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/disorder process
- Multiple treatment options at each decision point
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: $S_1$, $S_2$)
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

Common themes:

- *Sequence* of *key decision points*
- *Initial* treatment (e.g., at time of *presentation* or *diagnosis*)
- Treatment options at *subsequent* decision points depend on *response* to previous intervention/treatment(s)
Precision medicine

Patent heterogeneity:

- Genetic/genomic profiles
- Demographic characteristics
- Physiological characteristics
- Medical history, concomitant conditions
- Environment, lifestyle factors
- Adverse reactions, adherence to prior treatment
- ...

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

What is the “best” treatment sequence?

- Akin to conventional population inference

How can the clinician make the “best” decisions based on a patient’s characteristics?

- So as to achieve the most beneficial expected outcome
- Precision medicine
Treatment sequences

**Children with ADHD:** *Four* possible sequences

1. *Medication*; if no response then *intensify* dose, else *continue* medication
2. *Medication*; if no response then *augment* with behavioral therapy, else *continue* medication
3. *Behavioral therapy*; if no response then *intensify* therapy, else *continue* behavioral therapy
4. *Behavioral therapy*; if no response then *augment* with medication, else *continue* behavioral therapy

“**Best**” sequence: That leading to the *largest mean achievement score* if *all* children in the ADHD population were to follow this sequence
(Dynamic) treatment regime: A set of *sequential decision rules*

- Each rule corresponds to a *decision point*
- Each rule maps a *patient’s history* to the set of feasible *treatment options* given that history

“Best” (optimal) treatment regime: The set of rules leading to the *largest mean achievement score* if *all* children in the ADHD population were to follow these rules
**SMART**

**SMART:** Sequential, Multiple Assignment, Randomized Trial

- *Randomize* subjects to *feasible* options at *key decision points* where there is *equipoise*
- Collect not only *baseline* characteristics but additional *intervening* characteristics evolving between decision points

**Motivation and advantages:**

- Mimics *clinical practice*
- Allows evaluation and comparison of the *embedded treatment sequences*
- Yields rich data for estimation of *optimal treatment regimes*
Example: Acute Leukemia

Randomization at •s

Diagram:

- Acute Leukemia
  - C1
    - Response
      - M1
      - M2
    - No Response
      - S1
      - S2
  - C2
    - Response
      - M1
      - M2
    - No Response
      - S1
      - S2
Example: Children with ADHD

Randomization at •'s

- **ADHD**
  - Medication
    - Response
      - Continue Medication
    - No Response
      - Increase Medication Dose
      - Add Behavioral Therapy

- Behavioral Therapy
  - Response
    - Continue Behavioral Therapy
  - No Response
    - Intensify Behavioral Therapy
    - Add Medication
SMARTs in practice

Recent surge of interest:

- Recognition of treatment as sequential decision-making
- NIH RFAs
- Still much confusion among investigators and reviewers

SMART design principles:

- Open problem
- Base sample size on simple comparisons; e.g., comparison of initial treatments or of embedded sequences
- Comparison of overlapping embedded sequences requires specialized methods
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)
- Further intervention for *responders*? Maintain or intensify for *nonresponders*?
- **Ideally**: Use more *time- and resource-intensive interventions* only for those who need them
Optimizing behavioral cancer pain intervention

Figure 1. Trial Design with Focus on Randomization Pattern. (Figure 2 includes full assessment scheme.)

Cancer Patient with Average Pain Score ≥ 5

Randomize

PCST – Full (5 sessions)

NO

Randomize

Response ≥ 30% Pain Reduction

PCST-Plus (2 sessions)

PCST-Full Maintenance (5 weekly calls)

NO

PCST-Full Maintenance (5 weekly calls)

No further intervention

YES

Randomize

Response ≥ 30% Pain Reduction Assessed

PCST-Full (5 sessions)

YES

Randomize

Response ≥ 30% Pain Reduction

PCST-Full Maintenance for PCST-Brief (5 weekly calls)

Maintenance for PCST-Brief (5 weekly calls)

NO

Randomize

No further intervention

PCST-Brief (1 session of Relaxation/Impagery)
Eight embedded sequences: First four

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-Full; PCST-Full 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)
- **Exploratory analyses:** Estimation of an optimal regime
  - Identify key *patient characteristics*
Parental messaging to improve school attendance

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

- Two text messaging interventions aimed at parents
- In addition to “business as usual” at school (control)
- Further intervention for nonresponders? Augment or intensify?
Parental messaging to improve school attendance

High risk for absenteeism

Messaging I
- Response: Continue current intervention
- Non-Response: Augment

Messaging II
- Response: Continue current intervention
- Non-Response: Augment

"Business as usual"

ED-IES-16-R-0010: PI: Anja Kurki, American Institutes for Research/US Dept of Education Institute of Education Sciences
Four embedded sequences: Plus control

- Fall semester use Messaging I; Spring semester augment if nonresponse, continue if response
- Fall semester use Messaging I; Spring semester intensify if nonresponse, continue if response
- Fall semester use Messaging II; Spring semester augment if nonresponse, continue if response
- Fall semester use Messaging II; Spring semester intensify if nonresponse, continue if response
Parental messaging to improve school attendance

**Design and analysis:** Trial powered for *primary analysis*

- Parents/families randomized *within schools* – 60 schools, 430 consenting families/school

- **Primary analysis:** Messaging I vs. Messaging II vs. control (correction for multiple comparisons) based on binary *chronic absenteeism* during Fall (miss > 10% instructional time)

- **Response criterion:** Miss ≤ 10% instructional time in Fall

- **Secondary analyses:** Compare *embedded sequences* (correction for multiple comparisons)
  - Based on binary *chronic absenteeism* at end of Spring
  - Based on continuous *achievement scores* at end of Spring
  - Is it better to *augment* or *intensify*?

- **Exploratory analyses:** Estimation of an *optimal regime*
  - Identify key *school and family characteristics*
How best to intervene to encourage adolescent MSMs to practice safe sex?

- Target those who are not responsive to a standard intervention
- Ideally: Use more time- and resource-intensive interventions only for those who need them
- Similar design considerations
Behavioral interventions to prevent HIV

**SMARTs in Practice**

U01 MD011281, PI: Brian Mustanski, Northwestern University Medical Social Sciences, Psychiatry and Behavioral Sciences
How to treat women with locally advanced breast cancer who do not respond to initial therapy?

- **ISPY-2**: Adaptive phase II trial, *collaborative effort* of NCI, FDA, industry (FINH Biomarkers Consortium)
- **ISPY-2+**: Incorporate *SMART* with randomization of *nonresponders* (NCI P01 Program Project; PI, Laura Esserman, UCSF)
- Design *underway* involves *two* randomizations of nonresponders
Some lessons we’ve learned

**Lesson 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*

**Lesson 2:** *Sample size* based on *simple comparisons familiar* to reviewers
- Decision 1 treatments
- *Non-overlapping* embedded sequences

**Lesson 3:** Keep it *simple*
- *Small number* of *key decision points*
- *Small number* of *treatment options* at each
- Straightforward *response criteria*
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http://impact.unc.edu

- Statistical methods for *precision cancer medicine*
Some references


https://methodology.psu.edu/ra/adap-inter