

Utilizing Innovative Statistical Methods and Trial Designs in Rare Disease Settings

FDA-Duke Margolis Convening

March 19, 2018

**Utilizing Innovative Statistical Methods and Trial Designs
in Rare Disease Settings; Public Workshop**

March 19, 2018

Bayesian Borrowing For Confirmatory Clinical Trials

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Statistical Innovation Center
Eli Lilly & Company



Acknowledgements

- ◆ Michael Sonksen, PhD
- ◆ John Seaman, PhD
- ◆ Mitchell Thomann, PhD
- ◆ Forrest Williamson, PhD

Outline

- ◆ Bayesian approach overview
- ◆ Methods for borrowing and data sources
- ◆ Examples
- ◆ Conclusions

Key Messages

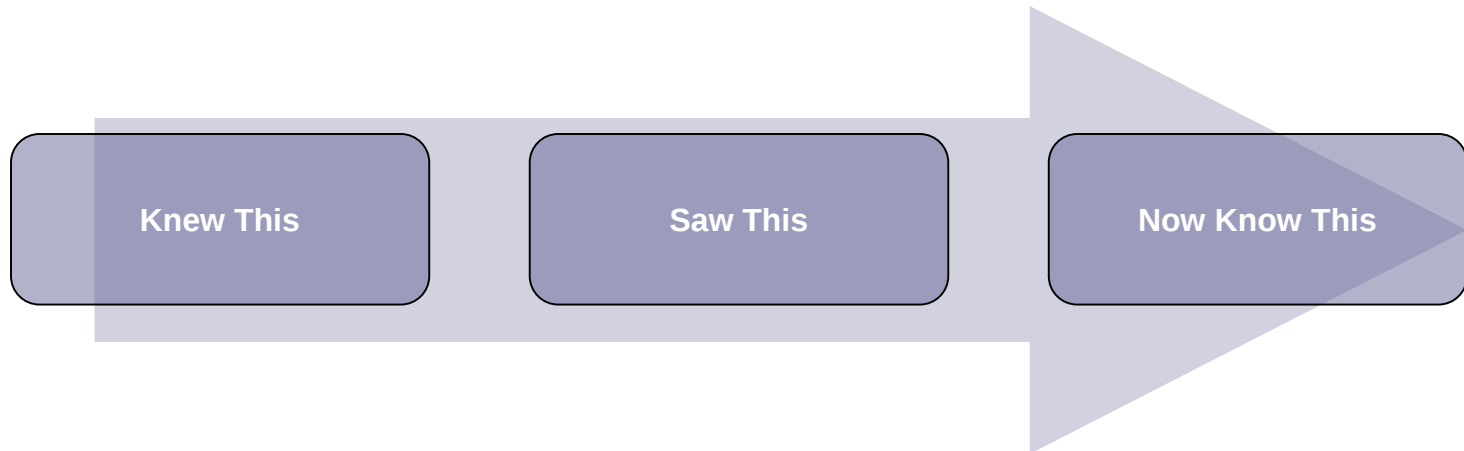
- ◆ Rare diseases are in desperate need of innovation
- ◆ Bayesian approach provides a formal framework for borrowing historical information
 - Offers an intelligent, complete use of all data to improve decisions
 - Best practices ensure transparent understanding of impact of borrowing
- ◆ Bayesian methods can improve the design and analysis of studies for rare diseases

The Bayesian Framework



Bayesian Statistics emulates the way we think

- ◆ We all learn from previous experience
 - Personally
 - Scientific decisions
 - Business decisions
- ◆ Pictorially, we can think of this as:



Value of Bayesian Approach



- ◆ Emulates how we naturally think (facilitates continual learning)
- ◆ Enables probability estimates of questions of interest
- ◆ Allows formal use of prior information, including priors built from previous studies
- ◆ Great flexibility in modeling and prediction
- ◆ Completely transparent

Borrowing Approaches and Data Sources



Borrowing Approaches

◆ Borrowing can be on control arm and/or treatment arm(s)

◆ Static vs Dynamic

- Static

- Pooling
- Single arm trials
- Power priors

- Dynamic

- Hierarchical modeling
- Mixture priors

Appeal of dynamic borrowing:

- Borrows more when current data are similar to historical data
- Protects against over-borrowing

◆ Static vs dynamic can differ for control/treatment

Overview of Potential Data Sources

- ◆ Expert opinion
- ◆ Natural history studies
- ◆ Summary level data (RCTs, observational)
- ◆ Individual-level patient data
 - Internal to Sponsor or at FDA (or other regulators)
 - Patient registries
 - Observational studies
- ◆ PK/PD modeling
- ◆ Pre-clinical data

Need to assess relevance of historical data to new data: similar indications, patient population, time since data collection, relevance of endpoints, timepoints, etc. (exchangability)

Role of Expert Opinion

- ◆ Large literature on this topic
- ◆ Elicit distributions of belief about key efficacy / safety endpoints
 - There are formal, well-tested protocols
 - May be used as portion of prior or down-weighted
- ◆ Elicit distributions about belief in relationships between endpoints, doses, populations, etc.
- ◆ Can use to inform about relevance of historical information
- ◆ Examples available (see, e.g., MYPAN)

General Comments about Borrowing

- ◆ How much to borrow?
 - ✓ What data is eligible to be included in the prior
 - ✓ Currently need to simulate operating characteristics
 - ✓ Consider “prior effective sample size” and “prior probability of success”
 - ✓ Should assess prior to posterior sensitivity
- ◆ May borrow different amounts for different treatments, based on medical need, etc.
- ◆ Note, borrowing may ‘dampen’ the effect in current trial (so borrowing does not always favor Sponsor)

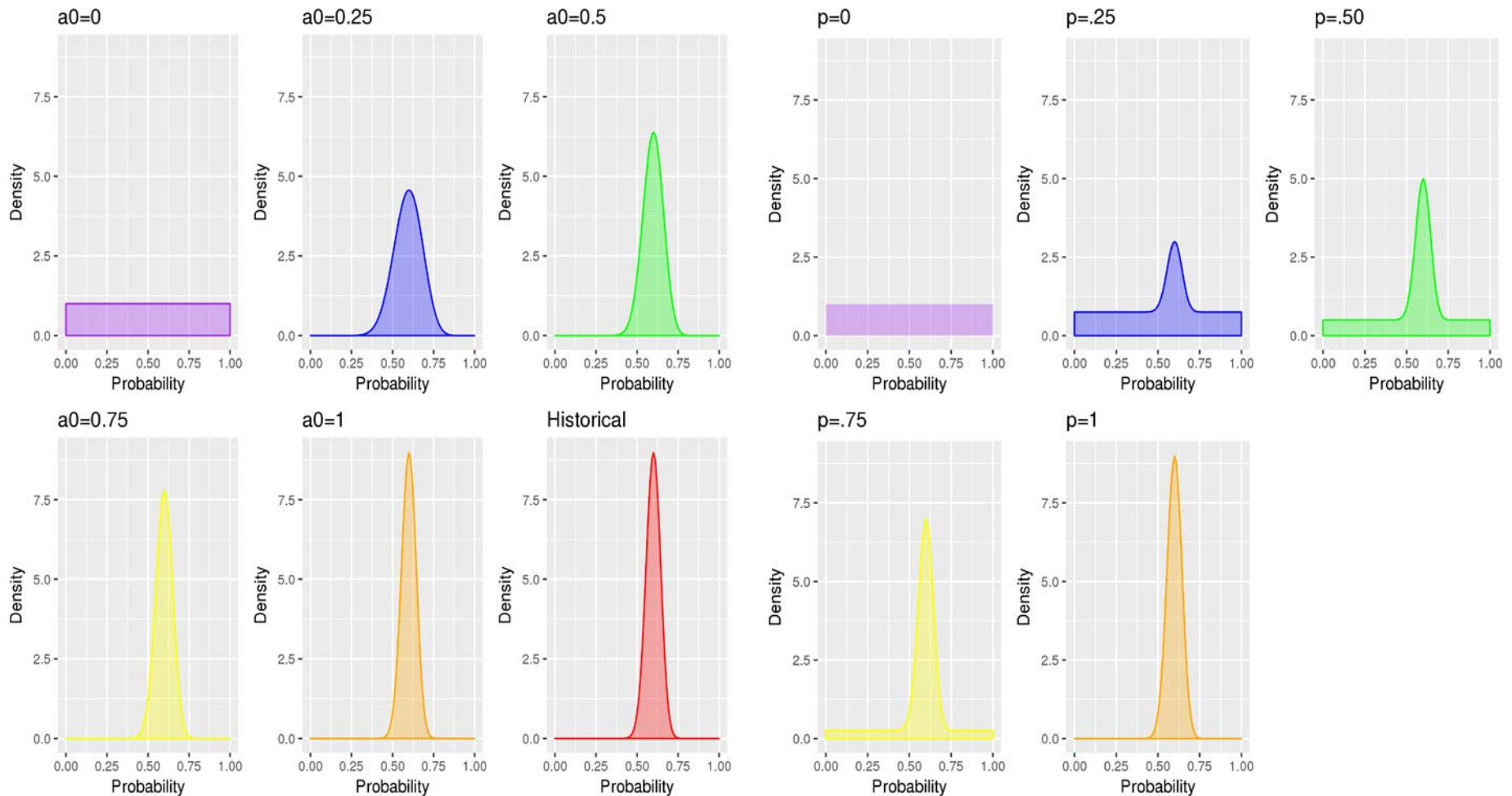
Examples

Lilly

Example 1: Borrowing historical control

- ◆ Previous data is available on the control group.
 - Specifically, a trial with 120 subjects and 72 responses.
 - Thus the historical rate is 60%.
- ◆ This historical information is kept constant throughout the simulation.
- ◆ The sample sizes for the current study are 70 for the controls and 140 for the new treatment.

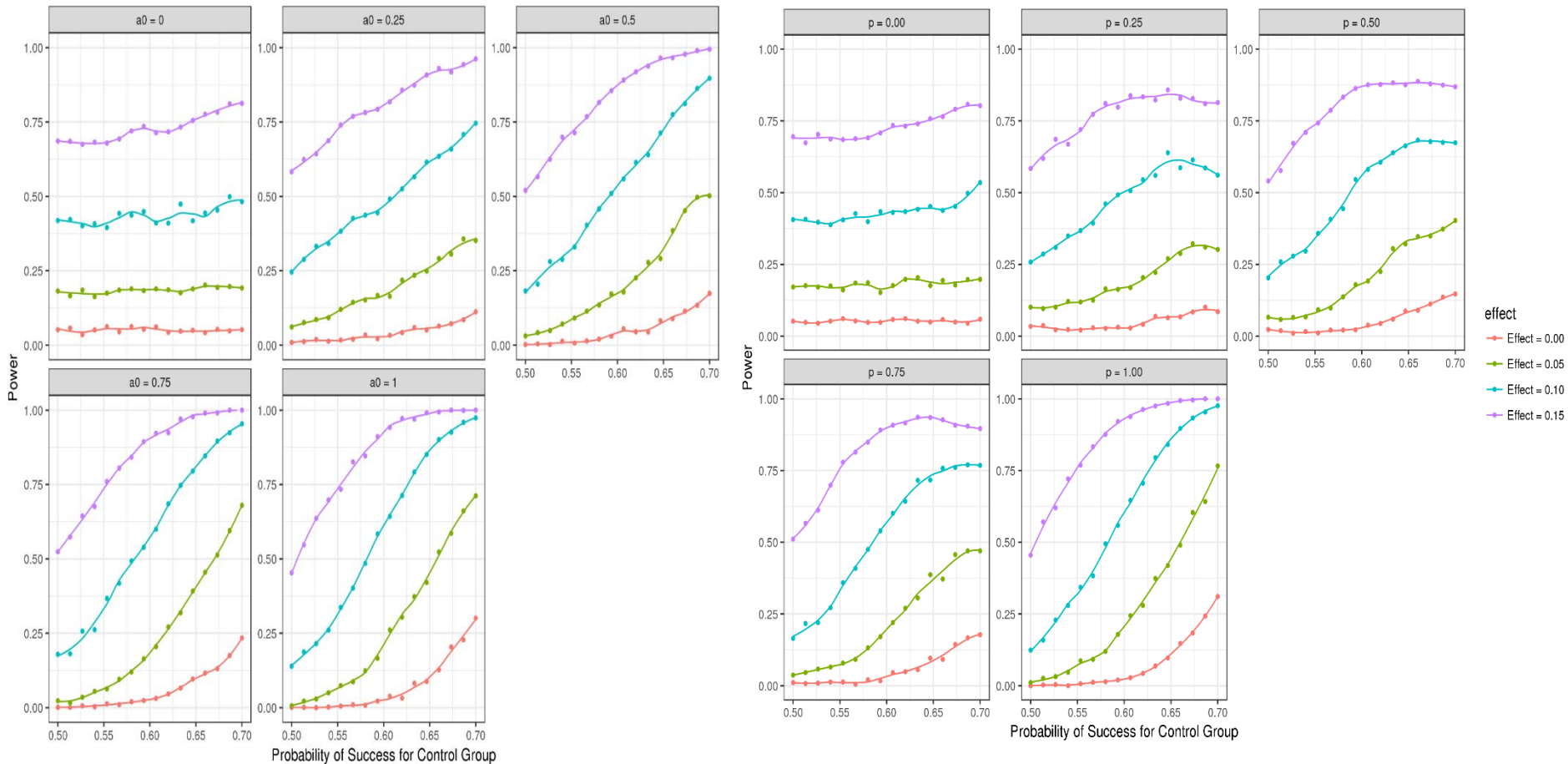
Example 1: Power Prior vs Mixture Priors



Power prior with various α_0 values

Mixture priors with beta(72, 48) and beta(1,1) at various mixing proportions

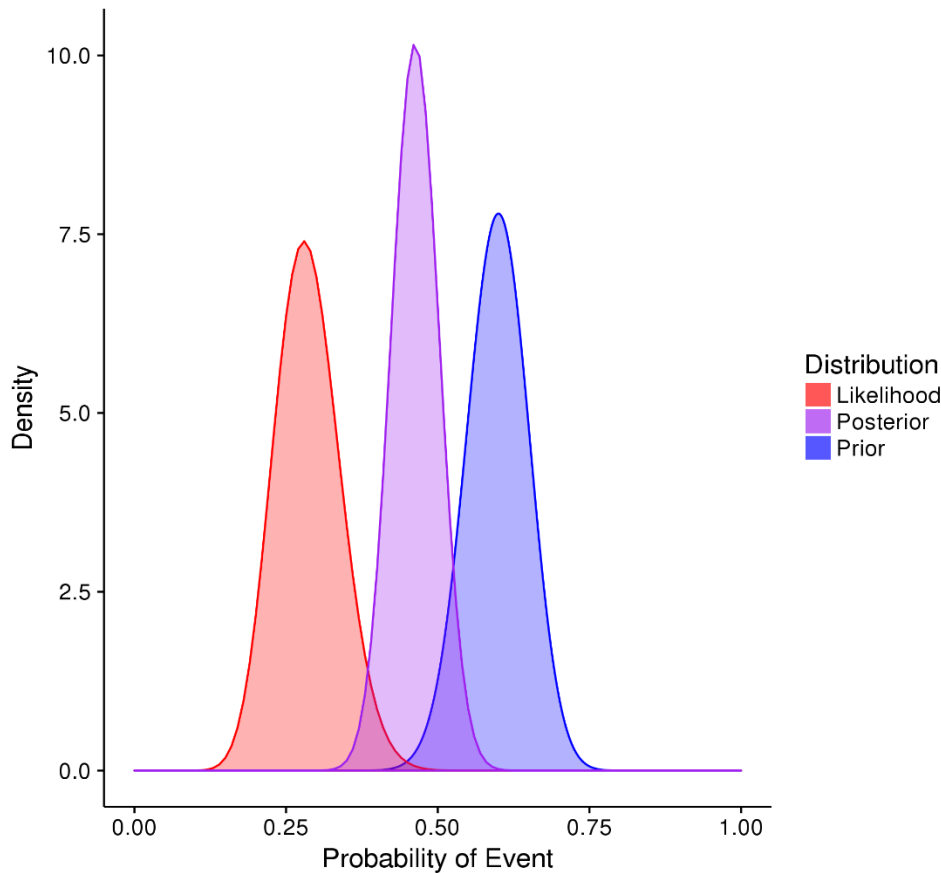
Example 1: “Power” Plots



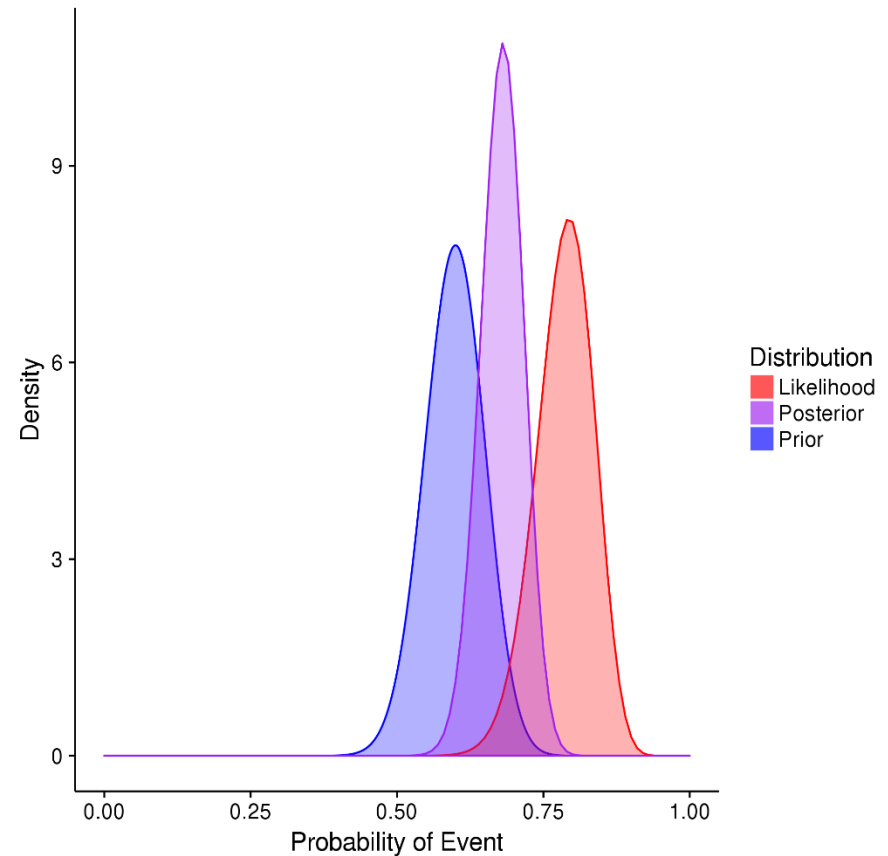
Plots of **power** for power priors (left) with various α_0 values and mixture priors (right) with various mixing proportions.

