Introduction to Sequential Decision Making, Treatment Regimes, and SMARTs

Marie Davidian

Department of Statistics
North Carolina State University
Clinical practice: Clinicians make a series of treatment decisions over the course of a patient’s disease or disorder

- Key decision points in the disease process
- Fixed schedule, milestone in the disease process, event necessitating a decision
- Several feasible treatment options at each decision point
- Accumling information on the patient
- Ideally: “Individualize” treatment to the patient
Clinical decision making

Premise: A patient’s *characteristics* are implicated in which treatment s/he should receive

- Genetic/genomic, demographic, physiological
- Laboratory measures
- Medical history, concomitant conditions
- Environment, lifestyle factors
- Adverse reactions, adherence to prior treatment
- Preference
- ...
Result: Treatment in practice involves *sequential decision making* based on *accruing individual information*

- Suggests *thinking about* and *studying* treatment from this perspective...
Example: Acute leukemia

Two decision points:

- **Decision 1**: Induction chemotherapy (2 options: C₁, C₂)
- **Decision 2**:
  - Maintenance treatment for patients who *respond* (2 options: M₁, M₂)
  - Salvage chemotherapy for those who *don’t respond* (2 options: S₁, S₂)
Example: Children with ADHD

Two decision points:

- **Decision 1**: Initial intervention
  (2 options: medication, behavioral therapy)

- **Decision 2**:
  - Continue initial intervention for children who *respond* (1 option: continue)
  - Modify initial intervention for those who *don't respond* (2 options: increase dose/intensify, add second intervention)
Clinical decision making

How are treatment decisions made?

- Clinical judgment
- Practice guidelines based on study results, expert opinion
- Synthesis of all information on a patient up to the point of a decision to determine next treatment action from among the feasible options

- Goal: Make the “best” decisions leading to the most beneficial expected outcome for the patient

Can clinical decision making be formalized and made evidence-based?
Informing clinical decision making

At any decision point: Would like a *rule* that takes as *input* all available information on the patient to that point and *outputs* a *recommended treatment action* from among the feasible *options*.
Informing clinical decision making

**Simplest rules:** Take as input no or minimal patient information
- E.g., acute leukemia
- *Decision 1:* Give $C_1$
- *Decision 2:* If response, give $M_2$, if nonresponse, give $S_1$

**Individualized rules:** More *complex rules* incorporating patient information
- “*Tailoring variables*”
Example of individualized rules: Acute leukemia

- **Decision 1:**
  
  If age $< 50$ years and WBC $< 10.0 \times 10^3/\mu l$, give chemotherapy $C_2$, otherwise, give $C_1$

- **Decision 2:**
  
  If patient responded and baseline WBC $< 11.2$, current WBC $< 10.5$, no grade 3+ hematologic adverse event, current ECOG Performance Status $\leq 2$, give maintenance $M_1$, otherwise, give $M_2$; otherwise
  
  If patient did not respond and age $> 60$, current WBC $< 11.0$, ECOG $\geq 2$ give $S_1$, otherwise, give $S_2$
Treatment regime: Aka *adaptive treatment strategy/intervention*

- A *set of decision rules*, each corresponding to a *decision point*
- Can be *simple* or *individualized/highly tailored*
- Defines an *algorithm* for making treatment decisions for an individual patient

**Precision medicine:**

- Development of *individualized treatment regimes* based on *data*
  formalizes selection of treatment based on a patient’s characteristics
Single decision regimes

**Assume:** There is an *outcome* of interest, e.g., survival time, achievement score

- *Large* outcomes are *good*
- $X = \text{all available information}$ on the patient
- Set of *treatment options*, e.g., $\{C_1, C_2\} = \{0, 1\}$

**Treatment regime $d$:** Comprises a *rule* $d_1(X)$ such that

$$d_1(X) = 0 \text{ or } 1 \text{ depending on } X$$

- Regime $d = \{d_1\}$
- Can be generalized to $> 2$ treatment options
Treatment regime

\[ d_1(X) = 0 \text{ or } 1 \text{ depending on } X \]

**Classical treatment comparison:** Acute leukemia *Decision 1*

- *Two regimes* of interest: “Give C₁” vs. “Give C₂”

  \[ d_1(X) = 0 \text{ for all } X \text{ vs. } d_1(X) = 1 \text{ for all } X \]

- *Class* of regimes of interest is \( \mathcal{D} = \{ \text{“Give C₁” , “Give C₂”} \} \)

- *Usual question*: If all patients in the population were to be given C₁, would mean outcome (mean survival time) be different from (better than) that if all were to be given C₂?

