MASTER PROTOCOLS IN COLLABORATIVE RESEARCH

Lisa LaVange, PhD

Professor and Associate Chair

UNC | GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
Biostatistics

ASA Biopharmaceutical Section/

Industry/Regulatory Workshop

Washington, DC

September 13-14, 2018

Outline

- Precision Medicine at FDA
- Master Protocols
- Rare Disease Drug Development Applications
- NIH Research

Precision Medicine

- Personalized medicine is getting the right product to the right patient (and in case of a drug or biologic) at the right dose
- Key challenge is to identify subgroups of patients to target at the right stage of drug development
- As medicines (or their targets) become more precise, traditional clinical trials become more difficult to conduct and/or less efficient
- Collaborative research paradigms, such as master protocols, are of increasing interest, as a result

Precision Medicine

- FDA statisticians involved in a number of precision medicine-related areas:
  - Diagnostic device evaluation (CDRH)
  - Enrichment study designs (CBER and CDER)
  - Master protocols/platform trials (CBER, CDER, CDRH)
  - Biomarker validation and qualification, e.g., BEST (CDER)
- In CDER, Woodcock and others were early advocates of sponsor collaborations whose purpose was to identify and match patients to targeted therapies more efficiently than stand-alone clinical trials

NEJM Article

Published July 2017

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

From the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD. Address reprint requests to Dr. LaVange at the Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Blvd., Silver Spring, MD 20993, or at lisa.lavange@fda.hhs.gov.

N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

A methodologic innovation responsive to this need involves coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure.[1-4] Such efforts are referred to as master protocols, defined as one overarching protocol designed to answer multiple questions. Master protocols may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classification, with multiple interventions,

Master Protocols

- Multiple diseases, multiple patient subgroups (biomarker-defined), and/or multiple therapies studied under one, over-arching protocol
- Also known as:
  - Umbrella or platform trials: one disease, multiple drugs
    - Example: NCI MATCH
  - Basket trials: one drug, multiple disease cohorts
    - Example: B225 trial of imatinib

Master Protocols

- Exploratory: Identify best treatment for biomarker-defined patient subgroup
  - Example: I-SPY II
- Confirmatory: Evaluate different therapies relative to control for a single disease in parallel
  - Example: Lung MAP
- Capitalize on similarities among trials and shared infrastructure to realize efficiencies
- Needed:
  - Regulatory buy-in
  - Sponsors with drugs to test

Master Protocols

Two avenues for innovation:

1. Establish a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data sharing and new data collection
2. Develop a common protocol for the network that incorporates innovative statistical approaches to study design and data analysis

Infrastructure advantages

- Established systems in place
  - Central randomization (e.g., via web portal)
  - Central electronic data capture system
  - In-network clinic personnel trained and experienced on existing systems
- Centralized governance structure
  - Use of central IRBs, a standing DMC, and/or other bodies
- Central labs, reading centers, etc., with QA oversight
- Common elements of trial protocols and common CRFs

→Gain efficiencies in study-start-up and conduct, trial monitoring, and data close-out

Innovative Design Possibilities

- Imbalanced randomization (e.g., 2:1, 3:1, or higher)
- Use of external or historical control data
  - In single-arm studies, or
  - In conjunction with concurrent controls (with 2:1 or higher) to increase power; potential adaptation
- Sharing of control groups across protocols – *within a specific pathway or marker subgroup*
- Model-based analysis methods (e.g., hierarchical Bayes) for pooled analysis of multiple disease or tumor types, markers, body sites, etc.

Rare Disease Master Protocols

DIAN-TU – Dominantly Inherited Alzheimer's Network – Trial Unit

- Rare form of Alzheimer's disease characterized by early onset and a more predictable progression
- DIAN-Observational study funded by NIH
  - Provides information on disease progression as a function of patient characteristics
- DIAN-TU is an adaptive platform clinical trial designed to study multiple therapies over time
  - Control patients shared across therapies, as appropriate (e.g., accounting for differences in mode of administration, etc.)
  - Analysis model incorporates predicted time of onset to reduce variability in time-to-event outcomes
- Protocol developed collaboratively with industry partners and incorporating input from FDA medical and statistical reviewers

Rare Disease Master Protocols

- PREVAIL platform trial in Ebola
  - NIAID and FDA collaboration
  - Trial studied one therapy vs palliative care; stopped early as outbreak declined
- ADAPT – master protocol to develop anti-bacterial agents in multi-drug resistant pathogens
  - ARLG (Antibiotic Resistance Leadership Group; https://arlg.org/studies-in-progress)
  - Trial designed to efficiently examine multiple therapies for the treatment of multiple categories of infections (hospital acquired pneumonia/ventilator assisted pneumonia, urinary tract infection, acute intra-abdominal)
  - Design team included representatives from industry, govt, and academia
  - Trial not yet initiated

NIH Research Collaboration

- NIH trial networks designed to examine multiple marketed therapies with objective of guiding practice of medicine
- Example: NHLBI-funded Precision Interventions for Severe and/or Exacerbation-Prone Asthma Network (PrecISE)
  - Designed to study multiple therapies in an adaptive platform trial
  - Biomarker-defined subgroups of patients to be targeted for each therapy
  - Precision medicine interim analyses to refine a priori definitions of target subgroups based on accumulating data
  - Futility analyses at interim to discontinue ineffective drugs early on and make room for additional therapies to enter the platform
  - UNC is the Data and Modeling Coordinating Center (Ivanova, Kosorok, LaVange, mPIs); enrollment to begin June 2019

Summary

- Dynamic nature of master protocols and adaptive platform trials well-suited for the fast pace of precision medicine drug development
- Infrastructure development requires more resources up front, but with the potential to produce savings as trials continue
- Considerable investment required, also up front, to establish the collaboration among interested parties
  - Obtaining buy-in from pharmaceutical sponsors can be particularly challenging, due to proprietary information being shared as well as competing commercial interests
- Involvement of patient advocacy groups (e.g., Friends of Cancer Research for Lung MAP) greatly enhances the ability to launch a master protocol in a timely fashion
- Two upcoming events of interest:
  - DIA workshop on master protocols Nov. 8-9 in Washington, DC
  - Faster Cures webinar on master protocols Dec. 10, 2018