Example 1: Impact of Borrowing on Results

$a_0=0.75$, Observed $y=20$, $n=70$.

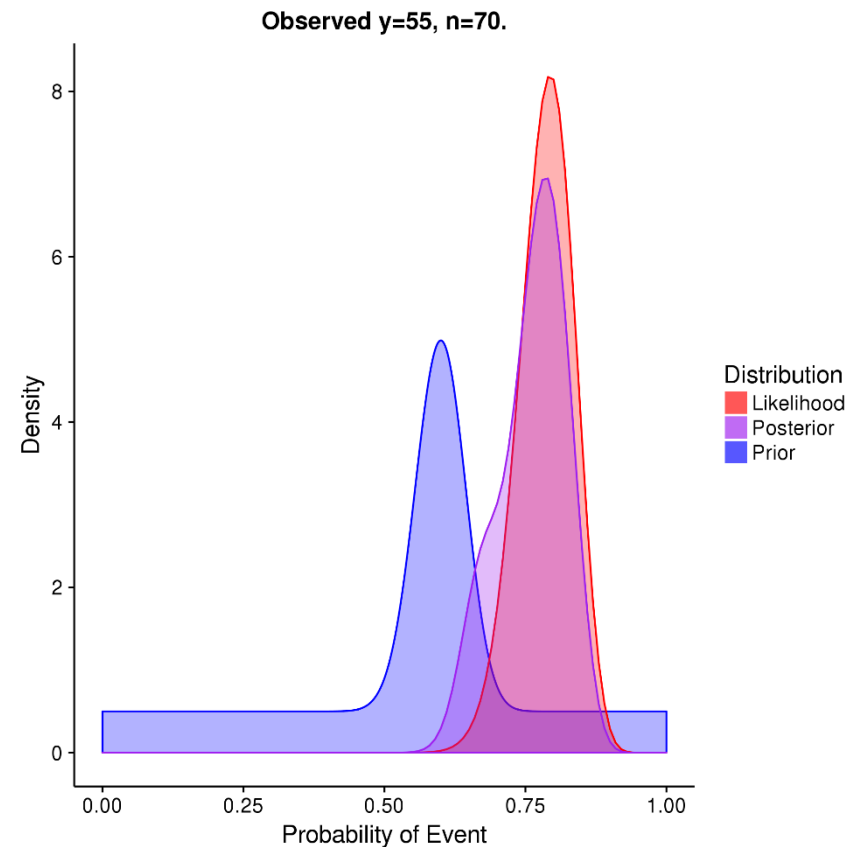
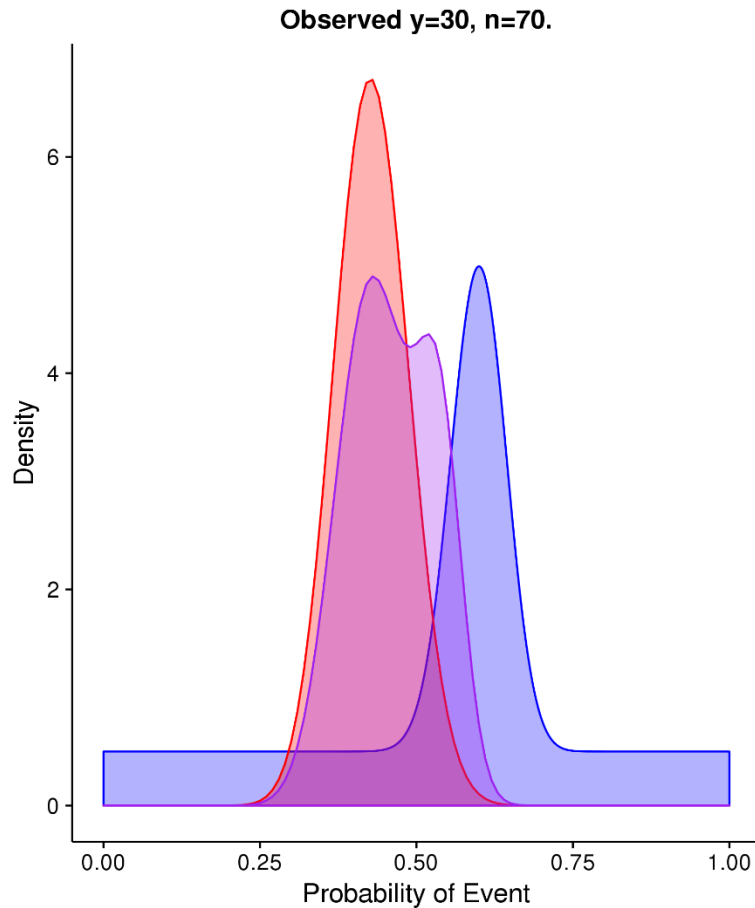


$a_0=0.75$, Observed $y=55$, $n=70$.



Plots of example posterior distributions for control arm, based on different trial outcomes, using power prior ($\alpha_0 = .75$)

Example 1: Impact of Borrowing on Results



Plots of example posterior distributions for control arm, based on different trial outcomes, using mixture prior ($p = .5$)

Example 2: Dynamic Borrowing of Adult Data to Pediatrics

- ◆ We are considering a pediatric rare disease trial in 50 patients: 40 active, 10 placebo (pbo)
- ◆ Primary Endpoint is binary response variable
- ◆ We want to use all relevant information to focus on bringing valuable scientific information to patients, prescribers and regulators
 - ✓ Network Meta-Analysis of studies was performed
 - ✓ Drug of Interest was featured in one study in adults

- ◆ We consider the new trial successful if

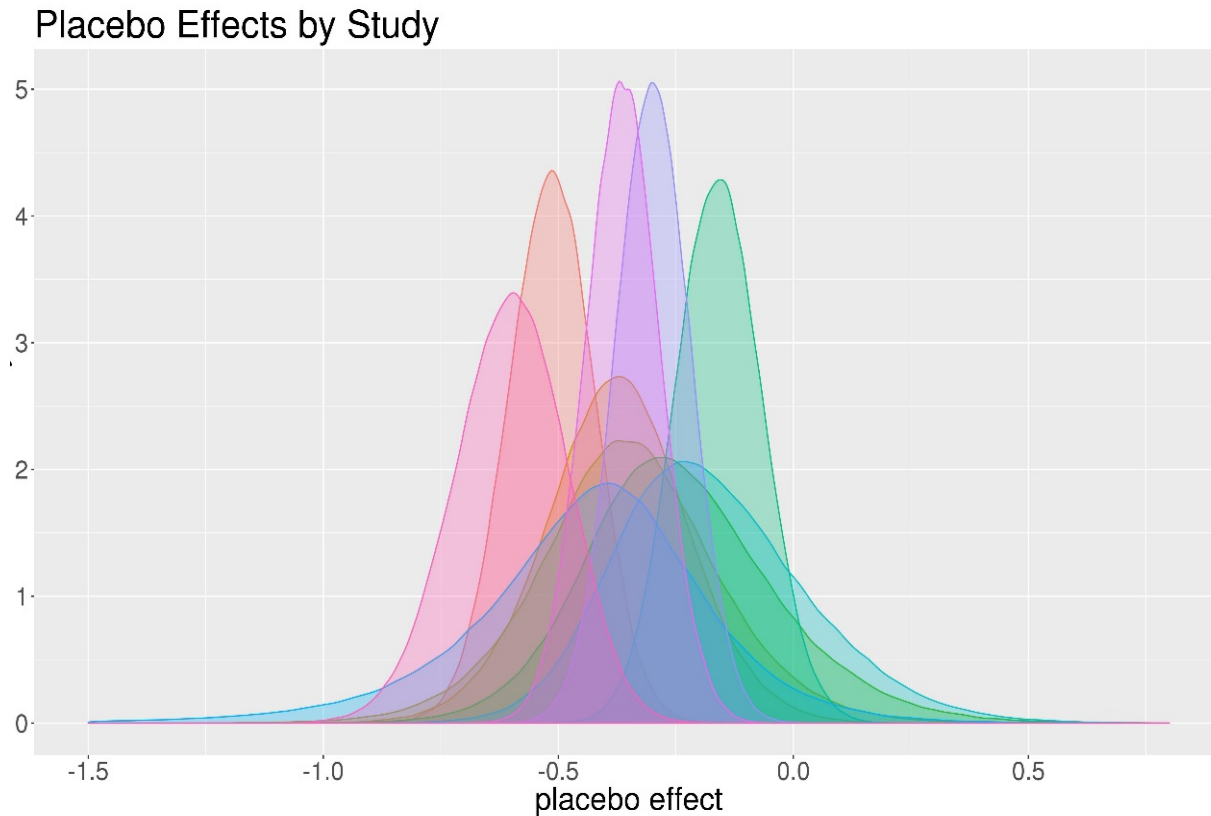
$$P(\text{effect} > 0.4) > 80\%$$

Could be based on medical impact of disease, patient/prescriber input

where effect is difference in log odds for drug vs pbo

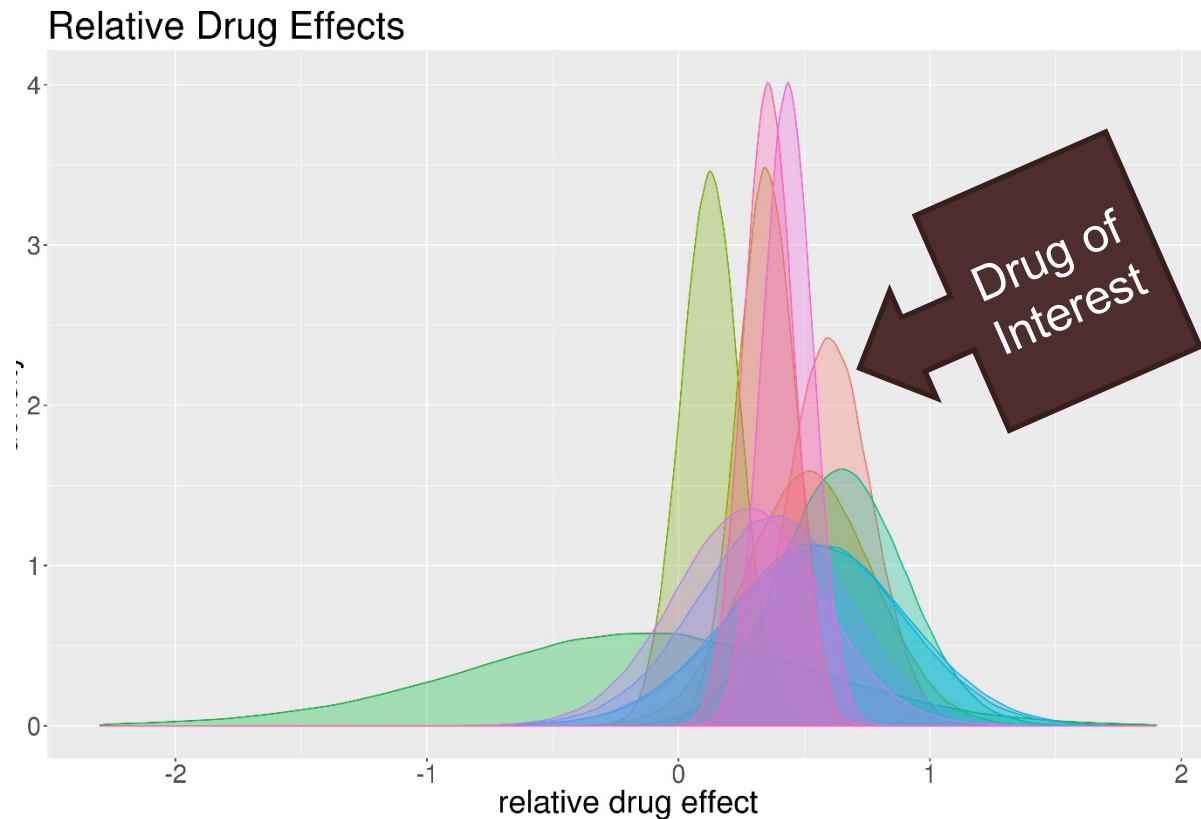
Example 2: Historical Adult Placebo Data

- ◆ 10 relevant studies (all controlled).
- ◆ 13 different dose / treatments.
- ◆ Average Control Rate = 0.4 ($n=1853$)

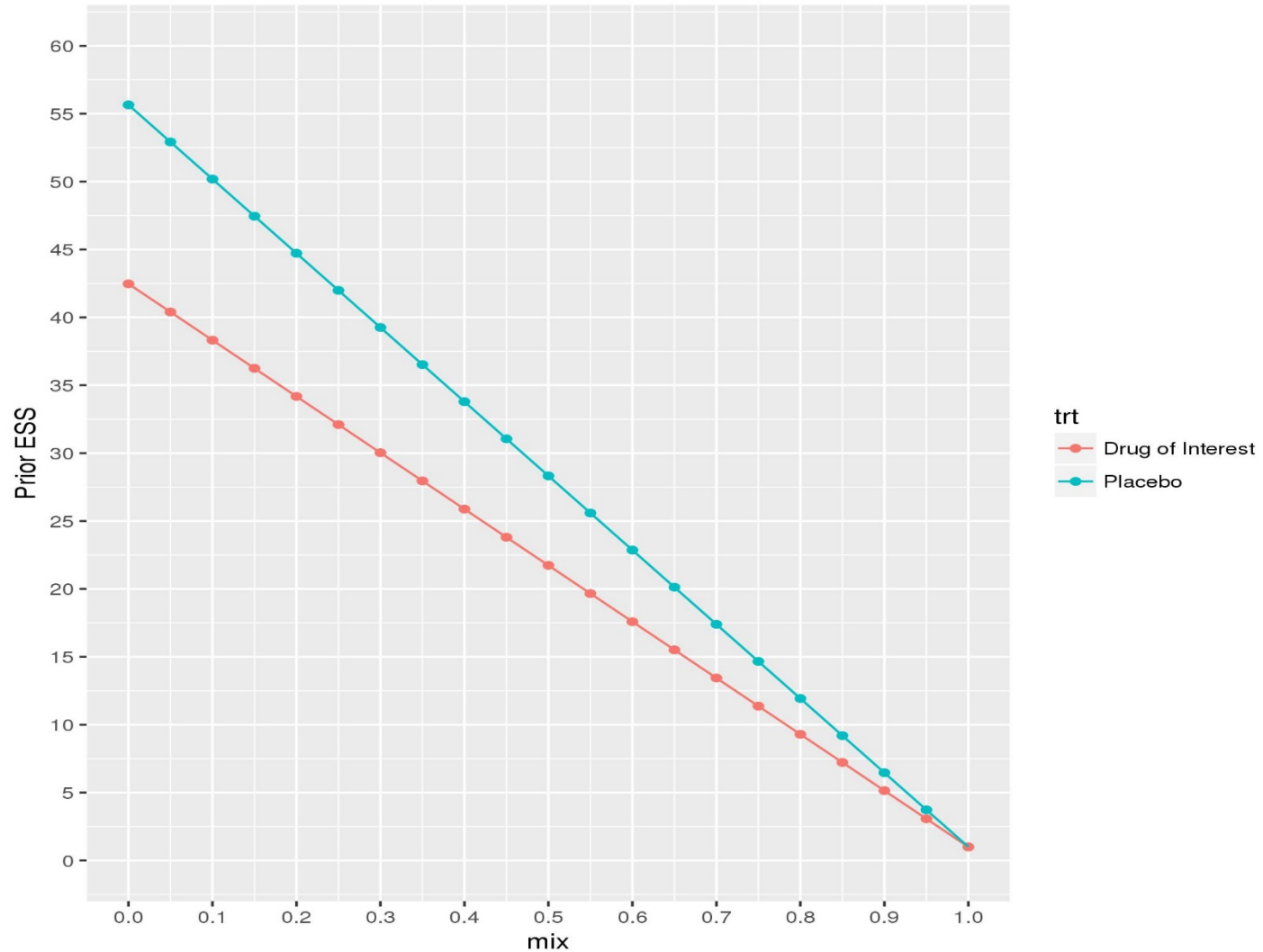


Example 2: Historical Adult Active Drug Data

- ◆ 10 relevant studies (all controlled)
- ◆ 13 different dose / treatments
- ◆ Drug of interest rate = 0.5 ($n=300$)

