BASS XXVIII

28TH ANNUAL BIOPHARMACEUTICAL APPLIED STATISTICS SYMPOSIUM

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Complex Innovative Designs

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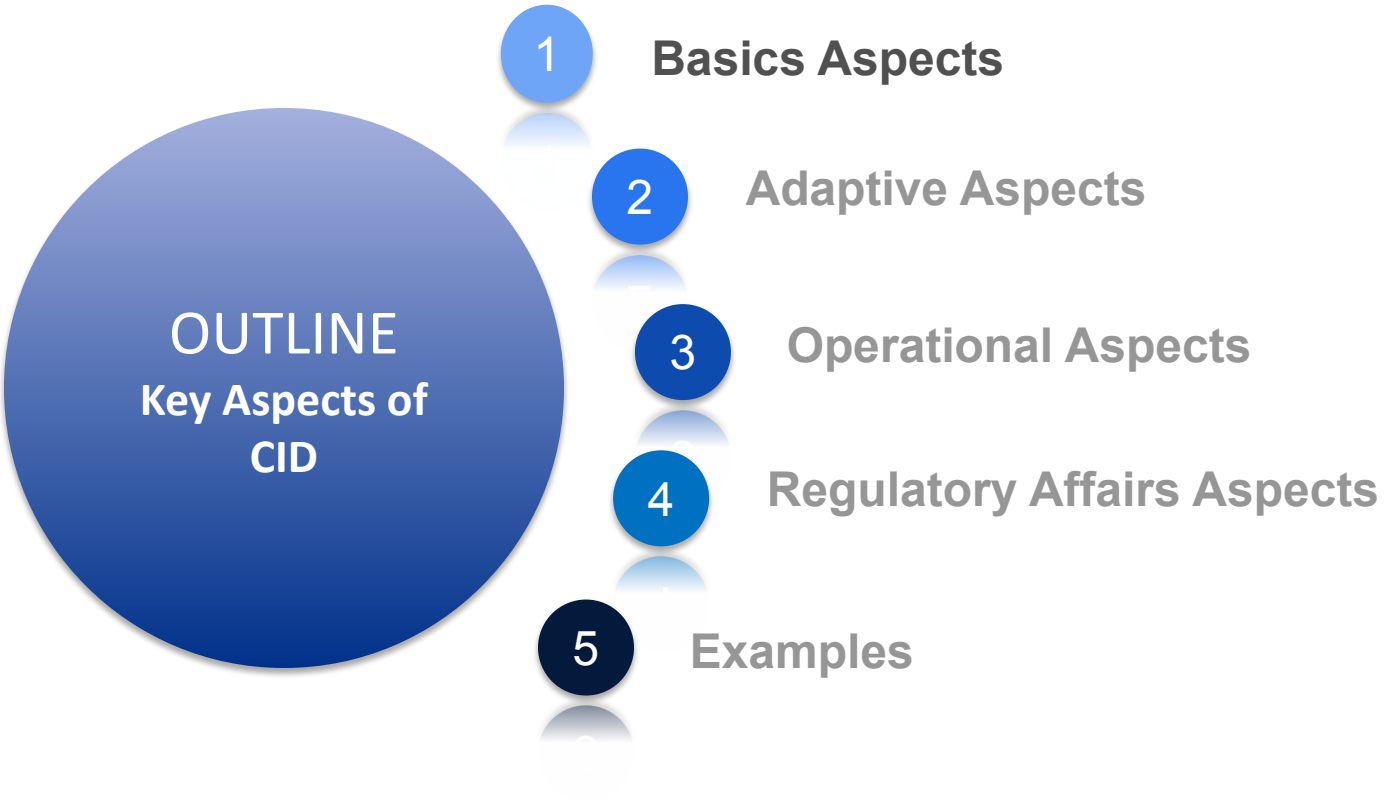
Quantitative Sciences

Janssen Pharmaceuticals Companies of Johnson & Johnson

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson


OUTLINE
Key Aspects of CID
1
Basics Aspects
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Adaptive Aspects
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Operational Aspects
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Regulatory Affairs Aspects
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Examples

Current Challenges in Drug Development

- Clinical trials are most commonly based on a "one population, one drug, one disease" strategy
- Each potential new therapy is typically tested independently from other therapies seeking to treat the same condition
- For every new trial, the protocol must be reviewed by a number of oversight entities
  - New phase III trials require an average of 36 administrative or regulatory approvals and averages more than 2 years
- The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease
- There is an urgent need to answer more questions more efficiently and, in less time

Innovation in clinical trial design can contribute to more rapidly advancing medical therapeutics

- Study multiple compounds in an operationally unified framework
  - Platform Trial, Umbrella, and Basket Trials
  - Unified infrastructure diminishes redundancies

- Coordinated application of patients as a precious resource enables efficiency in evaluation of multiple compounds
  - More efficient allocation of patients to randomized groups
    - Including increased fraction of patients assigned to investigational agents through use of common control group
    - May be more attractive for patients to participate in trial

