

Designing a Disease-Specific Master Protocol

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Acknowledgments

- This material on master protocols in oncology is collaborative with Dr. Raji Sridhara.

MASTER PROTOCOLS

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
 - Basket trials: one drug, multiple disease cohorts

Master Protocols

- Most examples to date in oncology/hematology
 - Example umbrella trial
 - NCI-MATCH
 - Example basket trial:
 - B225 trial of imatinib
- Recent interest in anti-bacterial drug development
 - Example:
 - ADAPT – multiple therapies; multiple body-sites of infection; multiple pathogens

Master Protocols

Two avenues for innovation:

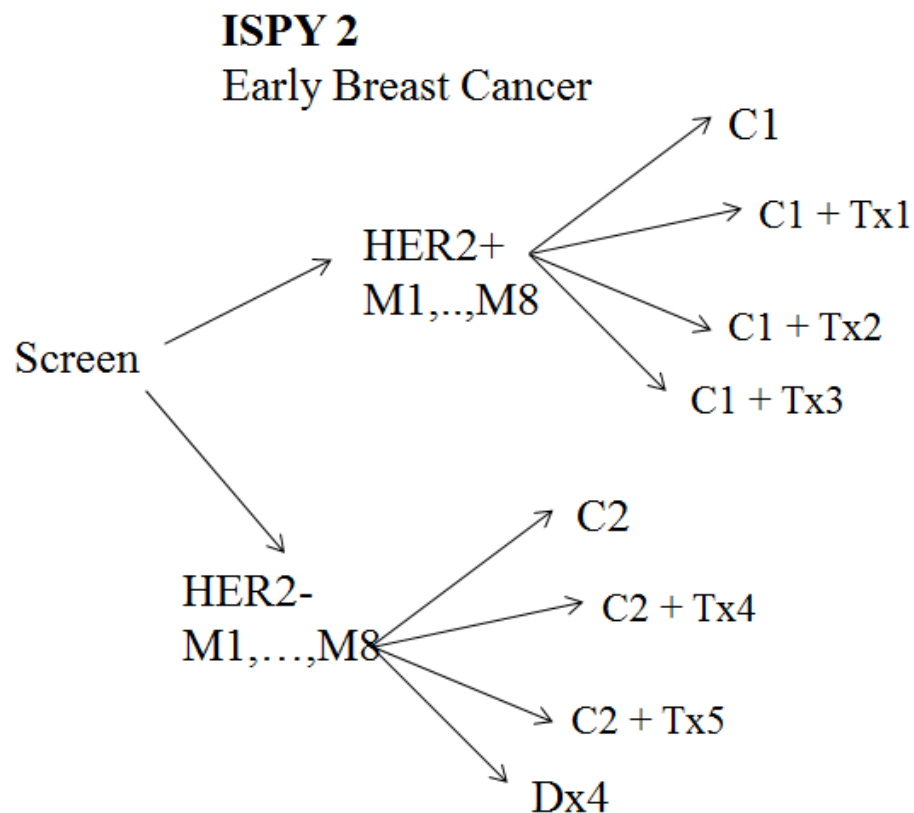
1. Establish a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data sharing and new data collection
2. Develop a common protocol for the network that incorporates innovative statistical approaches to study design and data analysis

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 (2nd stage)
- Capitalize on similarities among trials and shared infrastructure to realize efficiencies
- Needed:
 - Regulatory buy-in
 - Sponsors with drugs to test

