Statistical Leadership and Innovation in Practice

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Disclosure

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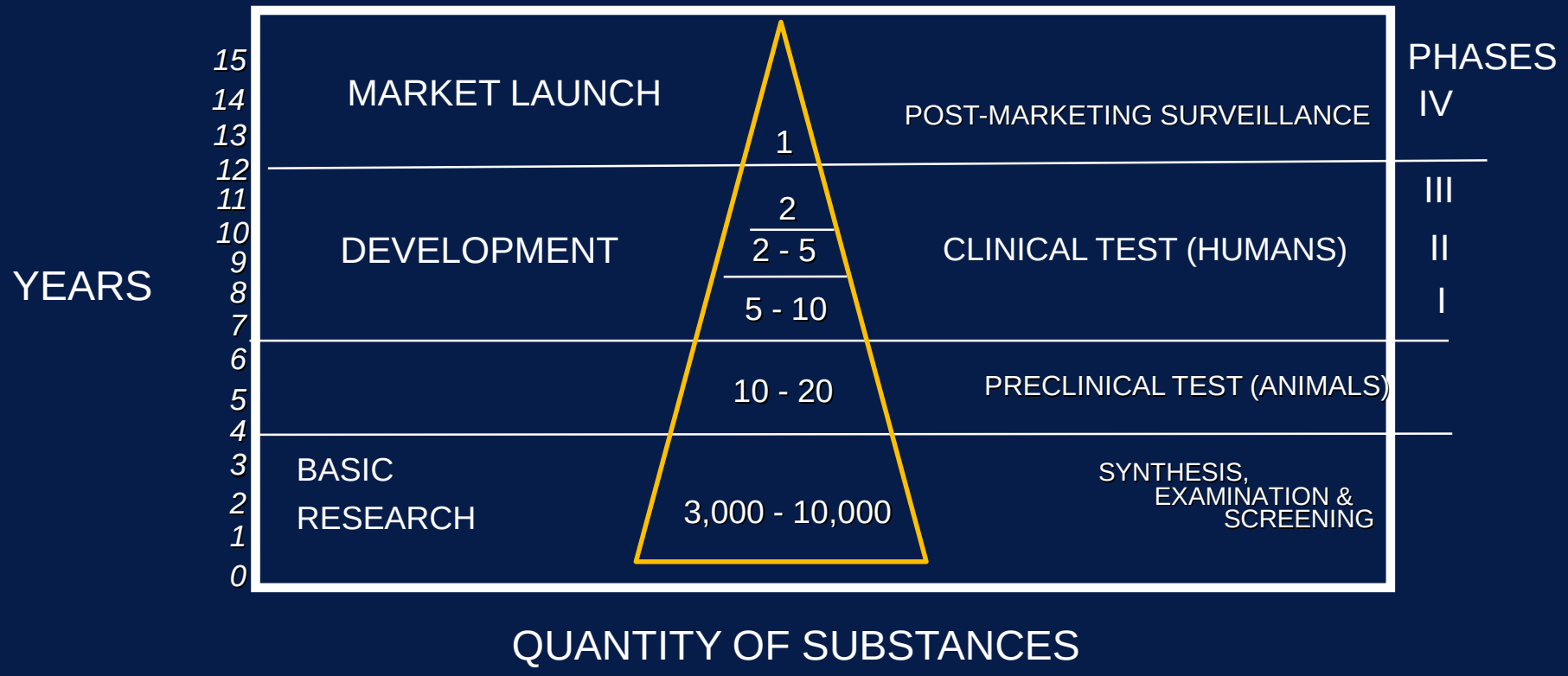
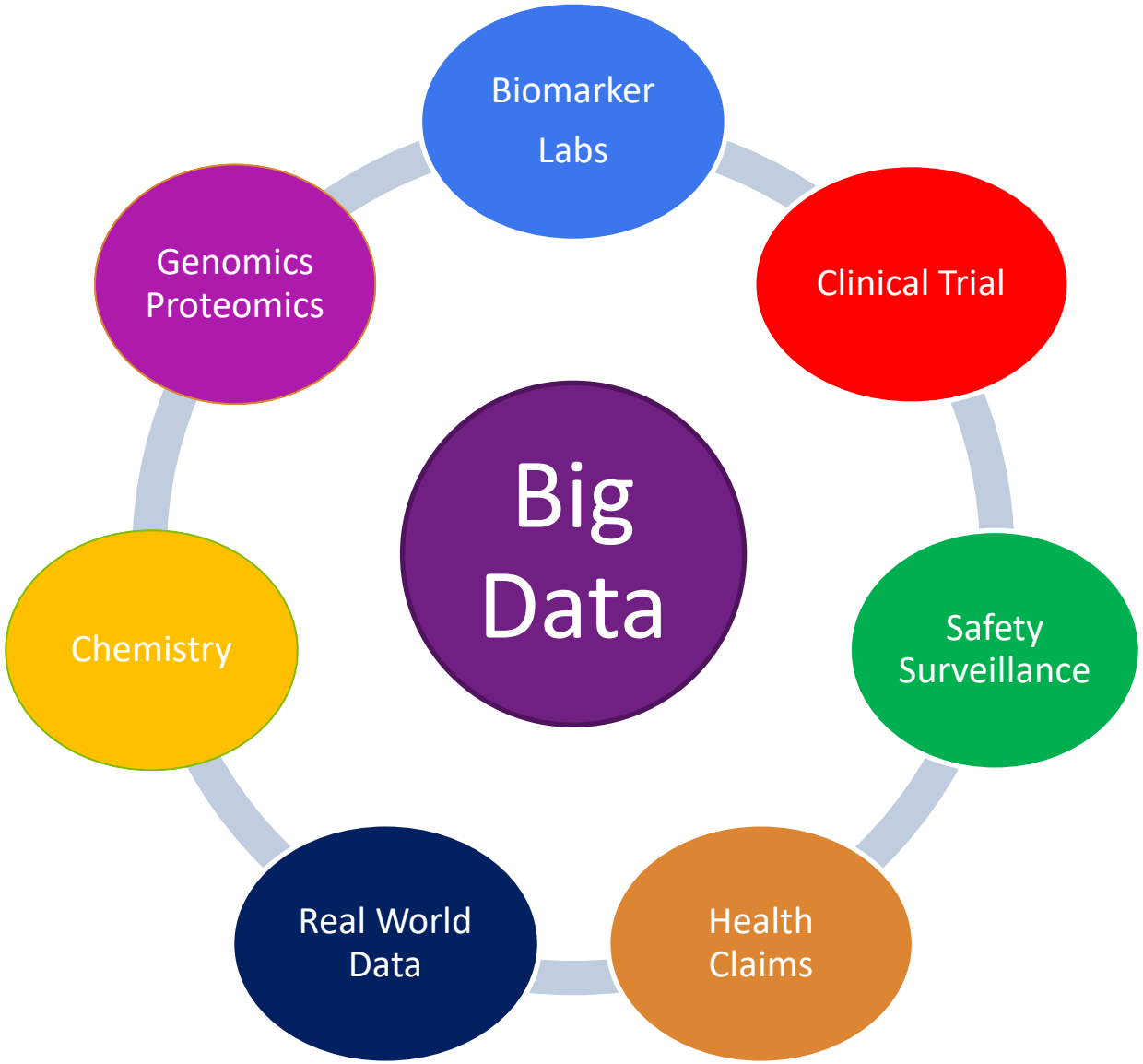
Ivan Chan is an employee of AbbVie Inc. and may own AbbVie stock.