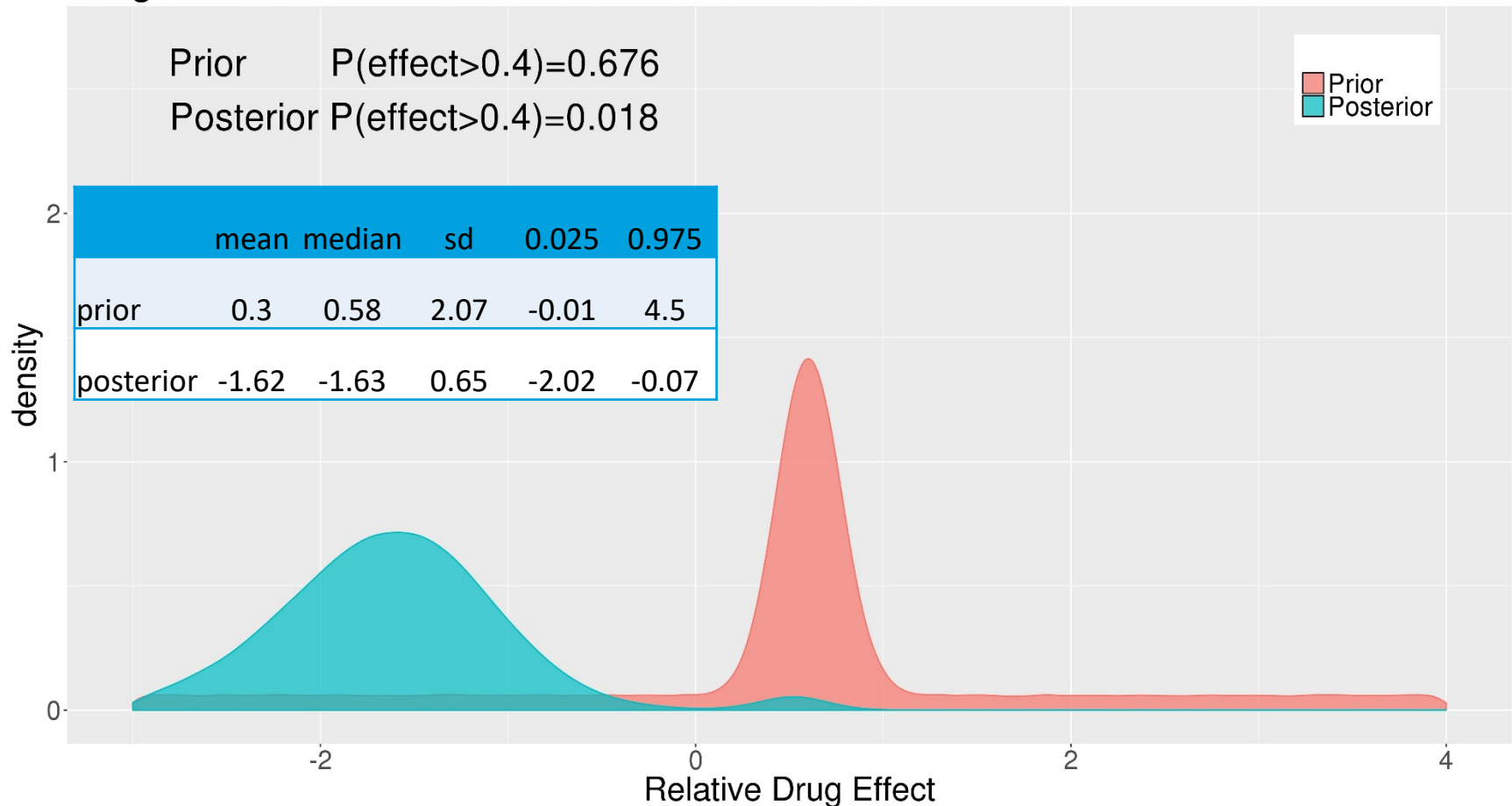


Example 2: Effective Sample Size



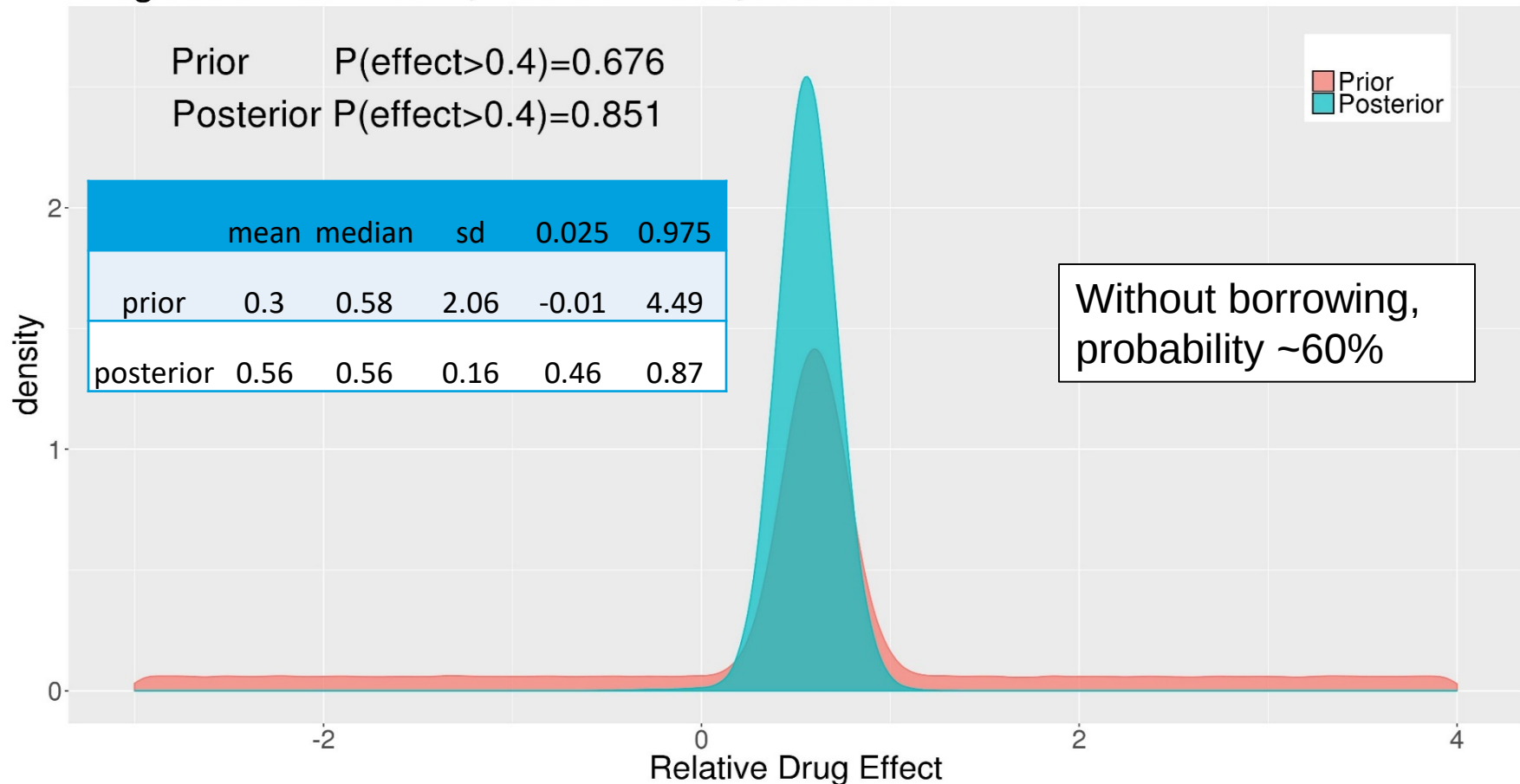
Example 2: An example outcome

Drug of Interest=5/40, Placebo=4/10, mix=0.5



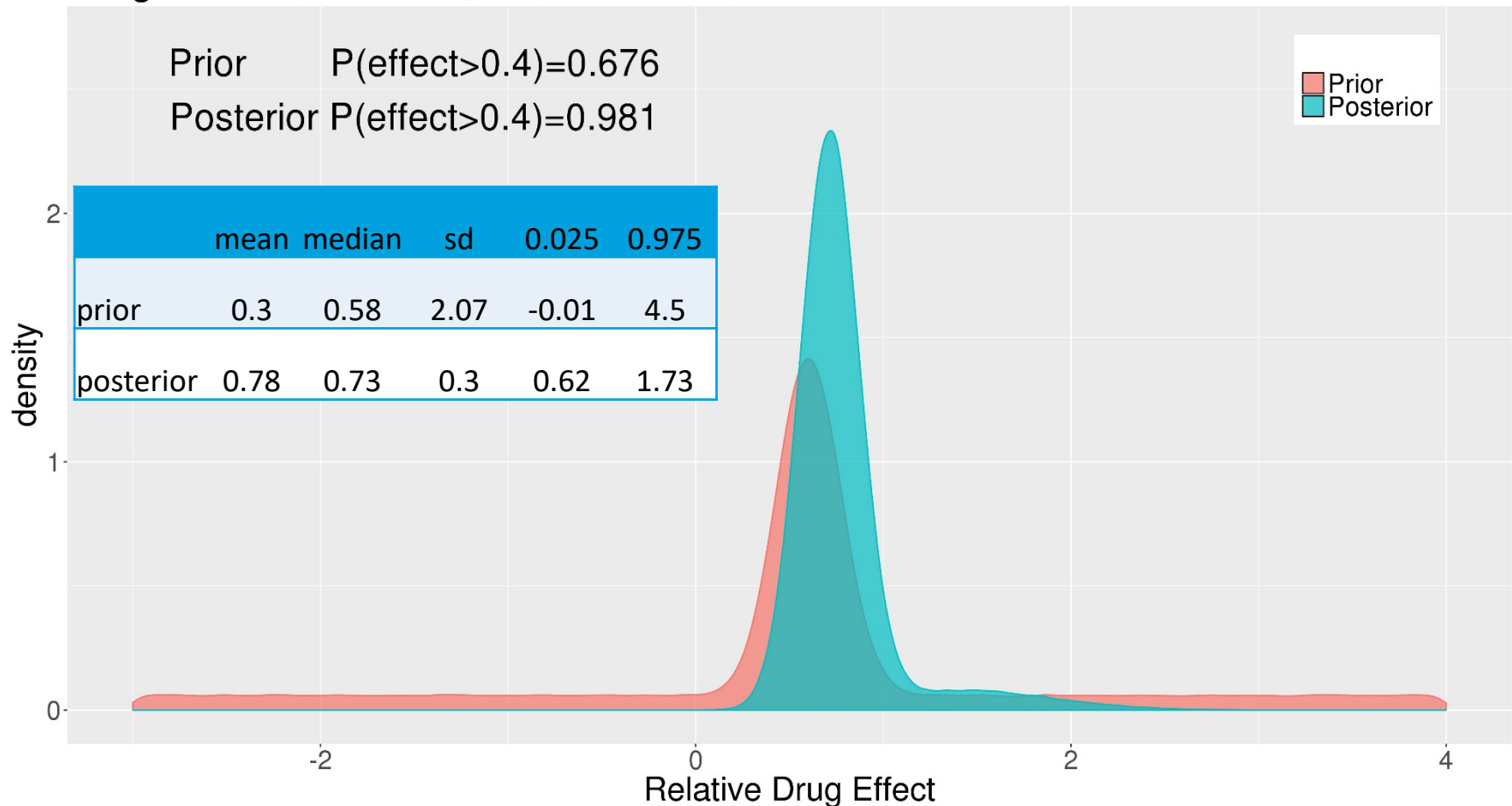
Example 2: An example outcome

Drug of Interest=20/40, Placebo=4/10, mix=0.5



Example 2: An example outcome

Drug of Interest=30/40, Placebo=4/10, mix=0.5



Conclusion

- ◆ Patients with rare diseases are in desperate need of innovation
- ◆ Need to leverage ALL sources of information
- ◆ Great flexibility in methods for borrowing
- ◆ Can incorporate patient/caregiver preferences and set thresholds accounting for unmet need, etc.
- ◆ Requires a shift in thinking from 2 studies $p < 0.05$ to continual learning via Bayesian approach

Thank you!

Backup

Key References

- ◆ Hampson, Whitehead, Eleftheriou, Tudur-Smith, Jones, Jayne, Hickey, Beresford, Bracaglia, Caldas, Cimaz, Dehoorne, Dolezalova, Friswell, Jelusic, Marks, Martin, McMahon, Peitz, van Royen-Kerkhof, Soylemezoglu, Brogan. (2015). Elicitation of Expert Prior Opinion: Application to the MYPAN Trial in Childhood Polyarteritis Nodosa. *PLoS One*, 10(3): e0120981.
- ◆ Viele, Berry, Neuenschwander, Amzal, Chen, Enas, Hobbs, Ibrahim, Kinnersley, Lindborg, Micallef, Roychoudhury, Thompson. (2014). Use of historical control data for assessing treatment effects in clinical trials. *Pharmaceutical Statistics*, 13(1): 41-53.

Motivation in Rare Diseases



- ◆ Significant challenges in rare disease setting
- ◆ Amongst other challenges, unlikely to be able to fully power phase 3
- ◆ Need to leverage all available data
 - Some rare diseases may be more common in adults
 - Other indications may have been considered for a given compound
 - Other external sources may be available

Example: MYPAN

- ◆ Childhood polyarteritis nodosa (PAN) is a rare and severe multi-systemic vasculitic disease
- ◆ Affects approximately 1 per million children
- ◆ MYPAN study (Mycophenolate mofetil for childhood PAN) is an open-label non-inferiority RCT of mycophenolate mofetil (MMF) versus Cyclophosphamide (CYC)
- ◆ Infeasible to conduct definitive study
- ◆ Aim instead to improve understanding of treatment options for PAN

Example: MYPAN

- ◆ Prior elicitation meeting was convened and opinion was sought on
 - the probability that a patients treated with CYC would achieve disease remission within 6-months, and
 - on the relative efficacies of MMF and CYC
- ◆ Individual elicitations first, then consensus; ESS influential in achieving consensus
- ◆ Expert opinion was combined with previously unseen data from a recently completed RCT in antineutrophil cytoplasmic autoantibodies (ANCA) associated vasculitis

Fig 2. Flow diagram illustrating the sequence of activities undertaken during the MYPAN prior elicitation meeting and the time allocated to each activity.

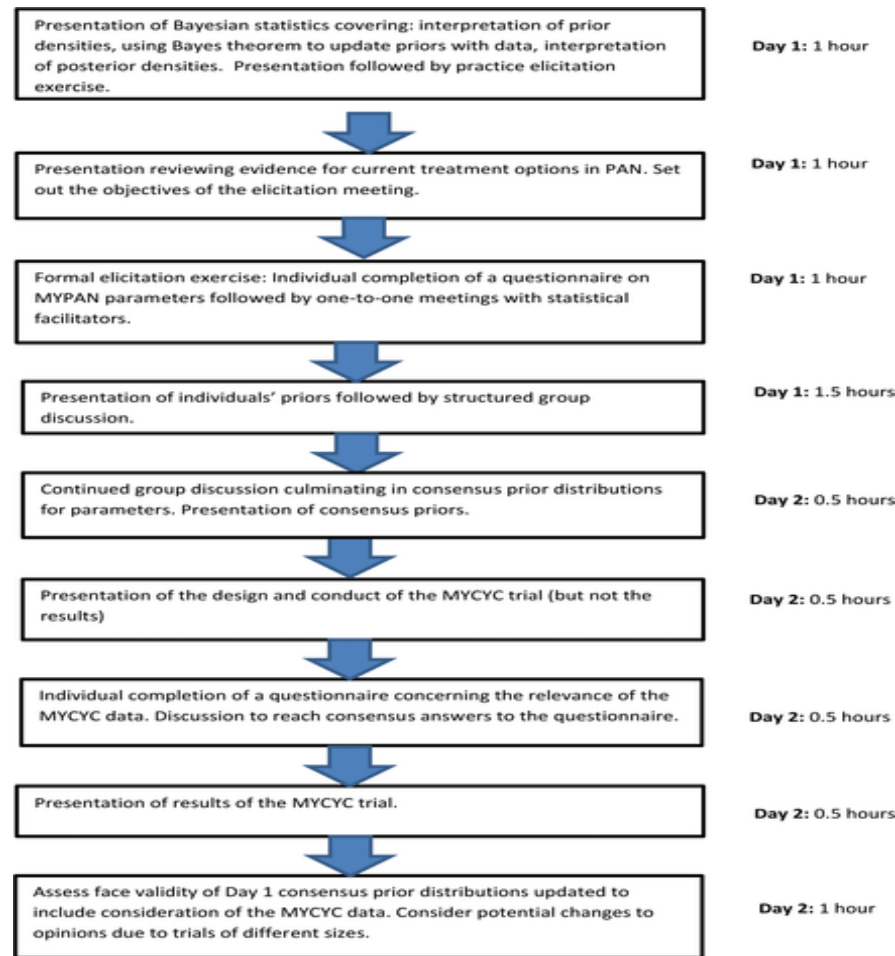
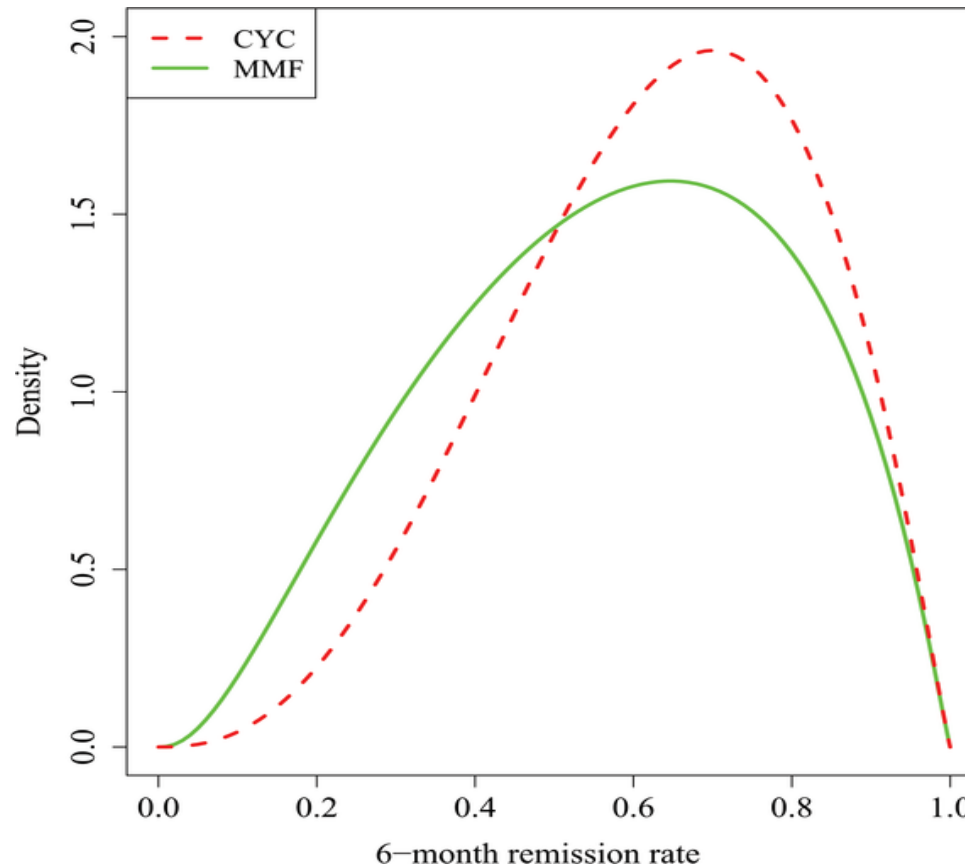


Fig 3. Expert prior opinion before introduction of the MYCYC data regarding 6-month remission rates using treatment with CYC or MMF for children with PAN.