- *Rephrased*: What is the “best” or optimal regime in \( \mathcal{D} \) achieving the largest mean outcome?
Treatment regime

\[ d_1(X) = 0 \text{ or } 1 \text{ depending on } X \]

Example individualized regimes: \( X = \{ \text{age, WBC, ECOG, AE, ...} \} \)

- Rule involving cut-offs or thresholds

\[
\begin{align*}
d_1(X) &= 1 (C_2) \text{ if age} < 50 \text{ and WBC} < 10 \\
&= 0 (C_1) \text{ otherwise}
\end{align*}
\]

written \textit{mathematically} as

\[
d_1(X) = \mathcal{I}(\text{age} < 50 \text{ and WBC} < 10)
\]

- Rule involving linear combinations

\[
d_1(X) = \mathcal{I}\{\text{age} + 8.7 \log(\text{WBC}) - 60 > 0\}
\]
Defining an optimal regime

Clearly: An *infinite number* of rules $d_1$ and thus regimes $d$ is possible

- The *class* of all possible regimes $\mathcal{D}$ is *infinite*
- Can we find the “*best*” regime in $\mathcal{D}$?
- I.e., an *optimal regime* $d^{\text{opt}}$ among all possible $d$?
- What do we mean by *optimal*?

Optimal decision at the time a patient presents:

- *Everything* the clinician knows about a patient is contained in $X$
- *Intuitively:* For a patient with a *particular set of information* $X$, the *optimal* decision is to give the treatment makes the *expected/predicted outcome* for such a patient *as large as possible*
Defining an optimal regime

Can we formalize this?

• I.e., give a precise definition of an optimal regime $d^{opt}$
• Possible through a formal *statistical causal inference framework* based on *potential outcomes*
• And suggests how to *estimate* an optimal regime from *data*
Causal inference framework

**Potential outcomes:** For a patient with information $X$ define

- $Y^*(1)$ is the outcome a patient *would have* under treatment 1
- $Y^*(0)$ *similarly*

- For any regime $d$ characterized by rule $d_1$, the outcome a patient *would have* if treatment were chosen using $d$ is

$$Y^*(d) = Y^*(1) \mathbb{I}\{d_1(X) = 1\} + Y^*(0) \mathbb{I}\{d_1(X) = 0\}$$

- For any regime $d$, $E\{Y^*(d)\}$ is the *expected (average) outcome* across the entire population if all patients *were to follow* $d$
- $d^{opt}$ is defined as the regime making $E\{Y^*(d)\}$ *as large as possible*; i.e.,

$$E\{Y^*(d^{opt})\} \geq E\{Y^*(d)\} \quad \text{for all } d \in \mathcal{D}$$
Causal inference framework

Classical treatment comparison: “Give C₁” vs. “Give C₂”

- “Give C₁” ⇒ \( d_1(X) = 0 \) for all \( X \)
  \[
  Y^*(d') = Y^*(0), \quad E\{ Y^*(d') \} = E\{ Y^*(0) \}
  \]

- “Give C₂” ⇒ \( d_1(X) = 1 \) for all \( X \)
  \[
  Y^*(d') = Y^*(1), \quad E\{ Y^*(d') \} = E\{ Y^*(1) \}
  \]

- \( d^{opt} : E\{ Y^*(0) \} \geq E\{ Y^*(1) \} \) or \( E\{ Y^*(1) \} \geq E\{ Y^*(0) \} \)?
Estimating an optimal regime

More generally: Can we estimate $d^{opt}$ satisfying this definition based on data?