Discovery and Development of a Successful Drug/Vaccine



Modified from PhRMA analysis, updated for data per Tufts Center for the Study of Drug Development (CSDD) database.

Big Data in Pharmaceutical Research



Acceleration of Research and Development

- Advancement of genomics to understand the disease
- Use of biomarker to guide smart R&D
- Innovative clinical trial development strategy
- COVID-19 pandemic highlighted the enormous need for innovation and accelerated development of drugs and vaccines
  - For example, started first vaccine trial 2 months after identification of the SARS-COV-2 genome sequence
  - Advanced vaccine development from Phase I to Phase III trials in <5 months
  - Tremendous collaboration between industry and government to shorten the development timeline to 12 to 18 months instead of years

Statisticians Play an Important Role in Research and Development

- Biomarker and genomics
- Design of experiments and clinical trials
- Statistical analysis and interpretation of data
- Statistical modeling and predictive analytics
- Strategic planning
  - Product label versus clinical development plan
  - Decision making and probability of success
- Interaction with regulatory and external experts
  - FDA, NIH, CDC, World Health Organization (WHO)
  - Key opinion leaders (KOL)

Adaptive Design Strategy

Features of Adaptive Design Strategy

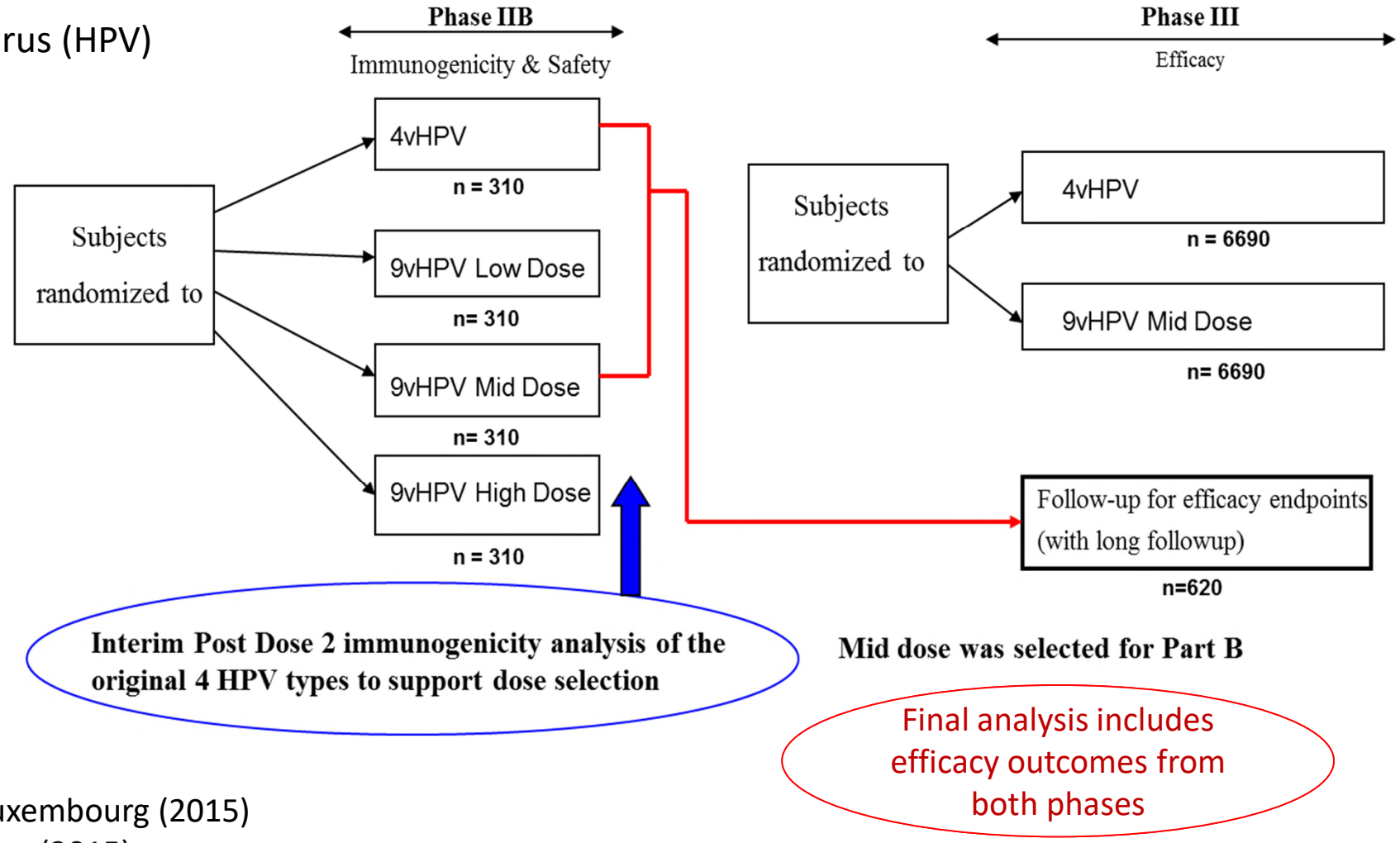
- Optimize dose-response assessment
- Interim stopping for futility or efficacy
- Drop the “losers” (dose selection)
- Adjust sample size/ response adaptive randomization
- Change of populations (enrichment)
- Seamless phase II/III trial
- Basket and platform trials
- Master protocol

Statistical Leadership in Practice

- PhRMA Working Group on Adaptive Designs
  - Formed in 2005 to contribute to a constructive dialogue on adaptive designs by engaging statisticians, clinicians, and other stakeholders in academia, regulatory agencies, and industry
  - Published white papers on adaptive designs
  - Promoted adaptive design trials in the industry and scientific community
- FDA Guidance on adaptive clinical trial designs (drafted in 2010 and finalized in 2019)
  - Allows a variety of adaptation rules as long as adequate evaluation of the operating characteristics is documented
  - Emphasizes simulations play an important role in understanding the trial operating characteristics

Example 1: Seamless Phase II/III Design with Dose Selection Based on Biomarker

Human Papillomavirus (HPV) Vaccine



Chen, Gesser, and Luxembourg (2015)
Li, Zhao, Sun and Chan (2015)

Improved Statistical Efficiency with Phase II/III Design

- Comprehensive simulations performed to evaluate operating characteristics
  - Demonstrated control of overall type I error in a wide range of scenarios (Li, Zhao, Sun and Chan 2015)
- Improved statistical efficiency (power gain) due to inclusion of Phase II subjects
  - Phase II contributes ~4.4% subjects but 10% of person-years of follow-up
- Cited as a successful example in FDA Guidance on Adaptive Designs (2019)

Example 2: Response Adaptive Randomization (RAR)