- Platform trials can attract multiple sponsors to collaborate

- Efficient learn & confirm trial design integrating phases of development
  - Efficiency for investigator sites – Maintain active operational infrastructure
  - Identify failing compounds sooner
    - Releases sponsor resources to develop other compounds sooner
  - Improve success of trials for successful compounds

Types of Adaptive Designs

Adaptive Design is defined as a *multistage* study design that uses *accumulating data* to decide how to *modify aspects* of the study without undermining the *validity* and *integrity* of the trial

Trial Level	Program Level	Portfolio Level
• Number of Subjects • Study Duration • Treatment Duration • Patient Population • Number of Treatments • Randomization Ratio • Number of Interim Analyses	*Seamless Adaptive Designs: Combining Conventional Phases in a Single Trial* • Seamless Phase I/II • MAD and POC • POC and ADRS (Adaptive Dose Ranging Studies) • Seamless Phase II/III	• Population Finder • Compound Finder • Indication Finder • Basket Trial • Umbrella Trial • Platform Trial

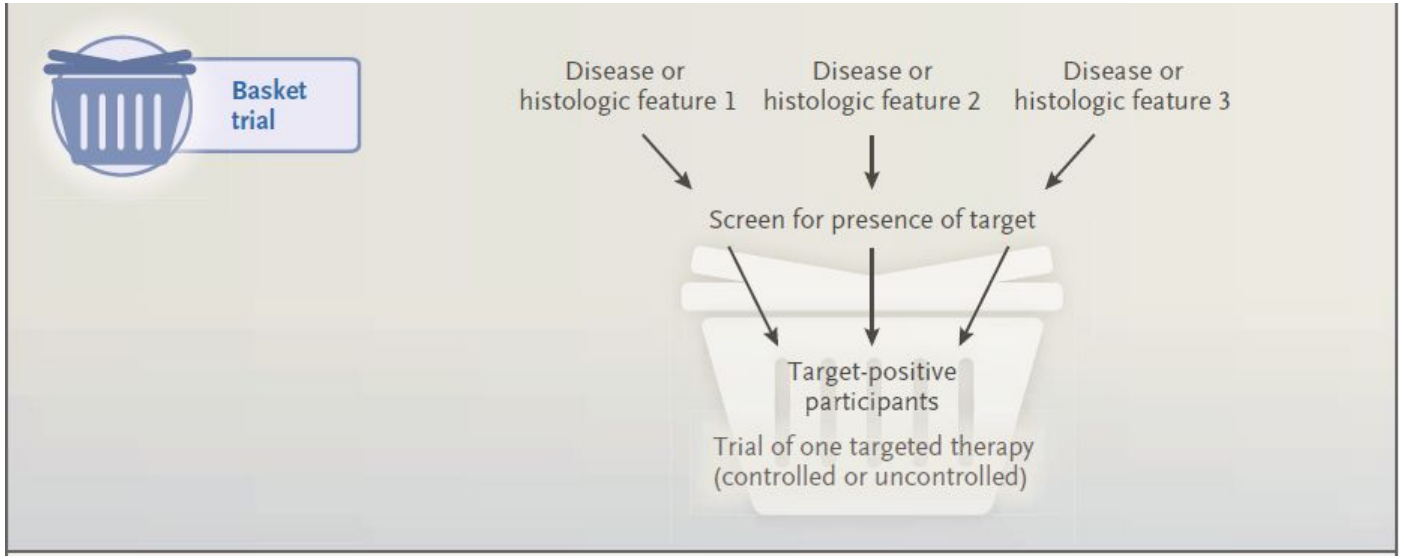
Krams M, Sharma A, Dragalin V et al. (2009). Adaptive Approaches in Clinical Drug Development. Pharm Med, 23: 139-148

Types of Adaptive Designs at the Portfolio Level

Population Finder	• The fixed aspect of the trial is the indication (e.g., breast cancer) and the treatment (e.g., epidermal growth factor receptor inhibitor) • The design aims to establish which subset of the population benefits most
Indication Finder	• The fixed aspect of the trial is the compound • The competing options are different indications • The design aims to establish which of the indications show therapeutic benefit
Compound Finder	• The competing options are several different compounds for the same indication • The design aims to identify the compound with the most impressive therapeutic index
Compound / Population Finder	• Multiple development candidates are assessed in parallel and matched with biomarker signatures of different subpopulations • The design aims to dynamically change the allocation of new patients with a given signature to different compounds

Krams M. and Dragalin V. (2014). Considerations and Optimization of Adaptive Trial Design in Clinical Development Programs. Springer, pp 69-90

