8. Sequential Multiple Assignment Randomized Trials (SMARTs)

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Basic SMART features

Sequential Multiple Assignment Randomized Trial (SMART): The gold standard study design for estimation/evaluation of multiple decision regimes

- Basic idea: Randomize (feasible) treatment options at key decision points
- At each of $K \geq 2$ stages, a participant may be randomly assigned to one of the treatment options feasible for her history to that point
- Each stage corresponds to a key decision point
- Mimics clinical practice: Treatment is adjusted when/if needed

Motivation for SMARTs:
- SRA holds; avoids challenges associated with observational data
- Compare full and partial treatment sequences
- Estimate an optimal regime
Example - Cancer pain management

SMART with $K = 2$ to study sequences of interventions for management of cancer pain:

- Stage 1: Randomization to Pain Coping Skills Training full dose (PCST-Full) or low dose (PCST-Brief)
- Response: % reduction in pain score $> \text{threshold}$ (i.e., reduction in pain score from baseline to the end of stage 1)
- Stage 2: Responders and nonresponders randomized to further options (maintenance, no further intervention, etc; see next slide)
Example - Cancer pain management

SMART with $K = 2$ to study interventions for cancer pain management:

```
R
PCST-Full
TREATMENT 0
Response?
R
PCST-Brief
TREATMENT 1
Response?
R
No further intervention
PCST-Full maintenance
TREATMENT 2
PCST-Plus
TREATMENT 4
PCST-Full maintenance
TREATMENT 2
PCST-Brief maintenance
TREATMENT 5
No further intervention
PCST-Brief maintenance
TREATMENT 5
R
PCST-Full
TREATMENT 0
```
Regimes embedded in a SMART

Embedded regimes:

- Participants in a SMART will have realized treatment experience consistent with having followed at least one simple, fixed treatment regime
- These regimes are referred to as *embedded regimes*
- Aka “*treatment sequences*”
- These embedded regimes are almost always *dynamic* because at the very least the rules at Decisions $k \geq 2$ assign treatment options based on past history (response status)
- The cancer pain management SMART embeds *eight* such sequences (next slide)
- Investigators often are interested in comparing embedded regimes/treatment sequences on the basis of their values and identifying the *best* embedded regime/treatment sequence (later)
Embedded regimes - cancer pain SMART

$(e_1)$ Give PCST-Full initially followed by PCST-Full maintenance if response or PCST-Plus if nonresponse

$(e_2)$ Give PCST-Full initially followed by PCST-Full maintenance regardless of response status

$(e_3)$ Give PCST-Full initially, followed by no further treatment if response or PCST-Plus if nonresponse

$(e_4)$ Give PCST-Full initially followed by no further treatment if response or PCST-Full maintenance if nonresponse

$(e_5)$ Give PCST-Brief initially followed by PCST-Brief maintenance if response or PCST-Full if nonresponse

$(e_6)$ Give PCST-Brief initially followed by PCST-Brief maintenance regardless of response status

$(e_7)$ Give PCST-Brief initially followed by no further treatment if response or PCST-Full if nonresponse

$(e_8)$ Give PCST-Brief initially followed by no further treatment if response or PCST-Brief maintenance if nonresponse
Common SMART issues

Concerns:

- Many design choices - can be overwhelming
- Concern over “sample splitting” resulting in low precision or power for detecting meaningful differences
- Involves complicated “subgroup analyses”
- These concerns are mostly unfounded

Confusion: SMARTs are often confused with adaptive clinical trial designs with a single point of randomization in which randomization probabilities are adjusted over time as evidence accrues

- Probably because dynamic treatment regimes have also been referred to as adaptive treatment strategies or adaptive interventions
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Basic SMART framework, $K = 2$

**Treatment options:** Sets of candidate treatment options $\mathcal{A}_1$ and $\mathcal{A}_2$ for stages 1 and 2 (Decisions 1 and 2)

- Overlap between $\mathcal{A}_1$ and $\mathcal{A}_2$ is possible
- All options are likely not feasible for all individuals, particularly those in $\mathcal{A}_2$; there will likely be feasible sets $\Psi_1(h_1) \subseteq \mathcal{A}_1$ and $\Psi_2(h_2) \subseteq \mathcal{A}_2$
- Often $\Psi_1(h_1) = \mathcal{A}_1$ for all $h_1$ (but need not be)
- Often $\Psi_2(h_2) \subset \mathcal{A}_2$ (strict subset) determined by a component or function of components of $h_2$
- For some $h_2$, $\Psi_2(h_2)$ may comprise a single option (see upcoming examples)
Basic SMART framework, $K = 2$

For a given participant:

- Baseline information $X_1$, baseline history $H_1 = X_1$ is recorded
- Option $A_1$ is assigned (via randomization) from $\psi_1(H_1)$
- Intervening information $X_2$ between stages 1 and 2 is recorded; history at beginning of stage 2 $H_2 = (X_1, A_1, X_2)$
- Option $A_2$ is assigned (via randomization) from $\psi_2(H_2)$
- If $\psi_2(H_2)$ comprises a single option, that option is assigned with probability 1 (equivalent to no randomization)
Example - Cancer pain management

SMART with $K = 2$ to study interventions for cancer pain management:
Basic SMART framework, $K = 2$

Example - cancer pain management:

- $\psi_1(h_1) = \{0, 1\}$ for all $h_1$
- Response defined as % reduction in pain score $> \text{threshold}$
- Response status $r_2 = 0 (1)$ for nonresponse (response) (a function of components of $h_2$)
- Feasible sets at stage 2 depend on $r_2$

$$\psi_2(h_2) = \begin{cases} 
\{2, 3\} & \text{if } r_2 = 1 \text{ and } a_1 = 0 \\
\{2, 4\} & \text{if } r_2 = 0 \text{ and } a_1 = 0 \\
\{3, 5\} & \text{if } r_2 = 1 \text{ and } a_1 = 1 \\
\{0, 5\} & \text{if } r_2 = 0 \text{ and } a_1 = 1 
\end{cases}$$
Data from SMART, $K = 2$

Data to be collected:

$$(X_{1i}, A_{1i}, X_{2i}, A_{2i}, Y_i), \quad i = 1, \ldots, n$$

- Outcome $Y$ usually ascertained at end of stage 2; coded so larger values are more beneficial
- We do not consider possibly censored time-to-event outcomes here, but this is certainly possible
Decision points

Key principle: Design should mimic *actual clinical decision-making*

- Stages are dictated by key decision points in the particular disease/disorder context
- E.g., in the cancer pain management example, response status is ascertained at 35 days after completion of stage 1 treatment; investigators deemed this to be sufficient time for patients to assess effect
- As noted previously, decision points need not be at fixed times but can be driven by interim patient information, so participants can enter stage 2 at different times
Example - Treatment for ADHD in children

Stage 1: Randomization to Low Intensity BMOD or MEDS

- Twelve weeks: Clinical assessment of ADHD severity at weekly clinic visits; response status based on this measure
- The first time child is deemed nonresponsive, he proceeds to stage 2
- Child who is never deemed nonresponsive proceeds to stage 2 at week 12
Example - Treatment for ADHD in children

Four embedded regimes:

(e₁) Give Low Intensity MEDS followed by continued Low Intensity MEDS if response or Intensify MEDS if nonresponse
(e₂) give Low Intensity MEDS followed by continued Low Intensity MEDS if response or Augment with BMOD if nonresponse
(e₃) give Low Intensity BMOD followed by continued Low Intensity BMOD if response or Intensify BMOD if nonresponse
(e₄) give Low Intensity BMOD followed by continued Low Intensity BMOD if response or Augment with MEDS if nonresponse
Timing/conditions for treatment change

**Primary interest:** Timing and/or conditions dictating treatment change

- How long to wait following initial stage 1 treatment before changing to a new treatment?
- How much of a change in symptoms/severity of disease or disorder should determine nonresponse?
Example - mHealth interventions in HIV+ men

AllyQuest: mHealth ARV therapy adherence app

- **AllyQuest+**: Intensified version
- Response status assessed at 3 months (adherence/viral suppression)
- 3 embedded regimes + control condition
- Key motivating question: Can individuals who are responsive to AllyQuest+ be stepped down to AllyQuest?
Evolution of a SMART design

**Illustrative example:** Interest in treatment sequences involving

- Two candidate stage 1 treatments, feasible for all individuals: New active treatment (coded 0) or standard of care (1)
- One maintenance therapy for responders (2)
- Two salvage therapies for nonresponders (3, 4)
- Under standard of care (1), response status ascertained/treatment changes typically made at 4 weeks
- Without additional information, possible SMART design on next slide; subjects are randomized with equal probability to options 0 or 1 at stage 1, are deemed responders/nonresponders at 4 weeks and transition to stage 2
Data:

- Stage 1 treatment $A_1 = 0$ or $1$
- Response status $R_2 = 0$ (nonresponse) or $1$ (response)
- $Y =$ final outcome after stage 2
Illustrative example, design 1

Possible comparisons: Facilitated by this design

- Comparison of response rate at 4 weeks (end of stage 1) based on

\[
\frac{\sum_{i=1}^{n} A_{1i} R_{2i}}{\sum_{i=1}^{n} A_{1i}} - \frac{\sum_{i=1}^{n} (1 - A_{1i}) R_{2i}}{\sum_{i=1}^{n} (1 - A_{1i})}
\]

(estimated difference in response rate at 4 weeks)

- Comparison of mean final outcome, marginalizing over stage 2 treatment, based on

\[
\frac{\sum_{i=1}^{n} A_{1i} Y_{i}}{\sum_{i=1}^{n} A_{1i}} - \frac{\sum_{i=1}^{n} (1 - A_{1i}) Y_{i}}{\sum_{i=1}^{n} (1 - A_{1i})}
\]
Illustrative example, design 2

**Concern:** 4 week follow-up period for assessment of response status may not be appropriate for both stage 1 treatments

- Accepted practice for standard of care
- But disagreement in the research community between 4 weeks and 8 weeks for active treatment
- Modify design: Trinary stage 1 randomization (see next slide)

**Tradeoff:**

- Can evaluate timing for active treatment, but at expense of larger, more complex trial
- I.e., with same sample size as design 1, design 2 allocates fewer subjects to each first stage option
Illustrative example, design 2

Decision Tree:
- **New Active Treatment Assess Resp. 4WK**
  - Response? (YES)
    - **TREATMENT 3** (Maintenance)
  - Response? (NO)
    - **Salvage 1**
- **New Active Treatment Assess Resp. 8WK**
  - Response? (YES)
    - **TREATMENT 3** (Maintenance)
  - Response? (NO)
    - **Salvage 2**
- **Standard of Care Assess Resp. 4WK**
  - Response? (YES)
    - **TREATMENT 3** (Maintenance)
  - Response? (NO)
    - **Salvage 2**
Illustrative example, design 3

Prioritization: Evaluating salvage therapies following standard of care *less important* than comparing 4- versus 8-week follow-up period under new active treatment

- Randomize only to active treatment with 4- or 8-week follow-up period
- Or a control condition in which treatment changes are made a clinician discretion
- Might consider unequal randomization probabilities at stage 1 to increase power for comparing embedded regimes (later)
Illustrative example, design 3

- **TREATMENT 0**
  - **New Active Treatment Assess Resp. 4WK**
  - **Response?**
    - **YES**
      - **TREATMENT 3**
      - **Maintenance**
    - **NO**
      - **R**
      - **TREATMENT 1**
      - **New Active Treatment Assess Resp. 8WK**
      - **Response?**
        - **YES**
          - **TREATMENT 4**
          - **Salvage 1**
        - **NO**
          - **R**
          - **TREATMENT 2**
          - **Active control**
    - **R**
    - **TREATMENT 5**
    - **Salvage 2**
Illustrative example, design 4

Alternatively:

- Researchers would like to decide after 4 weeks whether or not to continue new active treatment for another 4 weeks
- Randomize at stage 1 to new active treatment or control
- After 4 weeks randomize to being assessed for response immediately or continuing for another 4 weeks
- Is effectively equivalent to design 3 if subjects assigned to assessment of response at 8 weeks are evaluated for response at 4 weeks but do not move to stage 2 and randomization probabilities are chosen so that the proportions assigned to assessed at 4 and 8 weeks are the same in designs 3 and 4
Illustrative example, design 4
Settling on a design

**Important:** During the design process

- The focus should be on identifying pressing clinical questions and from these deriving a design
- Rather than the reverse, in which postulates candidate designs and then derives the clinical questions that potentially could be addressed using the design
- In my experience: Investigators often behave in the latter way
Feasible treatment options

Feasible options:

- In many cases are well-established by the science and questions motivating the SMART
- But in some cases are not, and the goal is to gain evidence
Switch away from the loser designs

**Motivation for a SMART:** Develop treatment strategies for patients who fail to respond to a standard treatment option
- Assign all subjects to the standard option in an initial *run-in period*
- Nonresponders are randomized to potential follow-up options

**Example - HIV prevention among adolescent men who have sex with men (MSM)**
- Standard intervention: Queer Sex Ed (QSE), an established web-based sex education program (coded as 0)
- Follow-up options: (1) Keep it Up! (KIU), new web-based sexual health intervention; (2) Attention Control (AC), static informational website serving as a control; (3) KIU booster; (4) AC booster; (5) KIU booster plus the Young Men’s Health Program (YMHP), involving viewing a motivational video; (6) YMHP alone; or (7) no intervention
Example: HIV prevention among adolescent MSM

- **TREATMENT 0**: Queer Sex Ed
  - Response? NO
  - **TREATMENT 7**: No further treatment

- **TREATMENT 1**: Keep it Up!
  - Response? NO
  - R
  - **TREATMENT 2**: Attention control
    - Response? NO
    - R
    - **TREATMENT 4**: Control booster
      - Response? NO
      - R
      - **TREATMENT 6**: YMHP

  - Response? YES
  - R
  - **TREATMENT 3**: Keep it Up! Booster
    - Response? NO
    - R
    - **TREATMENT 5**: Keep it Up! Booster and YMHP

  - Response? YES
  - R
  - **TREATMENT 1**: Keep it Up! Booster
Example: HIV prevention among adolescent MSM

Thus: Facilitates evaluation of follow-up interventions within the target population of adolescent MSM who do not respond to QSE (so for whom QSE is a “loser”)

- $R_1 = 0$ (1) indicates nonresponse (response) to QSE
- Among subjects with $R_1 = 0$, $R_2 = 0$ (1) indicates nonresponse (response) to stage 1 assigned treatment (KIU or AC)
- Feasible sets

$$
\Psi_1(h_1) = \begin{cases} 
\{7\} & \text{if } r_1 = 1 \\
\{1, 2\} & \text{if } r_1 = 0 
\end{cases}, \quad \Psi_2(h_2) = \begin{cases} 
\{7\} & \text{if } r_1 = 1 \\
\{3, 5\} & \text{if } r_1 = 0, r_2 = 0, \text{ and } a_1 = 1 \\
\{3\} & \text{if } r_1 = 0, r_2 = 1, \text{ and } a_1 = 1 \\
\{1, 6\} & \text{if } r_1 = 0, r_2 = 0, \text{ and } a_1 = 2 \\
\{4\} & \text{if } r_1 = 0, r_2 = 1, \text{ and } a_1 = 2.
\end{cases}
$$
Switch away from the loser designs

**Candidate treatment options:** Coded 0, 1, 2; try in sequence until response

- **Stage 1:** Randomize to 0, 1, 2; \( \Psi_1(h_1) = \{0, 1, 2\} \) for all \( h_1 \)
- \( R_2 = 0 \) (1) if nonresponder (responder) to stage 1 option
- Responders \( (R_2 = 1) \) receive no further treatment; nonresponders \( (R_2 = 0) \) move to stage 2
- **Stage 2:** Randomize among 2 options not yet received
  \[
  \Psi_2(h_2) = \begin{cases} 
  \{a_1\} & \text{if } r_2 = 1 \\
  \{0, 1, 2\} \setminus \{A_1\} & \text{if } r_2 = 0 
  \end{cases}
  \]
- Responders receive no further treatment; nonresponders receive remaining option
- Nonresponders switch away from inefficacious options (losers)
- 6 sequences: \((0, 1, 2), (0, 2, 1), (1, 0, 2), (1, 2, 0), (2, 0, 1), (2, 1, 0)\)
- Optimal regime: Minimize expected time to response
Example: Switch away from inefficacious options
**Stepped care designs**

**Motivation:** Determine “cost-effective” treatment regimes

- “Expensive” treatment options are given if, to whom, and for how long they are needed
- “Cost:” Measured by resource expenditures, risk of adverse events, treatment burden, any undesirable feature associated with a treatment option
- *Stepped care SMARTs* are used to identify regimes that produce large expected outcome at low cost
Example stepped care design 1
Example stepped care design 1