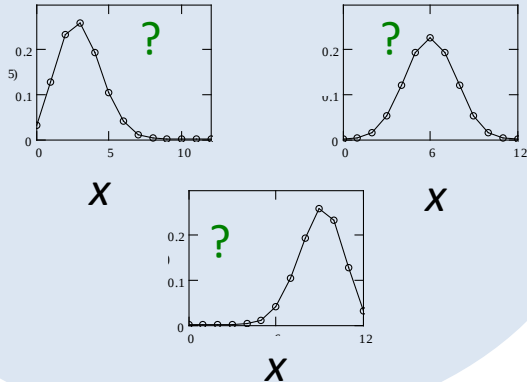


Hampson LV, Whitehead J, Eleftheriou D, Tudur-Smith C, Jones R, et al. (2015) Elicitation of Expert Prior Opinion: Application to the MYPAN Trial in Childhood Polyarteritis Nodosa. PLOS ONE 10(3): e0120981. <https://doi.org/10.1371/journal.pone.0120981>
<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0120981>

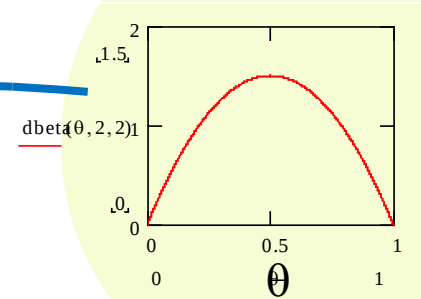
Combining Information

likelihood

$$0 < \theta < 1$$

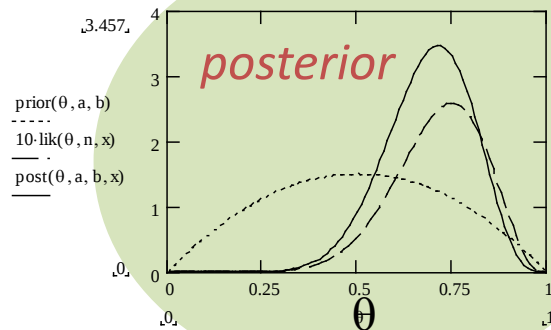


prior



Bayes' Theorem

The likelihood function represents all possible binomial distributions from which the sample might have originated—an infinite, uncountable number of possible distributions, one for each possible value of θ in $[0, 1]$.

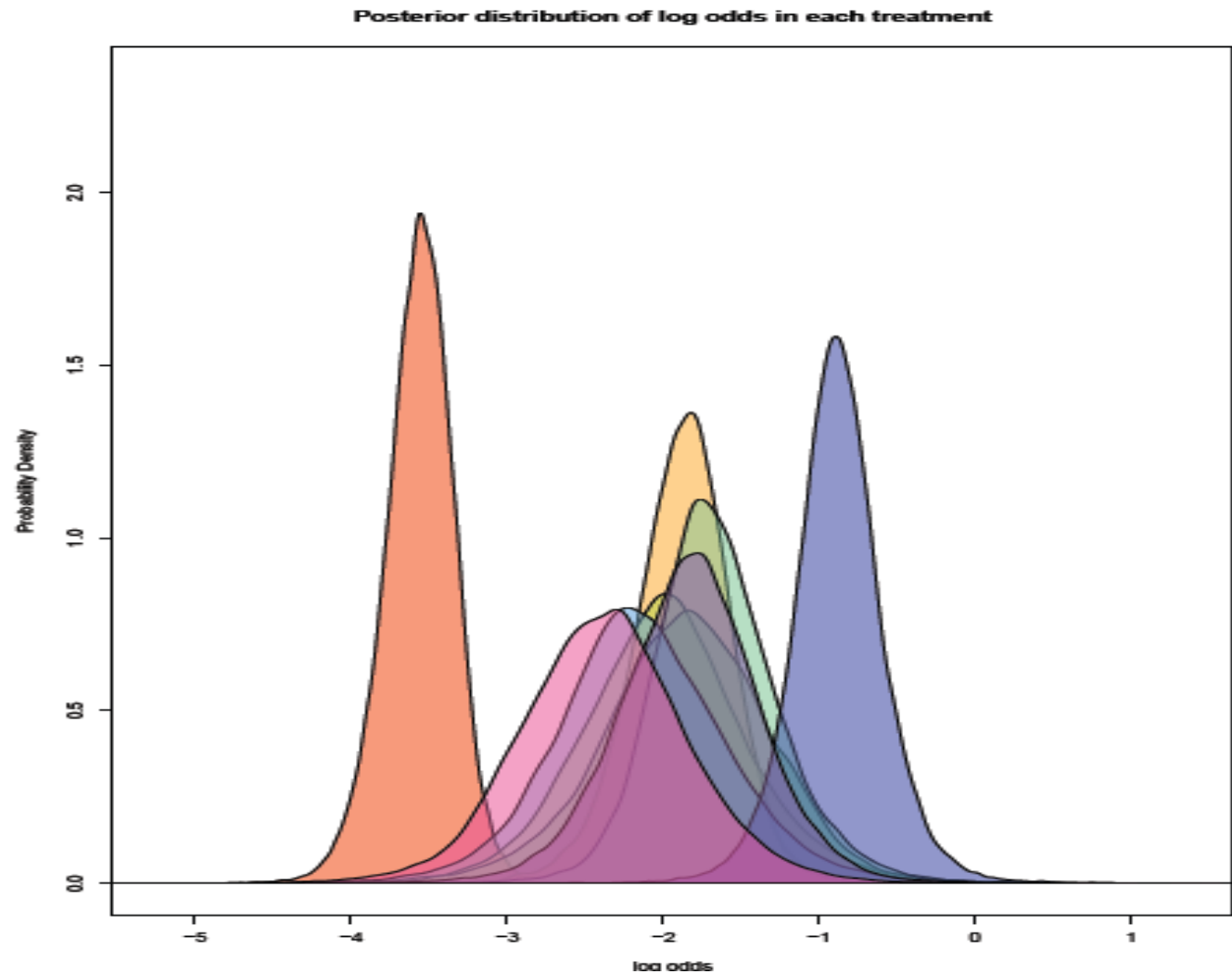


The prior distribution represents all we know before we obtain the current data. It may be based on past data, expert opinion, or both.

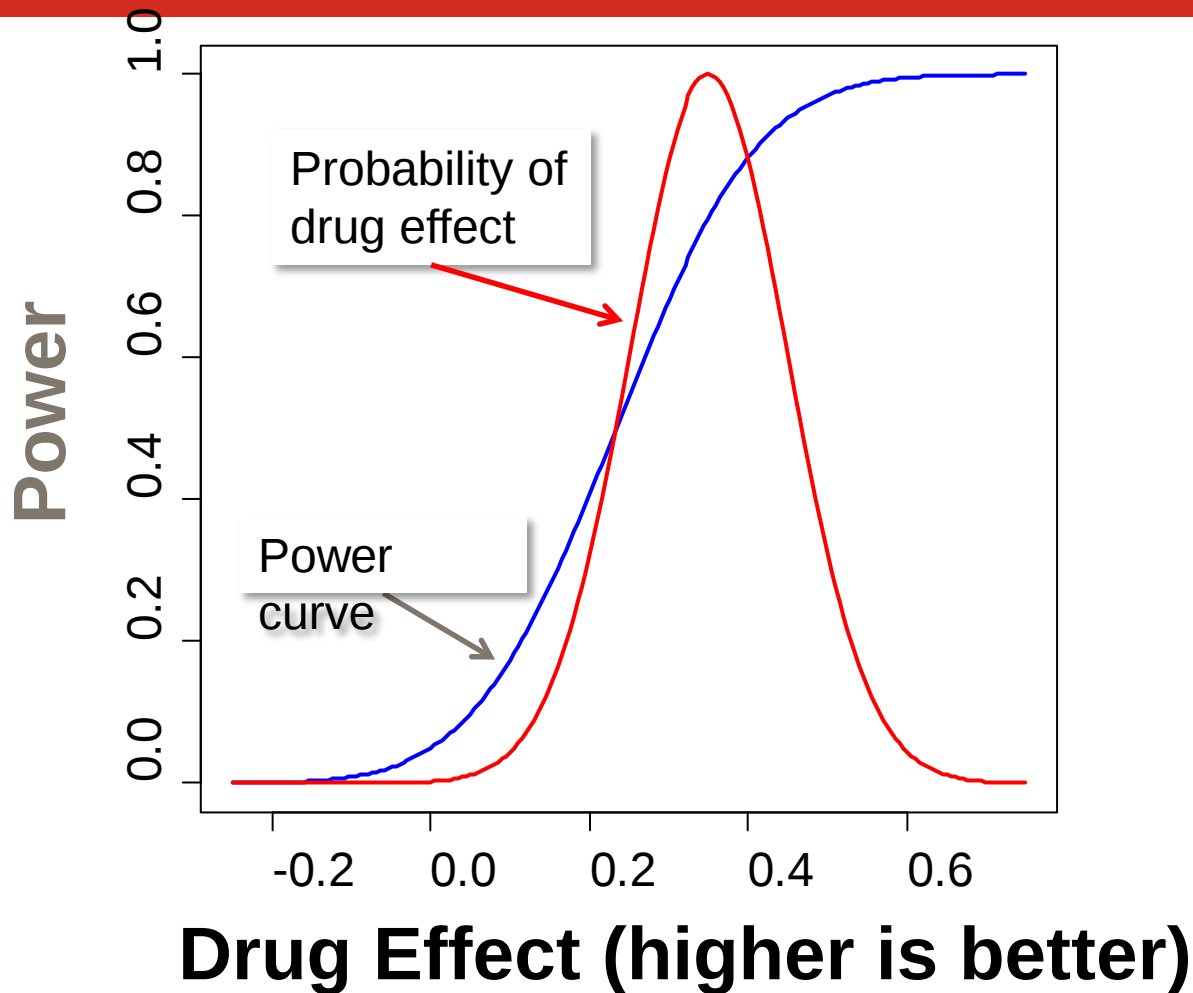
The posterior represents everything we know from prior information and new data.

Bayesian Synthesis of Data

Ttr_8
Ttr_7
Ttr_6
Ttr_5
Ttr_4
Ttr_3
Ttr_2
Ttr_1
XPlacebo



Probability of Phase 3 success

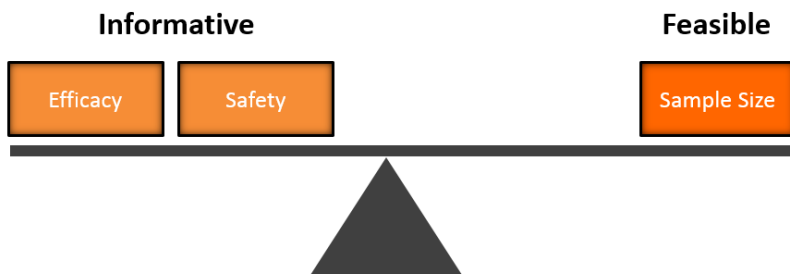


- Our current data informs **where we are likely to be on the curve**

1. Add in the uncertainty in the magnitude of the drug effect
2. **Average the power over the possible drug effect to get probability of study success (PrSS)**

Extrapolation

- ◆ In many cases for orphan indications, rare diseases and pediatric populations, **feasibility** is a concern
 - Fully powered trials in these diseases states and populations could yield a trial that would not finish in a reasonable amount of time)
- ◆ Extrapolation allows us to leverage information on efficacy of the experimental arm (as opposed to augmented/historical)
- ◆ Sources of pediatric extrapolation may include:
 - Other pediatric age groups
 - Other formulations of same active ingredient
 - Related pediatric indications
 - Adult indication for same (or related) pediatric indication



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Incorporating Early Phase Data in Phase 3 Designs

John Scott, Ph.D., FDA/CBER

March 19, 2018

The rare disease setting

- Need often very great
- Practical trial constraints often very high
- Moral obligation to make maximal use of available information
- Innovative trial designs can be part of that
- Also have a moral obligation not to make erroneous conclusions of effectiveness

Uses of external data in late phase trials

- For planning
 - Uncontroversial
- As a comparator in single-arm study
 - Later sessions may touch on this
- Partial borrowing of control data
- Partial borrowing of control and experimental data

General considerations for partial borrowing

- Scientific comparability of data sources
 - Population, endpoints, site, background care...
- Prospective planning
 - Was the external data intended to be used in this way? Affects comparability and assures “fair” use of data
- Can all relevant external data be appropriately considered in forming a prior?
 - Regression to the mean

Type I error considerations

- Conventional maximum Type I error probability $< .05$ may need reconsideration in a partial borrowing framework
 - Strict Type I error control eliminates benefit of borrowing
 - Type I error itself not a well-defined concept in Bayesian setting with informative priors
- May need to consider other concepts of error rate
 - Average Bayes error
 - Maximum posterior probability of null in rejection region

Thresholds and decision-making

- “How much to borrow” is a *very* complicated question
- Prior effective sample size or influence of prior on posterior
 - How do we decide a Phase II patient is 40% as relevant as a Phase III patient? Or that prior data should form no more than 15% of posterior?
- Calibrating to Type I error probability
 - Fundamentally arbitrary
- Dynamic borrowing
 - Makes amount of borrowing appear automatic
 - Still requires calibration
 - Relies exclusively on effect homogeneity, not clinical comparability
- Can decisions ultimately be calibrated to outcomes and values?