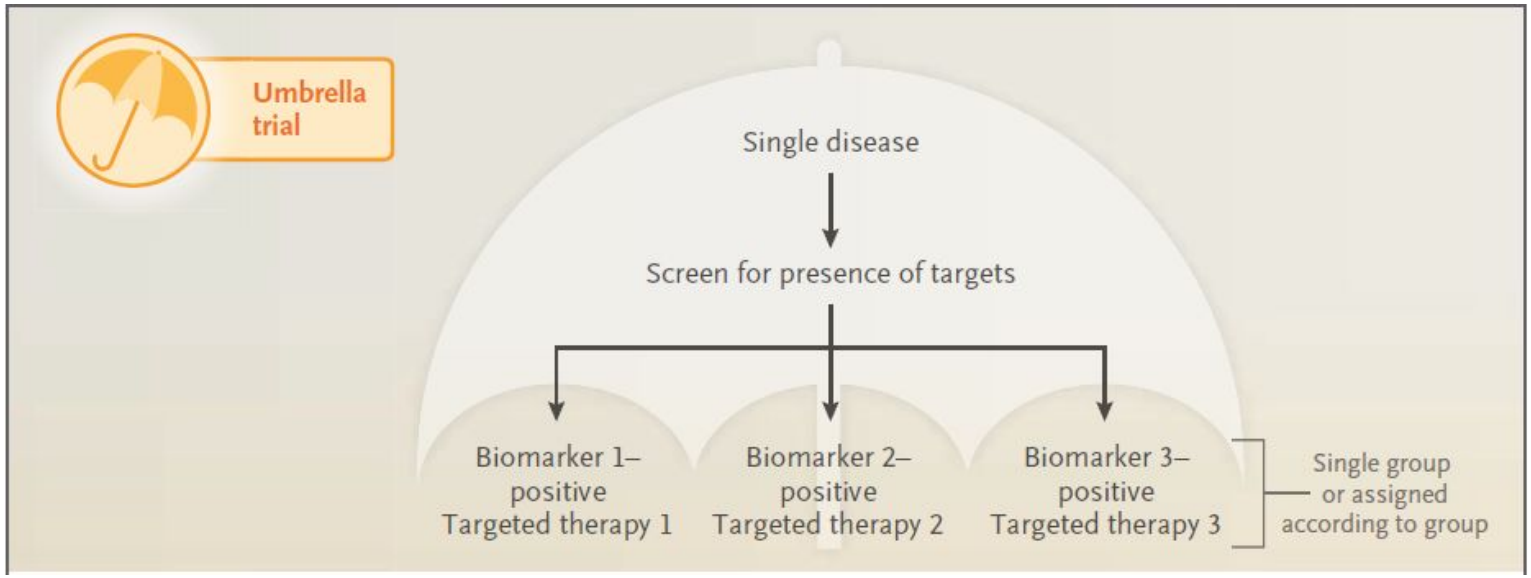
Basket Trial



- A basket trial involves multiple diseases or histologic features (i.e., in cancer).
- After participants are screened for the presence of a target, target-positive participants are entered into the trial.

Woodcock J. and LaVange LM (2017). *Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both*. NEJM, 377: 62-70