- Stage 1: Randomize to 2 inexpensive options
- Stage 2: Responders continue, nonresponders randomized among 2 expensive treatments (“stepped up”)
- Feasible treatments: $\psi_1(h_1) = \{0, 1\}$ for all $h_1$

$$
\psi_2(h_2) = \begin{cases} 
\{a_1\} & \text{if } r_2 = 1 \\
\{2, 3\} & \text{if } a_1 = 0 \text{ and } r_2 = 0 \\
\{4, 5\} & \text{if } a_1 = 1 \text{ and } r_2 = 0
\end{cases}
$$

- 4 embedded regimes:
  - ($e_1$) give inexpensive I, continue if response or step up to expensive I if nonresponse
  - ($e_2$) give inexpensive I, continue I if response or step up to expensive II if nonresponse
  - ($e_3$) give inexpensive II, continue II if response or step up to expensive III if nonresponse
  - ($e_4$) give inexpensive II, continue II if response or step up to expensive IV if nonresponse

- These regimes are step-up strategies; expensive options given only if needed
Example stepped care design 2

(b)

ST 790, Dynamic Treatment Regimes
Example stepped care design 2

- Stage 1: Randomized to an expensive or inexpensive option
- Stage 2: Responders to inexpensive option continue, nonresponders randomized among 2 expensive options
- Stage 2: Responders to expensive option are randomized to either continue or being “stepped down” to an inexpensive option, nonresponders randomized among 2 expensive options
- Feasible treatments: \( \Psi_1(h_1) = \{0, 1\} \) for all \( h_1 \)

\[
\Psi_2(h_2) = \begin{cases} 
0 & \text{if } a_1 = 0 \text{ and } r_2 = 1 \\
1, 2 & \text{if } a_1 = 0 \text{ and } r_2 = 0 \\
0, 1 & \text{if } a_1 = 1 \text{ and } r_2 = 1 \\
3, 4 & \text{if } a_1 = 1 \text{ and } r_2 = 0 
\end{cases}
\]

- 6 embedded regimes
- Optimal regime: Insight into if, how, when, and for whom expensive treatment should be given
Dosage adjustment designs

In some settings: Rather than being distinct treatment entities, the treatment options may be different doses of a drug or intervention

- Small number of possible doses: E.g., high versus low; can view each dose as a distinct option
- Large number of possible doses: Additional assumptions, considerations required
Dosage adjustment designs

Example - Treatment of bipolar disorder: Each “dose” comprises administration of antidepressant plus presence/absence of 4 binary factors – cognitive behavioral therapy (CBT), group therapy (GT), mood stabilizer drug A (MS-A), and mood stabilizer drug B (MS-B)

- $2^4 = 16$ possible combinations and thus doses (factorial arrangement)
- E.g., (CBT, GT, MS-A, MS-B) = (1, 1, 0, 0)
- Natural strategy: Select an initial dose and adjust depending on patient’s response
- Suggests: Studying initial and follow-up doses via a 2-stage SMART
Dosage adjustment designs

**In general:** $L$ binary factors, $2^L$ possible doses, encoded by $L$ binary factors

- Select an initial dose from the $2^L$ possible, the possibly adjust depending on response
- Set of options at each stage: $\mathcal{A} = \mathcal{A}_1 = \mathcal{A}_2 = \{0, 1\}^L$, possible option at stage $k = 1, 2$

$$a_k = (a_{k1}, \ldots, a_{kL})^T$$

$$a_{k\ell} = 0 \ (1) \text{ if } \ell \text{th factor is absence (present), } \ell = 1, \ldots, L$$

- For simplicity: $\Psi_1(h_1) = \mathcal{A}$ and $\Psi_2(h_2) = \mathcal{A}$ for all $h_1$ and $h_2$
- Focus here: Strategies in which a patient who responds to her initial dose continues on that dose and otherwise is switched to another dose
Dosage adjustment designs

Marginal structural model: For value of the fixed regime \((a_1, a_2)\) ("Give \(a_1\) followed by \(a_2\) if nonresponse")

- \(R_2^*(a_1)\) = indicator a randomly chosen individual would respond to \(a_1 \in \mathcal{A}\), \(R_2^*(a_1) = 0 (1)\) if nonresponse (response)
- \(Y^*(a_1, a_2)\) = outcome that would be achieved if given dose sequence \((a_1, a_2) \in \mathcal{A} \times \mathcal{A}\)
- \(\mu(a_1, a_2) = E\{Y^*(a_1, a_2)\}\) modeled as

\[
\mu(a_1, a_2; \alpha) = \alpha_0 + \sum_{\ell=1}^{L} \alpha_{1\ell} a_1\ell + \sum_{\ell<k} \alpha_{2,\ell k} a_1\ell a_1k
\]

\[
+ \{1 - R_2^*(a_1)\} \left( \sum_{\ell=1}^{L} \alpha_{3\ell} a_2\ell + \sum_{\ell<k} \alpha_{4,\ell k} a_2\ell a_2k + \sum_{\ell=1}^{L} \sum_{k=1}^{L} \alpha_{5,\ell k} a_1\ell a_2k \right)
\]

- No third-, higher-order interactions among factors, \(\alpha = (\alpha_0, \alpha_{11}, \ldots, \alpha_{5,LL})^T\) indexes main effects, second-order interactions
- So \(O(L^2)\) parameters versus \(O(2^{2L})\) for all possible combinations
Example - SMART for treatment of bipolar disorder

Embed full factorial design in a SMART:

With a model like that above, could embed a fractional factorial
Fit the model using methods for fitting marginal structural models
Choosing an interim outcome

Strong scientific theory/consensus exists on when/if to adjust treatment: Response criterion should be chosen to reflect this

No theory/consensus: Identify candidate criterion

- SMART 1: Randomize participants to response criterion/treatment option combinations; e.g., with 2 stage 1 options, 2 response criteria, randomize to 4 combinations
- SMART 2: Choose form of response criterion; e.g., with $\tilde{h}_2$ a function of $h_2$ and function $\tau(h_1; c)$, $c \in C$

$$\tilde{h}_2 > \tau(h_1; c) \text{ responder, } \tilde{h}_2 \leq \tau(h_1; c) \text{ nonresponder}$$

For example, in HIV $\tilde{h}_2 = CD4_2$ and $\tau(h_1; c) = c$

- With $A = A_1 = A_2$, randomize to $(A_1, C) \in A \times C$; nonresponder $\tilde{H}_2 \leq \tau(H_1; C)$ randomized to $A_2 \in A$, responders continue
- For $(a_1, c, a_2) \in A \times C \times A$, there is an associated embedded regime and subjects whose experience is consistent with it; can evaluate and compare
Randomization probabilities

**Standard practice:** Randomization to feasible options at each stage with *equal probability*

**However:** Depending on the goals, *unequal randomization probabilities* may be warranted

- Example - mHealth interventions in HIV+ men
- Primary analysis: Compare each embedded regime \((e_1)\) and \((e_3)\) to control condition, where

\[
(e_1) \text{ give AllyQuest+ and continue regardless of response status}
\]

\[
(e_3) \text{ give AllyQuest and continue if response or step up to AllyQuest+ if nonresponse}
\]

- \(n\) subjects, equal randomization, expected numbers assigned
  - control \(n/3\)
  - \((e_3)\) \(n/3\)
  - \((e_1)\) \((1 - \rho) n/3 + \rho n/6\), \(\rho = \text{prob of response to AllyQuest+}\

- Could adjust randomization probabilities to ensure equal expected sample size for \((e_1)\), \((e_3)\), control
Example - mHealth interventions in HIV+ men

- **AllyQuest+**
  - **Response?**
    - **NO**
      - Continue AllyQuest+
    - **YES**
      - Step-down to AllyQuest

- **AllyQuest**
  - **Response?**
    - **NO**
      - Step-up to AllyQuest+
    - **YES**
      - Continue AllyQuest

- **Control**
  - **Response?**
    - **NO**
      - **TREATMENT 0**
    - **YES**
      - **TREATMENT 1**

**R**

**TREATMENT 0**

**TREATMENT 1**

**TREATMENT 2**
As we have seen, there is great flexibility in the design of a SMART to address different questions. However, a SMART may not always be the best design. For example, if interest focuses on comparing predefined “treatment packages,” a standard $k$-arm clinical trial randomizing participants to competing packages may be more appropriate. Many researchers want to use a SMART design because they want to do a SMART! But they should consider if there are alternative designs that can address the scientific questions more effectively.
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Primary analysis in a SMART

In practice:

- Primary analyses that form the basis for power/sample size calculations are typically simple
- Comparison of response rates among stage 1 treatment options
- Comparison of fixed embedded treatment regimes
- Of course, these comparisons should genuinely be of primary scientific interest
Comparing response rates

**Situation 1:** $A_1$ with $m_1$ stage 1 options, feasible for all individuals

- Randomization probabilities for $a_1 \in A_1$
  \[
  \omega_1(H_1, a_1) = P(A_1 = a_1|H_1) = P(A_1 = a_1) = \omega_1(a_1)
  \]

- $R_2^*(a_1)$ is potential response to $a_1 \in A_1$, $R_2^*(a_1) = 0$ (1) nonresponse (response),
  \[
  E\{R_2^*(a_1)\} = p_{a_1}
  \]

- For $a_1, a'_1 \in A_1$, sample size to ensure level $\alpha$ test of
  \[
  H_0: E\{R_2^*(a_1)\} = E\{R_2^*(a'_1)\} (p_{a_1} = p_{a'_1}) \text{ vs. } H_1: E\{R_2^*(a_1)\} \neq E\{R_2^*(a'_1)\} (p_{a_1} \neq p_{a'_1})
  \]
  has sufficient power to detect
  \[
  |E\{R_2^*(a_1)\} - E\{R_2^*(a'_1)\}| = |p_{a_1} - p_{a'_1}| \geq \delta
  \]
  for clinically meaningful difference $\delta > 0$
Comparing response rates

**Formulation:** \( R_2^*(a_1) \perp A_1 \), and under SUTVA observed response status

\[
R_2 = R_2^*(A_1) = \sum_{a_1 \in A_1} R_2^*(a_1)I(A_1 = a_1)
\]

- Usual test of \( H_0 \) versus \( H_1 \) is based on \( T_n = \hat{p}_{a_1} - \hat{p}_{a'_1} \)

\[
\hat{p}_a = \left\{ \sum_{i=1}^{n} I(A_{1i} = a) \right\}^{-1} \left\{ \sum_{i=1}^{n} I(A_{1i} = a)R_{2i} \right\}
\]

\( T_n \) is a consistent estimator for

\[
p_{a_1} - p_{a'_1} = E\{R_2^*(a_1)\} - E\{R_2^*(a'_1)\} = E(R_2|A_1 = a_1) - E(R_2|A_1 = a'_1)
\]

- Straightforward as \( n \to \infty, n^{1/2}\{T_n - (p_{a_1} - p_{a'_1})\} \xrightarrow{D} \mathcal{N}(0, \sigma^2_{a_1,a'_1}) \)

\[
\sigma^2_{a_1,a'_1} = \frac{E[\{R_2^*(a_1) - p_{a_1}\}^2]}{\omega_1(a_1)} + \frac{E[\{R_2^*(a'_1) - p_{a'_1}\}^2]}{\omega_1(a'_1)}
\]

\[
= \frac{p_{a_1}(1 - p_{a_1})}{\omega_1(a_1)} + \frac{p_{a'_1}(1 - p_{a'_1})}{\omega_1(a'_1)}
\]
Comparing response rates

Thus: Under $H_0$, $n^{1/2} T_n / \hat{\sigma}_{a_1, a_1'} \xrightarrow{D} \mathcal{N}(0, 1)$

$$\hat{\sigma}^2_{a_1, a_1'} = \frac{\hat{p}_{a_1} (1 - \hat{p}_{a_1})}{\omega_1(a_1)} + \frac{\hat{p}_{a_1'} (1 - \hat{p}_{a_1'})}{\omega_1(a_1')}$$

- Test that rejects $H_0$ when $|T_n| / (\hat{\sigma}_{a_1, a_1'} / n^{1/2}) > z_{1-\alpha/2}$ has approx type I error $\alpha$ and power under $H_1$ with $|p_{a_1} - p_{a_1'}| \geq \delta$ at least

$$\Phi(-z_{1-\alpha/2} - n^{1/2} \delta / \sigma_{a_1, a_1'}) + \Phi(-z_{1-\alpha/2} + n^{1/2} \delta / \sigma_{a_1, a_1'}), \quad \Phi(z_u) = u \quad (8.1)$$

- To ensure power $(1 - \beta) \times 100\%$ to detect $\delta$ or greater, solve for $n$ such that $(8.1) \geq 1 - \beta$

- Standard: Ignore first term in $(8.1)$ (small) and solve for $n$ satisfying

$$\Phi(-z_{1-\alpha/2} + n^{1/2} \delta / \sigma_{a_1, a_1'}) = 1 - \beta,$$ yielding

$$n = \left\{ \sigma^2_{a_1, a_1'} (z_{1-\alpha/2} + z_{1-\beta})^2 \right\} / \delta^2$$

- With equal randomization to $m_1$ options in $A_1$, $\omega_1(a_1) = \omega_1(a_1') = 1/m_1$

$$n = m_1 \{p_{a_1} (1 - p_{a_1}) + p_{a_1'} (1 - p_{a_1'})\} (z_{1-\alpha/2} + z_{1-\beta})^2 / \delta^2 \quad (8.2)$$
Comparing response rates

Usage: Posit response rates $p_{a_1}$ and $p_{a'_1}$ for $a_1$ and $a'_1$, which imply $\delta$

- Alternatively, (8.2) involves a type of standardized effect size $\frac{\delta}{\sigma_{a_1,a'_1}}$; can posit a standardized effect size instead, although this may be challenging

- Basing sample size on posited response rates is dominant in medical applications; basing it on standardized effect size is dominant in the behavioral and educational sciences (e.g., “Cohen’s $d$”)

- Can use a Bonferroni correction for all $m_1(m_1 - 1)/2$ pairwise comparisons
Comparing response rates

**Generalization:** Randomization probabilities depend on $h_1$

$$\omega_1(h_1, a_1) = P(A_1 = a_1 | H_1)$$

- E.g., $m_1 = 2$, randomize participants with age $\leq c$ with prob $1/2$ but those with age $> c$ preferentially to one of the options
- E.g., if $A_1 = \{0, 1, 2\}$
  $$\psi_1(h_1) = \{0, 1, 2\} \text{ (} m_{11} = 3 \text{ options)} \text{ if age } \leq c \quad \omega_1(h_1, a_1) = 1/m_{11} = 1/3$$
  $$\psi_1(h_1) = \{0, 1\} \text{ (} m_{12} = 2 \text{ options)} \text{ if age } > c \quad \omega_1(h_1, a_1) = 1/m_{12} = 1/2$$

- Options $a_1, a'_1$ that are the focus of the comparison should appear in both feasible sets
- Here, randomization depends on $H_1$, so $R^*_2(a_1) \perp A_1 | H_1$
Comparing response rates

Formulation: Test of $H_0$ versus $H_1$ is based on $T_n = \hat{p}_{a_1} - \hat{p}_{a_1'}$ where

$$\hat{p}_{a_1} = \left\{ \sum_{i=1}^{n} \frac{I(A_{1i} = a_1)}{\omega_1(H_{1i}, a_1)} \right\}^{-1} \sum_{i=1}^{n} \frac{I(A_{1i} = a_1)R_{2i}}{\omega_1(H_{1i}, a_1)}$$

- Smaller sampling variation than simple IPW estimator

$$n^{-1} \sum_{i=1}^{n} \left\{ \frac{I(A_{1i} = a_1)R_{2i}}{\omega_1(H_{1i}, a_1)} \right\}$$

- Consistent estimator for $p_{a_1}$ if $\omega_1(h_1, a_1)$ are the true randomization probabilities

- Recall that estimating the $\omega_1(h_1, a_1)$ would lead to a more precise estimator; however, for simplicity in calculating sample size take them to be known

- Will yield conservative sample size estimation (a good thing)
Comparing response rates

Formulation: \( T_n \) is a consistent estimator for \( p_{a_1} - p_{a_1'} \), and a

\[
n \to \infty, \ n^{1/2} \{ T_n - (p_{a_1} - p_{a_1'}) \} \xrightarrow{D} \mathcal{N}(0, \sigma_{a_1, a_1'}^2)
\]

\[
\sigma_{a_1, a_1'}^2 = E \left[ \frac{\{ R^*_2(a_1) - p_{a_1} \}^2}{\omega_1(H_1, a_1)} \right] + E \left[ \frac{\{ R^*_2(a_1') - p_{a_1'} \}^2}{\omega_1(H_1, a_1')} \right]
\]

\[
\hat{\sigma}_{a_1, a_1'}^2 = n^{-1} \sum_{i=1}^{n} \left[ \left( \frac{R_{2i} - \hat{p}_{a_1}}{\omega_1(H_1_i, a_1)} \right) (A_{1i} = a_1) \right]^2 + \left[ \frac{(R_{2i} - \hat{p}_{a_1'}) l(A_{1i} = a_1')}{\omega_1(H_1_i, a_1')} \right]^2
\]