- I.e., estimate rule $d^{opt}_1(X)$ characterizing $d^{opt}$
- Evidence-based

Data: $(X, A, Y)$ from $n$ patients

- $X =$ recorded baseline characteristics
- $A =$ treatment option actually received
- $Y =$ outcome actually observed under treatment $A$
- $Y = Y^*(A)$
Estimating an optimal regime

Data sources:

- A conventional *randomized clinical trial* comparing treatment options 0 and 1
- An *observational point exposure study* of treatments 0 and 1 satisfying the assumption of *no unmeasured confounders*
- I.e., all characteristics used by clinicians/patients to make treatment decisions are *captured in* $X$

$$Y^*(0), Y^*(1) \perp A|X$$
Estimating an optimal regime

**Under these conditions:** Can show for any regime \( d = \{d_1\} \)

\[
E\{Y^*(d)\} = E_X \left[ E(Y|X, A = 1) \mathbb{I}\{d_1(X) = 1\} + E(Y|X, A = 0) \mathbb{I}\{d_1(X) = 0\} \right]
\]

- \( E(Y|X, A = 1) \) is the *expected/predicted observed outcome* for a patient with characteristics \( X \) who receives treatment \( A = 1 \)
- \( E(Y|X, A = 0) \) *similarly*

**Optimal regime** \( d^{opt} \) has rule:

\[
d^{opt}_1(X) =
\begin{cases} 
0 & \text{if } E(Y|X, A = 1) \leq E(Y|X, A = 0) \\
1 & \text{if } E(Y|X, A = 1) > E(Y|X, A = 0)
\end{cases}
\]

- Chooses the option that makes *expected/predicted outcome* for a patient with characteristics \( X \) *as large as possible*
Estimating an optimal regime

\[ d_{1}^{opt}(X) = \begin{cases} 
0 & \text{if } E(Y|X, A = 1) \leq E(Y|X, A = 0) \\
1 & \text{if } E(Y|X, A = 1) > E(Y|X, A = 0) 
\end{cases} \]

- \( E(Y|X, A) \) is the *regression* of observed outcome on characteristics and treatment option received

**Suggests:** Develop a *regression model* and *fit* to the data

- E.g., if \( X^{(1)}, X^{(2)} \) are functions of \( X \), a *linear regression* model (need *not* be linear)

\[
E(Y|X, A) = \alpha_0 + \alpha_1^TX^{(1)} + A(\beta_0 + \beta_1^TX^{(2)})
\]

- Or a *logistic regression* model

\[
\text{logit}\{ E(Y|X, A) \} = \alpha_0 + \alpha_1^TX^{(1)} + A(\beta_0 + \beta_1^TX^{(2)})
\]
Estimating an optimal regime

\[ d_{1}^{opt}(X) = \begin{cases} 
0 & \text{if } E(Y|X, A = 1) \leq E(Y|X, A = 0) \\
1 & \text{if } E(Y|X, A = 1) > E(Y|X, A = 0) 
\end{cases} \]

Models imply: Form of rules (algebra)

\[ d_{1}^{opt}(X) = \begin{cases} 
0 & \text{if } \beta_0 + \beta_1 T X^{(2)} \leq 0 \\
1 & \text{if } \beta_0 + \beta_1 T X^{(2)} > 0 
\end{cases} \]

Estimated optimal rule: Substitute \textit{estimates} for \( \beta_0, \beta_1 \)

\[ \hat{d}_{1}^{opt}(X) = I( \hat{\beta}_0 + \hat{\beta}_1 T X^{(2)} > 0 ) \]

Fancier models: The same idea applies to more flexible models, such as those from \textit{machine learning}
Estimating an optimal regime

Other approaches:

- Restrict attention to a class of regimes with rules of a particular form $d_1(X; \eta_1)$, e.g., acute leukemia
  
  $$d_1(X; \eta_1) = I(\text{age} < \eta_{11} \text{ and } \text{WBC} < \eta_{12}), \quad \eta_1 = (\eta_{11}, \eta_{12})$$

  and maximize an estimator for $E\{Y^*(d)\}$ directly in $\eta$

- Can choose the restricted class of regimes for interpretability, ease of implementation, etc