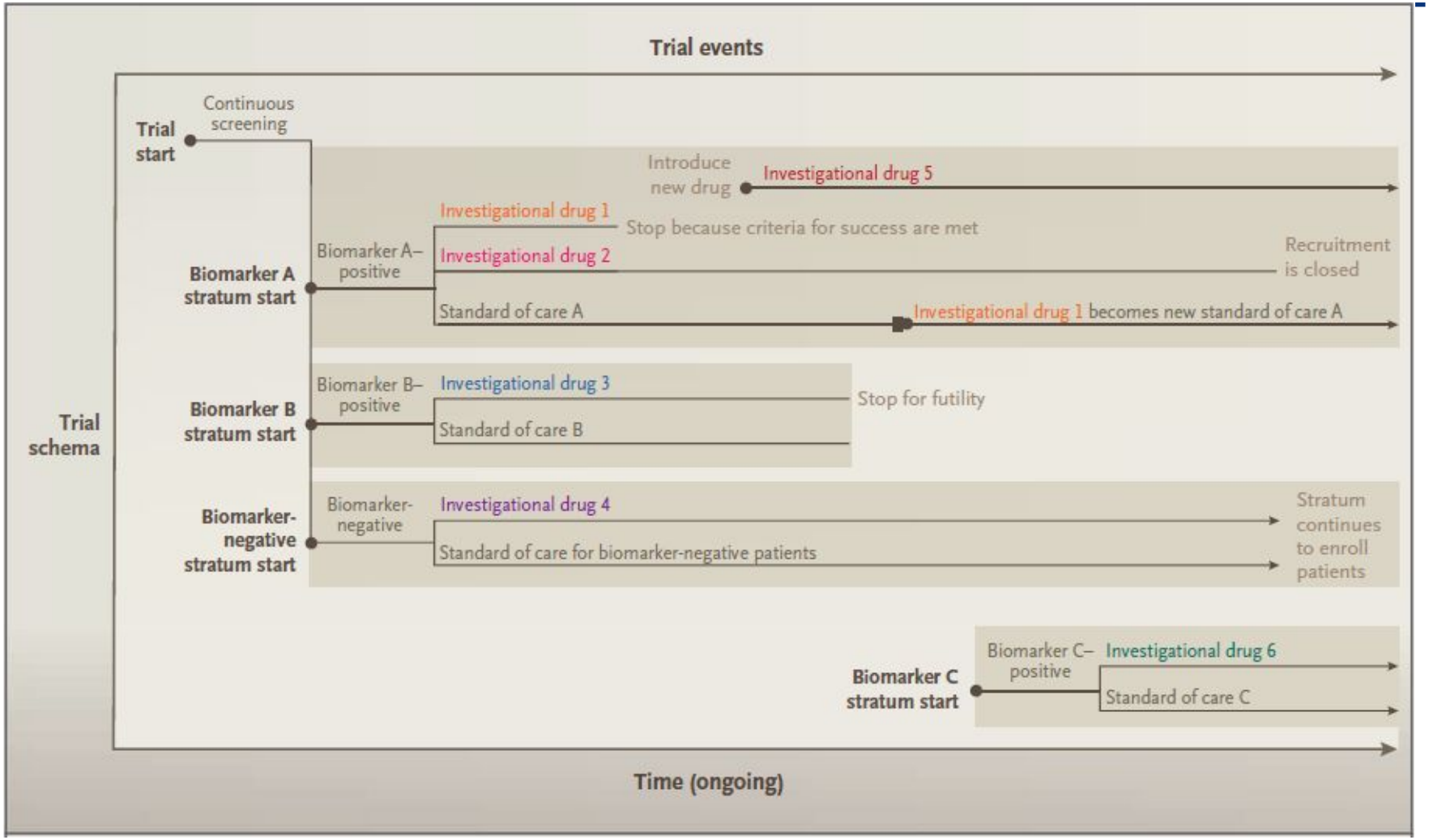
Umbrella Trial



- An **umbrella trial** evaluates various (often biomarker-defined) subgroups within a conventionally defined disease.
- Patients with the disease are screened for the presence of a biomarker or other characteristic and then assigned to a stratum on the basis of the results.
- Multiple drugs are studied in the various strata, and the design may be randomized or use external controls depending on the disease.

Woodcock J. and LaVange LM (2017). *Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both*. NEJM, 377: 62-70

Platform Trial



Platform trial: definition

An experimental infrastructure to evaluate simultaneously

- Multiple treatments and combinations of treatments
- In heterogeneous patient populations
- Using specialized statistical tools for allocating patients and analyzing results
- Designed around a group of related diseases rather than a single treatment
- Using pre-existing infrastructure for clinical operations and trial implementation

Saville BR & Berry SM. (2016). Efficiencies of Platform Clinical Trials: A Vision of the Future. Clinical Trials, 13 pp 358-366

Potential benefits of platform trials

- Share a common control group: total sample size for one multi arm Platform Trial can be less than multiple 2-arm trials
- Study multiple agents from different classes of drugs and/or target pathways and/or drug combinations entered simultaneously or in a staggered fashion as they become available for testing
- Number and type of treatment/therapies may change over time
- Consistency: each drug tested within similar conditions and trial environment
- Potential savings in screening and recruitment time
- Potential savings in trial costs in the long run by sustaining the installation and maintenance of a standing global trial platform

Process and operational efficiency

- One master protocol with common elements across sub-studies/appendices (ISA):
  - A new appendix for each new intervention cohort 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

Need for assessment of intended benefits

Platform trials are developed to have a positive impact on solutions for patients but...

it should be assessed whether the capitalization of improvement efforts occurs.

4 key questions can lead to the path to meaningful insight and evidence of intended improvement :

How to measure

- Measurements should provide a fair comparison to our current practices
- Reporting should not cause an administrative burden
- What can we measure providing what is already available?
- Who will obtain and report the data?

