Overview of Modern Clinical Trial Designs

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Objectives

• Consider reasons for revamping clinical trial designs to reflect wider representation of the population and more settings of real-world conditions.

• Outline the differences between classical and novel clinical trial designs and explain how they relate to established clinical trials.

• Explain the impact that innovative clinical trial design has on patients and how modern clinical trial designs include a diverse, patient-centered approach.
Clinical Trials Perspectives/Experience

• Recruitment?

• Retention?

• Diversity?
Clinical Trial Populations

Overview of Classical Clinical Trial Designs

- Clinical Trials
  - Experimental
  - Observational
    - Analytic
    - Cohort
    - Case-Control
  - Randomized Clinical Trial
  - Case-Sectional
  - Case Series
  - Case Report

Strength Levels:
- High
- Level 1
- Level 2
- Level 3
- Level 4
- Low
- Level 5

Classical versus Novel Clinical Trial Designs
• **Platform trial design**: A trial design in which multiple interventions can be evaluated over time.
  - Master protocol with subprotocol appendices
  - Basket trials, umbrella trials, and platform trials
    - Basket trial: a targeted therapy is evaluated for multiple diseases with a common factor.
    - Umbrella trials: multiple targeted therapies in a single disease that is stratified into multiple sub-studies based on specific factors.

• **Adaptive trial design**: Trial design evolves as information accrues according to prespecified rules and interim analyses based upon prespecified schedules.

• **Master protocol**: Main protocol designed to evaluate multiple interventional hypotheses with standardized elements (supplemented with intervention-specific appendices, other protocol-related appendices).
## Types of Master Protocols

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbrella</td>
<td>To study multiple targeted therapies in the context of a single disease</td>
</tr>
<tr>
<td>Basket</td>
<td>To study a single targeted therapy in the context of multiple diseases or disease subtypes</td>
</tr>
<tr>
<td>Platform</td>
<td>To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm</td>
</tr>
</tbody>
</table>

Master Protocols

Basket Trials
- One basket (genetic mutation) can contain multiple items (cancer types)

Umbrella Trials
- An umbrella (cancer type) can have multiple ribs (genetic mutations)

Platform Trials
- Multiple trains can (drugs) come and leave a platform (cancer type)

Platform Trial Design

**Umbrella/platform trial**

- Single histology
  - Biomarker 1
    - Treatment arm 1
  - Biomarker 2
    - Treatment arm 2
  - Biomarker 3
    - Treatment arm 3

**Basket trial**

- Histology 1
- Histology 2
- Histology 3
  - Biomarker positive
    - Biomarker driven treatment

**Figure 1.**
A, Study schema for an umbrella or platform trial.  
B, Study schema for a basket trial.

Platform Trial Design

Adaptive Platform Trials

• Need efficient trial strategies to evaluate multiple treatments and combinations of treatments, in patient populations over time.

• Efficiencies:
  • Concurrent control arm with multiple investigational interventions
  • Regulatory, ethical, operational

• Challenges: long-term commitment of resources, personnel
Comparison between Trial Designs

Traditional Fixed-Sample Design:
- Design
- Conduct
- Analyze

Adaptive Design:
- Design
- Conduct
- Analyze

- Adapt
- Review
Adaptive Trial Design – What Adaptations?

- Allows assessment of response to **treatment while the study is running**
- Can incorporate findings from within or outside the trial
  - Eligibility
  - Biomarker information
  - Treatments
  - Endpoints
  - Randomization
- This allows the trial to stay current with the latest updates and potentially increase recruitment and retention.
## Adaptive Designs (reference slide examples)

<table>
<thead>
<tr>
<th>Trial adaption, and cited examples of use</th>
<th>Type of adaptive design (AD) and example statistical methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changing the predetermined sample size in response to inaccurate assumptions of study design parameters to achieve the desired statistical power.</td>
<td>Sample size re-estimation (SSR) using aggregated interim data from all participants or interim data separated according to allocated treatment.</td>
</tr>
<tr>
<td>Stopping the trial early for efficacy, futility, or safety when there is sufficient evidence</td>
<td>Group sequential design futility assessment using stochastic curtailment.</td>
</tr>
<tr>
<td>Evaluating multiple treatments in one trial allowing for early selection of promising treatments or dropping futile or unsafe treatments and add to ongoing trial.</td>
<td>Multi-arm multi-stage (MAMS), dose/treatment-selection, drop-the-loser, or pick-the-winner, or add arm.</td>
</tr>
<tr>
<td>Changing the treatment allocation ratio to favor treatments indicating beneficial effects.</td>
<td>Response-adaptive randomization.</td>
</tr>
<tr>
<td>Multiple trial phases, in one trial under a single protocol.</td>
<td>Operationally or inferentially seamless AD.</td>
</tr>
<tr>
<td>Adjusting the trial population or selecting patients with certain characteristics that are most likely to benefit from investigative treatments.</td>
<td>Population or patient enrichment or biomarker AD.</td>
</tr>
<tr>
<td>Changing the primary research hypotheses or objectives or primary endpoints. For example, switching from non-inferiority to superiority.</td>
<td>Adaptive hypotheses.</td>
</tr>
<tr>
<td>Switching the allocated treatment of patients to an alternative treatment influenced by ethical considerations, for instance, due to lack of benefit or safety issues.</td>
<td>Adaptive treatment-switching.</td>
</tr>
<tr>
<td>Combination of at least two types of adaptations.</td>
<td>Multiple; inferentially seamless phase 2/3 or population enrichment; biomarker-stratified with RAR; adaptive platform trials.</td>
</tr>
</tbody>
</table>