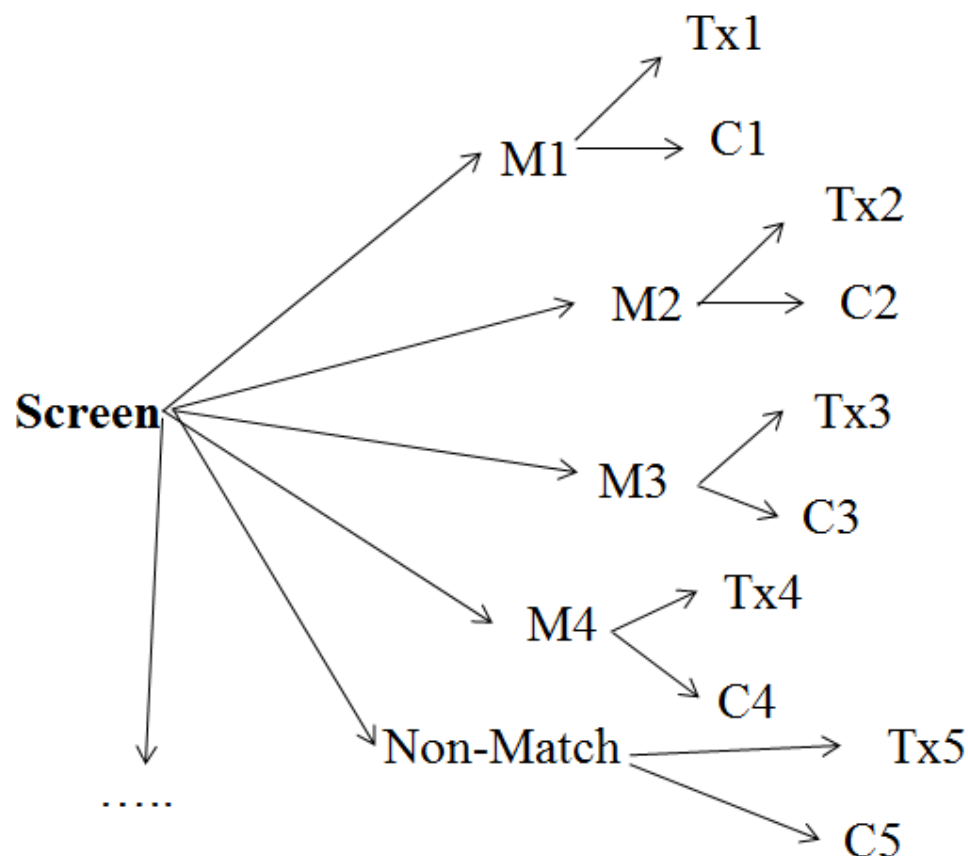
Example 1: I-SPY II

- Exploratory comparative platform trial
- Response-adaptive randomization

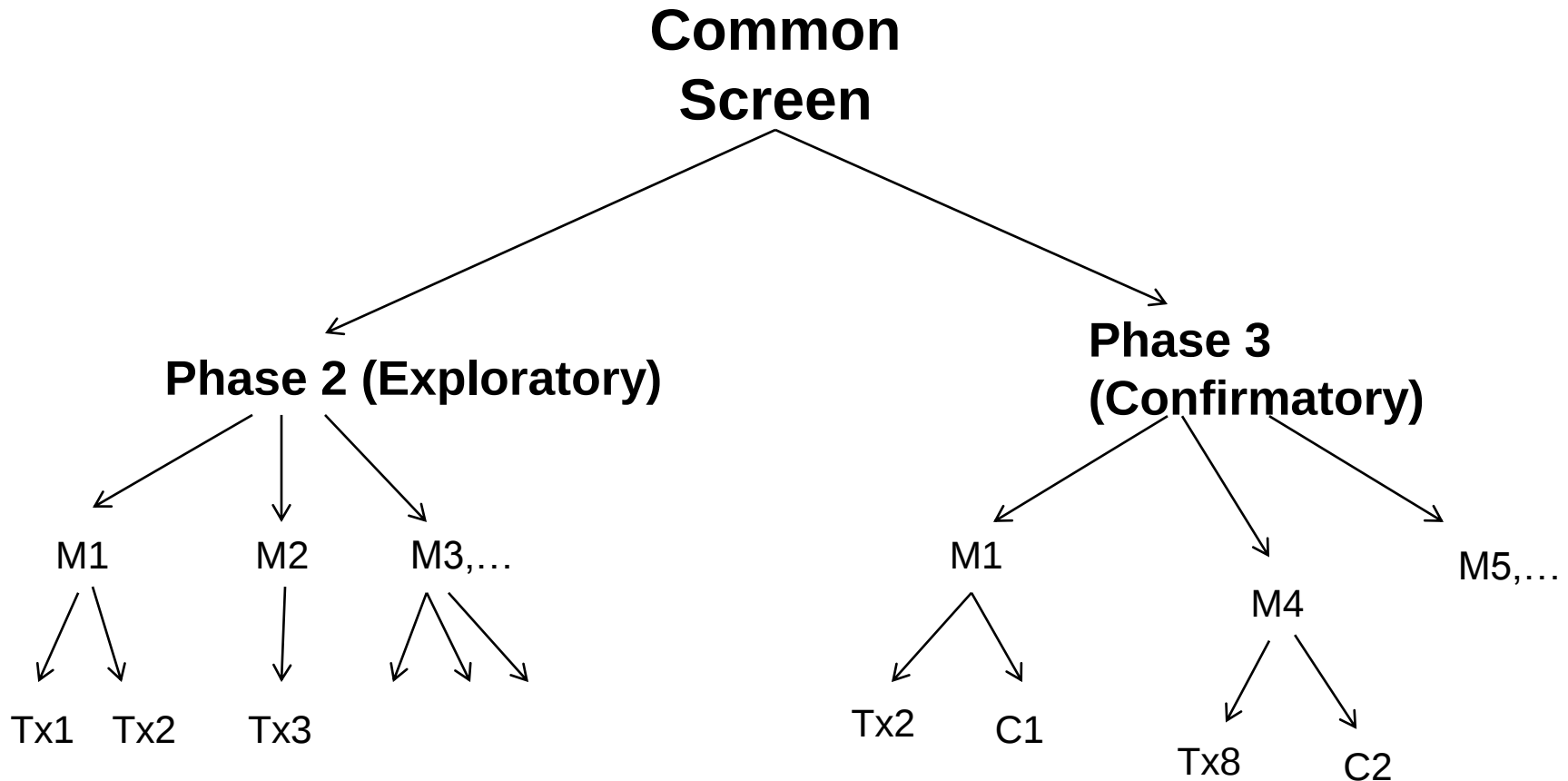


Example 2: Lung MAP

- Two-stage design in advanced squamous NSCLC
- 1st stage: analysis after 50 PFS events for futility and potential for accelerated approval with ORR
 - Non-null hypothesis (H_0 : HR = 0.75)
 - Only clinically meaningful PFS effect goes forward
- If > 1 marker, patient assigned to trial inversely with weight inversely proportional to biomarker prevalence
- FDA approval during trial → changes SOC → changes to design and analysis applied to all trials in the master protocol



Hypothetical Master Protocol in Oncology



Example: Tx8 activity assessed outside of the Phase 2 portion of the master protocol

Infrastructure advantages

- Streamlined enrollment procedures
 - Common screening platform to better match patients to trials for their particular disease/biomarker profile
- Centralized governance structure
 - Use of central IRBs, a standing DMC, single Steering Committee, etc.
- Established systems in place to improve trial processes
 - Central randomization (e.g., via web portal)
 - Central electronic data capture system
 - In-network clinic personnel trained and experienced on existing systems
- Common elements in case report forms (crfs)
 - Study start-up time reduced
 - Efficiencies realized during study conduct
 - Data quality improvements

Data Sharing

- Proposed trial network could encourage data sharing from studies conducted within the network, where appropriate
- Network could also facilitate new data collection
 - To aid in non-inferiority margin determination
 - As a source for prior information to support single study submissions or Bayesian approaches
- Chart data could provide perspective on past and current practices and patients, thereby informing future study designs
- Other types of studies could be conducted to support evidence from trials, e.g., case-control studies or retrospective cohort studies
 - Propensity score matching or other methods to control confounding

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
- Sharing of control groups across protocols – *within a specific pathway or marker subgroup*
- Model-based analysis methods for pooled analysis of multiple disease or tumor types, markers, body-sites of infection, etc.

BAYESIAN METHODS FOR PEDIATRIC TRIALS

Bayesian Methods

- Purpose is to borrow, information on adult patients for use in pediatric trials
- Two general approaches:
 1. Bayesian hierarchical modeling
 2. Adult data used as formal prior distributions in Bayesian design trials
- CDRH 2015 guidance describes (1)
- Drug Information Association (DIA)/FDA Bayesian statistics working group has developed a concept paper describing (1) and (2) both as useful approaches for pediatric trials

Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

**This guidance document is being distributed for comment purposes only.
Document issued on: May 6, 2015**

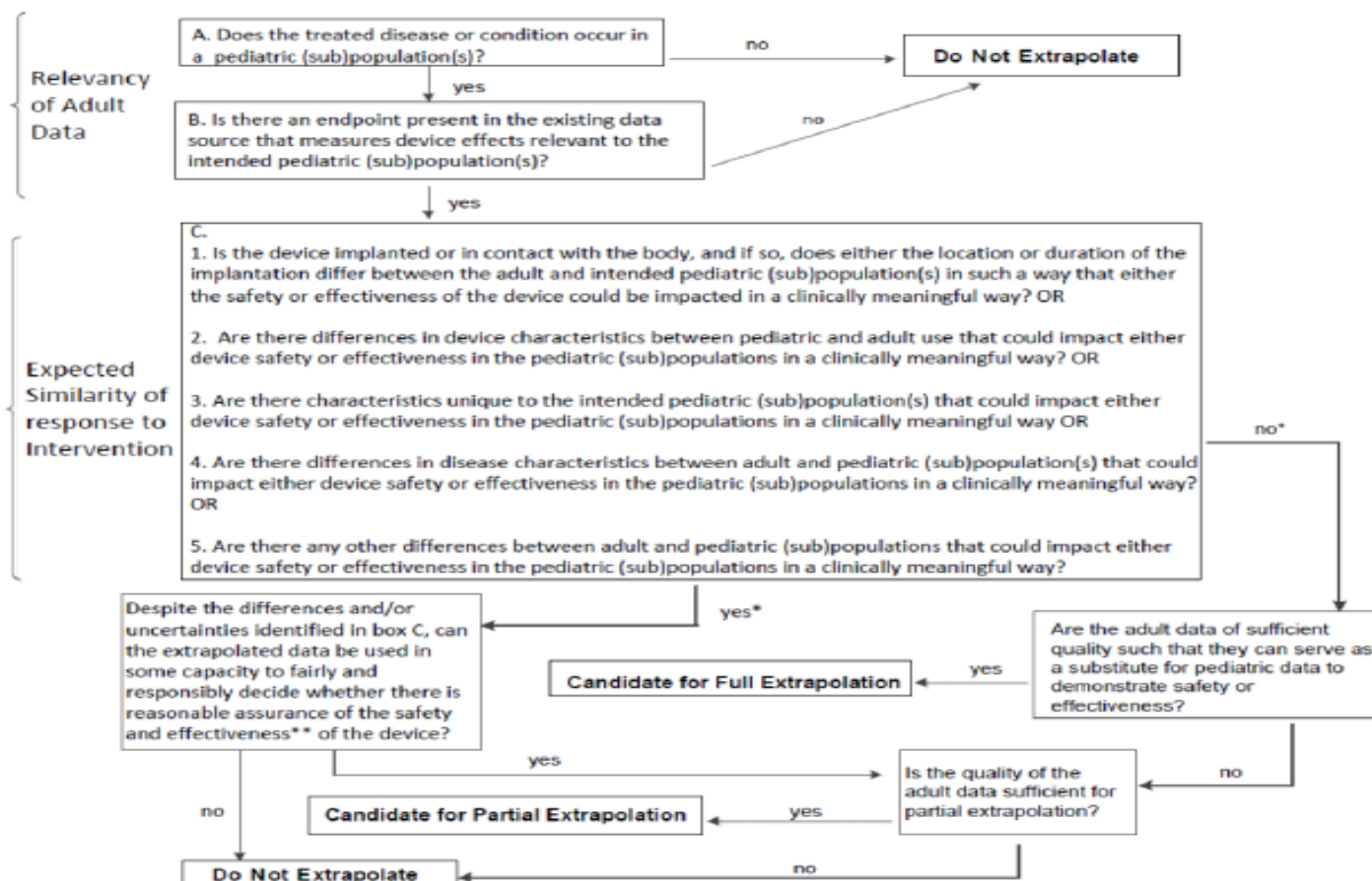
You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Jacqueline Francis (CDRH) at (301) 796-6405 (Jacqueline.Francis@fda.hhs.gov) or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-7800.