What to measure

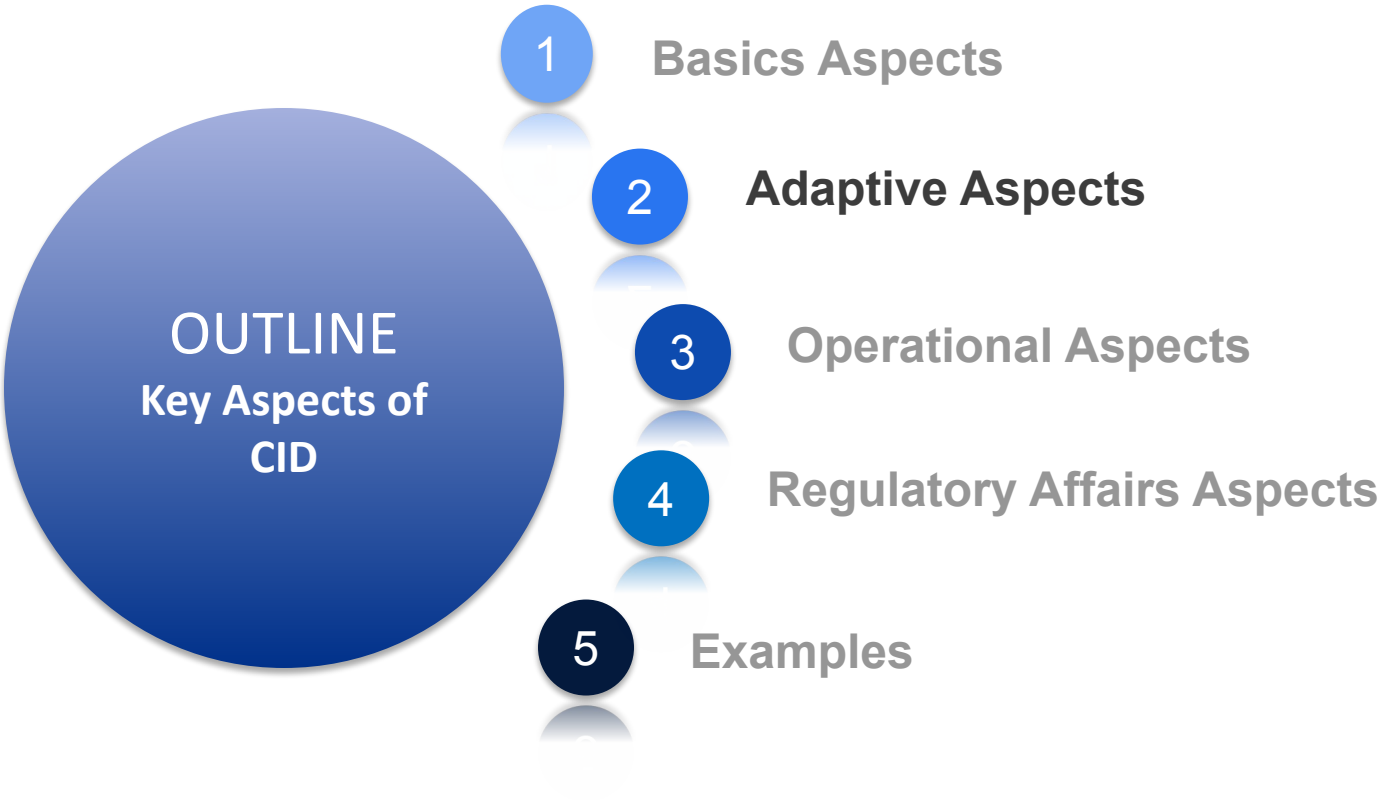
- A benefits-realization curve informs on the assumptions made on impact and strategy
- It supports to communicate with our stakeholders on the decisions made
- What KPIs can be identified to measure the projected benefit?
- When and to whom do we want to report?

Why change

- Productivity is driving us to improve our path to output
- Innovations however might also contribute to our competitive positioning
- What is our mission?

What do we want to accomplish

- Investments are to be made to change our operational approaches
- Focus is required to change something, to create benefit
- What are the Strategic Imperatives?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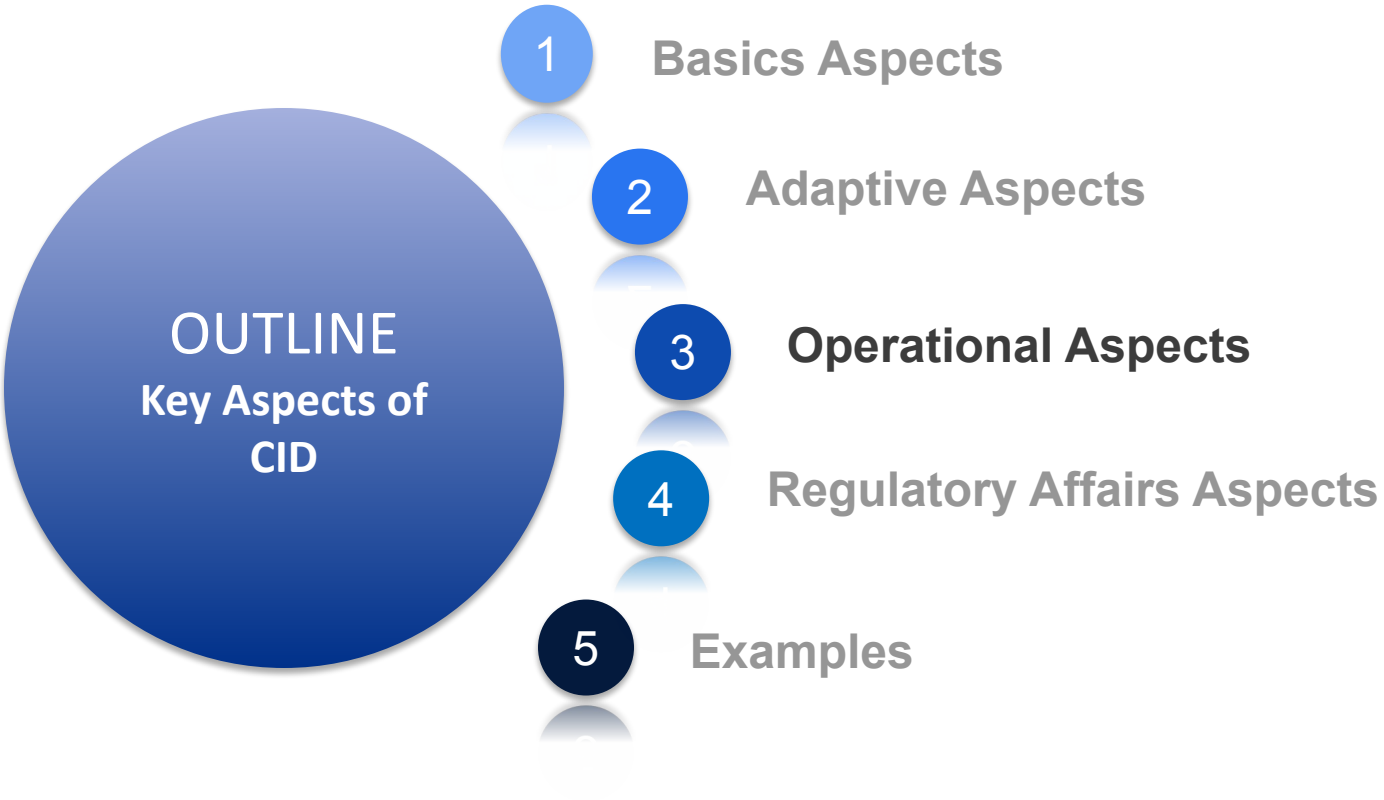
Adaptive design features in platform trials

