

SMART INNOVATIVE TRIAL DESIGN TO SUPPORT RESEARCH IN PRECISION RESUSCITATION MEDICINE

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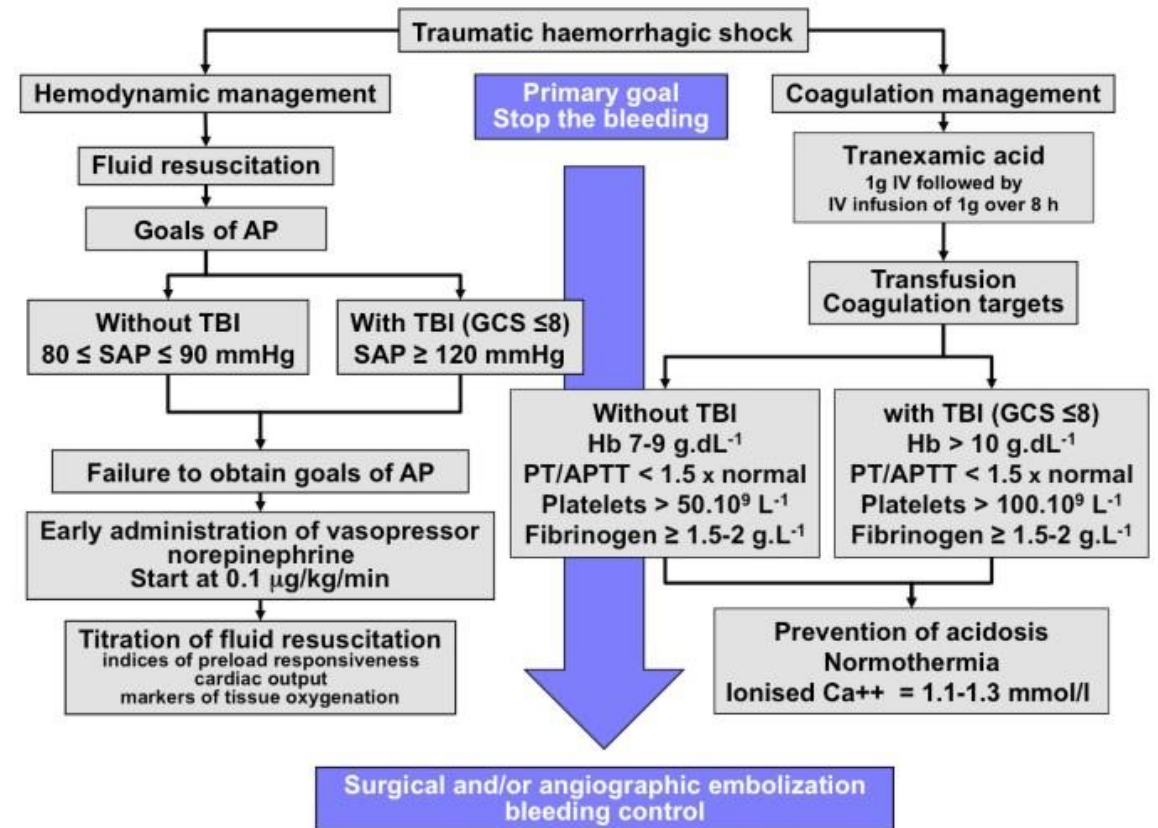
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RESUSCITATION PRACTICE VS. EVIDENCE

- Treatment of shock is a **complex process across multiple critical decision points**
- **Multiple interventions at a time and in a row depending on response to previous treatment and patient characteristics**
- Interventions based on experience, guidelines, clinical trials
 - Most trials test interventions at 1 point in the process
 - This ignore interactions: synergies, antagonisms