- Appropriate statistical method for analysis can control the overall type I error
- Heterogeneity of patient population need to be considered
- Successful implementation seen in phase 2 studies
  - Success of RAR in a phase 2/3 trial in diabetes (Skrivanek et al 2012)
    7 doses + Placebo + Active Control
    RAR between N=200 and 400 to select 2 doses for phase 3
    Phase 3 uses fixed randomization
- Regulatory acceptance of RAR in phase 3 varies
  - A recent RAR study in immunology
    2 doses + Placebo
    RAR after N=60 burn-in and adaptation is only within the 2 active doses
    Concerns raised by regulatory agency for the study to be considered as a pivotal trial

Recent Development

- PDUFA VI and 21st Century Cures Act Commitment on Complex Innovative Design project
  - FDA draft guidance on complex innovative trial designs (2019)
  - FDA Pilot Program will enhance sponsor interaction with the FDA on the implementation of innovative trial designs
- Broader implementation of innovative clinical trial designs will expand toolbox for accelerating drug development
  - Master/platform trials
  - Bayesian adaptive designs
  - Innovative use of external data
- Continued engagement between industry and regulatory agencies will enrich the experience and knowledge sharing

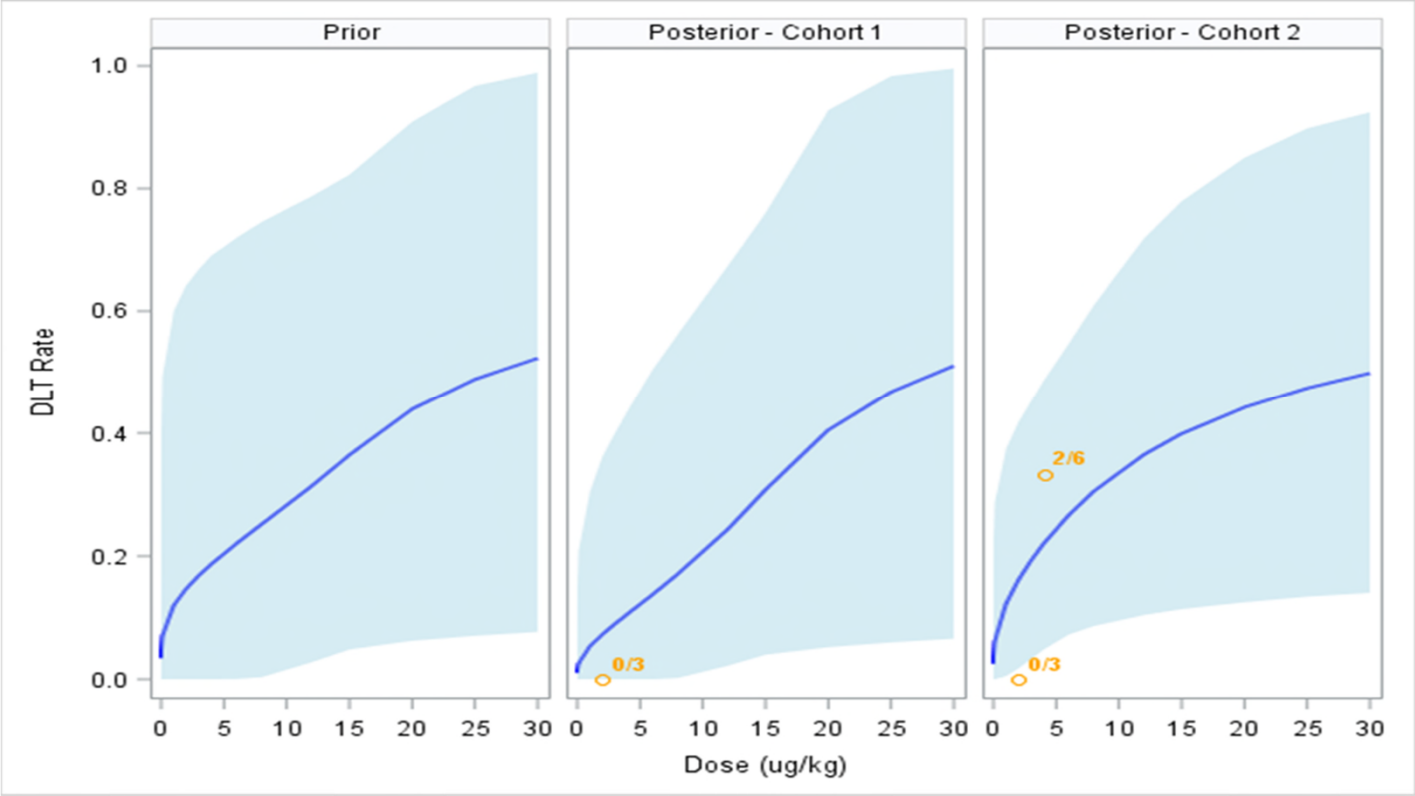
Bayesian Paradigm

Bayesian Paradigm in Drug Development

- Bayesian strategy has been gaining traction in drug development
  - Able to incorporate prior knowledge in the design and analysis
  - Able to accelerate decision making with less new data by leveraging prior information
  - Naturally suited for clinical trials with complex adaptation and predictive models
  - Advance in computational power
- FDA CDRH issued guidance on the use of Bayesian statistics for medical device clinical trials in 2010
- Recently FDA discussed the use of Bayesian design and analysis in its draft guidance on complex innovative trial designs for drugs and biologics (FDA Draft Guidance 2019)