- Adaptive designs can be used to create a seamless process in which new evidence about effectiveness is immediately used to improve patient care within the trial
- A platform trial can extend this process beyond a single treatment or few treatments and beyond a homogeneous population
- Match drugs with biomarker signatures
- Savings from common control
- Patients will benefit if we merge clinical trials and decision support into a single, continuous process
- Drug/biomarker pairs graduate to small, focused, more successful Phase III based on Bayesian predictive probabilities
- Better therapies move through faster

The Adaptive Platform Trials Coalition. (2019). Adaptive Platform Trials: Definition, Design, Conduct, and Reporting Considerations. Nature Review, Drug Discovery, 18, pp 797-807.

Simulations

- Prospective planning essential
- Many scenarios/examples
- Accrual rate matters
- Other arms and their efficacies matter
- **Extensive simulations of trial performance** to ensure:
  - the type I error rate control,
  - power and accuracy in estimation of treatment effect(s),
  - arm's duration in trial,
  - the rates of adverse events,
  - or dose finding
- are well defined and acceptable, across a very wide range of possible true treatment effect sizes, dose-response relationships, and population characteristics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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

Intervention-Specific Appendices (ISAs) Structure

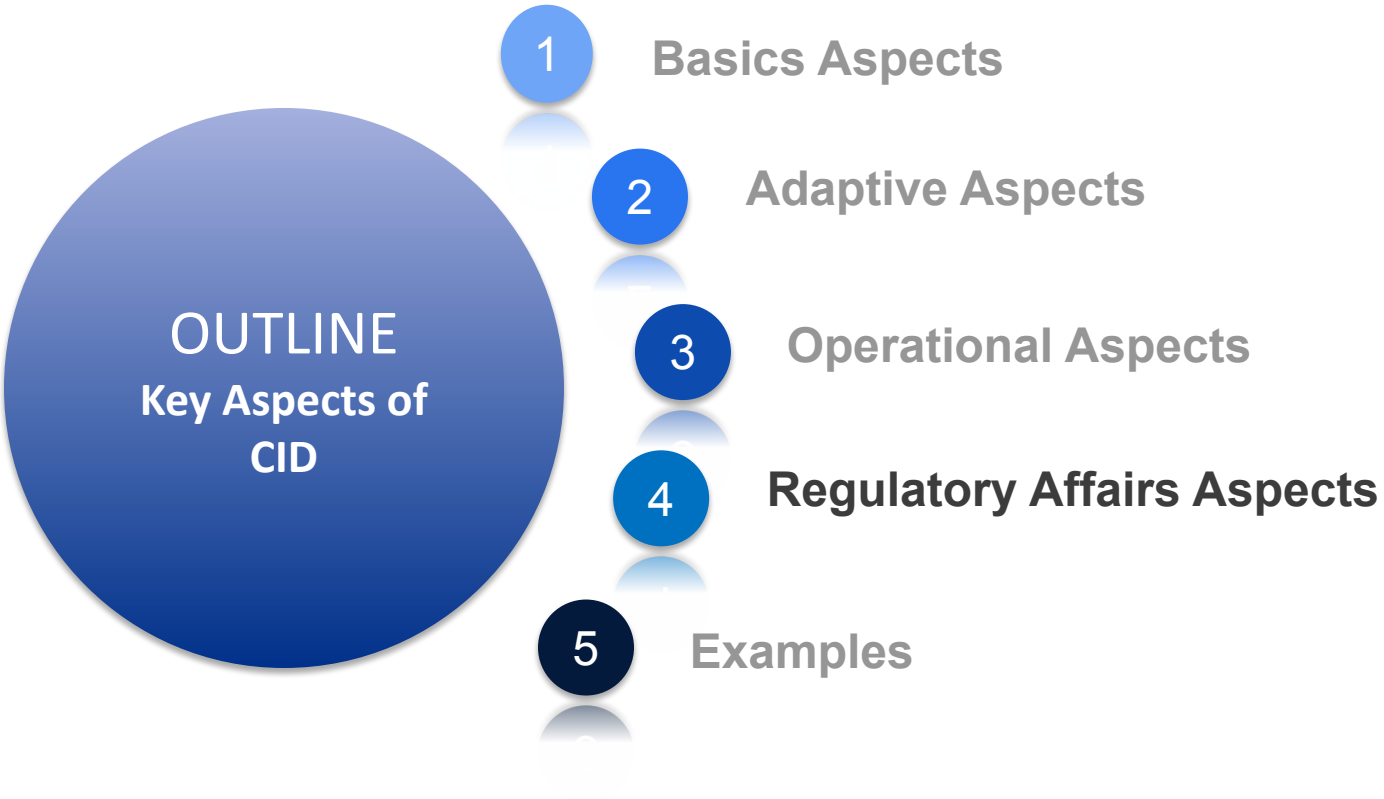
- **Background information**, including preclinical and clinical data, rationale for testing intervention in the disease and dose rationale
- **Intervention-specific data** including additional inclusion/exclusion, administration schedule, specific tests/procedures for biomarkers or safety, dose reduction 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