<https://annalsofintensivecare.springeropen.com/articles/10.1186/2110-5820-3-1>

NEED EVIDENCE FOR DTRS

- **Dynamic Treatment Regimen**, a.k.a. adaptive intervention, adaptive treatment strategy, stepped care, treatment policies
- Sequence of **individually tailored decision rules** that specify whether, how and/or when to alter the intensity, type, dose or delivery of intervention at critical decision points in the course of care, prevention, implementation, or education
- Guide/Formula for treatment
- Evidence-based
- **Goal: operationalize sequential decision making with the aim of improving clinical practice**



DTR EXAMPLE

*I'm a statistician and this likely a poor description of treatment

- FOR A PATIENT WHO EXHIBITS SIGNS OF SEVERE SHOCK, START BLOOD TRANSFUSION.
- IF INDIVIDUAL REMAINS HYPOTENSIVE, GIVE VASOPRESSOR.
- IF INDIVIDUAL IS NO LONGER HYPOTENSIVE, CONTINUE AND MONITOR FLUID RESUSCITATION WITH OXYGEN SUPPORT.

*****Start with A, If response, get B; if no response, get C.*****

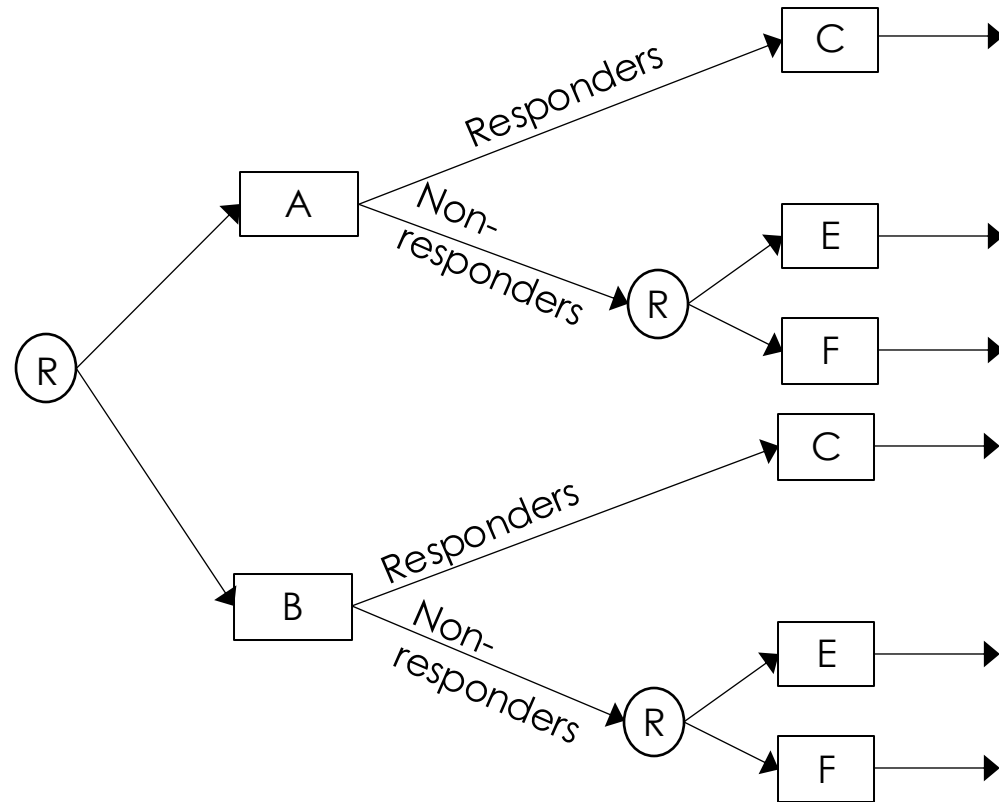
QUESTIONS TO DEVELOP DTR

1. What is the best **first-line** intervention(s)?
2. What is the best **measure of response** to see if the intervention is successful?
3. When is the best **time to measure response** to the initial intervention?
4. What is the best **subsequent** treatment among **non-responders**?
5. What is the best **subsequent** treatment among **responders**?
6. What **characteristics** are associated with treatment strategies for optimal outcome?