CDRH Pediatric Guidance

- Full extrapolation – existing (e.g., adult) clinical data are substituted for prospective clinical data on pediatric patients
 - Other data sources provide supportive evidence
- Partial extrapolation -- existing clinical data are combined via a statistical model with pediatric clinical data sources
- Statistical modeling requires availability of measured variables to help connect adult outcomes to pediatric outcomes
- A typical hierarchical model might have two levels: a patient level and a study level, with exchangeability evaluated at both levels

Figure 1. Pediatric Extrapolation Decision Tree

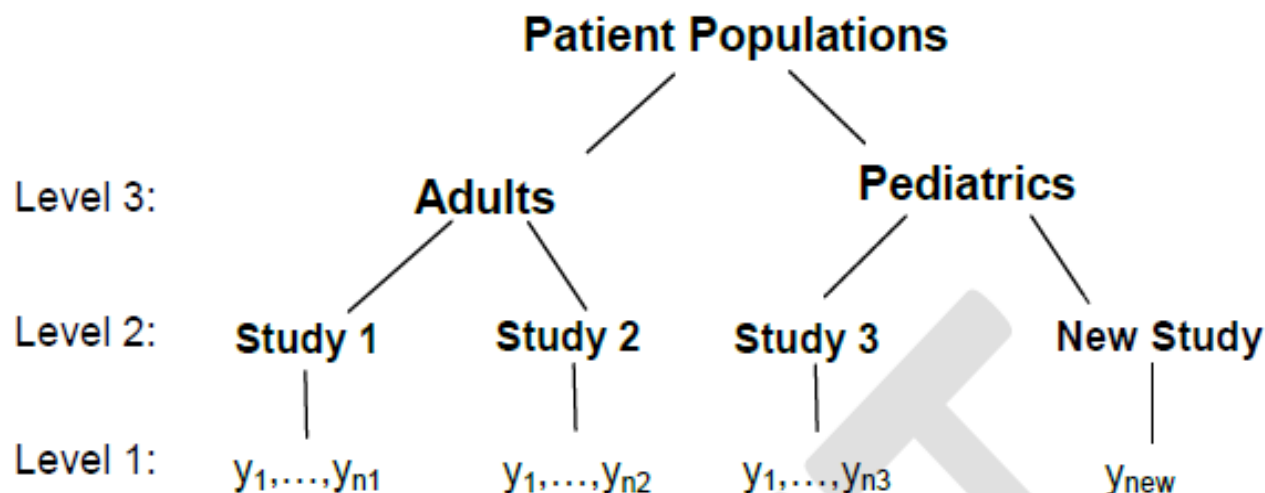


* Note that if all five questions in Box C are answered "no", the direction from C is "no". If at least one of the five is answered "yes", the direction from C is "yes".

**—"The agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that a device is safe and effective. Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. 21 CFR 860.7(c)(1)&(2)."

CDRH Pediatric Guidance

Figure 2. Three-Level Hierarchical Model Structure Example: Studies Within Patient Populations Have Different But Related Effects



Level 1: Patients (y) exchangeable within studies

Level 2: Studies exchangeable within patient populations

Level 3: Patient populations are exchangeable

Use of Adult Data as Priors

- Guillain-Barré syndrome (GBS) – similar in children and adults, but children recover faster
- Treatment options: plasma exchange and IV immune globulin (IVIg)
- 2 trials in adults comparing IVIg to plasmapheresis showed little difference between treatments in median time to ambulation (n = 388 total)
- Trials in children small and of poor quality, e.g., case series compared to unmatched historical controls
- Can adult data be leveraged to keep pediatric trial of feasible size?
 - 200-600 ped GBS cases per year → ~100-300 potentially eligible for a trial

A Bayesian approach to randomized controlled trials in children utilizing information from adults: the case of Guillain-Barré syndrome

Steven N Goodman^a and John T Sladky^b

Background Guillain-Barré syndrome (GBS) is a rare neurologic disease that occurs at all ages, causing a progressive, ascending paralysis that usually resolves over weeks or months. The disease appears to be identical in children and adults, except that children recover more quickly, with fewer residua. For patients who lose the ability to walk independently, the main treatment options are plasmapheresis or intravenous immune globulin (IVIg), treatments that have shown to have identical effectiveness in adults in two large RCTs involving 388 patients. The effectiveness of the treatments in children has only been studied in small, poorly controlled studies. If one could capture all eligible patients in the United States, only about 100–300 children would be available for a trial annually.