Two-Part Consenting Process Structure

- Part One: Master Informed Consent Form (ICF)
  - All participants receive the same ICF
  - Describes both screening and treatment
  - ICF includes general trial overview and describes all the required tests/procedures and risks (e.g., risk of being randomized)
  - Table summarizing all available interventions

- Part Two: ISA-Specific ICF
  - Participant receives ISA ICF once they have received randomization assignment (i.e., ISA A versus ISA B)
  - ICF includes only treatment information (e.g., administration schedule, intervention-specific risk factors, any additional safety tests/labs/assays, as applicable)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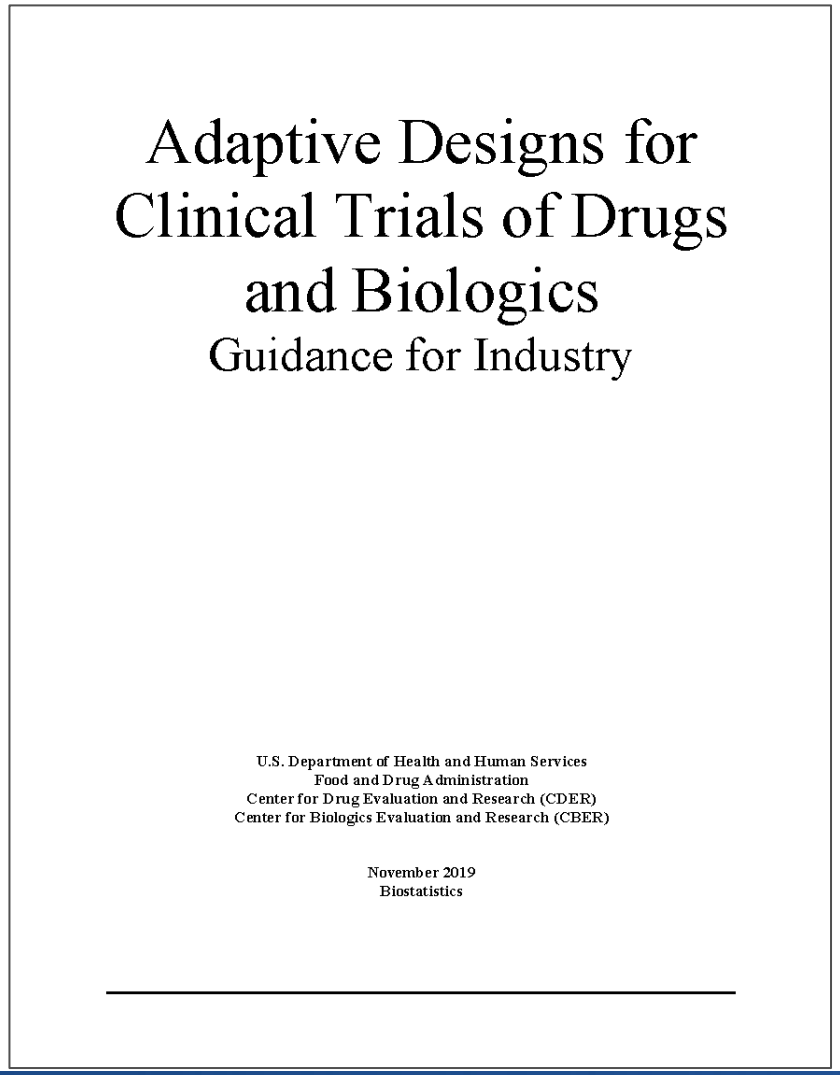
FDA Guidances