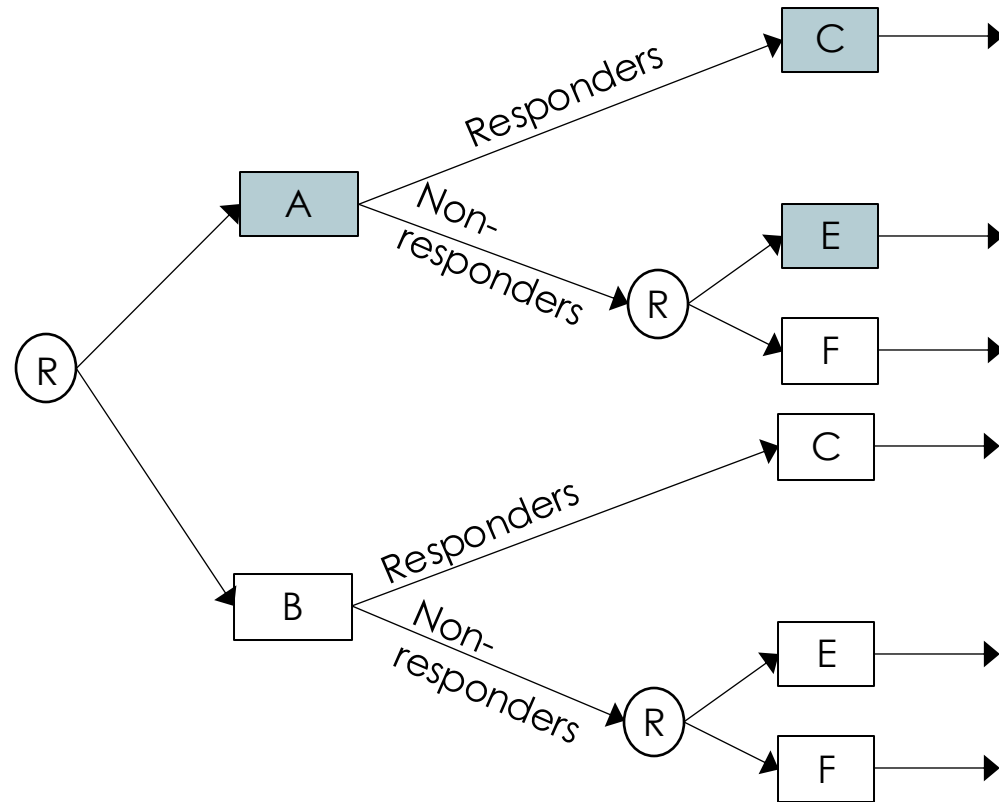
SMART CLINICAL TRIAL DESIGN

- **Sequential, multiple assignment, randomized trial**
- A type of **multi-stage randomized design**
- Trial participants are **randomized** to a set of treatment options at **critical decision points** over the course of treatment
 - Critical decisions occur in short time frame
- **All individuals** participate in all stages of the trial
- Subsequent randomization is based on information leading up to that point
- DTRs embedded in design
- Goal: **Develop/Construct effective DTRs**
- Many have been funded by NIH, PCORI, DoD