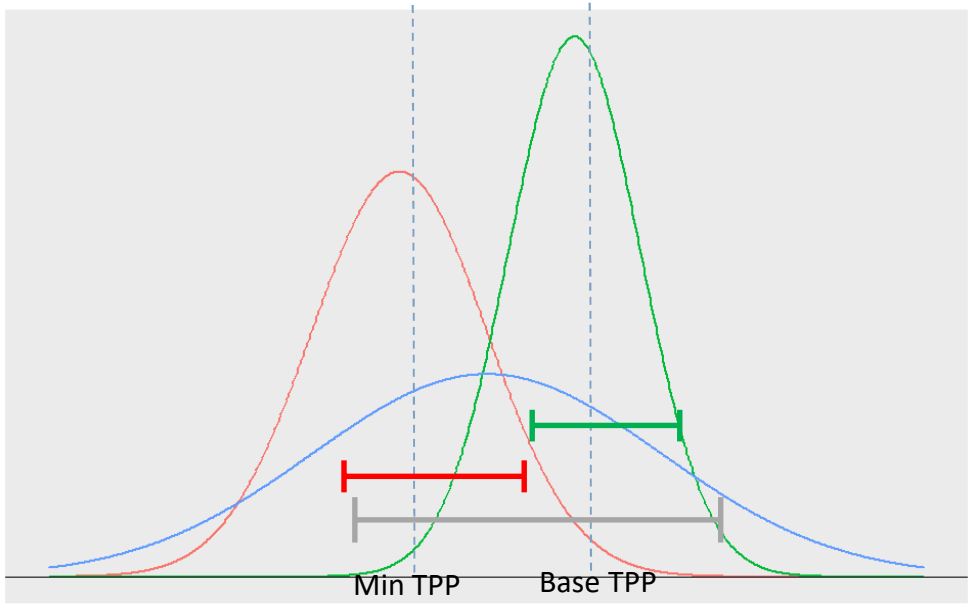
Applications of Bayesian Strategy (1)

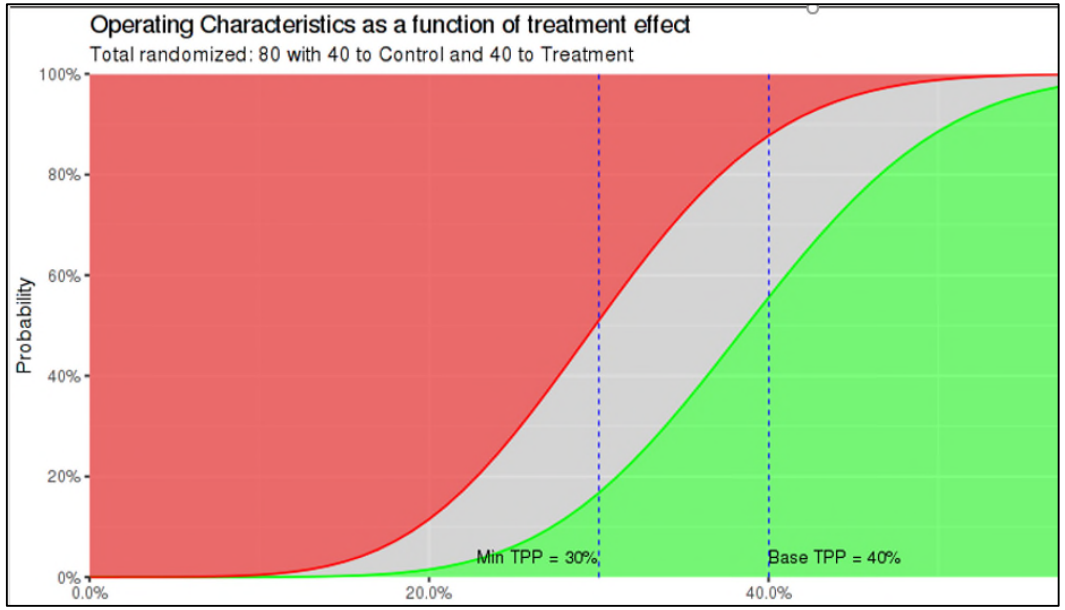
- Adaptive dose finding in early development studies
  - ➢ Bayesian Optimal Interval Design (BOIN) and Continual Reassessment method (CRM) have superior performance than the traditional 3+3 design



