Modern Biostatistical Considerations for Designing Responsible Trials
Responsible Clinical Trials

- Medical research is conducted to propose new treatment or therapies to promote patient well-being
  - Clinical trials are considered a gold-standard method to propose new evidence

- Researchers have an obligation to conduct these trials in a responsible manner
  - Efficient use of Resources
  - Ethical Conduct
  - Scientifically Valid Design
Responsible Clinical Trials

- Efficient use of Resources
  - Research Time
  - Funding
  - Research subjects

- Ethical Conduct
  - Limit exposure to inherent risks of research
  - Hippocratic oath

- Scientifically Valid Design
  - Experiment/Trial can answer stated Research Question
  - Ex: sample size, randomization, sample selection (generalizability)
Biostatistician’s Role in Research

- **MYTH:** Biostatisticians have limited clinical experience and won’t be of any help in study design

- **MYTH:** After a study is designed, it is advisable to get a biostatistician’s approval

- **MYTH:** Once a study is in progress, contact with the biostatistician is unnecessary until study conclusion
Biostatistician’s Role in Research

• FACT: Biostatistician’s are:
  ○ Full-time researchers with experiences in a myriad of situations that can help guide the direction of research
  ○ Accustomed to working with clinicians and researchers and understand the sometimes contradictory nature of responsible research
  ○ Able and willing to be involved while research questions are being formulated to offer advice on research goals
Randomized Controlled Trials

• Phase I
  ○ Safety and toxicity

• Phase II
  ○ Exploratory studies

• Phase III
  ○ Confirmatory evidence
Phase I Studies

Goals for early-phase clinical trials:

- Determine safety and toxicity of proposed drug/treatment
- Establish the Maximum Tolerated Dose (MTD)
  - MTD is defined as dose that keeps dose limiting toxicities (DLT) at or below a desired threshold (20%, 30%, etc.)

Restrictions

- Small sample sizes (often between 10-30)
- Unknown dose-toxicity response curve
- Unknown efficacy at given doses
3+3 Design

- Most commonly used technique for identifying MTD
  - Works for small samples
  - Simple to implement
  - Widely used
  - But...
    - Threshold = 33.3% Only
    - No Guarantees
    - No statistical validity
Continual Reassessment Method (CRM)

- CRM
  - Estimates dose-response curve *directly*
    - Predicts most likely MTD at each step
  - Can update after each patient or use cohorts of 2 or 3 subjects
  - Escalation with Overdose Control (EWOC)
    - Begin with lower threshold
    - Gradually increase
  - More accurate than 3+3
    - And more safe
Continual Reassessment Method (CRM)

Anesthesiology
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**Maximum Tolerated Dose of Nalmefene in Patients Receiving Epidural Fentanyl and Dilute Bupivacaine for Postoperative Analgesia**

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Continual Reassessment Method (CRM)

Table 2. Effect of Each Successively Calculated Nalmefene Dose on the Corresponding Patient’s Postoperative Analgesia

<table>
<thead>
<tr>
<th>Pt (yr)</th>
<th>Sex</th>
<th>Surgery</th>
<th>NAL Dose (µg/kg)</th>
<th>ROA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Thoracic</td>
<td>0.25</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>U abdominal</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Colorectal</td>
<td>0.75</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>U abdominal</td>
<td>0.25</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Thoracic</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Thoracic</td>
<td>0.50</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>Thoracic</td>
<td>0.25</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>Thoracic</td>
<td>0.25</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>Thoracic</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>Thoracic</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>Thoracic</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>Thoracic</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>Thoracic</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>U abdominal</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>U abdominal</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>Thoracic</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>Thoracic</td>
<td>0.75</td>
<td>No</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>Thoracic</td>
<td>0.75</td>
<td>Yes</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>U abdominal</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
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<td>0.50</td>
<td>Yes</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>U abdominal</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>22</td>
<td>F</td>
<td>Thoracic</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>23</td>
<td>M</td>
<td>Thoracic</td>
<td>0.50</td>
<td>Yes</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>Thoracic</td>
<td>0.50</td>
<td>No</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>Thoracic</td>
<td>0.50</td>
<td>No</td>
</tr>
</tbody>
</table>

NAL = nalmefene; Pt = patient number; ROA = reversal of analgesia; U abdominal = upper abdominal.
Continual Reassessment Method (CRM)

Fig. 1. The 95% posterior probability intervals (vertical bars) of reversal of analgesia (ROA) for the four doses of nalmefene based on results from all 25 patients. If the upper (U) and lower (L) probability limits of a given vertical bar are denoted as \( P_U \) and \( P_L \), respectively, and as \( P_{ROA} \) the probability of ROA at the dose corresponding to that bar, then the formal probability statement for each dose is \( \mathbb{P}(P_L < P_{ROA}(\text{dose}) < P_U | \text{final data}) = 0.95 \). In particular, the value \( P_U \) is the 97.5th percentile and \( P_L \) is the 2.5th percentile of the distribution of \( P_{ROA} \) given the final data from the 25 patients. For example, the bar at the 0.05-\( \mu \)g/kg nalmefene dose is the graphical representation of the statement, \( \mathbb{P}(0.073 < P_{ROA}(0.05) < 0.305 | \text{final data}) = 0.95 \). The dot in each interval is the median (fiftieth percentile) \( P_{ROA} \) of that dose.
Say you are in the middle of a clinical trial:

- Should you continue if there is already evidence that one treatment works (or that another doesn’t)?
  - Rather than conduct the whole study, you may wish to stop if you are reasonably sure of the outcome
    - Interim Analyses
    - Early Termination

- Rather than stop the study, maybe you can adjust it to treat patients as ethically as possible while also answering research question
  - Adaptive Allocation
Early Termination

- Three reasons to end a trial early
  - Toxicity
  - Efficacy
  - Futility

- Interim Analysis Approaches for Early Termination
  - Simon’s Two-Stage Design (Simon, *Controlled Clinical Trials*, 1989)
    - Used to stop for futility (no chance of an effect)
    - Often used to stop for efficacy (already an effect)
Early Termination

- Bayesian Approach
  - After each subject is accrued and observed...
    - Estimate probability of treatment efficacy, toxicity or futility
      - e.g. $P(p_T > p_C) = $ probability treatment success rate is greater than control success rate
    - If probability is greater than threshold $\Rightarrow$ stop
      - Thresholds often set to 85%, 90% or 95%
    - If probability is not greater than threshold $\Rightarrow$ continue
  - Repeat until threshold crossed or all subjects accrued
  - Can plan to stop for efficacy, toxicity and/or futility in same trial
Early Termination
Adaptive Allocation

- Standard Clinical Trials allocate at fixed rates
  - Equal Allocation → 1:1 or 50/50
    - Each group has the same number of subjects
  - Unbalanced Allocation → 2:1, 3:1
    - Groups purposely left unbalanced

- What if one treatment is clearly superior (or inferior)
  - Patients could “miss out” or otherwise be harmed
  - What about patients allocated to “losing” treatment after sufficient evidence is attained?
Adaptive Allocation

- Adjusts allocation ratio to account for relative treatment success (or failure)
  - As evidence builds that one treatment is superior, probability that subjects will be assigned to that treatment is increased
    - Update ratio after each new patient is accrued and observed
    - Ratio is tied directly to treatment means and proportions
      - And also treatment variability
  - Benefits:
    - Patients treated as ethically as possible under research conditions
    - Patients are still randomized → statistical validity is maintained
  - May be a power – ethics trade off
    - Power may decrease as adaptation increases (unequal groups)
Adaptive Allocation
Phase III studies

- Many modern clinical trial methodologies exist to help alleviate some of the contradictory requirements of research
  - Early stopping rules
    - Futility
    - Efficacy
  - Adaptive allocation
  - Seamless design
• Traditional design
  ○ Conduct and conclude Phase II prior to Phase III
    -* Phase II and Phase III are separate studies*
    -* Information from Phase II is only incorporated in the design aspect of Phase III*

• Seamless design
  ○ Phase II/III studies are run concurrently
    -* Phase II subjects are used in Phase III analyses*
    -* More efficient use of subjects and resources*
Traditional Design

Phase II

Random

Dose A

Control

Phase III

Random

Dose B

Control

Analysis

Analysis
Seamless Design

Phase II/III

Dose A
Random
Dose B
Control

Analysis

Analysis
Seamless Designs

- Able to incorporate other modern design features
  - Adaptive allocation, early stopping, etc...

- Not limited to Phase II/III
  - Pre-clinical to clinical
  - Phase I/II
Dynamic Treatment Regime (DTR)

- **Study design that mirrors clinical care decision making**
  - Assign to initial treatment regimen
    - If condition improves, patient remains on initial treatment
    - If condition fails to improve, change to secondary treatment option

Initial Treatment

- Patient improves

- Patient remains the same or worsens

Initial Treatment

Secondary Treatment
First, all participants were randomized. Children received either JAE and EMT or JAE, EMT and AAC as the first treatment to improve verbal capacity.

After 12 weeks, children’s vocabulary was reassessed. Those who did not respond to initial treatment of JAE+EMT were re-randomized.

Responsive children continued on the same treatment. Non-responsive children were assigned to either intensified treatment or were assigned to receive AAC in addition to continuing treatment.
RFA=Radiofrequency ablation
AAD=Antiarrhythmic agent
PVC=Premature ventricular contractions
Dynamic Treatment Regimes (DTR)

- **DTR requires:**
  - Longitudinal follow-up, multi-stage
  - At least one secondary or complementary treatments
  - Randomization
    - NOT a crossover trial

- **Recommended if:**
  - Sequence of treatment(s) is important
  - Interest in particular subgroup of subjects
    - Responders/Non-responders
    - Adherence
Summary

- Modern characteristics of trials can be incorporated
  - Increase efficiency
  - Address ethical issues
  - Scientifically validated

- MYTH: Biostatisticians can have a large impact in a small time-frame
  - FACT: For any request, biostatisticians should be given at least 6 weeks following an in-person meeting.
    - Example: Investigator recently requested assistance for a May 2017 LOI deadline. YAY!!!!
Biostatistics Resources at VCU

• MYTH: There is no biostatistics support available at VCU
  - C. Kenneth & Dianne Wright Center for Clinical and Translational Research
    - Research Innovator
  - Massey Cancer Center
    - Biostatistics Shared Resource
  - Department of Biostatistics
    - Biostatistical Consulting Laboratory (BCL)
    - Faculty collaborations
  - Clinical Department Resources
THANK YOU!!!