SMART DESIGN EXAMPLE 1



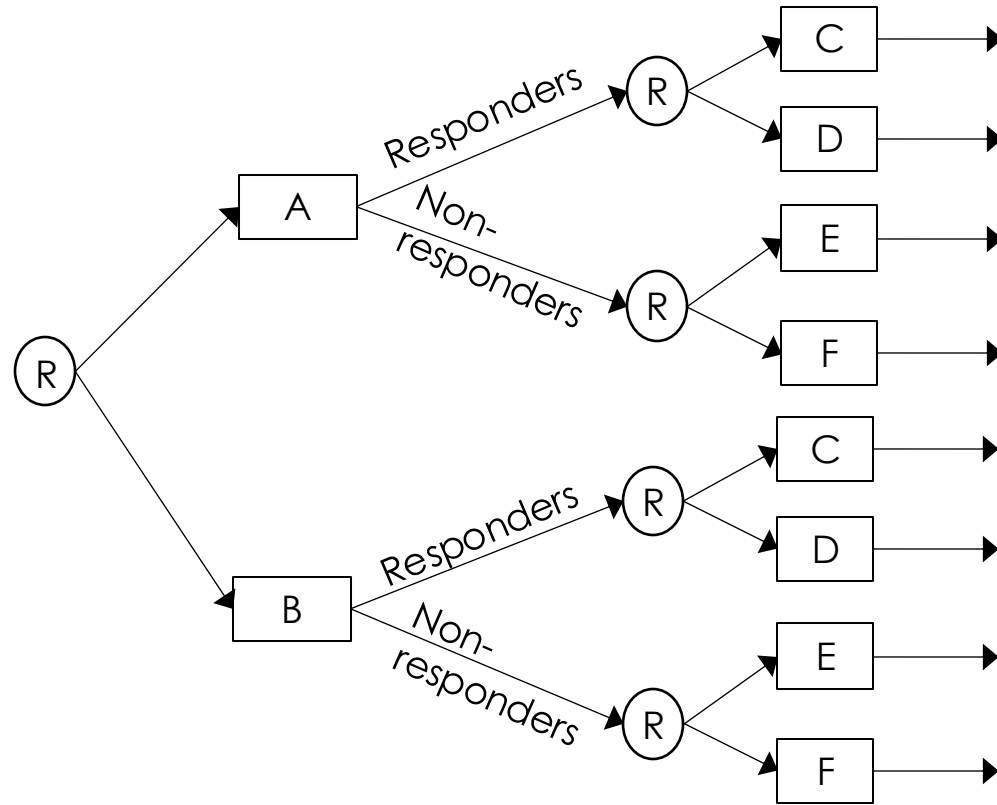
SMART DESIGN EMBEDDED DTRS



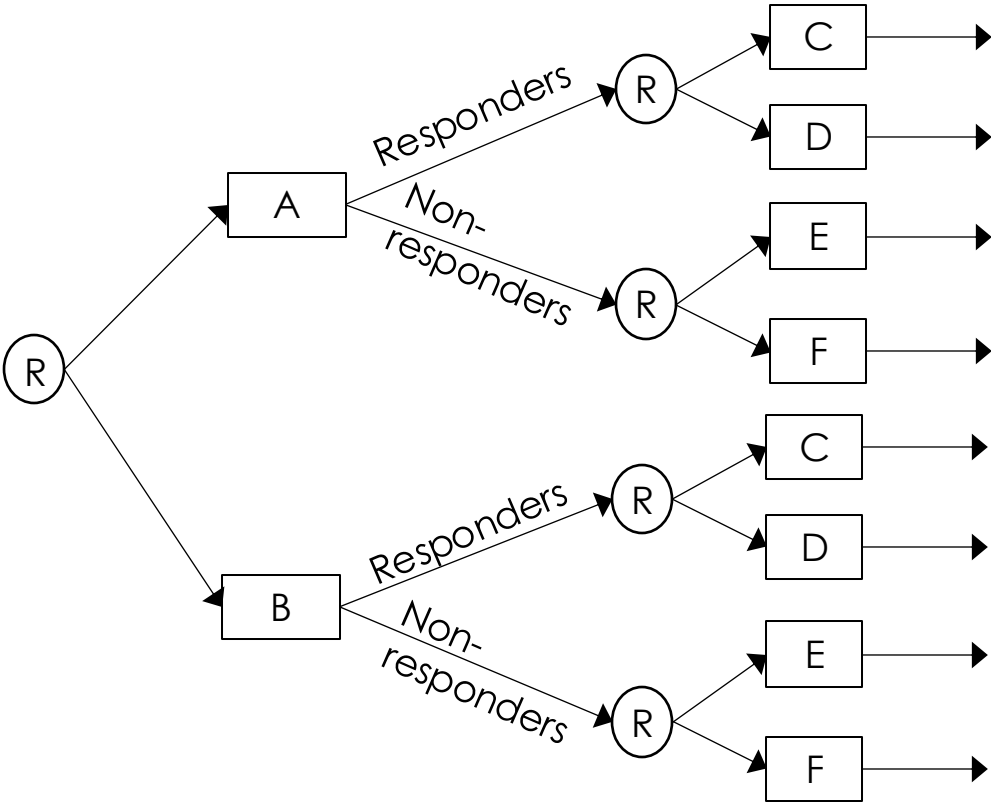
1. **A,C,E**
2. A,C,F

3. B,C,E
4. B,C,F

SMART DESIGN EXAMPLE 2



NUMBER OF DTRS: 8



- 1. A,C,E
- 2. A,C,F
- 3. A,D,E
- 4. A,D,F

- 5. B,C,E
- 6. B,C,F
- 7. B,D,E
- 8. B,D,F

SMART BENEFITS

- **Delayed Effects** – treatment synergies or antagonisms
- **Prescriptive Effects** – initial treatment may elicit symptoms to better match individual to subsequent treatment
- **Sample Selection Effects** – individuals who enroll in, remain in or are adherent in a SMART may be different (more representative) from those in other designs

SMART QUESTIONS OF INTEREST

- **Simultaneously address the effectiveness of treatments at each stage and the effectiveness of embedded DTRs**
- Which sequential treatments work better than standalone treatment?
- Investigate the interplay between treatment strategies and disease development.
- Tailor treatment to response and characteristics
- Identify characteristics associated with optimal outcome
- **Approximate clinical care**

SAMPLE SIZE/POWER & ANALYSIS

- Aims that do not consider DTRs, use standard methods
 - E.g. Two arm comparison as usual
 - May need an estimate of responders/non-responders (subsets) to up weight sample size
- Aims that include DTRs: SMART specific methods
 - Account for restricted randomization, simultaneous estimation of DTR effects
 - Various applets and R packages exist (see <https://d3c.isr.umich.edu/available-software/>)

SUMMARY

- **Dynamic treatment regimens** are evidence-based guidelines for clinical practice