Applications of Bayesian Strategy (2)

- Predictive models and Go/No-Go decision framework
  - ➢ Predictive model in trials with complex adaptations
  - ➢ Probability of success in proof of concept trials and from phase 2 to phase 3 based on accumulating data (Pulkstenis et al 2017)
  - ➢ Predicted probabilities of success based on interim data (Lee and Liu 2008)





Applications of Bayesian Strategy (3)

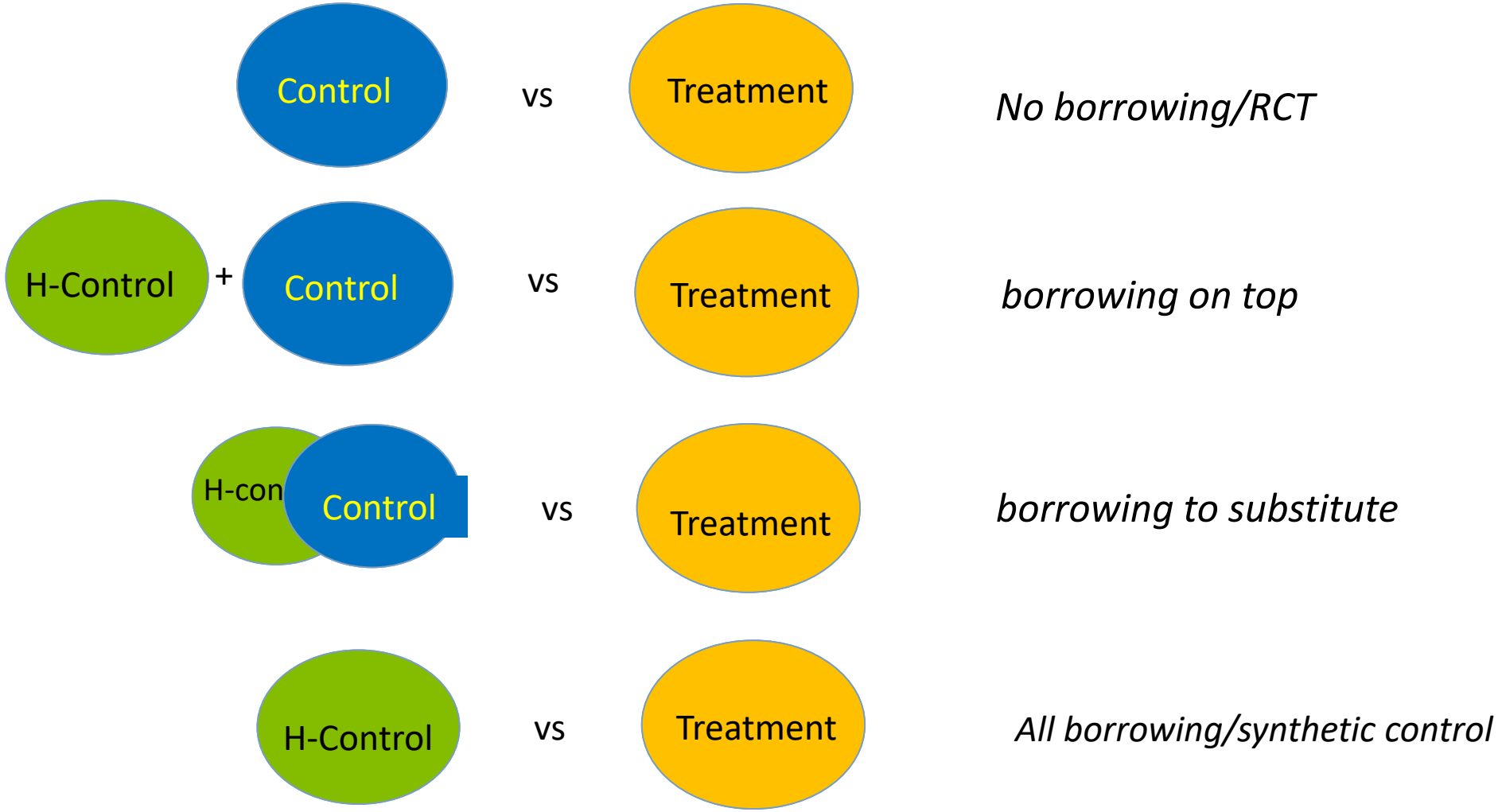
- Use of hierarchical model for subgroup analysis
  - ➢ Shrinkage estimate can reduce the variability of individual estimates
  - ➢ FDA successfully applied this approach to Drug Trial Snapshot (RINVOQ)
  - ➢ Use MCMC simulations to obtain model estimates

Use of External Data in Regulatory Decision Making

How Can we Increase the Efficiency of R&D?