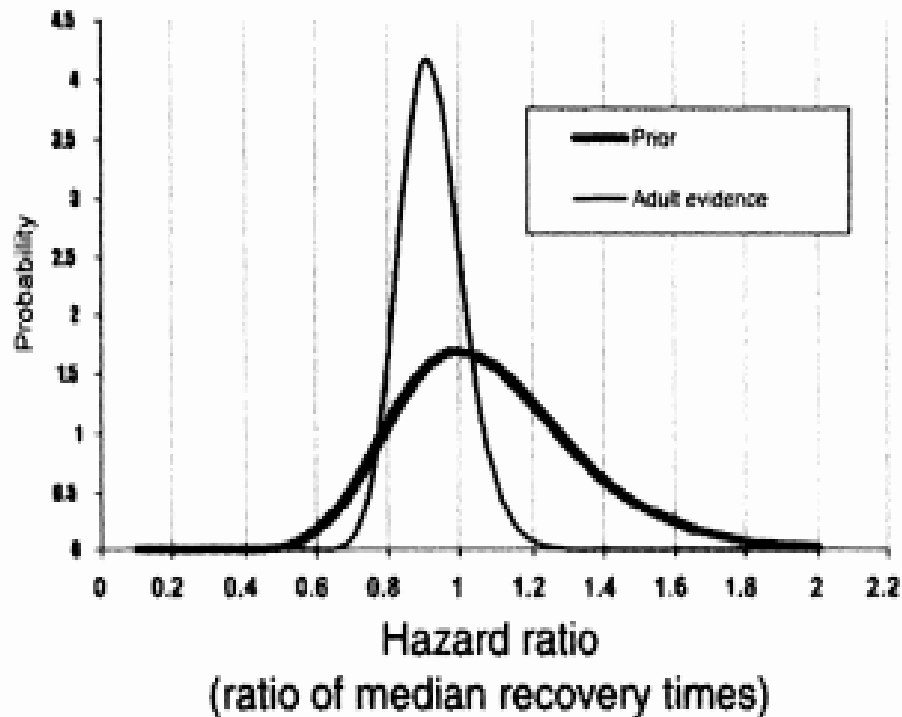
Methods The goal of this case was to demonstrate how Bayesian methods could be used to incorporate prior information on treatment efficacy from adults to design a randomized noninferiority trial of IVIg versus plasmapheresis in children. A Bayesian normal–normal model on the hazard ratio of time to independent walking was implemented.

Results An evidence-based prior was constructed that was equivalent to 72 children showing exact equivalence between the therapies. A design was constructed based on a Bayesian normal–normal model on the hazard ratio, yielding a sample size of 160 children, with a preposterior analysis demonstrating a “Type I” error rate of 5% and a power of 77%.

Conclusions This case study illustrates a rational approach to constructing an evidence-based prior that would allow information from adults to formally augment data from children to minimize unnecessary pediatric experimentation. The frequentist properties of a Bayesian design can be evaluated and reported as they would be for a standard design. Discussion of the appropriate prior for such designs is both a necessary and desirable feature of Bayesian trials. *Clinical Trials* 2005; 2: 305–310. www.SCTjournal.com

2004 FDA Workshop:
Bayesian Methods

Special issue of
Clinical Trials
Published from talks
(2005)



Example of the use of adult data to form a prior distribution for peds

Figure 2 Evidence from adults and prior probability curve used for children on the hazard ratio of IVIg versus plasmapheresis for the endpoint of time to independent ambulation.

GBS Example

- Use of prior corresponded to roughly 72 pediatric patients studied
- Sample size of actual study, designed with monitoring after every 40 patients, up to a maximum of 160
 - Expected $n = 104$ if IVIg inferior to plasmapheresis
 - Expected $n = 156$ if IVIg non-inferior
- For comparison, frequentist analysis ignoring prior information from adult data requires 450 or greater
- For above, 7 days to ambulation considered the non-inferiority margin ($\sim HR = 1.3$)
- Caution—Bayesian approach requires that biological processes in disease and treatment support extrapolation from one population to the other

Using prior distributions to synthesize historical evidence: comments on the Goodman–Sladky case study of IVIg in Guillain–Barré syndrome

Joel B Greenhouse^a and Howard Seltman^a

One feature of the Bayesian approach is that it provides methods for synthesizing what is known about a question of interest and provides a formalism based on the laws of probability for incorporating this auxiliary knowledge into the planning and the analysis of the next study. In this comment, we use elements of the Goodman–Sladky case study to illustrate (1) the use of Bayesian methods to quantify historical information about an intervention through the specification of a prior distribution, (2) an approach to the analysis of the sensitivity of the conclusions of a Bayesian analysis to the specification of the prior distribution, and (3) we comment on the role of research synthesis for combining information about an intervention from different data sources as a tool to help summarize evidence about the intervention. *Clinical Trials* 2005; 2: 311–318. www.SCTjournal.com