- A **SMART** is a clinical trial design that can provide evidence for effective DTRs
- The **sample size** of a SMART is highly dependent on the primary aim; analytic methods depend on the objective
- **R packages and applets** are available to help in design and analysis for a SMART: (<https://d3c.isr.umich.edu/software/> & other R packages e.g. DTR)

RESOURCES: ARTICLES & TEXTS

- Website
 - <https://d3c.isr.umich.edu/experimental-designs/sequential-multiple-assignment-randomized-trials-smarts/>
- Articles:
 - Kidwell KM, Almirall D. *Sequential, Multiple Assignment, Randomized Trial Designs*. JAMA. 2023;329(4):336–337. doi:10.1001/jama.2022.24324
 - Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SA. A “SMART” design for building individualized treatment sequences. *The Annual Review of Clinical Psychology*, 2012. 8:21-48.
 - Almirall, D., Nahum-Shani, I., Sherwood, N.E., Murphy, S.A. *Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research*. *Translational behavioral Medicine*, 2014. 4(3):260-274.
- Texts:
 - **Adaptive Treatment Strategies in Practice: Planning Trials and Analyzing Data for Personalized Medicine**. Ed. Kosorok & Moodie. 2016. ASA-SIAM.
 - **Dynamic Treatment Regimes: Statistical Methods for Precision Medicine**. Tsiatis, Davidian, Holloway, Laber. 2020. CRC Press.

THANK YOU

Interested in learning more?

<https://smart-workshops.com>

- SMART Workshop, June 13-14– recorded to learn asynchronously
 - <https://smart-workshops.com/smart-design-info>
- Small sample SMART Workshop, Aug 13-14– recorded to learn asynchronously
 - <https://smart-workshops.com/snsmart-design-info>

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