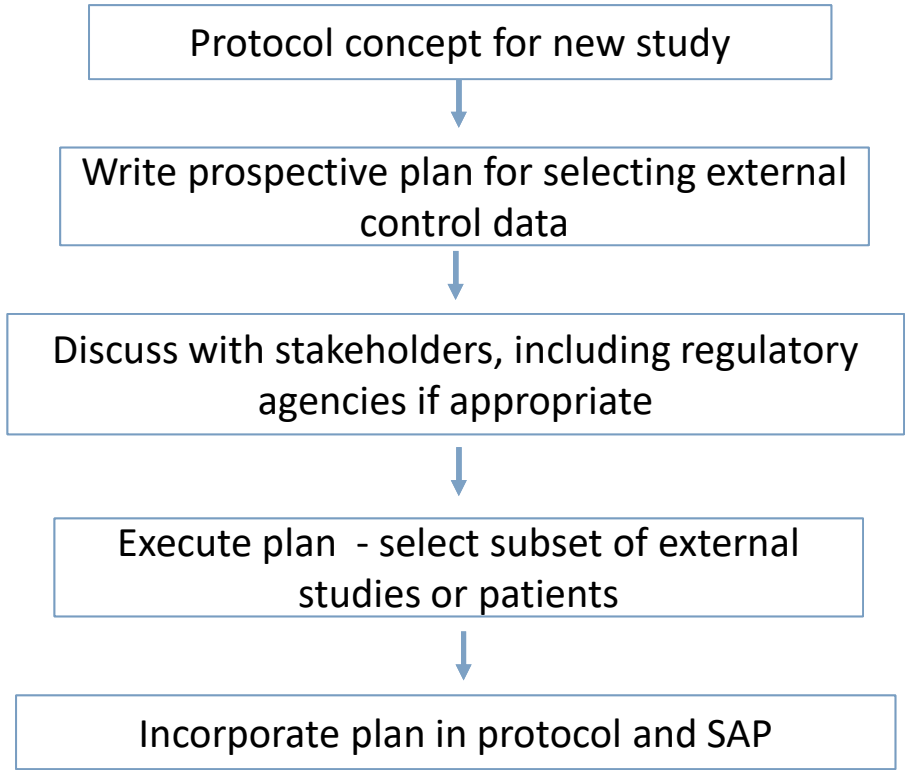
- Clinical trials represent a big chunk of the R&D cost
- Finding innovative ways to design more efficient clinical trials is very important for drug development
- Leveraging external data in similar patient population can significantly reduce the cost of clinical trials
- FDA draft guidance on Complex Innovative Trial Design (2019) discusses the considerations for leveraging external data in clinical trials

External/Historical Data Borrowing – Full Spectrum of Possibilities



Careful Selection of External Controls to Reduce Risk Bias
(Lim et al, Therapeutic Innovations and Regulatory Science 2019)

- Assess suitability of current trial to incorporate external controls
- Prospectively plan the selection of external control studies
- Define the optimal set of external controls



Example: Rheumatoid Arthritis POC trial

Design

- A proof of concept (POC) dose ranging trial in immunology (rheumatoid arthritis)
- 4 dose levels of a new treatment vs placebo
- Primary endpoint is change from baseline in disease activity score (DAS28) at week 12

Historical data

- Previous trials exist in similar disease setting
- Can we borrow some historical placebo data?
  - Reduce the number of concurrent placebo subjects
  - Increase the precision/power of study

Historical Data Borrowing - Data Source

- **Determine the number of historical controls to borrow**
  - *Initial plan for n=40 per group in POC trial without borrowing*

Historical Data (n, placebo mean, SD):
Study 1: (n=176, -0.8 (1.5));
Study 2: (n=131, -0.6 (1.5));
Study 3: (n=55, -1.1 (1.6))