- Can recast this as a classification problem and use established machine learning methods to determine the form of the rule (e.g., SVM, CART)

- Estimated optimal rule is a “black box”

- Can be considered a form of artificial intelligence
Evidence-based decision support

**Result:** From any of these approaches

- An estimated *evidence-based optimal regime* based on *formal statistical principles* that can be used to inform selection of treatment
- Provides *evidence-based decision support*
- Insight on *key characteristics (tailoring variables)* that should be incorporated in decision making
Example: Acute leukemia

Two decision points:

- **Decision 1**: Induction chemotherapy (2 options: $C_1$, $C_2$)
- **Decision 2**:
  - Maintenance treatment for patients who *respond* (2 options: $M_1$, $M_2$)
  - Salvage chemotherapy for those who *don’t respond* (2 options: $S_1$, $S_2$)
Multiple decisions

Two decisions (leukemia example):

- **Decision 1:** $X_1 =$ information available at baseline, set of treatment options, e.g., $\{C_1, C_2\}$
- **Decision 2:** $X_2 =$ additional information collected between Decisions 1 and 2, treatment options, e.g., $\{M_1, M_2, S_1, S_2\}$
- $X_2$ includes responder status

Regime: A set of rules $d = \{d_1, d_2\}$

- $d_1(X_1)$ dictates treatment at Decision 1 given information available at that point, $X_1$
- $a_1$ is treatment determined by $X_1$ at Decision 1, i.e., $d_1(X_1)$
- $d_2(X_1, a_1, X_2)$ dictates treatment at Decision 2 given all accrued information at that point, $(X_1, a_1, X_2)$
Optimal multiple decision regime

Optimal regime $d^{opt}$: *Intuitively*, should satisfy

- If a patient with *baseline characteristics* $X_1$ were to receive treatment *at all decisions* according to the rules in

$$d^{opt} = \{d_1^{opt}, d_2^{opt}\},$$

his/her *expected/predicted outcome* is *as large as possible*
Optimal multiple decision regime

**Defined in terms of potential outcomes:** For options $a_1$ and $a_2$ at Decisions 1 and 2

- $X_2^*(a_1)$ is the *potential information* accruing on a patient following $a_1$ at Decision 1
- $Y^*(a_1, a_2)$ is the outcome a patient *would have* following $a_1$ at Decision 1 and $a_2$ at Decision 2
- If a patient were to *follow* the rules in regime $d$
  - Treatment at Decision 1 is *determined by* $X_1$, $a_1 = d_1(X_1)$
  - Treatment at Decision 2 is *determined by* $X_1$ and $X_2^*(a_1)$, $a_2 = d_2\{X_1, a_1, X_2^*(a_1)\}$
- $Y^*(d)$ is the outcome a patient *would have* if treatments $a_1$ and $a_2$ at Decisions 1 and 2 were chosen using $d$

**Optimal regime:** $d^{opt}$ makes $E\{Y^*(d)\}$ *as large as possible*
Can we estimate $d^{opt}$ from data?

- Can we use data and regression modeling at each decision point as before?
- I.e., consider each decision separately and use data from separate studies comparing the options at each?
- Not quite…
Complications for multiple decisions

**Delayed effects:** For example

- $C_1$ may not appear best initially in terms of response but may have enhanced effectiveness over the *long term* for survival when followed by $M_1$
- *Result* – Must use data from a *single study* (same patients) reflecting the *entire sequence of decisions*

**Required data:** $(X_1, A_1, X_2, A_2, Y)$ recorded from $n$ patients

- $A_1 =$ treatment *actually received* at Decision 1
  - $A_2 =$ treatment *actually received* at Decision 2
- $X_2 =$ *intervening information* *actually observed*
- $Y =$ outcome *actually observed*
- $Y = Y^*(A_1, A_2)$
Data sources

Longitudinal observational study:

- Records baseline, intervening information and treatments actually received
- **Challenge:** All characteristics used by clinicians/patients to select treatment options *at all decisions* must be *captured in* $X_1, X_2$
- Must satisfy a *no unmeasured confounders* assumption at *every* decision point