- Test that rejects \( H_0 \) when \( |T_n|/ (\hat{\sigma}_{a_1, a_1'} / n^{1/2}) > z_{1-\alpha/2} \) has approx type I error \( \alpha \) and power under \( H_1 \) with \( |p_{a_1} - p_{a_1'}| \geq \delta \) at least

\[
\Phi(-z_{1-\alpha/2} - n^{1/2} \delta / \sigma_{a_1, a_1'}) + \Phi(-z_{1-\alpha/2} + n^{1/2} \delta / \sigma_{a_1, a_1'})
\]
Comparing response rates

Complication: Dependence on $\omega_1(H_1i, a_1)$ and $\omega_1(H_1i, a'_1)$

- One approach: As in Murphy (2005), use an upper bound on $\sigma^2_{a_1,a'_1}$ given by

$$\tilde{\sigma}^2_{a_1,a'_1} = \frac{p_{a_1}(1 - p_{a_1})}{\min_{h_1} \omega_1(h_1, a_1)} + \frac{p_{a'_1}(1 - p_{a'_1})}{\min_{h_1} \omega_1(h_1, a'_1)}$$

- Conservative sample size calculation: Solve for $n$ such that

$$\Phi(-z_{1-\alpha/2} - n^{1/2} \delta / \tilde{\sigma}_{a_1,a'_1}) + \Phi(-z_{1-\alpha/2} + n^{1/2} \delta / \tilde{\sigma}_{a_1,a'_1}) \geq 1 - \beta$$

and disregard first term to obtain

$$n = \left(\tilde{\sigma}^2_{a_1,a'_1}(z_{1-\alpha/2} + z_{1-\beta})^2\right) / \delta^2$$

- Must posit response rates $p_{a_1}$ and $p_{a'_1}$, implying $\delta$
Comparing response rates

Example: As above, with \( A_1 = \{0, 1, 2\} \)

\[
\psi_1(h_1) = \{0, 1, 2\} \quad (m_{11} = 3 \text{ options}) \text{ if age } \leq c \\
\psi_1(h_1) = \{0, 1\} \quad (m_{12} = 2 \text{ options}) \text{ if age } > c
\]

\[
\omega_1(h_1, a_1) = 1/m_{11} = 1/3 \\
\omega_1(h_1, a_1) = 1/m_{12} = 1/2
\]

- Suppose \( a_1 = 0 \) and \( a_1' = 1 \), in which case

\[
\min_{h_1} \omega_1(h_1, 0) = \min_{h_1} \omega_1(h_1, 1) = 1/m_{11} = 1/3
\]

and for posited \( p_0 \) and \( p_1 \), \( \delta = p_1 - p_0 \) and

\[
\tilde{\sigma}^2_{0,1} = 3\{p_0(1-p_0) + p_1(1-p_1)\}
\]
Comparing response rates

Discussion:

• Sizing a SMART for comparison of stage 1 response rates is equivalent to sizing a randomized trial with binary outcome, so is familiar to investigators

• This comparison should be of genuine primary scientific interest

• E.g., in the cancer pain management SMART, the primary analysis was comparison of response rates to PCST-Full and PCST-Brief because there was no previous study of this

• If primary interest is instead in comparing treatment sequences, comparison of stage 1 treatment options may not be meaningful

• E.g., It is possible that the stage 1 option with the highest response rate is embedded in a regime that is worst among all regimes embedded in the SMART with respect to the final outcome of interest

• Sizing a SMART for comparison of fixed treatment regimes on the basis of the final outcome (as the primary analysis) may be more appropriate
Comparing fixed regimes

**Usually:** Comparison of regimes *embedded* in the SMART

**Simplest case:** Comparison of *nonoverlapping* regimes based on final outcome

- I.e., regimes with different stage 1 treatment option
- In this case, the sets of subjects with realized treatment experience consistent with each regime are disjoint and thus independent
- Often of great clinical interest: For example, comparing the most intensive or expensive embedded regime to the least intensive or expensive (cost, resource utilization, patient burden)
Comparing fixed regimes

**Formulation, simplest case:** $d = \{d_1, d_2\}$ and $d' = \{d'_1, d'_2\}$ are two fixed, nonoverlapping regimes

- i.e., satisfying

$$d_1(h_1) \neq d'_1(h_1) \text{ for all } h_1 \in H_1$$

so do not recommend the same stage 1 treatment option for any baseline history

- $Y^*(d)$ and $Y^*(d') = the potential final outcomes under $d$ and $d'$,

with *values*

$$\nu(d) = E\{Y^*(d)\} \text{ and } \nu(d') = E\{Y^*(d')\}$$

- Goal: Choose sample size $n$ to ensure a level $\alpha$ test of

$$H_0 : \nu(d) = \nu(d') \text{ vs. } H_1 : \nu(d) \neq \nu(d')$$

has sufficient power to detect

$$|\nu(d) - \nu(d')| \geq \delta$$
Comparing fixed regimes

**IPW estimator for \( \nu(d) \):** Consistent estimator

\[
\hat{\nu}(d) = \left[ \sum_{i=1}^{n} \frac{I\{A_{1i} = d_1(H_{1i})\} I\{A_{2i} = d_2(H_{2i})\}}{\omega_1\{H_{1i}, d_1(H_{1i})\} \omega_2\{H_{2i}, d_2(H_{2i})\}} \right]^{-1} \\
\times \sum_{i=1}^{n} \frac{I\{A_{1i} = d_1(H_{1i})\} I\{A_{2i} = d_2(H_{2i})\} Y_i}{\omega_1\{H_{1i}, d_1(H_{1i})\} \omega_2\{H_{2i}, d_2(H_{2i})\}} \\
= \left[ \sum_{i=1}^{n} \frac{I\{A_{1i} = d_1(H_{1i})\} I\{A_{2i} = d_2(H_{2i})\}}{\omega_1(H_{1i}, A_{1i}) \omega_2(H_{2i}, A_{2i})} \right]^{-1} \\
\times \sum_{i=1}^{n} \frac{I\{A_{1i} = d_1(H_{1i})\} I\{A_{2i} = d_2(H_{2i})\} Y_i}{\omega_1(H_{1i}, A_{1i}) \omega_2(H_{2i}, A_{2i})}
\]

(8.3)

- Regard randomization probabilities \( \omega_k(h_k, a_k), k = 1, 2 \) as known
Comparing fixed regimes

Sample size: \( T_n = \hat{V}(d) - \hat{V}(d') \) is a consistent estimator for \( V(d) - V(d') \) and \( n^{1/2}[T_n - \{V(d) - V(d')\}] \xrightarrow{D} \mathcal{N}(0, \sigma_{d,d'}^2) \)

\[
\sigma_{d,d'}^2 = E \left[ \frac{\{ Y^*(d) - V(d) \}^2}{\omega_1 \{ H_1, d_1(H_1) \} \omega_2 \{ H_2, d_2(H_2) \}} \right] + E \left[ \frac{\{ Y^*(d') - V(d') \}^2}{\omega_1 \{ H_1, d'_1(H_1) \} \omega_2 \{ H_2, d'_2(H_2) \}} \right]
\]

• Consistent estimator for \( \sigma_{d,d'}^2 \)

\[
\hat{\sigma}_{d,d'}^2 = n^{-1} \sum_{i=1}^{n} \left[ \frac{\{ Y_i - \hat{V}(d) \} I\{ A_{1i} = d_1(H_{1i}) \} I\{ A_{2i} = d_2(H_{2i}) \}}{\omega_1(H_{1i}, A_{1i}) \omega_2(H_{2i}, A_{2i})} \right]^2 + n^{-1} \sum_{i=1}^{n} \left[ \frac{\{ Y_i - \hat{V}(d') \} I\{ A_{1i} = d'_1(H_{1i}) \} I\{ A_{2i} = d'_2(H_{2i}) \}}{\omega_1(H_{1i}, A_{1i}) \omega_2(H_{2i}, A_{2i})} \right]^2
\]
Comparing fixed regimes

