Introduction to Platform Trials

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Statistical Modeling and Methodology
Outline

- Introduction to platform trials and motivation
- Example walk through of a platform trial
- Protocol structure
  - Master protocol
  - Intervention Specific Appendix (ISA)
- Benefits and Risks
- Examples of ongoing platform trials
- Conclusions
What is a Platform Trial?

An experimental infrastructure to evaluate multiple treatments and/or combinations of treatments in heterogeneous patient populations.

- Not all interventions are included, or even known, at the start of the platform
- Specialized statistical tools for allocating patients and analyzing results
- Pre-existing infrastructure for clinical operations and trial implementation
Traditional trial

Drug 1

DA 1

Standard Trial:
- Single treatment
- Homogeneous patients in one Disease Area (DA), One Question
Adaptive Designs

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<th>Drug 1</th>
<th>DA 1</th>
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Adaptive Designs

- Altering randomization
- Sample size adjustment
- More complex statistical models – longitudinal
- Incorporation of historical data or borrowing
Basket Studies

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<th>Drug 1</th>
<th>DA 1</th>
<th>DA 2</th>
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Basket Studies

- Multiple DA
- Targeted therapies
- Rare disease types
- Limited resources
Basket Studies

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Basket Studies

- Borrowing of information (hierarchical models)
- One DA gives you information about another DA
- Recent statistical advance allow for finding a compound that may only work in one DA
- SARC – Sarcoma study of 10 subtypes, 2001 prior to the term “basket” study
## Multi-arm Designs

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- One DA
- Multiple compounds
  - All compounds are included from the beginning of the study
  - Compare among all treatments
  - Compare to only control
- Major issue – difficult to get companies to allow their compounds to be compared to other, non-control, treatments.
- All K compounds may not be available at the start of the study, then what?
### Multi-arm Designs

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- Adaptive designs – outcome adaptive randomization can be helpful in this setting when a control is present, but can lead to other issues.
- Very difficult to have multiple compounds ready to start at the same time – need to plan accordingly.
# Platform Trials

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Phase 2 Trial (Cancer)

**Approach 1**

- Start
  - Population of patients
- Finish
  - Population of patients

**Approach 2**

- Start
  - Population of patients
- Randomize
- Standard of Care
- Experimental arm
- Finish
  - Population of patients
Phase 2 Trial (Cancer)

High Failure Rate in Phase 3 (60%-70%)

Population of patients

Start

Finish

Approach 1

Approach 2

Randomize

Standard of Care

Experimental arm

Population of patients

Start

Finish

Population of patients

Population of patients
Population of Patients

Population of patients

Planed Subgroups
Has any treatment reached the goal for graduation?

A treatment “graduates” if the probability it is better than SOC is greater than 0.8
Platform Trial

Start

Population of patients

1  4  2  3

Randomize

Finish

Graduate to Phase III

Arm 1

1  4

Standard of Care
Experimental arm 1
Experimental arm 2
Experimental arm 3
Population of patients

Start

Arm 1

Finish

Graduate to Phase III

Standard of Care
Experimental arm 1
Experimental arm 2
Experimental arm 3

What about subgroups 2 and 3?
Platform Trial

Start

Population of patients

Arm 1

1 4

Randomize

Finish

Standard of Care

Experimental arm 4

Experimental arm 2

Experimental arm 3
Platform Trial

Start

Population of patients

Arm 1

Randomize

Finish

Graduate to Phase III

Arm 3

Standard of Care

Experimental arm 4

Experimental arm 5

Experimental arm 3

1

2

3

4

1

1
Platform Trial

Population of patients

Start

Arm 1

Arm 3

Finish

Standard of Care
Experimental arm 4
Experimental arm 5

Randomize
Protocol

- We already have a protocol designed for one intervention, how is it different?
  - This is a great starting point

- How do we know how well this will work in practice?
  - Simulation

- How do we organize a protocol when we don’t know exactly what treatments are in the platform when we write it?
Protocol Organization

Master Protocol

ISA 1

ISA 2

ISA 3
Master Protocol Structure

- The overall study design
- Study population inclusion and exclusion criteria
- Randomization scheme
- Consent process
- Primary, secondary and other outcomes
- Statistical methodology, and the planned analyses that are common across all interventions
- Study assessments and procedures, including efficacy assessments, safety assessments, adverse event and serious adverse event reporting
- Data collection procedures
- Data monitoring committee
- Platform level decision rules, eg graduation or futility
Intervention-Specific Appendices (ISAs) Structure

- Each ISA typically contains a control and an experimental (maybe more than one dose)
- If multiple doses/treatments define how patients are randomized within an ISA and how decisions are made
- Background information, including preclinical and clinical data, rationale for testing intervention in the disease and dose rationale
- Intervention-specific data including additional inclusion/exclusion, administration schedule, specific tests/procedures for biomarkers or safety, dose reduction guidelines, and adverse events of special interest
- Pharmacy information, including administration schedule
- As part of each ISA, an integrated inclusion/exclusion criteria, concomitant and prohibited medication section, and T&E should be provided
Example – Two Possible Approaches