Regulatory interactions

- Novel and complex approaches may be a learning process for both applicants and FDA
- May require intense planning and discussion
- Public workshop tomorrow (3/20/18) on FDA campus on Complex and Innovative Trial Design
 - Trial design possibilities
 - Use of simulations in trial design
 - FDA's pilot program to evaluate novel design proposals



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CYSTIC FIBROSIS FOUNDATION
THERAPEUTICS
DEVELOPMENT NETWORK

Utilizing Patient Registry and Natural History Data to Advance Therapeutic Development for Rare Diseases

Nicole Mayer Hamblett, PhD

Professor, Pediatrics, Adjunct Professor, Biostatistics

University of Washington

Co-Executive Director, CF Therapeutics Development Network Coordinating Center,
Seattle Children's Hospital



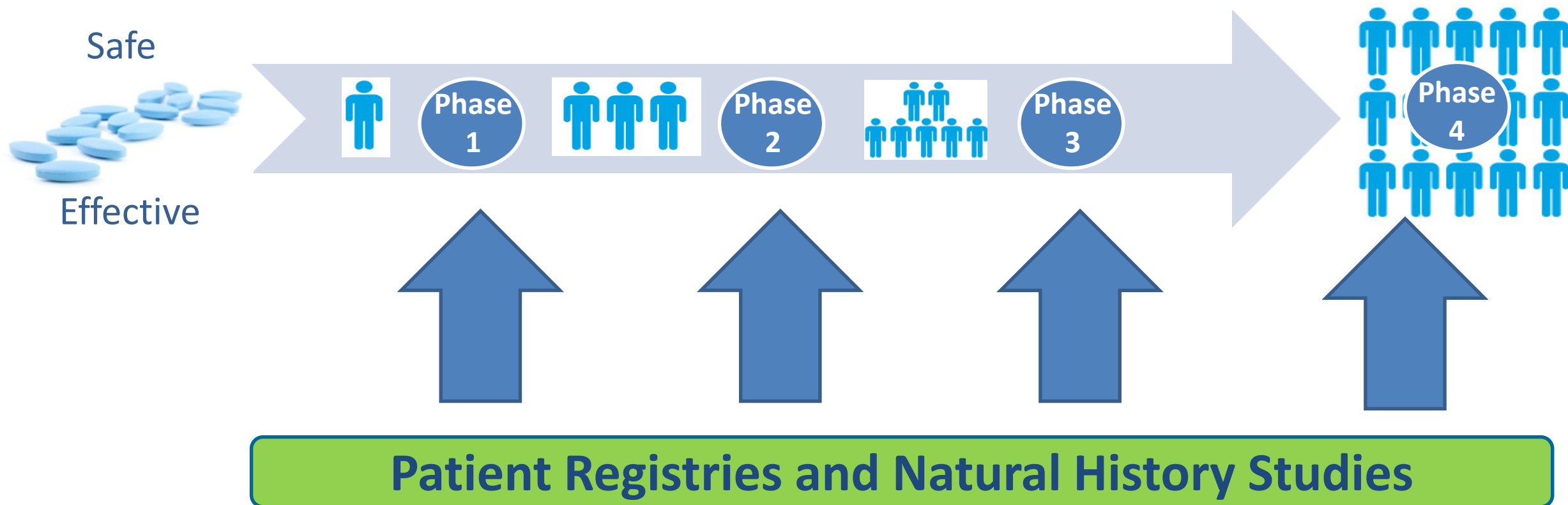
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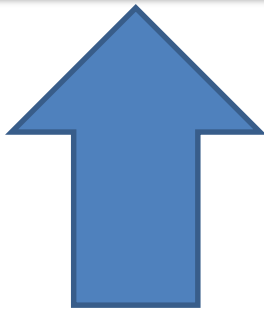
SCHOOL OF PUBLIC HEALTH
UNIVERSITY of WASHINGTON

A Critical Foundation to a Rare Disease Therapeutics Pipeline



A Critical Foundation to a Rare Disease Therapeutics Pipeline

**Sufficient Data
Resources to
Identify
Patients and
Capture
Disease Course**



Patient Registries and Natural History Studies

Registries and Natural History Studies

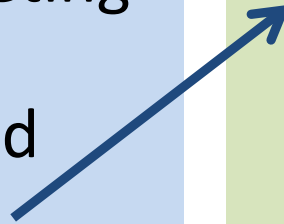
Not Necessarily the Same

- Patient Registries

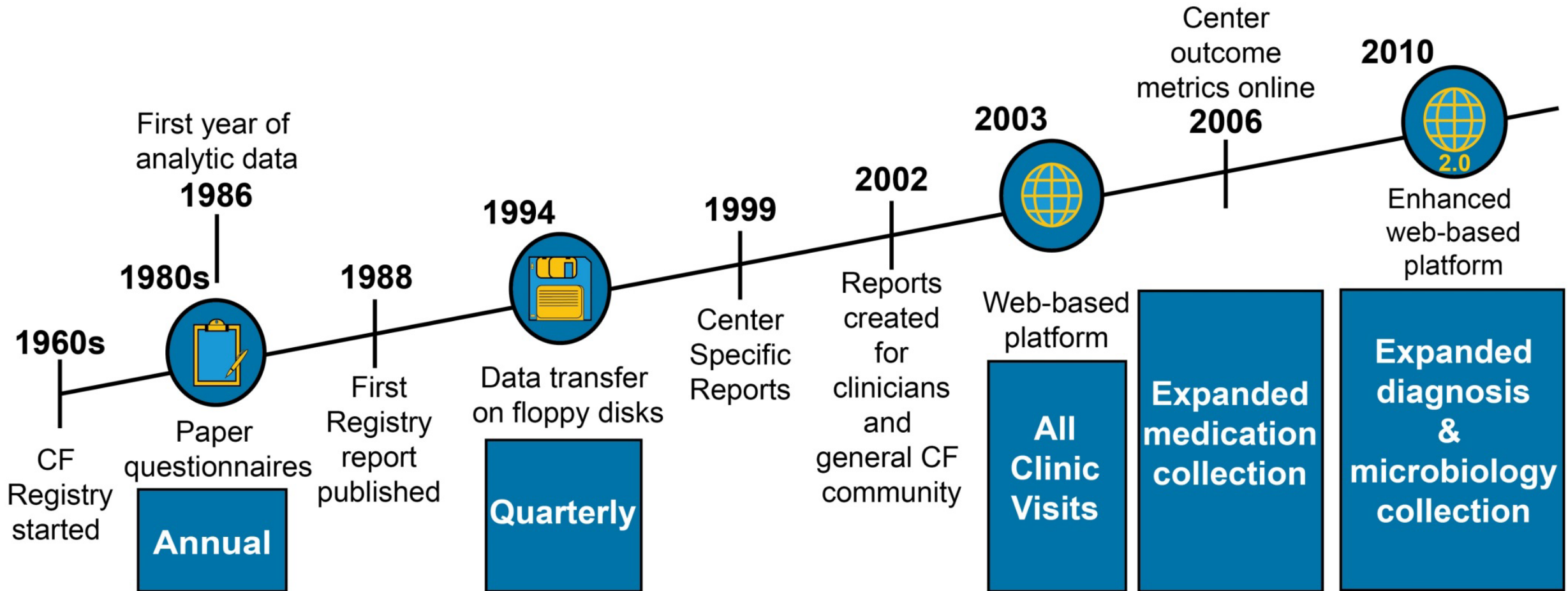
- Broad in scope
- Can be used for patient communication, recruitment
- Used to fulfill post-marketing commitments
- Can include an embedded natural history study

- Natural History Studies

- Freestanding or included within the scope of a registry
- Focused on describing the disease
- Enable track disease course on a more comprehensive and granular level

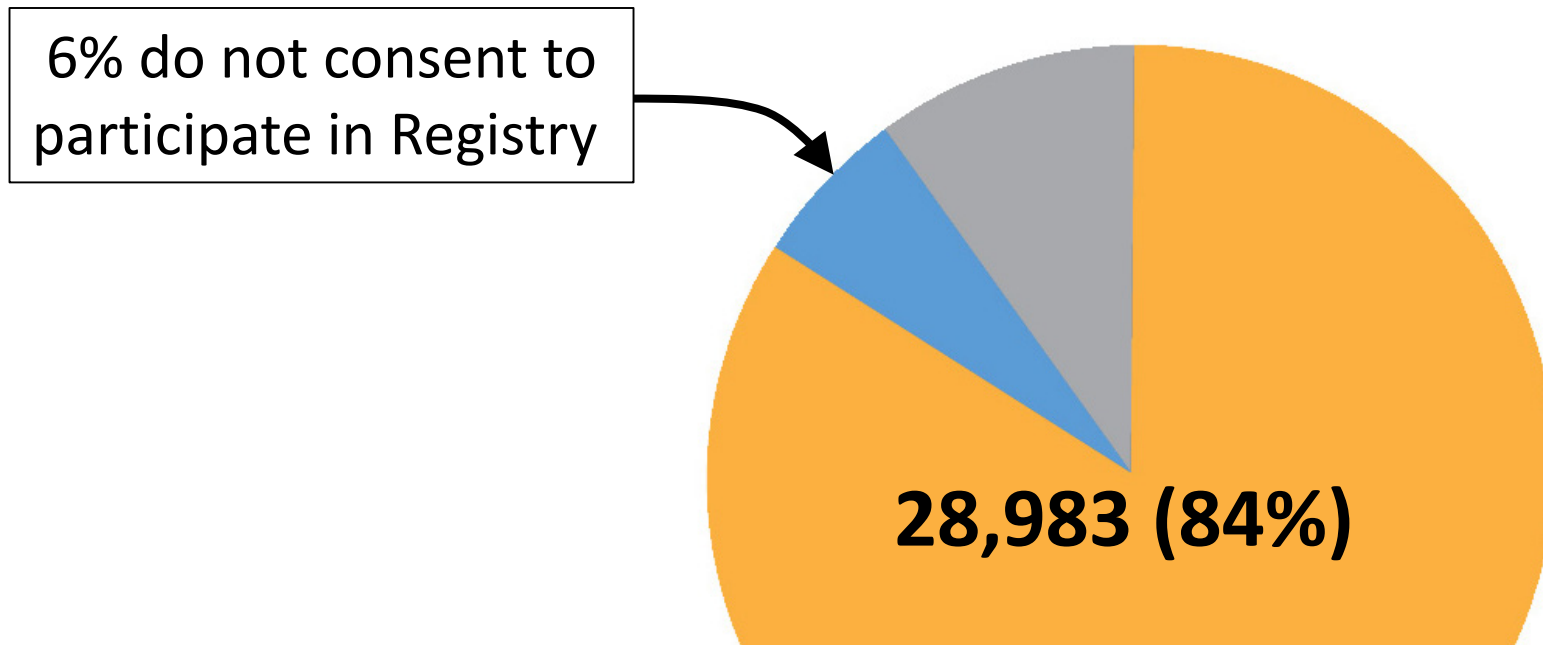


The Cystic Fibrosis National Registry Through the Decades



A Clear Focus on Capturing the Population

**Approximately 84% of Individuals in the US with CF
Followed in the CF Foundation Patient Registry**

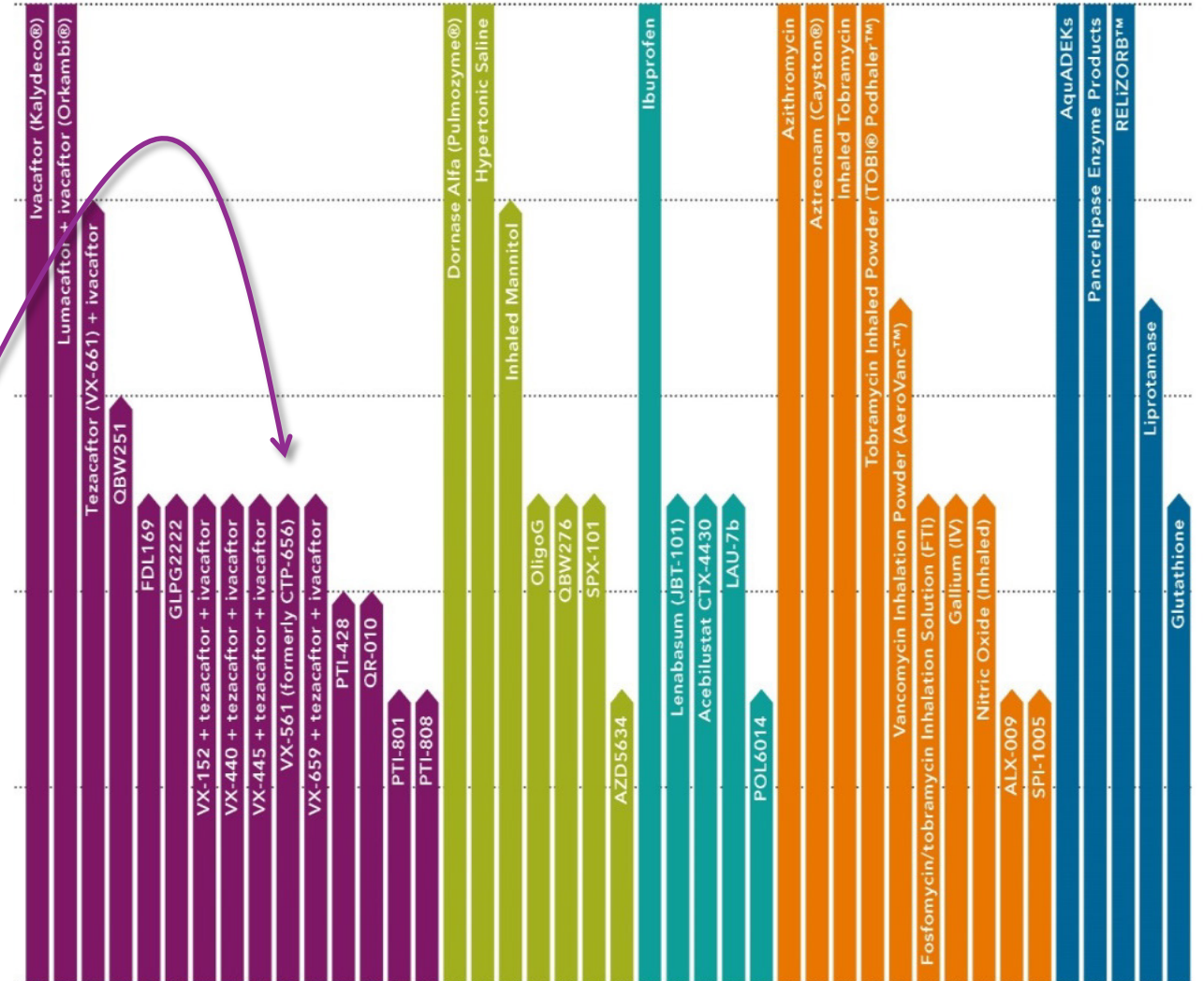


There are over 1700 different *CFTR* mutations which less than 50 CF adults in the U.S. carry – a considerable challenge for developing mutation specific therapies

Leveraging the Entire Population through a Registry

Who and where are these patients?

- Timely identification of ‘**potentially eligible patients**’
- Currently 19 trials in “CF**SmartReports**”
- Available to all programs in the CF Care Center Network



Significant Investments in Registries and NH Studies *and Infrastructure*



Natural Histories Patient Registry



Building Industry Partnerships for Disease Rather than Product-Based Registries

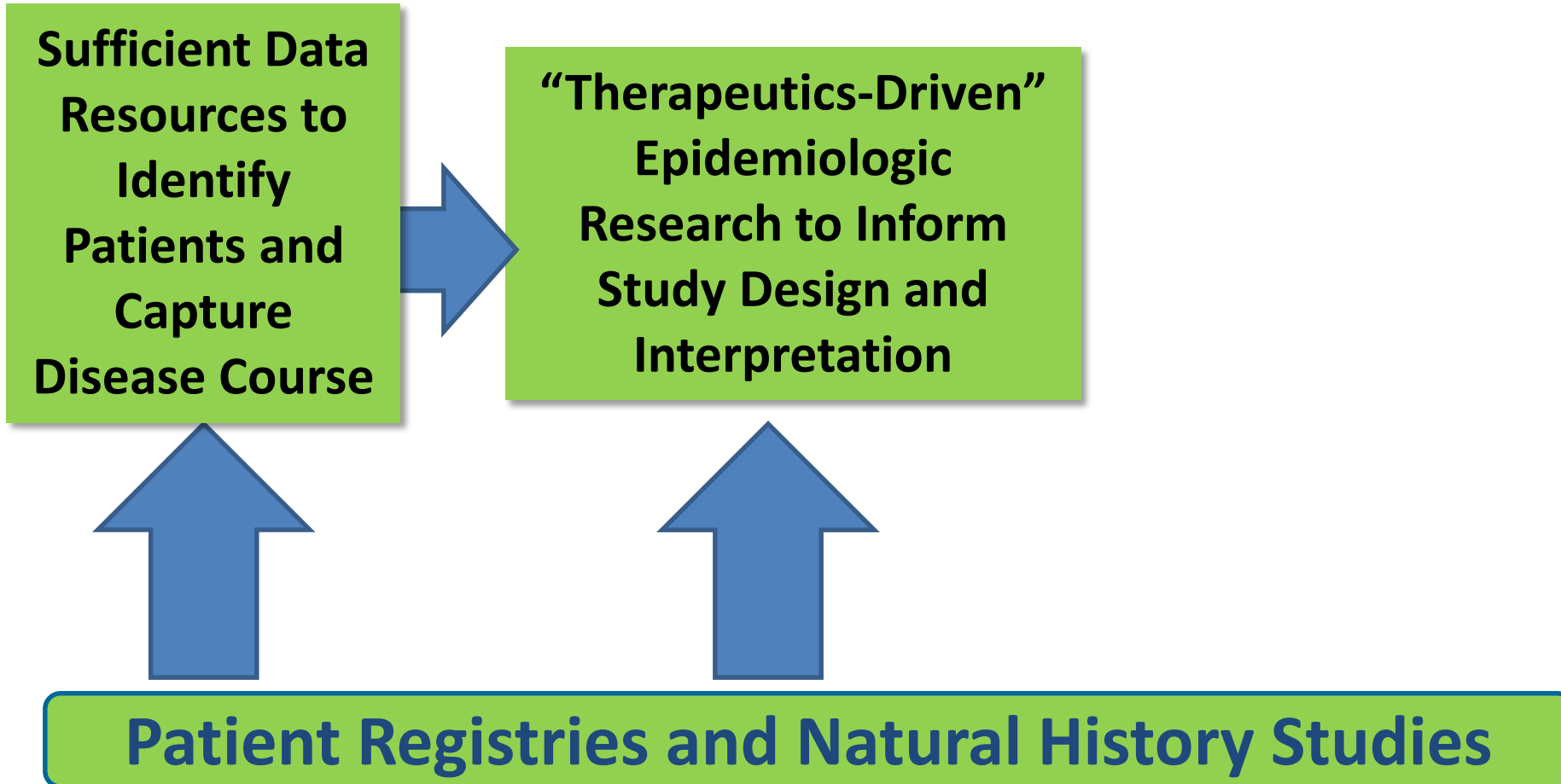
- Avoids duplicative infrastructure
- Removes limitations of product specific registries
 - Eligibility (“on” label only, remove patients switching or off therapy)
 - Limited enrollment size
 - Lack of comparators/controls

