderate depression for peri-menopausal (otherwise healthy) women
  - often comes with mild hypertension, insomnia, anxiety, and constipation
- A possible Whole System Herbal Therapy involves:
  - Dietary Change
  - Exercise
  - Multi-herb medicine
- Outcome: difference in Ham-D score before and after treatment
Dietary Change and Exercise

- Replace (augment) a standard American diet (high in animal fats, low in fiber) with a Mediterranean diet (rich in vegetables, fruits, fiber, and olive oil)

- Walking at least 30 minutes per day
- Belly breathing and progressive relaxation twice daily
Multi-herb Medicine

A tincture of **lime flowers** (for high blood pressure), **dandelion root** (to increase the function of liver to improve detoxification), **valerian** (for insomnia), and **lemon balm** (for anxiety) in equal parts, 60 drops three times daily.
Thus, a whole system herbal therapy can be viewed as a multi-factor treatment

Different factors of the example therapy are:

- **Diet** (Mediterranean vs. standard)
- **Exercise** (yes vs. no)
- **Lime Flowers** (present vs. absent)
- **Dandelion Root** (present vs. absent)
- **Valerian** (present vs. absent)
- **Lemon Balm** (present vs. absent)
- **Herbal tincture** (yes vs. no)

Let’s not worry about **correct dosage** at the moment
Two Important Research Questions

- Does the herbal therapy work?
  - An RCT of the therapy vs. appropriate control answers this

- Which factors of the therapy work, and which don’t? And how do they interact, if at all?
  - This is important for optimizing the effectiveness of therapy
  - The RCT design doesn’t directly address this question

The Common Approach

- A series of RCTs plus non-experimental analysis:
  - 2-group RCT of the therapy vs. appropriate control
  - non-experimental post hoc analysis on data from RCT (e.g., dose-response)

- Example: A behavioral intervention study called Fast Track (CPPRG, 1992, 1999)
Issues

- **Philosophical:** Opening the “black box” is necessary to understand the science better
- **Statistical:** Weak inference from non-experimental post hoc analyses (Holland, 1986; Rosenbaum and Rubin, 1984)
- **Practical:** Expensive and time-consuming in the long-run

A Remedy

Embedding RCT procedure into a larger framework to open the black box, by including additional phases of experimentation
Multi-phase Optimization Strategy, or MOST

- A principled framework for developing, optimizing, and evaluating multi-factor treatments
- MOST consists of three ordered phases of experiment:
  - Screening of candidate factors
  - Refining of screened factors to optimize the treatment
  - Confirming effectiveness of optimized treatment in a standard RCT
Screening Phase Overview

- Aims to explore a number of candidate factors to identify the few active ones, rather than fine-tuning them.
- 2-level designs are usually good enough at this phase.
- Often uses balanced fractional factorial designs:
  - have been successfully used in engineering applications for decades (e.g., Box et al., 1978).
  - many statistical softwares for constructing these designs: SAS, JMP, Matlab, Minitab...
Refining Phase Overview

- Finds the **best doses** of active factors by response surface analysis
- Settles confusion about any **unanticipated** effects that appear significant at the screening phase – use factorial designs again

Now let’s talk a little more about **factorial designs** ...
Each row represents a treatment group in the experiment.

In general, for $k$ factors, there will be $2^k$ treatment groups.
Suppose $y$ is the outcome variable ...

- **Main effect** of each factor is clearly defined and estimated:

\[
\text{effect} \ (X_1) \ = \ (\bar{y} \text{ when } X_1 \text{ is } +) - (\bar{y} \text{ when } X_1 \text{ is } -)
\]

averaged over levels of other factors ...

- Similarly **interactions** are defined and estimated:

\[
\text{effect} \ (X_1X_2) \ = \ (\bar{y} \text{ when } X_1X_2 \text{ is } +) - (\bar{y} \text{ when } X_1X_2 \text{ is } -)
\]
Towards Fractional Factorial Designs

Problem with Full Factorial Design:
- number of treatment groups \(2^k\) grows exponentially with number of factors \(k\)
- thus highly impractical in terms of cost and feasibility

Fractional Factorial Design – A Solution:
- “cleverly” chooses only a fraction of the \(2^k\) groups, based on scientist’s substantive input, and studies them
- still does a good job in estimating important effects, under reasonable assumptions

Let’s consider a simple example...
Balanced Fractional Factorial Designs

- In the fractional factorial design on the right, all factors occur at + and − levels same number of times: balanced

- In balanced factorial designs, the sample size and hence statistical power for testing each main effect is the same as testing that factor in a single-factor 2-group trial.
**A Smoking Cessation Study**

- An ongoing NCI-funded web-based smoking cessation program at the University of Michigan (Strecher et al.)
- **Goal:** To determine the impact of potentially active factors of smoking cessation program among adult smokers
- **Treatment:** web-based behavioral therapy (5 factors) + nicotine patch
- **Individually tailored** treatment based on age, gender, ethnicity, education ...
- **Outcome:** 7-day point prevalence at 6 month – “Did you smoke a cigarette in the last 7 days?” – yes/no
Smoking Cessation Factors

The behavioral therapy involves **online messages** ...

- Two levels of **message exposure**: single vs. multiple
- Two levels of **message source**, efficacy expectations, outcome expectations, and success story: high vs. low tailoring depth
MOST has been successfully implemented ... 

- Fractional factorial design with 16 treatment groups has been used in the screening phase.
- Note that a full factorial design would need $2^5 = 32$ treatment groups – 50% savings!
- Screening Phase Sample size:
  - Intent-to-treat: 1846
  - Compliant: 952
- Refining phase is ongoing ...

This huge sample size is NOT a necessity for MOST to work! It's only a luxury they could afford!
Impact of Individual Smoking Cessation Factors

The “black box” has been opened ...

Compliant analysis ($n = 952$): Impact measured by $t$-statistic
Discussion

- MOST relies on randomized experiments at every phase, rather than non-experimental post-hoc analysis.
- Uses balanced fractional factorial designs:
  - choice of “good” fractional designs is driven by scientist’s subject matter knowledge
  - same statistical power to detect main effects as a single-factor 2-group trial
- MOST eliminates inactive factors from the therapy, hence cost-effective
- MOST performed substantially better than the common approach (a series of RCTs + post hoc analysis) in an extensive simulation study conducted by us.
MOST, as a methodology, has a lot of promise for application in Whole System Herbal research!

Questions? Comments?

... Thank you!
A Simulation Study

Purpose

To compare the performance of MOST with that of the common approach (a series of RCTs + post hoc analysis), in finding an optimized multi-component therapy, to be evaluated in a confirmatory 2-arm RCT.
Generative Model

Mimics actual behavioral study settings, e.g., Fast Track
Simulation Summary

What we did

- Generated $N = 1000$ data-sets, each of size $n = 2500$, from the generative model
- Separately applied MOST and the common approach on each simulated data-set, to find an optimized therapy
- Evaluated the effectiveness of both of them in a large confirmatory RCT

We found that

On average, MOST finds a more effective therapy than the common approach, under a wide variety of scenarios