Platform Trial - Randomized

Ability to drop arms early and flexibility to add new arms

Standard-of-care

Intervention 1

Intervention 2

New arm introduced

Arm dropped

New arm introduced

Intervention 3

Intervention 4

Platform Design – Randomized Response Adaptive
Risk of Bias in Platform Trials

- Prespecified plans for interim and statistical analyses used in the trial
  - Prespecified plans applied equally to all interventions
- Concurrent/nonconcurrent randomized participants for statistical comparisons
- Information flow/results
  - Investigational Drug Steering Committee (IDSC), Trial Committee, Participants
- Follow reporting guidelines in publications
# Summary - Traditional and Platform Trials

Table. General Characteristics of Traditional and Platform Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Traditional Trial</th>
<th>Platform Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td>Efficacy of a single agent in a homogeneous population</td>
<td>Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous</td>
</tr>
<tr>
<td>Duration</td>
<td>Finite, based on time required to answer the single primary question</td>
<td>Potentially long-term, as long as there are suitable treatments requiring evaluation</td>
</tr>
<tr>
<td>No. of treatment groups</td>
<td>Prespecified and generally limited</td>
<td>Multiple treatment groups; the number of treatment groups and the specific treatments may change over time</td>
</tr>
<tr>
<td>Stopping rules</td>
<td>The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment</td>
<td>Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)</td>
</tr>
<tr>
<td>Allocation strategy</td>
<td>Fixed randomization</td>
<td>Response-adaptive randomization</td>
</tr>
<tr>
<td>Sponsor support</td>
<td>Supported by a single federal or industrial sponsor</td>
<td>The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination</td>
</tr>
</tbody>
</table>

Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.
Trial Management

Traditional Trial Design

- Preparation for opening trial
  - Before trial opens
- Managing data for open comparisons
  - Trial open for recruitment

Adaptive Platform Protocol Design

- Preparation for opening trial
  - Before trial opens
- Managing data for open comparisons
  - Trial open for recruitment
- Preparation for opening new comparison
- Preparation for opening new comparison
- Preparation for opening new comparison
Key Considerations: Preplan and Prespecify

- Selection criteria of new research questions & interventions
- Clinical leadership
- Scientific peer review
- Funding/sustainability
- Biomarker development and cohort selection
- Investigator/site engagement & feasibility of accrual
- Protocol development
- Ethics and regulatory assessment and version control
- Clear terminology
- Contracts and drug supply
- CRFs and database changes
- Site implementation
- Trial management priorities
  - New, ongoing, IA
Revamping clinical trial designs to reflect wider representation of the population

• Adaptive clinical trial designs allow for pre-specified trial design changes during the trial when data becomes available.
  • The adaptive design may begin with a narrow population if there are concerns about safety, then expand to a broader population based on interim safety data from the trial that provide support for increasing inclusion.
  • Broadening the inclusion criteria based upon interim assessments
  • As the trial progresses, data may reveal the need to decrease the frequency of study visits, thus allowing more flexibility in visit windows and potentially supplementing with electronic communication as appropriate.
    • Thus, easing the burden on the trial participants and potentially increasing recruitment and retention.
New clinical trial design allows for more representative settings of real-world conditions

- Adaptive designs allow for more **flexibility** to the clinical trials and for **modifications during the course** of the trial in order to streamline and optimize the process.
- This innovative approach has the potential to:
  - Reduce resource use
  - Decrease time to trial completion
  - Limit allocation of participants to inferior interventions, and
  - Improve the likelihood that trial results will be scientifically or clinically relevant
Pragmatic Clinical Trial Design

• The idea was actually introduced in 1967 by Schwartz and Lellouch
• Pragmatic trials are designed to evaluate the **effectiveness** of interventions in real-life routine practice
• Pragmatic trials produce results that can be **generalized** and **applied** in routine practice settings.
• Pragmatic trials may test the same intervention as an explanatory trial, but they are conducted in real-world clinical practice settings, with typical patients and by qualified clinicians.

“If we want more evidence-based practice, we need more practice-based evidence.”