Sample size: Under $H_0$, $n^{1/2} T_n/\hat{\sigma}_{d,d'} \xrightarrow{D} \mathcal{N}(0,1)$, so test that rejects $H_0$ when $n^{1/2} |T_n|/\hat{\sigma}_{d,d'} \geq z_{1-\alpha/2}$ has approx type I error $\alpha$ and power under $H_1$ exceeding

$$\Phi(-z_{1-\alpha/2} - n^{1/2} \delta/\sigma_{d,d'}) + \Phi(-z_{1-\alpha/2} + n^{1/2} \delta/\sigma_{d,d'})$$

- To ensure power $\geq (1 - \beta) \times 100\%$, choose $n$ so this $\geq 1 - \beta$
- Disregarding first term: $n = \sigma_{d,d'}^2(z_{1-\alpha/2} + z_{1-\beta})^2/\delta^2$
- Conservative sample size obtained via upper bound on $\sigma_{d,d'}^2$ (Murphy, 2005); using $E[\{Y^*(d) - \nu(d)\}^2] = \text{var}\{Y^*(d)\}$

$$\tilde{\sigma}_{d,d'}^2 = \frac{\text{var}\{Y^*(d)\}}{\min_{x_2} \omega_1 \{x_1, d_1(x_1)\} \omega_2 \{x_2, d_2(x_2)\}}$$

$$+ \frac{\text{var}\{Y^*(d')\}}{\min_{x_2} \omega_1 \{x_1, d'_1(x_1)\} \omega_2 \{x_2, d'_2(x_2)\}}$$
Comparing fixed regimes

Practical use: Based on knowledge or preliminary data

- Posit $\nu(d)$ and $\nu(d')$ and thus $\delta$, or posit $\delta$ directly
- And specify $\text{var}\{Y^*(d)\}$ and $\text{var}\{Y^*(d')\}$ (may be reasonable to take these to be equal)
- Or specify standardized effect size $\frac{\delta}{\sigma_{d,d'}}$
Example - Cancer pain management

SMART with $K = 2$ to study interventions for cancer pain management:

Diagram:

- **PCST-Full**
  - Response?
    - YES
      - **PCST-Plus**
      - TREATMENT 4
    - NO
      - **PCST-Full maintenance**
      - TREATMENT 2

- **PCST-Brief**
  - Response?
    - YES
      - **PCST-Brief maintenance**
      - TREATMENT 5
    - NO
      - **PCST-Full**
      - TREATMENT 0
      - No further intervention
      - TREATMENT 3

- TREATMENT 0
- TREATMENT 1
- TREATMENT 2
- TREATMENT 3
- TREATMENT 4
- TREATMENT 5
Comparing fixed regimes

**Goal:** Compare *most and least intensive* embedded regimes

(e₁) Give PCST-Full followed by PCST-Full maintenance if response or PCST-Plus if nonresponse

(e₈) Give PCST-Brief followed by no further treatment if response or PCST-Brief maintenance if nonresponse

• \( d = e₁ \), so \( d₁(h₁) \equiv 0 \) for all \( h₁ \), \( d₂(h₂) = 2r₂ + 4(1 - r₂) \)

• \( d' = e₈ \), so \( d'₁(h₁) \equiv 1 \) for all \( h₁ \), \( d''₂(h₂) = 3r₂ + 5(1 - r₂) \)

\[
T_n = \frac{\sum_{i=1}^{n} Y_i I(A_{1i} = 0) I(A_{2i} = 4 - 2R_{2i})}{\sum_{i=1}^{n} I(A_{1i} = 0) I(A_{2i} = 4 - 2R_{2i})} - \frac{\sum_{i=1}^{n} Y_i I(A_{1i} = 1) I(A_{2i} = 5 - 2R_{2i})}{\sum_{i=1}^{n} I(A_{1i} = 1) I(A_{2i} = 5 - 2R_{2i})}
\]

\[
\hat{\sigma}_{d,d'}^2 = 16 \sum_{i=1}^{n} \{ Y_i - \hat{\nu}(d') \}^2 I(A_{1i} = 0) I(A_{2i} = 4 - 2R_{2i})
\]

\[
+ 16 \sum_{i=1}^{n} \{ Y_i - \hat{\nu}(d') \}^2 I(A_{1i} = 1) I(A_{2i} = 5 - 2R_{2i})
\]
Comparing fixed regimes

**Outcome:** $Y = \%$ reduction in pain from baseline

- Previous studies: $SD(Y) \approx 30\%$; take $\text{var}\{Y^*(d)\} = \text{var}\{Y^*(d')\} = 30^2$
- With all $\omega_k(h_k, a_k) \equiv 1/2$ for all $h_k, a_k \in \Psi_k(h_k)$

\[
\sigma^2_{d,d'} = 4[\text{var}\{Y^*(d)\} + \text{var}\{Y^*(d')\}] = 8(30^2)
\]

- Goal: Detect $\delta = 10\%$ at level $\alpha = 0.05$ with 80% power $\Rightarrow n \approx 566$
- Goal: $\delta$ that can be detected with 80% power and $n = 350$ $\Rightarrow \delta \approx 12.73\%$
- Alternative goal: Detect standardized effect size $e = \delta/\sigma_{d,d'} = 0.15$

- Conventional standardized effect size (continuous outcome): Cohen’s $d = \delta/\sigma$, $\sigma^2 = \text{var}\{Y^*(d)\} = \text{var}\{Y^*(d')\}$

- Here: $d = \sqrt{8}e \approx 0.42$ “small to medium” effect size (Cohen, 1998) $\Leftrightarrow \delta \approx 12.73\%$
Comparing fixed regimes

**Overlapping regimes:** \( d = \{d_1, d_2\}, \quad d' = \{d'_1, d'_2\} \) have stage 1 rules that can assign the *same* stage 1 treatment option; i.e.,

\[
d_1(h_1) = d'_1(h_1) \quad \text{for some} \quad h_1 \in \mathcal{H}_1
\]

- There will be subjects with realized treatment experience consistent with having followed *both* \( d \) and \( d' \)
- Simplest case: \( d_1(h_1) \) and \( d'_1(h_1) \) assign the same option in \( \mathcal{A}_1 \) for all \( h_1 \)
Illustrative example, design 1

Embedded regimes: Identify $d$ and $d'$ with

$(e_1)$ New Active Treatment followed by Maintenance if response, Salvage 1 if nonresponse

$(e_2)$ New Active Treatment followed by Maintenance if response, Salvage 2 if nonresponse

Subject receives New Active Treatment, responds: Consistent with both
Comparing fixed regimes

**Result:** A subject with realized treatment experience consistent with having followed the rules in both $d$ and $d'$ contributes to both $\widehat{V}(d)$ and $\widehat{V}(d')$

- $\widehat{V}(d)$ and $\widehat{V}(d')$ are no longer based on disjoint groups of subjects so are **correlated**
- This complicates calculation of sample size formulæ

**Demonstration:** Define

$$W(d') = \frac{I\{A_1 = d_1(H_1)\}I\{A_2 = d_2(H_2)\}}{\omega_1\{H_1, d_1(H_1)\}\omega_2\{H_2, d_2(H_2)\}}$$

$$= \frac{I\{A_1 = d_1(H_1)\}I\{A_2 = d_2(H_2)\}}{\omega_1(H_1, A_1)\omega_2(H_2, A_2)}$$

- If $d$ and $d'$ are nonoverlapping, $W(d')W(d') \equiv 0$ almost surely
Comparing fixed regimes

Formulation: \( T_n = \hat{\mathcal{V}}(d) - \hat{\mathcal{V}}(d') \), theory of M-estimation shows

\[
n^{1/2} [T_n - \{ \mathcal{V}(d) - \mathcal{V}(d') \}] \xrightarrow{D} \mathcal{N}(0, \varsigma_{d,d'}^2)
\]

\[
\varsigma_{d,d'}^2 = \sigma_{d,d'}^2 - 2E[ W(d) \{ Y^*(d) - \mathcal{V}(d) \} W(d') \{ Y^*(d') - \mathcal{V}(d') \}]
\]

and \( \sigma_{d,d'}^2 \) is defined on Slide 627

- If \( d \) and \( d' \) are nonoverlapping, \( W(d) W(d') \equiv 0 \Rightarrow \varsigma_{d,d'}^2 = \sigma_{d,d'}^2 \), and sample size is as before

- Otherwise, with \( W_i(d) \) denoting evaluation at \( A_{ki}, H_{ki}, k = 1, 2 \)

\[
\hat{\varsigma}_{d,d'}^2 = \hat{\sigma}_{d,d'}^2 - 2n^{-1} \sum_{i=1}^{n} W_i(d) W_i(d') \{ Y_i - \hat{\mathcal{V}}(d) \} \{ Y_i - \hat{\mathcal{V}}(d') \}
\]