Clinical trial?
SMART: Sequential, Multiple Assignment, Randomized Trial

- Randomize subjects at each decision point
- Record treatments $A_1$ and $A_2$ received
- Collect not only baseline information $X_1$ but intervening information $X_2$

Advantages:

- Allows evaluation of simple regimes (treatment sequences)
- Yields rich data for estimation of an optimal treatment regime

Pioneered by Susan Murphy, Phil Lavori, Ree Dawson, and others
Acute Leukemia: Randomization at \( \bullet \)s
Two decision points:

- **Decision 1**: Initial intervention
  (2 options: medication, behavioral therapy)

- **Decision 2**:  
  - Continue initial intervention for children who *respond*  
    (1 option: continue)  
  - Modify initial intervention for those who *don’t respond*  
    (2 options: increase dose/intensify, add second intervention)
Children with ADHD: Randomization at decision points

1. **ADHD**
   - Medication
     - Response → Continue Medication
     - No Response → Increase Medication Dose → Add Behavioral Therapy
2. Behavioral Therapy
   - Response → Continue Behavioral Therapy
   - No Response → Intensify Behavioral Therapy → Add Medication
Embedded regimes in a SMART

**Leukemia SMART:** *Embeds* 8 simple regimes/sequences

1. Give $C_1$ followed by $M_1$ if response, else $S_1$ if nonresponse
2. Give $C_1$ followed by $M_1$ if response, else $S_2$ if nonresponse
   :
7. Give $C_2$ followed by $M_2$ if response, else $S_1$ if nonresponse
8. Give $C_2$ followed by $M_2$ if response, else $S_2$ if nonresponse
Embedded regimes in a SMART

**ADHD SMART:** Similarly embeds 4 simple regimes/sequences

1. *Medication followed by increased dose if nonresponse, else continue*

2. *Medication followed by added behavioral therapy if nonresponse, else continue*

3. *Behavioral therapy followed by intensified behavioral therapy if nonresponse, else continue*

4. *Behavioral therapy followed by added medication if nonresponse, else continue*

- In a SMART, *randomization* guarantees there will be subjects whose *actual treatments received* are *consistent with* following *all* of the embedded regimes
- Allows evaluation and comparison of *treatment sequences* (including identifying the “*best*”)
Embedded regimes in a SMART

Estimation of mean outcome: If all patients in the population received treatment according to an embedded regime

- Leukemia SMART: A subject whose realized experience is

\[ C_1 \Rightarrow \text{Response} \Rightarrow M_1 \]

is consistent with having followed EITHER OF

1. Give \( C_1 \) followed by \( M_1 \) if response, else \( S_1 \) if nonresponse
2. Give \( C_1 \) followed by \( M_1 \) if response, else \( S_2 \) if nonresponse

- Based on all subjects with experience consistent with each regime

- Estimated optimal embedded regime: That with largest estimated mean outcome
Estimating an individualized optimal regime

Data sources, again:

- **SMART:** Collection of *extensive, detailed information* at *baseline* and *intermediate* to Decisions 1 and 2 supports estimation of an *optimal regime*
- **Longitudinal observational study:** Depends on quality of information available

**Estimating** $d^{opt}$: $d^{opt} = \{ d_1^{opt}(X_1), d_2^{opt}(X_1, A_1, X_2) \}$

- Start at the *final decision* and work *backward*
- *Backward induction*
Sequential regression (Q-learning)

**Decision 2:** Given the patient’s *accrued history to this point*, determine the *optimal rule* to be used *now*

- Decision 2 options coded \{0, 1\}; can show

\[
d_{2}^{\text{opt}}(X_1, A_1, X_2)
\]

\[
= 0 \text{ if } E(Y|X_1, A_1, X_2, A_2 = 1) \leq E(Y|X_1, A_1, X_2, A_2 = 0)
\]

\[
= 1 \text{ if } E(Y|X_1, A_1, X_2, A_2 = 1) > E(Y|X_1, A_1, X_2, A_2 = 0)
\]