There is also Low Hanging Fruit

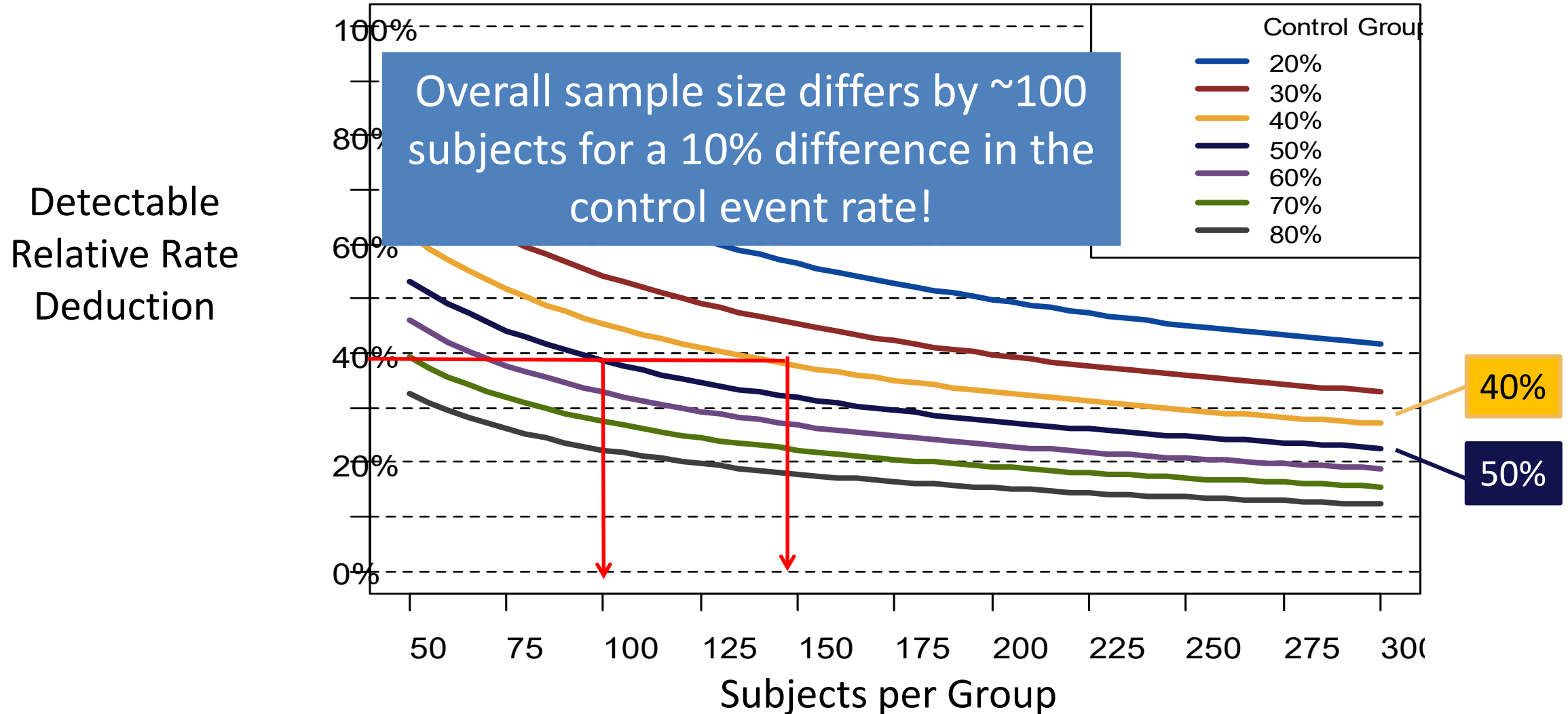
- Complementary natural history data is available through completed clinical trials
 - *Placebo data donation from industry sponsors to a central data archive*
- These data mitigate issues related to missing data and endpoint consistency inherent with registry and NH data



A Critical Foundation to a Rare Disease Therapeutics Pipeline



Therapeutics Driven Epidemiologic Research: *Informing Study Design and Endpoint Selection*

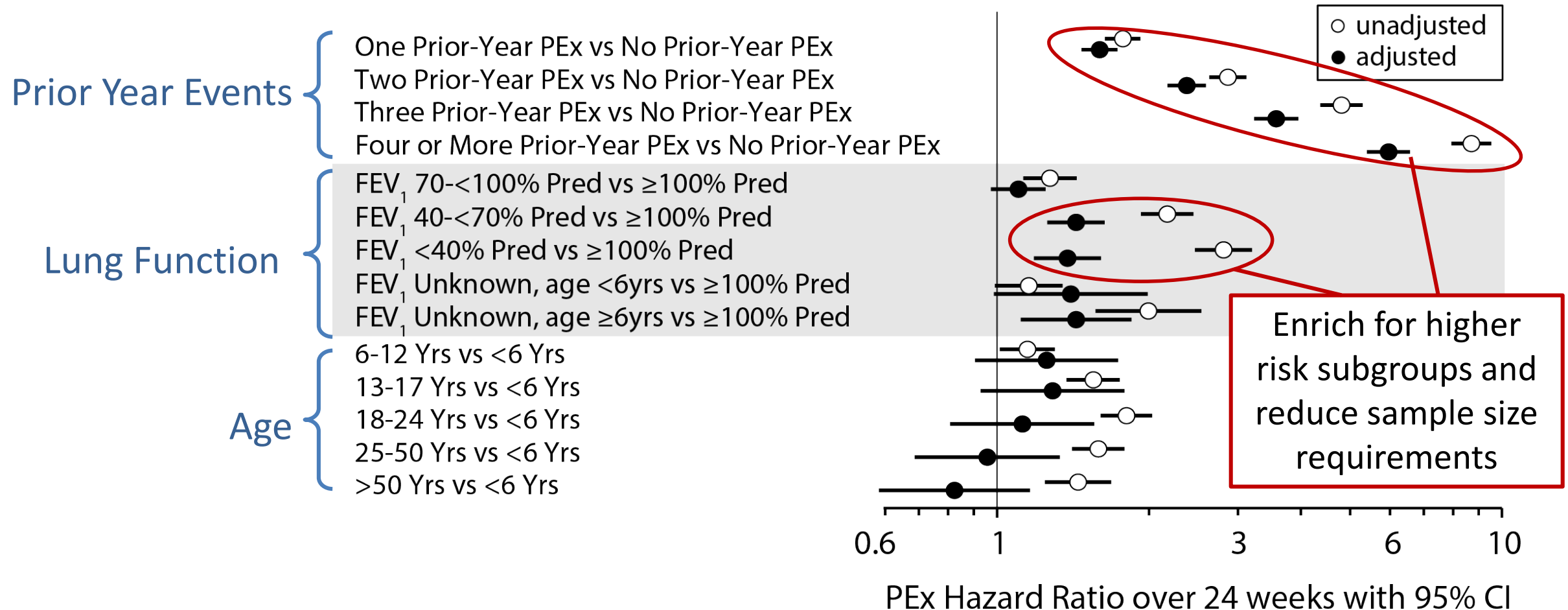


80% power, two-sided $\alpha = 0.05$

So.....We Need to Learn Everything we Can about this Endpoint

- What are the event rates of this endpoint?
- Are there patient subgroups with higher rates of this endpoint?
- Can we can enrich our study population and reduce overall recruitment burden?

Association of Potential Eligibility Criteria and Risk of PEx: US CF Patients, 2010-2014



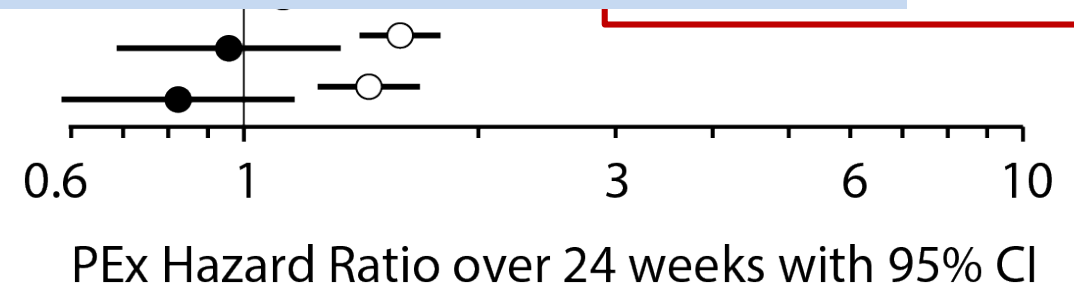
Association of Potential Eligibility Criteria and Risk of PEx: US CF Patients, 2010-2014

Limitations to Consider

Do these events reflect rates with the most current SOC?

Is the endpoint consistent between the registry and how we will collect it for clinical trials?

Age
25-50 Yrs vs <6 Yrs
>50 Yrs vs <6 Yrs



Therapeutics Driven Epidemiologic Research: *Providing Context to Clinical Trial Results*

Discontinuations Due to AE

In a chronic disease setting, very difficult to determine whether AEs attributable to treatment or disease

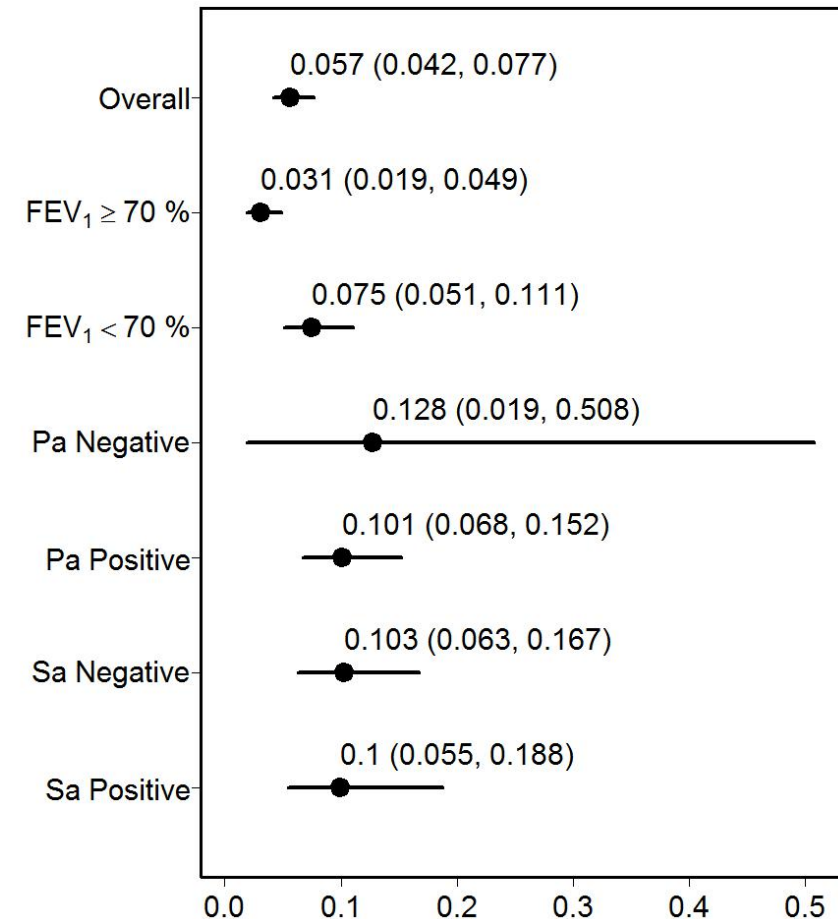
.....even when there is a placebo group

Phase 3 Controlled Studies	Double-Blinded Period	
System Organ Class/ Preferred Term	N= 361 (%)	Control N= 239 (%)
Patients with Any AE Leading to Study Drug Discontinuation	41 (11)	15 (6)
General Disorders and Administration Site Cond.	12 (3)	3 (1)
Condition Aggravated	8 (2)	3 (1)
Chest Discomfort	3 (1)	0
Respiratory, Thoracic and Mediastinal Disorders	32 (9)	9 (4)
Hemoptysis	6 (2)	0
Cough	18 (5)	6 (3)
Bronchospasm	2 (0.6)	0
Pharyngolaryngeal Pain	3 (1)	0
Throat Irritation	1 (0.3)	1 (0.4)
Wheezing	0	2 (1)
Nervous System Disorders	1 (0.3)	1 (0.4)
Headache	1 (0.3)	1 (0.4)
Infection and Infestations	0	2 (1)
Lower Respiratory Tract Infxn.	0	1 (0.4)
Pneumonia	0	1 (0.4)

Therapeutics Driven Epidemiologic Research: *Providing Context to Clinical Trial Results*

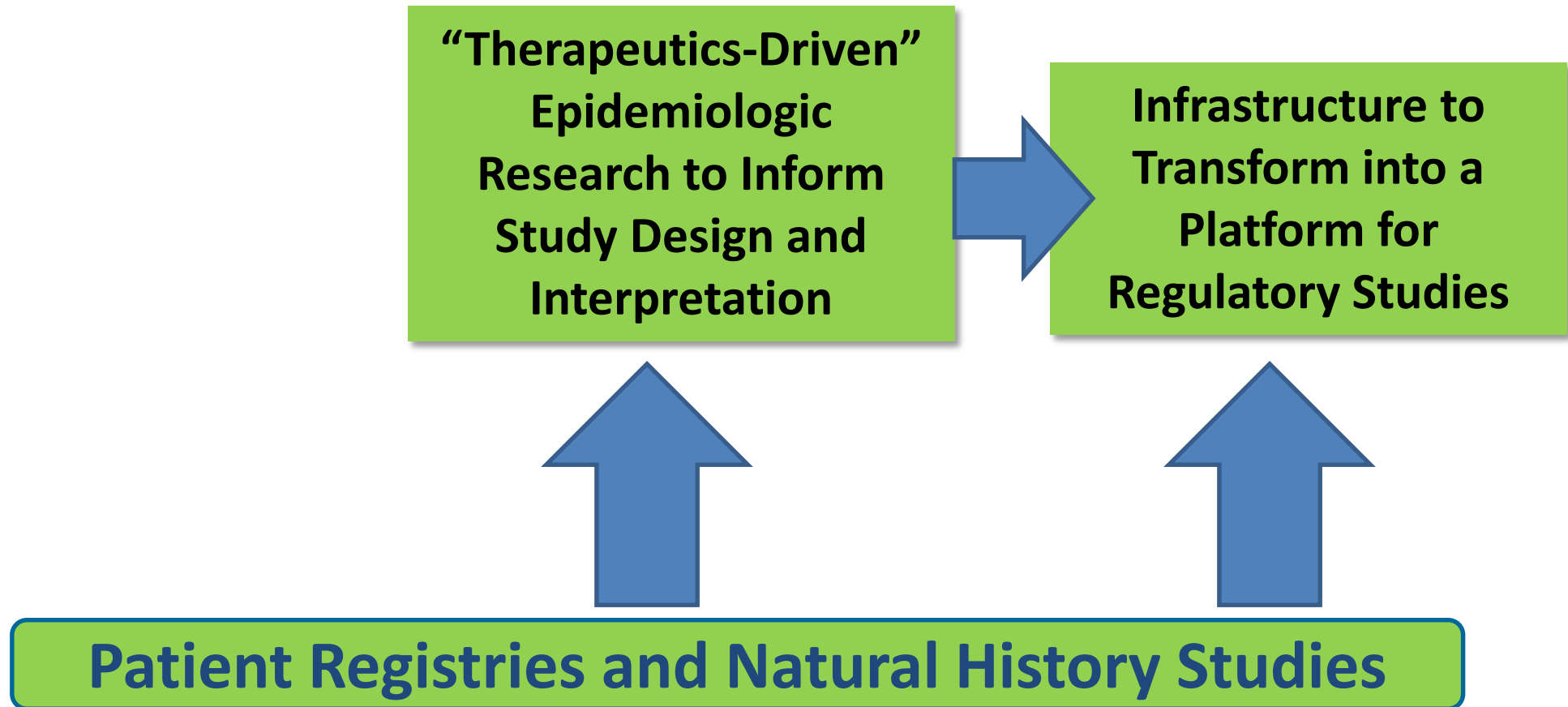
- Natural history data: N=1008 participants (placebo or SOC control) from eight completed randomized trials
- All studies collected AEs with standardized coding

Event Rates in Adults by Disease Severity



Hemoptysis Events per Month (95% CI)

A Critical Foundation to a Rare Disease Therapeutics Pipeline

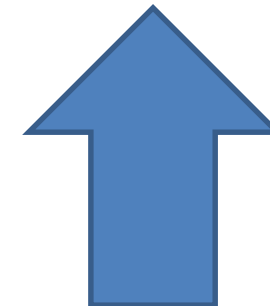


A Critical Foundation to a Rare Disease Therapeutics Pipeline

Source for historical or concurrent controls
Fulfillment of post-marketing studies

**Infrastructure to
Transform into a
Platform for
Regulatory Studies**

Patient Registries and Natural History Studies

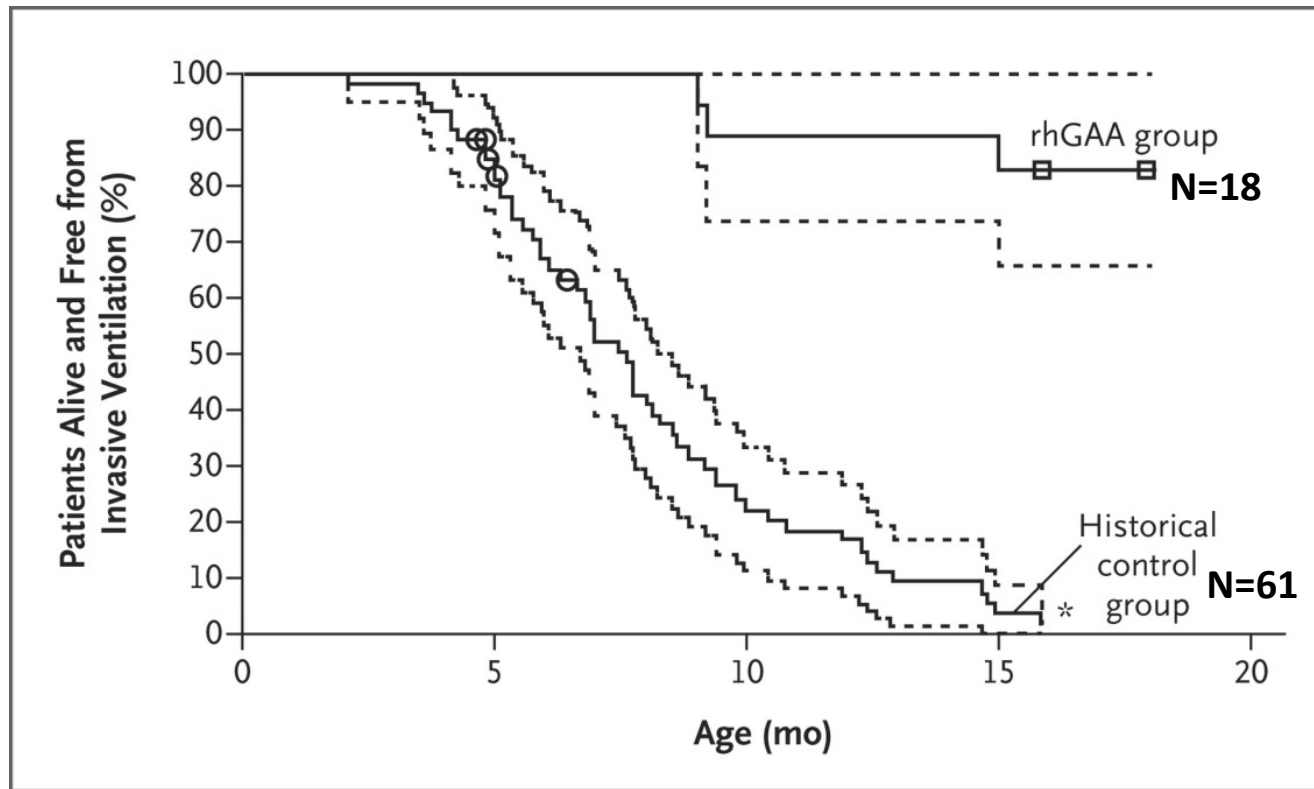


THE CHANGING FACE OF CLINICAL TRIALS

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*

Drug-Development Challenges for Small Biopharmaceutical Companies

Richard A. Moscicki, M.D., and P.K. Tandon, Ph.D.