\( W_i(d) W_i(d') \) is nonzero only for \( i \) for whom \( d \) and \( d' \) lead to the same treatment experience
Comparing fixed regimes

**Sample size:** Under $H_0$, $n^{1/2} \frac{T_n}{\hat{\varsigma}^2_{d,d'}} \xrightarrow{D} \mathcal{N}(0, 1)$

- In principle this can form the basis for a test procedure as before
- However: Power depends on $\varsigma^2_{d,d'}$, which involves both $\sigma^2_{d,d'}$ and the unknown covariance term

$$-2E[W(d)\{Y^*(d) - \mathcal{V}(d)\} W(d')\{Y^*(d') - \mathcal{V}(d')\}]$$

which depends on the nature of the overlap of $d$ and $d'$

- Thus, specifying $\varsigma^2_{d,d'}$ is problematic in practice, as would be specifying a standardized effect size $\delta/\varsigma_{d,d'}$
Comparing fixed regimes

**Simplification:** Above, $e_1$ and $e_2$ differ only in stage 2 salvage option
$\Rightarrow$ comparison of $e_1$ and $e_2$ reduces to comparison of Salvage 1 and Salvage 2 among nonresponders to New Active Treatment based on final outcome (with variance $\sigma^2$)

- Result: Sample size $n$ for the SMART can be based on conventional two-sample comparison of means
- E.g., for given $\delta$ and $\sigma^2$ and thus $\delta/\sigma$, and equal randomization at each stage, the number of nonresponders required to detect $\delta$ with 80% power at level 0.05 when $\delta/\sigma = 0.5$ is
  \[
  4(1.96 + 0.84)^2/(0.5)^2 \approx 126
  \]
- To find $n$, note $\approx n/2$ subject will be assigned to New Active Treatment at stage 1, so if a proportion $\theta$ of these will be nonresponders
  \[
  n = 2(126)/\theta
  \]

Must posit nonresponse probability $\theta$
More complex comparisons: Investigators often pose vague goals; e.g., “compare first-stage treatments” or “identify the optimal first-stage treatment” based on the final outcome

- Formalizing these imprecise goals leads to questions involving *marginalizing* or *maximizing* over stage 2

- E.g., Compare mean outcomes for different stage 1 treatments $a_1$ if all individuals in the population received $a_1$ and then received stage 2 options with the probabilities used to randomize to these in the SMART

- E.g., Compare mean outcomes for different $a_1$ if all individuals received $a_1$ and then received stage 2 options according to the standard of care in the population

- E.g., Compare mean outcomes for different $a_1$ if all individuals received $a_1$ and then received the optimal stage 2 option for their histories (so maximizing over stage 2 options)
Marginalizing

**Define:** Potential outcome for a randomly chosen individual in the population who receives option \( a_1 \in A_1 \) at the first stage and then is assigned stage two treatment \( \mu_2(H_2) \) depending on her history

\[
Y^*\{a_1, \mu_2(H_2)\}
\]

- \( H_2 \) understood to equal \((\overline{X}_2, a_1)\) (stage one treatment fixed at \( a_1 \))
- \( \mu_2(h_2) \) is a *stochastic process* indexed by \( h_2 \in H_2 \) taking values \( a_2 \in A_2 \) according to a probability distribution

\[
\mu_2(h_2) = a_2 \text{ with probability } \omega_{\mu,2}(h_2, a_2)
\]

where \( \sum_{a_2 \in A_2} \omega_{\mu,2}(h_2, a_2) = 1 \) for \( h_2 = (\overline{X}_2, a_1) \in H_2 \)

- **Thus:** For given \( a_2 \) and such \( h_2 \), \( \omega_{\mu,2}(h_2, a_2) \) is the probability of assignment to option \( a_2 \) at second stage under an assignment mechanism that is *possibly different* from that in the SMART
Marginalizing

Marginalizing over the second stage: Compare mean (final) outcomes for two or more first-stage treatment options, marginalizing over second-stage treatment received in the SMART

- In the SMART, stage-two treatments are assigned according to known randomization probabilities $\omega_2(h_2, a_2)$
- Thus, these mean outcomes reflect a “world” in which second-stage treatments are administered in the population with probabilities identical to these randomization probabilities
- I.e., for $a_2 \in A_2$ and $h_2 = (\bar{x}_2, a_1)$,

$$\mu_2(h_2) = a_2 \text{ with probability } \omega_{\mu,2}(h_2, a_2) = \omega_2(h_2, a_2)$$
Marginalizing

Marginalizing over the second stage: Compare mean (final) outcomes for two or more first-stage treatment options, marginalizing over second-stage treatment received in the SMART

- Mean outcome for $a_1$, marginalizing over second stage treatment

$$
\varepsilon_1(a_1) = E[Y^* \{a_1, \mu_2(H_2)\}]
$$

mean outcome if all individuals in the population were to receive $a_1$ at stage one, then receive an option in $A_2$ according to the same probabilities used to randomize subjects in the SMART

- Thus: For two Decision 1 options $a_1$ and $a_1'$, interested in

$$
\varepsilon_1(a_1) - \varepsilon_1(a_1')
$$

- May be relevant in settings where the second-stage treatment options have effects that are qualitatively similar across first-stage treatments
Marginalizing

Marginalizing with respect to standard of care: Compare mean (final) outcomes for two or more first-stage treatment options, marginalizing over the way stage-two treatments are assigned in clinical practice (i.e., standard of care)

- $\omega_{\mu,2}(h_2, a_2)$ are probabilities with which individuals with history $h_2$ are assigned to $a_2$ under standard of care
- Mean outcome if all individuals in the population were to receive option $a_1$ at the first decision point and then be treated according to standard of care thereafter

$$\mathcal{E}_2(a_1) = E[Y^* \{a_1, \mu_2(H_2)\}]$$

- Reflects a “world” in which second-stage treatments are administered in the population according to the standard of care
- Relevant if one wishes to recommend a stage-one treatment option assuming that the standard of care will be followed subsequently
Marginalizing

**Goal:** For distinct \( a_1, a'_1 \in A_1 \), test

\[
H_0 : \mathcal{E}_j(a_1) = \mathcal{E}_j(a'_1) \quad \text{vs.} \quad H_1 : \mathcal{E}_j(a_1) \neq \mathcal{E}_j(a'_1), \quad j = 1, 2
\]

- Based on estimator for \( E[Y^*\{a_1, \mu_2(H_2)\}] \)
- Can be shown (Murphy et al., 2001)

\[
E[Y^*\{a_1, \mu_2(H_2)\}] = E\left\{ \frac{I(A_1 = a_1) \omega_{\mu,2}(H_2, A_2) Y}{\omega_1(H_1, A_1) \omega_2(H_2, A_2)} \right\}
\]

(8.4)

\[
E\left\{ \frac{I(A_1 = a_1) \omega_{\mu,2}(H_2, A_2)}{\omega_1(H_1, A_1) \omega_2(H_2, A_2)} \right\} = 1
\]

provided that \( \omega_{\mu,2}(h_2, a_2) = 0 \) whenever \( \omega_2(h_2, a_2) = 0 \) so probability under the treatment assignment mechanism associated with \( \mu_2(h_2) \) is absolutely continuous with respect to that for the SMART
Marginalizing

\[ E[Y^* \{a_1, \mu_2(H_2)\}] = E \left\{ \frac{I(A_1 = a_1) \omega_{\mu,2}(H_2, A_2) Y}{\omega_1(H_1, A_1) \omega_2(H_2, A_2)} \right\} \]  \hspace{1cm} (8.4)

- (8.4) places point mass at \( a_1 \) but recognizes that stage-two treatment is assigned with probabilities dictated by \( \mu_2(h_2) \)
- Reweights the information from the SMART to reflect the hypothetical “world” in which stage two treatment is assigned according to the probability distribution of \( \mu_2(h_2) \)
- The regime assigning \( a_1 \) at Decision 1 and stage-two treatment according to \( \mu_2(h_2) \) is a random treatment regime; see Murphy et al. (2001)
Marginalizing

Estimator for $E[Y^*\{a_1, \mu_2(H_2)\}]$:

\[
\left\{ \sum_{i=1}^{n} \frac{I(A_{1i} = a_1) \omega_{\mu,2}(H_{2i}, A_{2i})}{\omega_1(H_{1i}, A_{1i}) \omega_2(H_{2i}, A_{2i})} \right\}^{-1} \sum_{i=1}^{n} \frac{I(A_{1i} = a_1) \omega_{\mu,2}(H_{2i}, A_{2i}) Y_i}{\omega_1(H_{1i}, A_{1i}) \omega_2(H_{2i}, A_{2i})}
\]  