• Approach 1: Run two POC studies to evaluate different compounds

• Approach 2: Platform trial where the 2\textsuperscript{nd} compound is added to the platform

• Assumptions:
  – Compound 2 is expected to be available about 25-30 months after the first one
  – Platform is more difficult to get started, approx. 6 months longer
  – Each POC is smaller and will only have about 60 sites
  – Platform is larger and thus have about 90 sites
  – Recruitment per site stays the same

• In terms of time, how do this options compare?
Platform Study CD: Hopes, Dreams, Aspirations

The graph compares two study designs:

- **Study 1**: Standard Study Design
- **Study 2**: Platform Study Design

The y-axis represents the number of patients, and the x-axis shows the months. The graph illustrates the progression of patient numbers over time for both study designs.
Process and Operational Efficiency

• One master protocol with common elements across sub-studies/appendices:
  – A new appendix for each new intervention added
  – Informed consent, data close-out, etc.
  – Clinical monitors trained on common elements

• Centralized governance structure: central IRB, DMC, other bodies (e.g. standardized clinical, laboratory, biomarker, or imaging assessments) to reduce start up time

• Central labs, reading centers, centralized QA: increase data quality and reduce across clinics variability

• Utilize pre-existing infrastructure over time when new therapies enter the study: for sites operations and data collection
Sharing Information Between ISAs

Start Platform
Any Concerns on Information Sharing?
Sharing Information Between ISAs

Start Platform
Sharing Information Between ISAs
Sharing Information Between ISAs
Sharing Information Between ISAs
Information Sharing

• Easier to justify sharing of control patients between ISAs that are in the platform during same time frame
• Harder to justify sharing between ISAs that have no overlap and are separated by a “significant” amount of time.
• Statistical approach
  – Test and pool
  – Model time trends
  – Discount patients enrolled prior to the start of an ISA
  – Hierarchical model for borrowing
• Why is this important?
  – Borrowing control patients between ISAs allows the randomization in each ISA to favor the new treatment, eg 3:1 or 4:1 so fewer patients receive placebo or control
  – Increase power without increasing sample size
Benefits and Risks of Platform Trial

Benefits
• Smaller number of patients on placebo/control
• Leverage common control group
• Improve decision making by avoiding cross-study comparisons which include different designs, different countries, different sites
• Accelerate downstream programs
• Understand performance of novel endpoints across multiple compounds
• Uniform collection of biomarkers to inform other programs
• Increased number of sites allows for quicker enrollment

Risks
• Delayed initiation of Compound 1
• Increased resources and costs up-front
• Trial design is novel for HAs, IRBs, Sites….may impede transition to Compound 2
• Evaluation of design is not a trivial task
• Various centers may not want to write a “blank check” to allow any, unknown, compound to be used in their center
Great Idea – Can it be done?

• It has been done and is being done

• Examples
  – I-SPY2 – Breast cancer
  – EPAD – Alzheimer's
  – DIAN – Alzheimer’s
  – A few in development within Janssen
I-SPY2

- First platform trial in Breast cancer
- ISPY-1 → ISPY-2 (Bayesian Approach)
- Identify which patient subgroups are likely to respond to specific drug combinations (used biomarker subgroups)
- Model relationship between baseline and longitudinal markers (depending on therapy) to predict pCR
- Better treatment of patients in trial
- Graduate drugs within patient subgroups to smaller, more focused Phase 3
- Evaluate multiple treatment at one time
Alzheimer Platform Trials

- **IMI-EPAD**
  - Patients enter a Longitudinal Cohort Study (LCS) and then can be directed into the POC platform trial.

- **DIAN**
  - Platform trial for patient with dominantly inherited Alzheimer
  - Strong historical data used build disease progression model

- Both trials leverage the use of placebo control patients borrowed across the treatment cohort
  - Decreases the number of patients on placebo
  - Increase likelihood of detecting beneficial compounds
Simulations

- Prospective planning essential
- Many scenarios/examples
- Accrual rate matters
- Other interventions and their efficacies matter

- Extensive simulations of trial performance to ensure:
  - the type I error rate,
  - power and accuracy in estimation of treatment effect(s)
  - Intervention’s duration in trial
  - the rates of adverse events
  - or dose finding
- Well defined and acceptable, across a very wide range of possible true treatment effect sizes, dose-response relationships, and population characteristics
R Simulation Package

- Currently working on a package in R to simulate platform trials
  - Utilized internally for 2 platforms and 1 non-platform trial
- Similar structure from one platform trial to another
- Many differences from one platform to another
- Why not a nice GUI?
  - Developed with minimal usage of S3 classes to make a low learning curve for most statisticians while remaining flexible
  - Having the R source code allows for different options and extensions
  - Transparent to the nature of what is going on in the trial
  - Many statisticians are familiar with R
- Release the package on GitHub.com
  - Allow everyone to access the code and package
  - Allow others to contribute
  - Test code
Where we are now!
Where we want to be
Conclusions

• Platform offer a novel way of sharing information between ISAs and evaluating interventions
• Plan...Plan...Plan
• Simulate...Simulate....Simulate
  – Simulate some more

• Team concept is critical
Thank you!
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