Kishnani et. al. *Neurology* 2007

- Enzyme replacement therapy in Pompe disease with rhGAA
- Placebo controlled trial unethical
- Used historical controls for regulatory approval

Ideal Attributes for use of Historical Controls

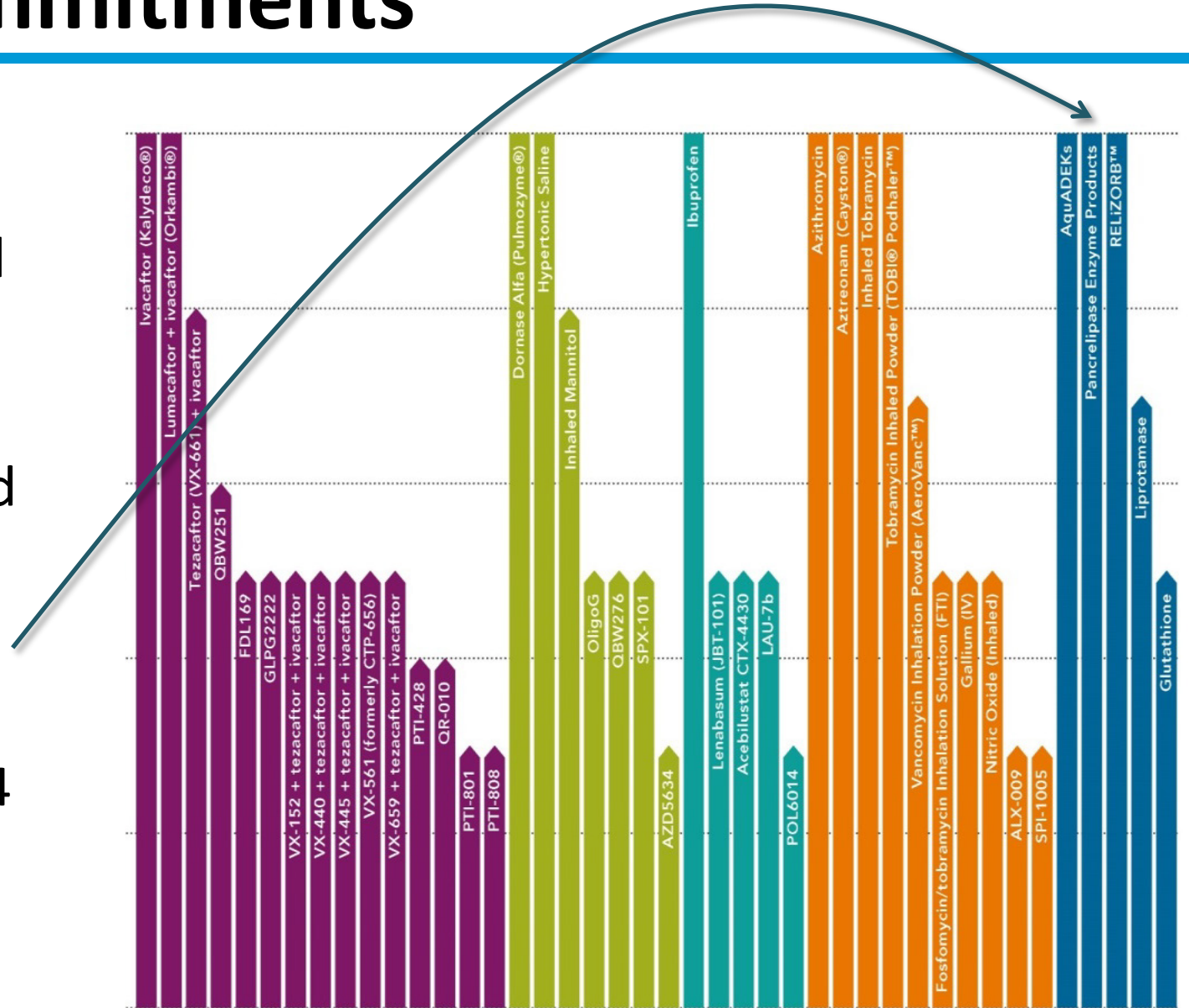
- Objective, well defined endpoint
- Large treatment effect

Using Registry and NH Data for Regulatory Studies: *The Groundwork*

- Consistency between trial and registry endpoints
 - Definition, timing of data collection
- Understanding of historical trends and clinical trial participation bias
- Infrastructure for quantifying and ensuring data quality

Leveraging a Disease Registry for Post-Marketing Commitments

- 10-year prospective observational study to assess risk of fibrosing colonopathy (FC) for reformulated pancreatic enzymes in CF
- FC is a rare event – the incidence can more accurately be estimated by leveraging the registry population
- Solution: Registry-embedded master protocol negotiated with 4 industry sponsors to meet post-marketing requirements for each sponsor

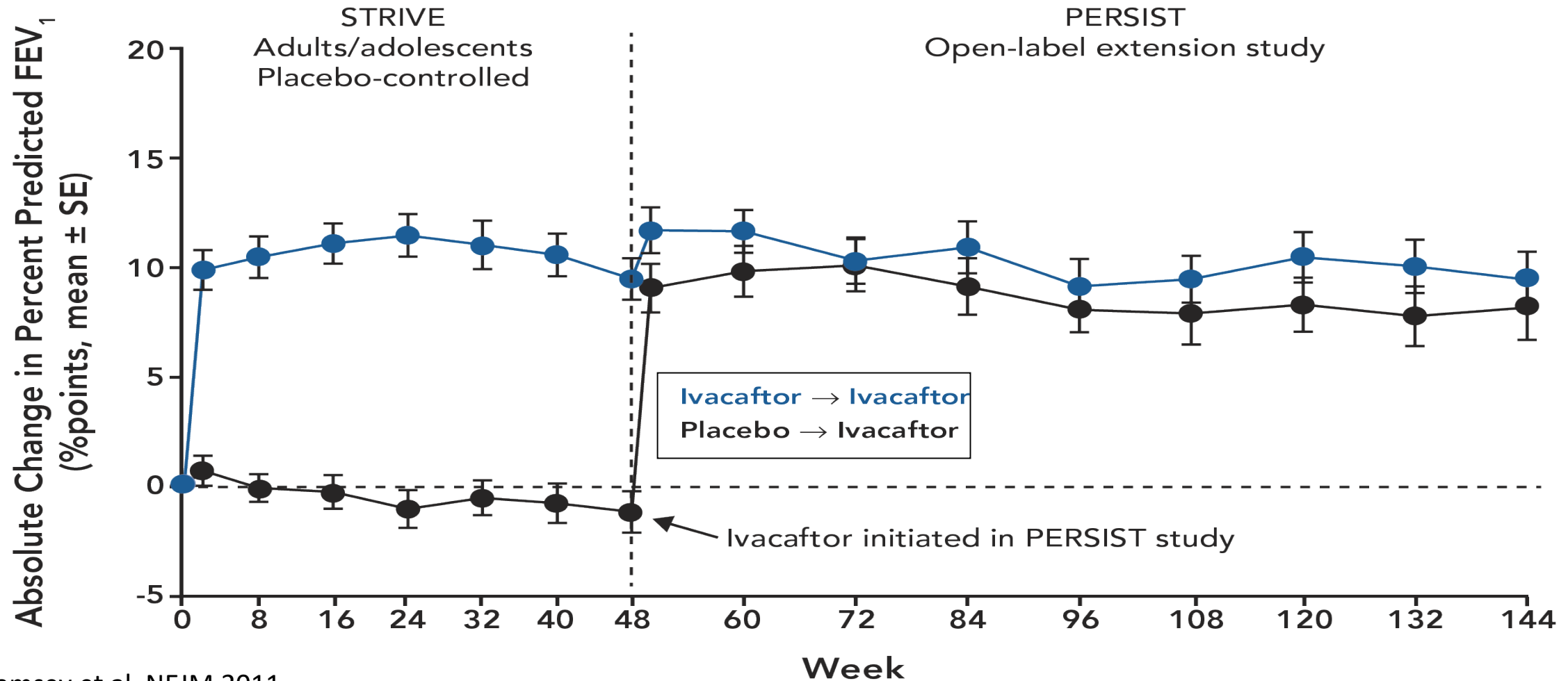


Leveraging a Disease Registry for Post-Marketing Commitments

- Newer and flexible approval pathways for rare diseases often require post-market long term effectiveness studies
- Optional consent to collect registry IDs included in many of our therapeutic trials
- Enables long-term linkage and follow up via the registry



Ivacaftor Efficacy in RCTs Limited to Acute Outcomes



Rate of FEV₁ Decline Slower in Ivacaftor Patients as Compared to Concurrent Registry Controls

Difference in Rate of FEV₁
Decline:
0.8%
(95% CI 0.06,1.55)

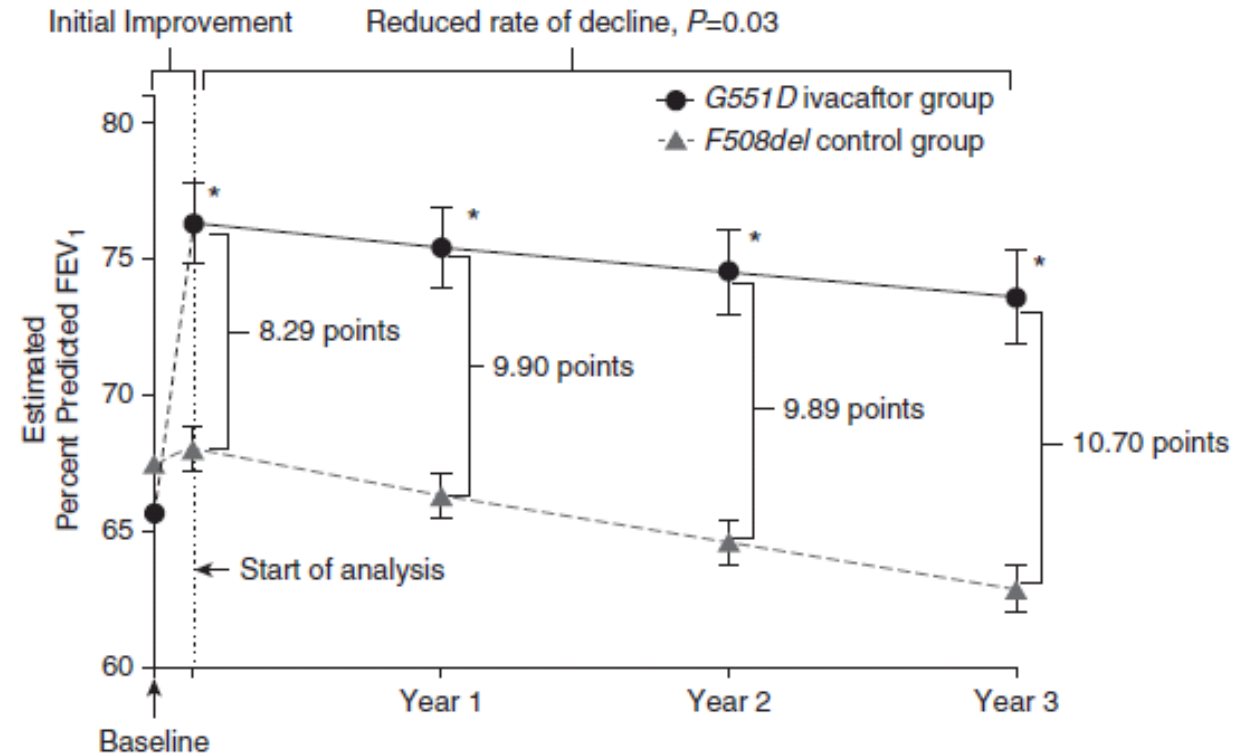
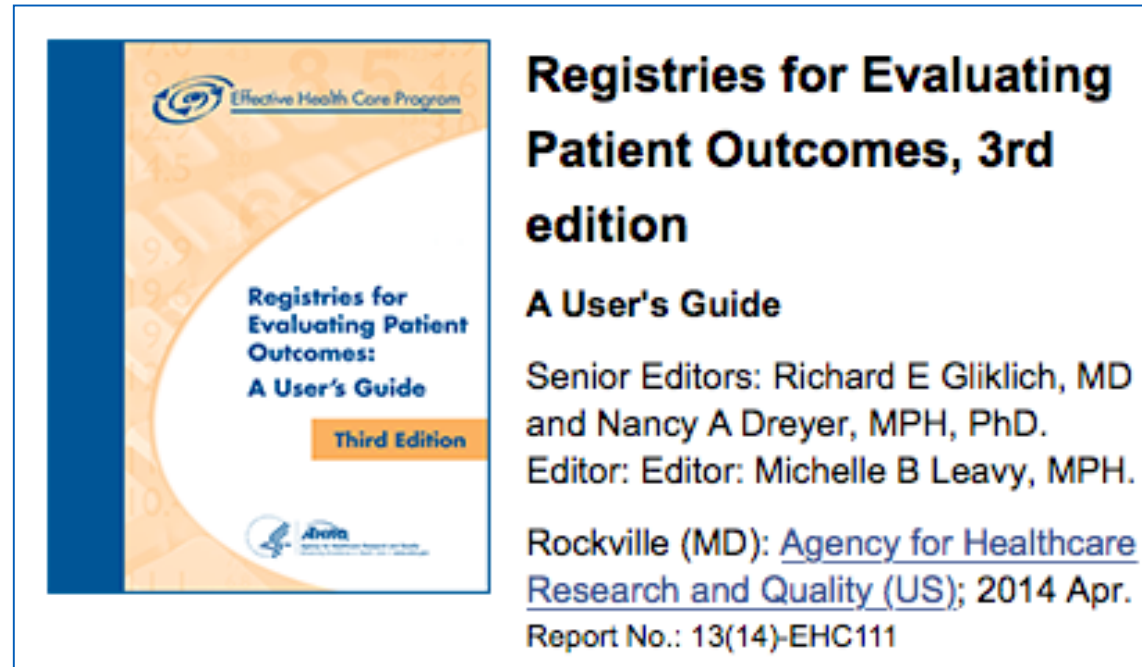


Figure 2. Estimated percentage predicted FEV₁ measures (±SE) at Years 1, 2, and 3. * $P < 0.001$.

Five controls were matched to each ivacaftor patient using propensity scores based on risk factors for increased rate of FEV₁ decline.

Methods for Addressing Bias a Necessity

- Confounding by indication cannot be avoided
 - Propensity scores or IVs
- Selection bias
 - Sensitivity analyses to evaluate the impact of cohort selection
- Missing data
 - Evaluate the impact of missing data on key results

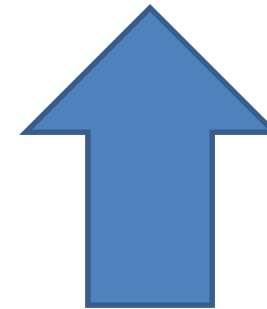
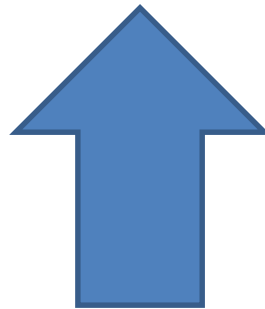
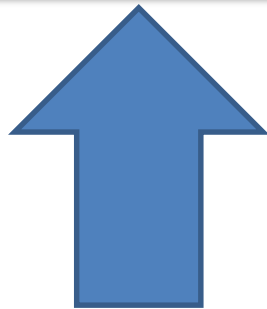


A Critical Foundation to a Rare Disease Therapeutics Pipeline

**Sufficient Data
Resources to
Identify
Patients and
Capture
Disease Course**

**“Therapeutics-Driven”
Epidemiologic
Research to Inform
Study Design and
Interpretation**

**Infrastructure to
transform into a
platform for
regulatory studies**



Patient Registries and Natural History Studies

Success is Ultimately Driven by Commitment from Our Community



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CF COMMUNITY **BLOG**

Vote for the Questions You Want Answered by the Patient Registry

Members of the cystic fibrosis community can have an even greater say in research when they vote for the Insight CF questions they most want answered. Readers have until June 21 to vote.