- \(E(Y|X_1, A_1, X_2, A_2)\) is the *regression* of outcome on both treatments and all accrued characteristics

- Can develop and fit a *regression model* and *estimate* \(d_{2}^{\text{opt}}(X_1, A_1, X_2)\) as before
**Decision 1:** Trickier

- Decision 1 options coded \{0, 1\}
- Must take into account that the *optimal rule* at Decision 2 will be followed *in the future*
- I.e., \(d_{1}^{\text{opt}}(X_1)\) must select treatment at Decision 1 to make the *expected/predicted outcome* as large as possible *acknowledging that* \(d_{2}^{\text{opt}}(X_1, A_1, X_2)\) will be used to determine treatment at Decision 2
- Best explained by *illustration*
Sequential regression (Q-learning)

Illustration:

- Develop a regression model for Decision 2, e.g.,

\[
E(Y|X_1, A_1, X_2, A_2) = \alpha_{20} + \alpha_{21}^T X_1^{(1)} + \alpha_{22}^T X_2^{(1)} + \alpha_{23}^T X_1^{(1)} A_1 \\
+ A_2(\beta_{20} + \beta_{21}^T X_2^{(2)} + \beta_{22} A_1),
\]

fit to the data \((X_1, A_1, X_2, A_2, Y)\) from \(n\) subjects, and estimate

\[
\hat{d}_{2}^{opt}(X_1, A_1, X_2) = I(\hat{\beta}_{20} + \hat{\beta}_{21}^T X_2^{(2)} + \hat{\beta}_{22} A_1 > 0)
\]

- For each subject, obtain

\[
\tilde{A}_2 = \hat{d}_{2}^{opt}(X_1, A_1, X_2),
\]

the estimated optimal treatment option at Decision 2 (may or may not be the same) as \(A_2\) actually received by the subject.)
Sequential regression (Q-learning)

Illustration:

- For each subject, form $\tilde{Y}$, the estimated predicted outcome s/he would have if the optimal option $\tilde{A}_2$ were received at Decision 2:

$$
\tilde{Y} = \hat{\alpha}_{20} + \hat{\alpha}_{21}^T X_1^{(1)} + \hat{\alpha}_{22}^T X_2^{(1)} + \hat{\alpha}_{23}^T X_1^{(2)} A_1
+ \tilde{A}_2(\hat{\beta}_{20} + \hat{\beta}_{21}^T X_2^{(2)} + \hat{\beta}_{22} A_1)
$$

- Develop a regression model for Decision 1 with $\tilde{Y}$ as the “outcome,” e.g.,

$$
E(\tilde{Y}|X_1, A_1) = \alpha_{10} + \alpha_{11}^T X_1^{(1)} + A_1(\beta_{10} + \beta_{11}^T X_1^{(2)}),
$$

fit to the “data” $(X_1, A_1, \tilde{Y})$ from $n$ subjects, and estimate

$$
\hat{\alpha}_{1}^{opt}(X_1) = \mathcal{I}(\hat{\beta}_{10} + \hat{\beta}_{11}^T X_1^{(2)} > 0)
$$

- Fancier models are possible (e.g., flexible machine learning)
Estimating an optimal regime

Other approaches:

- Restrict attention to a class of regimes with rules of a particular form \( d_1(X_1; \eta_1) \) and \( d_2(X_1, A_1, X_2; \eta_2) \) and maximize an estimator for \( E\{Y^*(d)\} \) directly in \( \eta \).

- Can choose the restricted class of regimes for interpretability, ease of implementation, etc.

- Can recast estimation at each decision as a classification problem and use established machine learning methods to determine the form of the rules at each decision (e.g., SVM, CART).

- Estimated optimal rules are “black boxes.”

- Can be considered a form of artificial intelligence.
Evidence-based decision support

**Result:** From any of these approaches

- An *evidence-based regime* based on *formal statistical principles* that can be used to inform selection of treatment at each decision point
- Provides *evidence-based decision support*
- Insight on *key characteristics* (*tailoring variables*) that should be incorporated at each decision point
Optimizing behavioral cancer pain intervention

How best to use behavioral interventions to manage cancer patients’ pain?