- **Maximum sample size to borrow from historical controls**

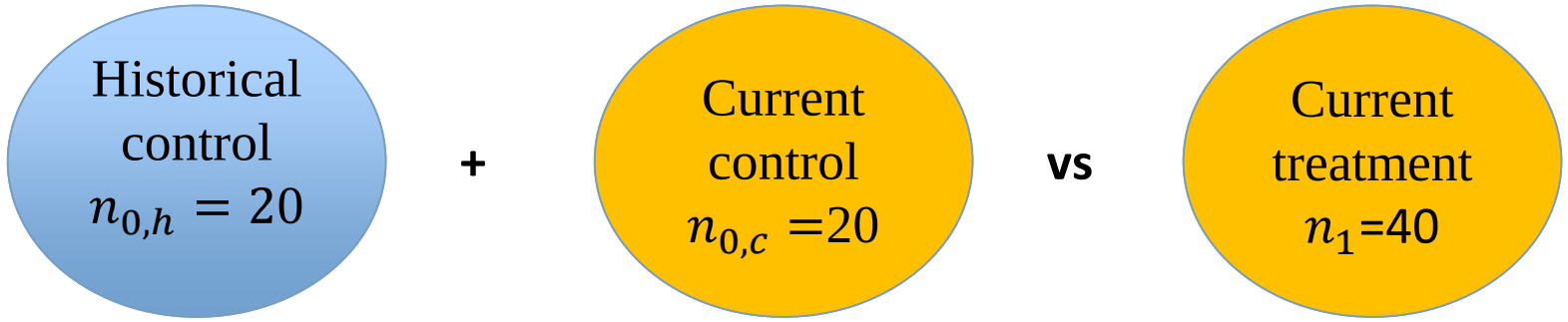
Meta Analysis Method	τ	mean	SE	Effective sample Size (N)
Pooled	0	-0.77	0.080	362
DerSimonia-Laird	0.149	-0.79	0.121	62
REML	0.147	-0.79	0.120	64

τ: between trial variability

Historical Data Borrowing – Sample Size

Recommend to borrow n=20 subjects from historical controls

- Reduce the sample size in concurrent controls
- Minimize potential bias
- Ensure safety comparison with randomized controls
- Allow flexibility in borrowing at analysis stage
- Reduce >$5 million study cost and 2 months enrollment time



Synthetic Controls

- When individual patient-level data are available, one can incorporate the external data in the analysis by appropriate matching
- A synthetic control arm can be created using external patient-level data by appropriating matching on baseline characteristics
  - Previous clinical trial data
  - Real-world data
- Propensity score matching is a common method

  Propensity score (PS) = Prob of a subject assigned to treatment in current trial or synthetic control given all baseline covariates

Case Study of Using Synthetic Controls in Non-Small Cell Lung Cancer
(Davi et al, Friends of Cancer Research, 2019)

- Evaluate the utility of synthetic controls
- Use propensity score matching on baseline demographic variables
- Demonstrate the synthetic controls perform similarly to the controls in the randomized trial (Target) in overall survival

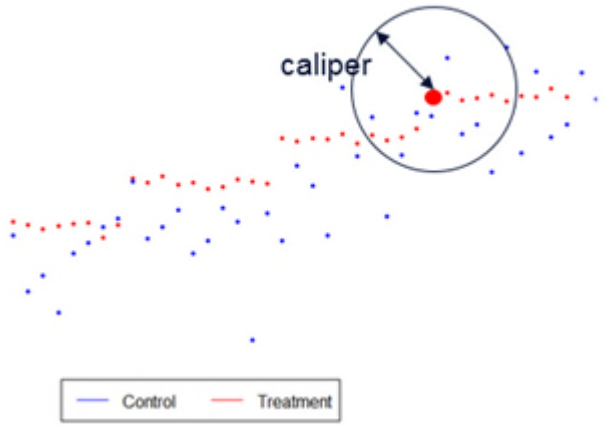
Comparison of Overall Survival (Months) in Control Arms in Target Study					
Before Matching			After Propensity Score Matching		
Quartile	Historical Pool	Control in Target	Quartile	Synthetic Control	Control in Target
75	19.8 (18.4, 22.1)	17.4 (14.9, 20.1)	75	17.0 (14.9, 19.6)	16.6 (14.3, 19.6)
50	10.4 (9.6, 11.1)	8.9 (8.2, 9.6)	50	9.2 (8.2, 10.7)	8.8 (7.9, 9.6)
25	5.1 (4.4, 5.6)	4.6 (4.1, 5.0)	25	4.4 (3.6, 5.3)	4.6 (4.1, 5.0)
Log-rank p-value = 0.03 HR (Target vs Hist Pool) = 1.16, 95% CI (1.02, 1.32)			Log-rank p-value = 0.65 HR (Target vs Synthetic C) = 1.04, 95% CI (0.88, 1.23)		

Example: Synthetic Placebo Control for Immunology Study

- A POC study comparing a new drug X to Adalimumab for RA
- Creating a synthetic placebo arm from 3 previous trials with propensity score matching on baseline covariates

PS analysis → Matching → Analysis: pairwise comparison

PS analysis	Matching	Analysis: pairwise comparison	
T: 45	T: 45	New drug:	30
P:	P: 45	ADA:	15
		Placebo:	45



Propensity score matching

Matching Ratio (Treated: Placebo)	N_X: N_ADA: N_PBO	Two-Group Comparison Power (ADA vs. PBO)
1:1	30:15:45	82%
1:2	30:15:90	87%
1:3	30:15:135	88%

Summary

- Innovative designs and analytic strategies have increased the success rate of drug development
- Statisticians' leadership and innovative thinking plays an important role in drug development

"***Leadership is not a position or a title, it is action and example***."

- Donald McGannon

Key References

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