By [Laurie Eddy](#)

June 7, 2017

Acknowledgments

- Cystic Fibrosis Foundation and CF Therapeutics Development Network
- Bruce Marshall
- Aliza Fink
- Alex Ebert
- Christopher Dowd
- Dutch VanDevanter
- Wayne Morgan

Utilizing Innovative Statistical Methods and Trial Designs in Rare Disease Settings

March 19, 2018

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Master Protocols in Rare Diseases: The Potential and the Challenges

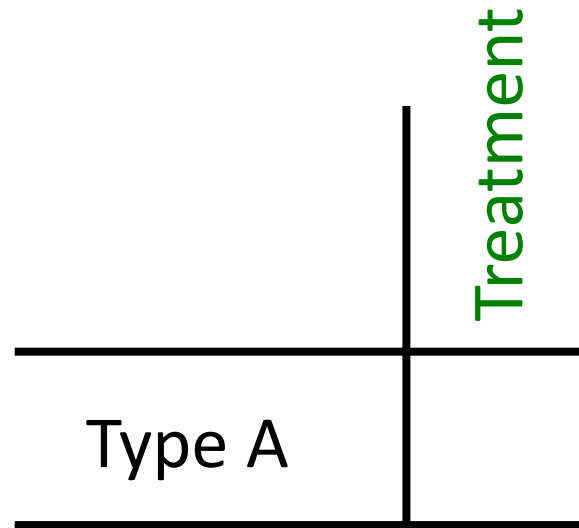
Scott M. Berry, PhD

Berry Consultants, LLC

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March 19, 2018

Traditional Trial



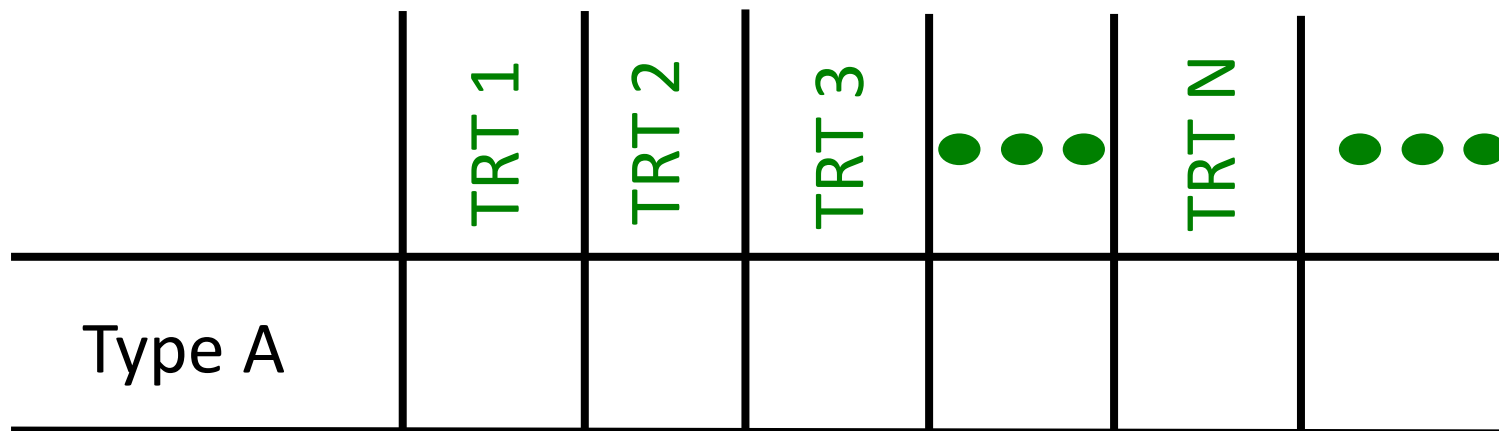
“Standard Trial: Single treatment,
Homogeneous patients, Single question ”

Basket Trial Designs

	Treatment
Type A	
Type B	
Type C	
⋮	
Type K	

- Single Treatment (doses?)
- Multiple Subgroups of interest
 - Severity of disease
 - Genetic markers
 - Demographic covariates
 - MOA related
 - Timing of Intervention
 - ...

Platform Trial Designs



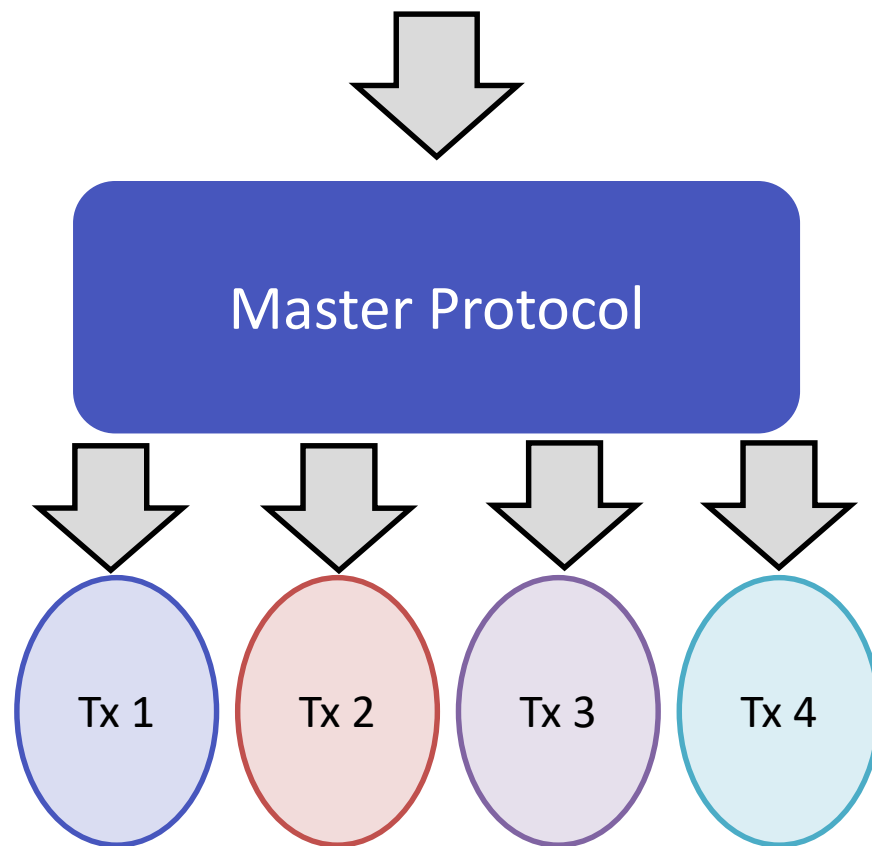
- Platform Trial -- “Master Protocol”
- Perpetual Trial?

Platform (Basket) Trial Designs

	TRT 1	TRT 2	TRT 3	...	TRT N	...
Type A						
Type B						
...						
Type K						
...						

Adaptive Platform Trial Design: Master Protocol

- There is one Protocol
- The master protocol assigns patients
- Protocol is disease focused
- No treatment names in protocol
- Treatment arm appendices
- Evolving arms—perpetual?



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.

Woodcock & LaVange:

“Two types of innovation are hallmarks of master protocols: the use of a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data collection and sharing; and the use of a common protocol that incorporates innovative statistical approaches to study design and data analysis, enabling a broader set of objectives to be met more effectively than would be possible in independent trials”

Woodcock & LaVange:

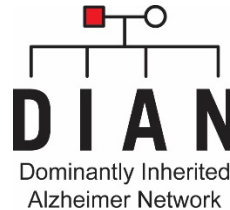
“Two types of innovation are hallmarks of master protocols: the use of a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data collection and sharing; and the use of a common protocol that incorporates innovative statistical approaches to study design and data analysis, enabling a broader set of objectives to be met more effectively than would be possible in independent trials”

Woodcock & LaVange:

“Two types of innovation are hallmarks of master protocols: the use of a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data collection and sharing; and **the use of a common protocol that incorporates innovative statistical approaches to study design and data analysis, enabling a broader set of objectives to be met more effectively than would be possible in independent trials**”

Background Information

- Randy Bateman, PI

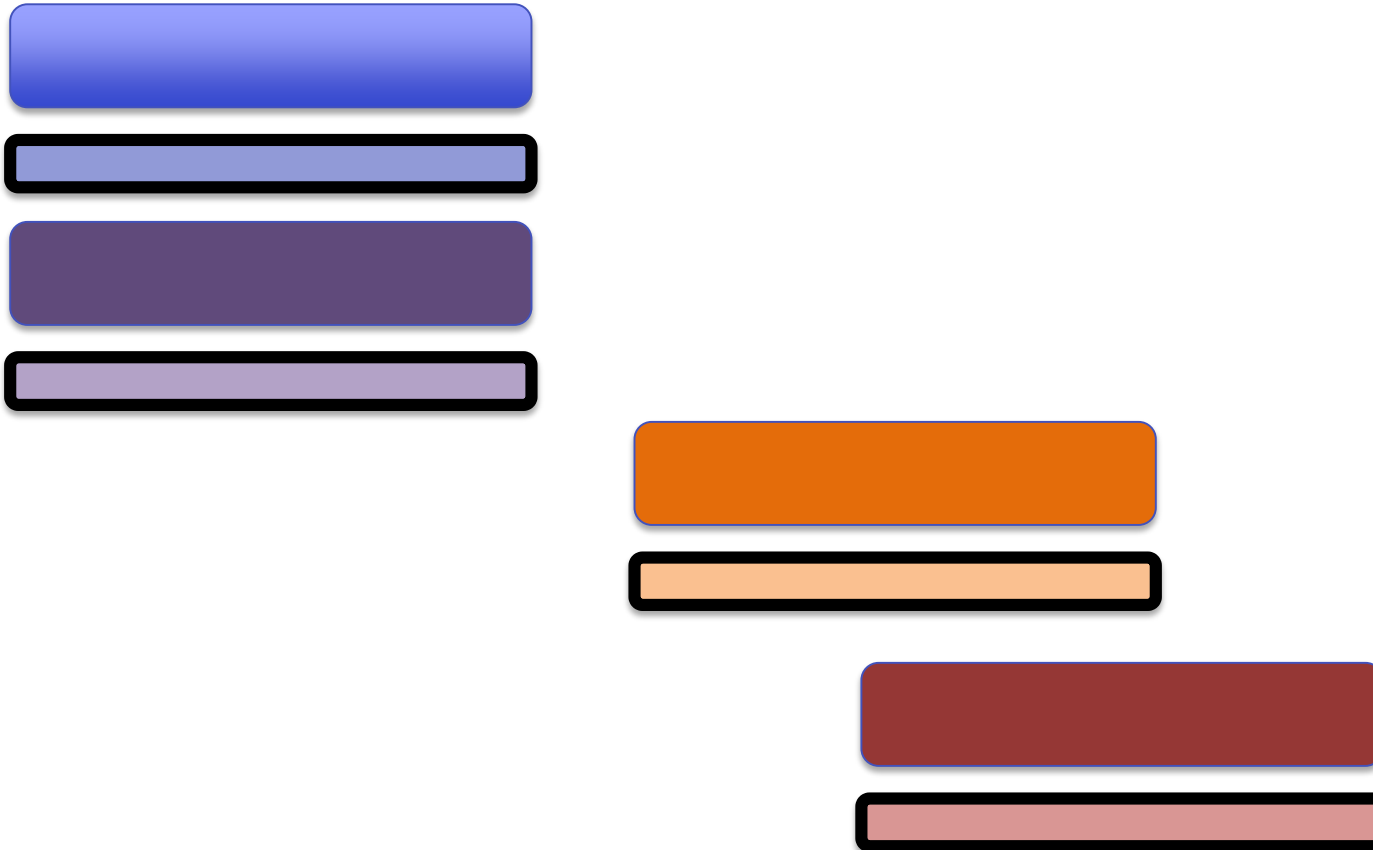


- Dominantly Inherited Alzheimer Network (DIAN) is an international research partnership of leading scientists determined to understand a rare form of Alzheimer's disease (ADAD) that is caused by a gene mutation.
- Autosomal Dominant Alzheimer's Disease (ADAD) is caused by rare inherited gene mutations in the APP, PSEN1, or PSEN2 genes which lead to early-onset AD (<60 years old)
 - 40-80% of 41.2/100,000 (AD < 60 y.o)

Trial Design

- A Master Protocol: A common platform for multiple treatments
 - Patients enrolled equally to any “drug cohorts”
 - Enrolled 3:1; Active:PBO
 - All patients blinded to their active/PBO but not across arms
- Primary analysis for the trial is based on cognitive progression model; pooled placebo

Trial Design



Time

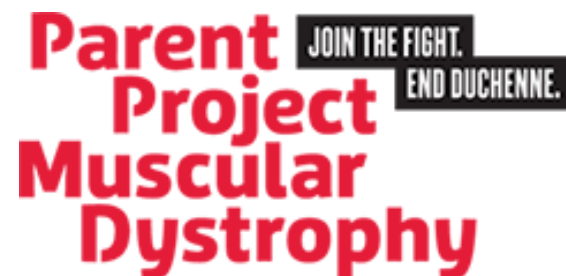
Improvement in Power

DPR Reduction	1-Arm (60:20)		Pool (60:40)
	MMRM	CPM	CPM
0%	0.025	0.008	0.008
10%	0.050	0.057	0.104
20%	0.093	0.259	0.535
30%	0.162	0.634	0.901
40%	0.267	0.911	0.988
50%	0.407	0.989	0.999
60%	0.562	1.000	1.000
70%	0.709	1.000	1.000
80%	0.829	1.000	1.000
90%	0.915	1.000	1.000

More than increase in power...

- iSpy-2: Neoadjuvant breast cancer
- Building of longitudinal modeling (MRI $\rightarrow$ pCR)
- Surrogacy of pCR $\rightarrow$ EFS?
- 14 different arms with differing pCR rates and evaluation of the surrogacy on EFS
 - Same protocol/procedures/endpoints
 - Patient-level data of pCR $\rightarrow$ EFS

PPMD Trial (in progress)



- Creation of a perpetual master protocol for DMD
- Phase 2/3 trial design
- Wide range of disease severity & re-randomization
- Common endpoints/procedures/protocol
- Randomized with a common control arm across all investigational arms

Challenges

- The upfront work; costs; efforts – takes longer to build a platform than single trial
- Building an integrated inferential design for synergy, yet attractive for intervention owners
- Design is disease-focused; arm friendly
- Writing a master protocol, modular appendices, and SAP
- Financing of the trial (start-up, per arm, CROs?)
- Arm selection/recruitment... sponsors feeling they “lose control”

Statistical Challenges

- Complex simulations & modeling
- RAR, subgroup effects, longitudinal models, borrowing controls, modeling time,... success, and futility...
- Blinding, Consent, & Randomization
- Arm specific exclusions?
- Who knows what and when in a perpetual trial?
- Consort diagram for a publication?

Potential

- Better inferences per arm
- **Better understanding of the disease**
- More arms (combinations) and more “shots on goal”
- Better for patients (in and out)
- Cheaper & faster
- Enormous advantages for rare diseases

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Commentary on Master Protocols for Rare Diseases

Michael Proschan

NIAID

Desired Trial Features When The Disease is Not Rare

- ~~Large sample size~~
- ~~Replication of trials~~
- ~~Results convincing even with simple analyses~~
- ~~Results robust to alternative/sensitivity analyses~~
- ~~Protection against multiple comparisons~~
- ~~Substantial data on safety~~

Need to Make Most of Available Data

- Master protocol approach does this through:
 - Sharing control arm for multiple treatment arms
 - Eliminating poorly performing arms & re-randomizing patients to remaining arms
 - Incorporating covariates & using model-based approach
 - Conserving resources by using same master protocol for different treatments, different diseases
 - Avoiding methods that are overly conservative with small sample sizes (e.g., Fisher's exact test)

Concerns & Safeguards

- Must protect against temporal trends
 - Compare arms to concurrent control
 - I would avoid response-adaptive randomization
 - Can result in long strings of same treatment
 - Can be inefficient without substantial “burn in” period of standard randomization
 - I would “burn in” for entire trial
- Covariate-adaptive randomization & adjusting for covariates used in randomization may be cat’s meow
 - If using unequal allocation, remember problems in Genzyme Late Onset Treatment Study in Pompe disease (Proschan, Brittain, and Kammerman, 2011, *Biometrics* **67**, 1135-1141)
 - Use solution by Kuznetsova & Tymofeyev (2012) *Stat Med* **31**, 701-723

Concerns & Safeguards

- Bayesian methods & prior distributions
 - Natural approach in adaptive settings
 - Need for skeptical prior quickly overwhelmed by data
 - Need to explain rationale for prior: avoid black boxes

Concerns & Safeguards

- Sharing control arms is good, but raises questions:
 - How many arms are too many?
 - Is it better to choose best single candidate or include multiple treatment arms? How do you decide?
 - Is adjustment for multiple comparisons needed if there are many arms?
 - We would not adjust in separate trials, but is this a fair argument?
 - “Bad” control arm affects all comparisons
 - Lose credibility about other comparisons if one turns out to be a false positive

Bottom Line

- Compromise is needed
 - Traditional approach with large sample size & robust analysis is not feasible
- Master protocol approach offers more advantages than disadvantages
- I would
 - Compare with concurrent controls
 - Avoid response-adaptive randomization

Sweet 16!

- Florida State 75, Xavier 70: Go 'Noles!

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Opportunity for Public Comment

March 19, 2018

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Synthesis Discussion

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