Introduction

Every randomized controlled clinical trial (RCT) takes place in the context of uncertain evidence about the efficacy of the intervention of interest. The goal of an RCT, therefore, is to bring differing opinions concerning the intervention to consensus. Yet paradoxically, analytic methods used to evaluate evidence from a trial typically do not incorporate previous results and knowledge, even though the scientific method is predicated on learning from the accumulation of evidence. Nevertheless,

inform the design of a study of the same interventions in children with GBS. In these comments, we would like to use elements of this case study to illustrate 1) the use of Bayesian methods to quantify historical information about an intervention through the specification of a prior distribution, 2) an approach to the analysis of the sensitivity of the conclusions of a Bayesian analysis to the specification of the prior distribution, and 3) to comment on the role of research synthesis for combining information about an intervention from different data sources as a tool to help summarize evidence

Companion article:
How to choose
a prior and how to
conduct sensitivity
analysis on the
choice

Summary

- Pediatric and rare disease trials are increasingly challenging
- Trial networks with established infrastructure and use of a common protocol can address some of these challenges
 - Optimize trial design and conduct to realize efficiencies and improve data quality through centralization of processes, systems, and training
- Innovative trial designs could be considered, given the network infrastructure and resources available to implement such designs
 - In pediatric trials, methods of borrowing information from adult clinical trials, when available and under appropriate conditions, can be leveraged to improve pediatric trials
- Overall objective is to reduce time and cost of developing promising drugs for children



BACK-UP SLIDES

Imbalanced Randomization

- Alternative to single-arm studies in settings with significant recruitment challenges
- Design includes an active control arm with highly imbalanced randomization (e.g., 2:1, 3:1, or higher)
- Leverage external control data via frequentist or Bayesian methods during analysis to increase power
- Consider interim assessment of similarity between concurrent control patients and external control patients*
 - If highly similar, randomization could cease
 - If highly dissimilar, could revert to 1:1 randomization
- External data can be up- or down-weighted in analysis, with use of Bayesian methods*

*Viele K, Berry S, Neuenschwander B, et al. Use of historical control data for assessing treatment effects in clinical trials (2013) *Pharm. Stat.*

Shared Control Subjects

- Use of common protocol with standard procedures, visit schedules, and CRFs may allow control patients to be shared across trials
- Example:
 - Drug A's trial is actively recruiting with 1:1 randomization allocation of Drug A vs. standard of care (SoC)
 - Drug B's trial is approved to begin recruitment in same study population
 - Randomization of eligible patients changes at this point to 1:1:1 corresponding to Drug A: Drug B: SoC
 - If enrollment is completed for Drug A's trial, while Drug B's trial is still ongoing, then
 - Randomization allocation reverts to 1:1 for Drug B: SoC
 - Control patients in Drug A's trial have their data unmasked for analysis of the Drug A protocol but remain masked in Drug B's trial

Shared Control Subjects

- Essential to this process is a CRO/Coordinating Center able to establish appropriate firewall procedures to maintain masking of patients among the various trials
- Sharing control patients does not imply that comparisons among active drugs are carried out
- Trial close-out for one protocol while the other is ongoing, and some control patients are shared, will impact operations at the clinics
- *Assuming logistical considerations can be addressed*, the benefit to sharing control patients could be substantial in terms of both recruitment time and trial costs

Multiple Disease Types

- For cases where disease or tumor types correspond to rare diseases, and studying each type is not feasible due to low prevalence
- Mode-based approaches that account for heterogeneity across types may be useful
- Bayesian hierarchical modeling is one such approach*
 - Assume subgroups are exchangeable in the hierarchical model
 - Covariate adjustment may be needed for exchangeability
 - Test for overall treatment effect (does the drug work?) supplemented by subgroup-specific estimates of treatment effects that are ‘smoothed’ under the model
 - Clustering can separate disease types with positive results versus those with less favorable results

*See, e.g., Berry SM, Broglio KR, Groshen S, and Berry DA. Bayesian hierarchical modeling of patient subpopulations: Efficient designs of Phase II oncology clinical trials (2013). *Clinical Trials*.