(8.5)

Marginalizing over second stage: $\omega_{\mu,2}(h_2, a_2) = \omega_2(h_2, a_2)$

- (8.5) becomes

\[
\hat{E}_1(a_1) = \left\{ \sum_{i=1}^{n} \frac{I(A_{1i} = a_1)}{\omega_1(H_{1i}, A_{1i})} \right\}^{-1} \sum_{i=1}^{n} \frac{I(A_{1i} = a_1) Y_i}{\omega_1(H_{1i}, A_{1i})}
\]

- For $a_1, a_1' \in A_1$, estimator for $\mathcal{E}_1(a_1) - \mathcal{E}_1(a_1')$ is

\[
T_n = \hat{E}_1(a_1) - \hat{E}_1(a_1')
\]

- Operationally, inference on $\mathcal{E}_1(a_1) - \mathcal{E}_1(a_1')$ is the same as for difference of two mean outcomes in a conventional clinical trial
Marginalizing

Marginalizing over second stage: Test $H_0 : \mathcal{E}_1(a_1) = \mathcal{E}_1(a'_1)$

- $n^{1/2}[T_n - \{\mathcal{E}_1(a_1) - \mathcal{E}_1(a'_1)\}] \xrightarrow{D} \mathcal{N}(0, \sigma_{a_1,a'_1}^2)$

$$\sigma_{a_1,a'_1}^2 = E \left( \left[ \frac{Y - \mathcal{E}_1(a_1)}{\omega_1(H_1, a_1)} \right]^2 \right) + E \left( \left[ \frac{Y - \mathcal{E}_1(a'_1)}{\omega_1(H_1, a'_1)} \right]^2 \right)$$

- Estimated consistently by

$$\hat{\sigma}_{a_1,a'_1}^2 = n^{-1} \sum_{i=1}^{n} \left( \left[ \frac{Y_i - \hat{\mathcal{E}}_1(a_1)}{\omega_1(H_{1i}, a_1)} \right]^2 + \left[ \frac{Y_i - \hat{\mathcal{E}}_1(a'_1)}{\omega_1(H_{1i}, a'_1)} \right]^2 \right)$$

- Reject $H_0$ when $\frac{n^{1/2}|T_n|}{\hat{\sigma}_{a_1,a'_1}} \geq Z_{1-\alpha/2}$ provided $|\mathcal{E}_1(a_1) - \mathcal{E}_1(a'_1)| \geq \delta$

- Approximate sample size formula

$$n = \frac{\sigma_{a_1,a'_1}^2 (Z_{1-\alpha/2} + Z_{1-\beta})^2}{\delta^2}$$
Marginalizing over second stage: First stage randomization does not depend on $h_1$, $\omega_1(h_1, a_1) = \omega_1(a_1)$

- $\mathcal{E}_1(a_1) = \omega_1^{-1}(a_1)E\{ Y|A_1 = a_1 \} = E(Y|A_1 = a_1)$

\[
\sigma_{a_1, a_1'}^2 = \frac{\text{var}(Y|A_1 = a_1)}{\omega_1(a_1)} + \frac{\text{var}(Y|A_1 = a_1')}{\omega_1(a_1')}
\]

- Posit values for $\text{var}(Y|A_1 = a_1)$, $\text{var}(Y|A_1 = a_1')$, values for $\mathcal{E}_1(a_1)$ and $\mathcal{E}_1(a_1')$ (or for $\delta$)
- E.g., $\text{var}(Y|A_1 = a_1) = \text{var}(Y|A_1 = a_1') = \sigma^2$, $\omega_1(a_1) = \omega_1(a_1') = 1/m_1$

\[
n = \frac{2m_1 \sigma^2(z_{1-\alpha/2} + z_{1-\beta})^2}{\delta^2}
\]
Marginalizing

Marginalizing over second stage: First stage randomization does depend on $h_1$; can show (Murphy et al., 2001)

$$E \left[ \frac{\{Y - \mathcal{E}_1(a_1)\}^2 I(A_1 = a_1)}{\omega_1^2(H_1, a_1)} \right] = E \left( \frac{E[\{Y - \mathcal{E}_1(a_1)\}^2 | H_1, A_1 = a_1]}{\omega_1(H_1, a_1)} \right)$$

$$\leq \frac{E \left( E[\{Y - \mathcal{E}_1(a_1)\}^2 | H_1, A_1 = a_1] \right)}{\min_{h_1} \omega_1(h_1, a_1)}$$

$$E \left\{ E \left( [Y^* \{a_1, \mu_2(H_2)\} - \mathcal{E}_1(a_1)]^2 | H_1 \right) \right\} = \frac{\var[Y^* \{a_1, \mu_2(H_2)\}]}{\min_{h_1} \omega_1(h_1, a_1)}$$

- Upper bound on $\sigma_{a_1,a_1'}^2$

$$\sim \sigma_{a_1,a_1'}^2 = \frac{\var[Y^* \{a_1, \mu_2(H_2)\}]}{\min_{h_1} \omega_1(h_1, a_1)} + \frac{\var[Y^* \{a_1', \mu_2(H_2)\}]}{\min_{h_1} \omega_1(h_1, a_1')}$$
Marginalizing

Marginalizing with respect to standard of care: $\mu_2(h_2)$ has probability distribution reflecting assignment of stage-two treatment options under the standard of care in the population

- Usually *unknown*; could be estimated from *historical data* or elicited from experts
- Test $H_0 : \mathcal{E}_2(a_1) = \mathcal{E}_2(a'_1)$ versus $H_1 : \mathcal{E}_2(a_1) \neq \mathcal{E}_2(a'_1)$
- Estimator for $\mathcal{E}_2(a_1)$

\[
\hat{\mathcal{E}}_2(a_1) = \left\{ \sum_{i=1}^{n} W_{\mu,i}(a_1) \right\}^{-1} \sum_{i=1}^{n} W_{\mu,i}(a_1) Y_i
\]

\[
W_{\mu}(a_1) = \frac{I(A_1 = a_1) \omega_{\mu,2}(H_2, A_2)}{\omega_1(H_1, A_1) \omega_2(H_2, A_2)}
\]
Maximizing

More complicated: Maximization leads to nonstandard asymptotic behavior of the test statistic under the null hypothesis

- For $e_{j_{a_1}}^{a_1}$, $e_{J_{a_1}}^{a_1}$ embedded regimes assigning $a_1$ at stage 1,
  
  $Y^*(e_{j}^{a_1})$ is the potential outcome if all individuals in the population were treated according to $e_{j}^{a_1}$

- Mean outcome if all individuals received $a_1$ followed by optimal stage-two treatment based on $h_2$

  $$\mathcal{E}_3(a_1) = \max_{j=1,\ldots,J_{a_1}} E\{Y^*(e_{j}^{a_1})\}$$

  want to test $H_0: \mathcal{E}_3(a_1) = \mathcal{E}_3(a_1')$

- With two regimes $e_{1}^{a_1}, e_{2}^{a_1}$ beginning with $a_1$ and two regimes $e_{1}^{a_1'}, e_{2}^{a_1'}$ beginning with $a_1'$, the test statistic is

  $$T_n = \max \left\{ \hat{\nu}(e_{1}^{a_1}), \hat{\nu}(e_{2}^{a_1}) \right\} - \max \left\{ \hat{\nu}(e_{1}^{a_1'}), \hat{\nu}(e_{2}^{a_1'}) \right\}$$
Additional sample size criteria

Sizing a SMART for estimation of an optimal regime: Can derive sample size formulæ that ensure

- Sufficient power to detect a clinically meaningful difference in mean outcome (value) under an optimal treatment regime and under some comparator treatment strategy, such as standard of care in the population
- The value under the estimated optimal regime is within a prespecified tolerance of that under a true optimal regime with high probability

Remarks:

- Sample size focused on these criteria is much harder and may involve nonstandard inferential techniques
- In practice, the primary analysis for which the trial is sized is much simpler but being able to evaluate sample size for more complex goals supports these as secondary analyses
8. Sequential Multiple Assignment Randomized Trials (SMARTs)

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Further topics

Development needed:

- Handing missing data in a SMART
- Adaptive randomization in a SMART – updating randomization probabilities as information accumulates on relative benefits of the embedded regimes

Biggest issue: More widespread adoption and acceptance of SMARTs
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