- *Pain Coping Skills Training* (PCST) – can be *brief* (1 session) or *full* (5 sessions); which is better?
- Further intervention for *responders*? Maintain or intensify for *nonresponders*?
- *Ideally*: Use more *time- and resource-intensive interventions* only for those who need them
- What is the best *intervention sequence*?
- *Optimal intervention regime*?
Optimizing behavioral cancer pain intervention

R01 CA202779, PI: Tamara Somers, Duke University Psychiatry and Behavioral Sciences
Eight embedded regimes: First four *intervention sequences*

1. Start with PCST-Full, PCST-Plus (*augment*) if nonresponse, PCST-Full maintenance (*continue*) if response

2. Start with PCST-Full, PCST-Plus (*augment*) if nonresponse, nothing further if response

3. Start with PCST-Full, PCST-Full maintenance (*continue*) if nonresponse, PCST- Full maintenance (*continue*) if response

4. Start with PCST-Brief, PCST-Brief maintenance (*continue*) if nonresponse, nothing further if response
Design and analysis: Powered for *primary analysis* \( n = 327 \)

- *Primary analysis*: PCST-Full vs. PCST-Brief based on % reduction in pain from baseline to end of Stage 1
- *Response criterion*: \( \geq 30\% \) reduction in pain
- *Secondary analyses*: Based on % reduction in pain from baseline to end of Stage 2 and at 6-month follow-up
  - Compare *most and least intensive sequences*
  - Compare *8 embedded sequences* (correction for multiple comparisons) and find “*best*”

- *Exploratory analyses*: Estimation of an *optimal regime*
  - Identify key *patient characteristics*
Parent messaging and student attendance

How to intervene with parents to encourage school attendance in children at high risk for chronic absenteeism?

American Institutes for Research, funded by Institute for Education Sciences, US Dept of Education
I-SPY 2.2 platform trial in breast cancer

How to treat women with locally advanced breast cancer who do not respond to initial therapy?

- **I-SPY 2**: Adaptive phase II platform trial, *collaborative effort* of NCI, FDA, industry (FINH Biomarkers Consortium)
- **Adaptive randomization**: Assign as many participants as possible to better options based on data from previous participants
- **I-SPY 2+**: Incorporate *SMART* with repeated randomization of nonresponders
I-SPY 2.2 platform trial in breast cancer

P01 CA210961, PI: Laura Esserman, UCSF
1. *Science* is paramount
   - Decision points, treatment options, response criteria, . . . should be based on *science*, not “*I wanna do a SMART*”
   - E.g., treatment sequences should occur *naturally in practice*

2. *Sample size* based on *simple comparisons*
   - Decision 1 treatments
   - *Non-overlapping* embedded sequences

3. Keep it *simple*
   - *Small number* of *key decision points*
   - *Small number* of *treatment options* at each
   - Straightforward *response criteria*
• Thinking in terms of *sequential treatment decisions* is *gaining popularity*

• SMARTs and estimation of optimal treatment regimes are *becoming more common*

• But statistical methods research is *way ahead* of what is actually being done in practice

• **Goal:** Broaden acceptance of thinking sequentially and of conducting SMARTs and analyses evaluating treatment regimes
Issues

- Flexibility versus interpretability? Machine learning approaches lead to “black boxes” but interpretability may sacrifice performance.
- What if more than one outcome is of interest? E.g., balancing efficacy and toxicity in cancer treatment?
- Design principles (e.g., sample size, primary analysis) for SMARTs? How to do adaptive randomization in a SMART? How to do interim analysis of a SMART?
- Assessment of uncertainty (e.g., standard errors)?
- Once an optimal regime is estimated, should it be compared to standard of care in a conventional clinical trial?
Dynamic Treatment Regimes
Statistical Methods for Precision Medicine

Anastasios A. Tsiatis
Marie Davidian
Shannon T. Holloway
Eric B. Laber
Thought leaders

Susan Murphy and Jamie Robins
More on the SMARTs

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5681223/

**Parent messaging and student attendance:**