## Key Differences

<table>
<thead>
<tr>
<th>Explanatory</th>
<th>versus</th>
<th>Pragmatic</th>
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</thead>
<tbody>
<tr>
<td>Can the intervention work?</td>
<td>Question</td>
<td>Does the intervention work when used in real world practice?</td>
</tr>
<tr>
<td>Well-resourced, ideal</td>
<td>Setting</td>
<td>Real world practice</td>
</tr>
<tr>
<td>Highly selective, excludes many, poor adherence, homogenous</td>
<td>Participants</td>
<td>Little or no selection beyond the clinical indication of interest, heterogenous</td>
</tr>
<tr>
<td>Strictly enforced, adherence is closely monitored</td>
<td>Intervention</td>
<td>Applied flexibly</td>
</tr>
<tr>
<td>Short-term surrogates, process measurements</td>
<td>Outcomes</td>
<td>Directly relevant to participants, funders, communities, and healthcare providers</td>
</tr>
<tr>
<td>Indirect: little effort made to match the design of the trial to the decision-making needs of those in the usual setting in which the intervention will be implemented</td>
<td>Relevance to Practice</td>
<td>Direct: the trial is designed to meet the needs of those making decisions about treatment options in the setting in which the intervention will be implemented</td>
</tr>
</tbody>
</table>
# Explanatory versus Pragmatic Trials

<table>
<thead>
<tr>
<th>Explanatory</th>
<th>Continuum</th>
<th>Pragmatic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHAT?</strong></td>
<td><strong>WHY?</strong></td>
<td><strong>WHO?</strong></td>
</tr>
<tr>
<td>Can treatment work?</td>
<td>Does treatment work?</td>
<td>Informs decision makers</td>
</tr>
<tr>
<td>EFFICACY</td>
<td>EFFECTIVENESS</td>
<td>Maximises generalisability:</td>
</tr>
<tr>
<td>- Hypothesis testing</td>
<td>- Comparing treatment strategies</td>
<td>- Protocol reflecting usual care</td>
</tr>
<tr>
<td>- Ideal circumstances</td>
<td>- Usual care</td>
<td></td>
</tr>
<tr>
<td><strong>HOW?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess cause – effect of drug</td>
<td></td>
<td>Broad inclusion</td>
</tr>
<tr>
<td>Minimize variation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rigid protocol</td>
<td></td>
<td></td>
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<tr>
<td>Selective inclusion</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>METHOD?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Data collection &gt; usual care</td>
<td>- Data collection = usual care</td>
<td></td>
</tr>
<tr>
<td>- Outcomes research relevant</td>
<td>- Outcomes clinically relevant</td>
<td></td>
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</tbody>
</table>
Why do we need Pragmatic Trials?

• We are not reaching patients with complex, comorbid conditions and those most in need.
• Traditional research rarely happens in typical clinical settings, thus findings often aren’t feasible for real-world uptake.
• We are not asking questions important to providers, patients, administrators, or policymakers.
Key Messages: IMPACT

• Modern clinical trial designs offer several practicable and desirable benefits which facilitate faster answers and allow clinical trials to serve as a tool to move treatment on for patients much more quickly.

• The use of shared resources across multiple comparisons must be cost-saving compared to separate two-arm non-adaptive trials to address the same questions.

• There are notable design, operational and logistical challenges which require careful attention.


• Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics. FDA Guidance for Industry. https://www.fda.gov/media/120721/download


THANK YOU ...

• For your time and attention today
<table>
<thead>
<tr>
<th>Area</th>
<th>Proposed Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research question</td>
<td>Define criteria for review of new interventions</td>
</tr>
</tbody>
</table>
| Trial Management Group      | Collaborative Group  
  Study chair/principal investigator: overall trial oversight  
  Co-chairs/PIs: clinical and scientific leadership for addition of new trial interventions                                                                 |
| Scientific peer review      | Ongoing discussion with key funding stakeholders/partners  
  Planning for adequate support of central and site resources  
  Addition of new comparison discussed in early stages to assess feasibility of funding                                                                 |
| Biomarker                   | Clearly define cohort and identify biomarkers, assure feasibility and laboratory QC                                                                                                                                 |
| Protocol                    | Consider futureproof changes in trial design (e.g. modular)                                                                                                                                               |
| Ethics/Regulatory approval  | Rationale for addition of new interventions discussed early with regulatory bodies                                                                                                                                 |
| CRF and database            | Timelines for implementing changes are key for timely implementation                                                                                                                                          |
| Site implementation         | Engage early (e.g. via survey) to gauge interest in new research question  
  Discuss activation criteria with centers  
  Pre-set timelines for local approval of new comparison (if control arm is shared)                                                                                                                     |
| Other                       | Constant assessment of priorities and competing tasks (e.g. new, ongoing versus interim analysis tasks)  
  Importance of adequate resourcing for trial management team                                                                                                                                           |