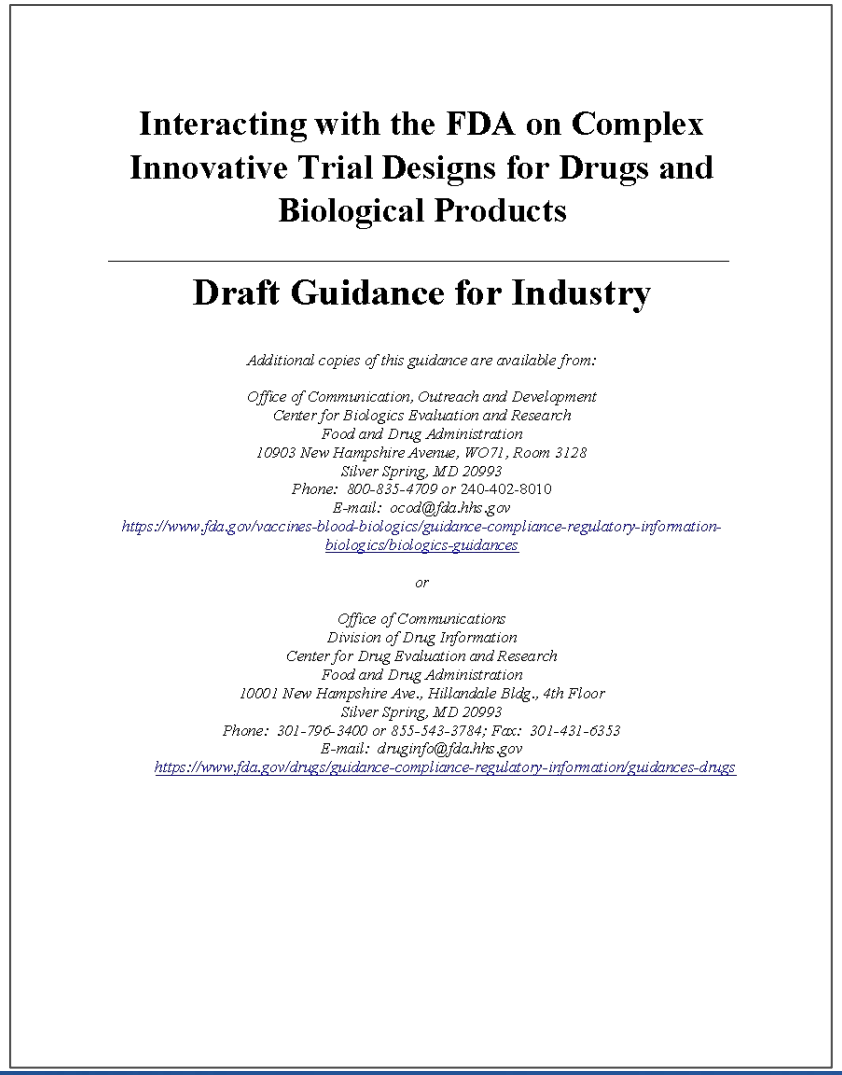


Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2019
Biostatistics



Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

Draft Guidance for Industry

Additional copies of this guidance are available from:

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, WO71, Room 3128
Silver Spring, MD 20993
Phone: 800-835-4709 or 240-402-8010
E-mail: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

or

Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993
Phone: 301-796-3400 or 855-543-3784; Fax: 301-431-6353
E-mail: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

FDA's viewpoints on master protocols: Points to Consider

FDA's experience with master protocols is evolving. Recognizing the complexity of these studies, FDA issued a draft guidance for master protocols in oncology[2]. However, other Divisions may have different considerations, and it is encouraged to discuss any master protocol design in a formal meeting with the FDA.

Study Design

- Use of a common control arm where multiple drugs are evaluated in a single disease
  - Account for potential changes in the control arm (e.g., changes in SOC, shifts in placebo response over time)
- Master protocol and SAP should describe conditions that would result in adaptations based on interim analyses or futility rules
- Consider study design elements such as assessment time points and a candidate's MOA or clinical study results when evaluating for platform study

Statistics

- Master protocols employing adaptive designs should provide all information described in draft guidance's *Adaptive Designs for Clinical Trials of Drugs and Biologics* and *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*

Safety

- Independent Safety Assessment Committee (ISAC) and/or Independent Data Monitoring Committee (IDMC) recommended
- Master protocol should describe rules for re-enrollment, and participants with AEs should be excluded from other trials until AE(s) have resolved

Biomarker Development

- Recommend early discussion of biomarker development plans with FDA when using to inform patient selection for trials
  - Master protocol should explain why use of the biomarker is appropriate, employ analytically validated IVD tests, and contain a prespecified plan for allocation of participants potentially eligible for more than one sub study

[1] Based on (1) FDA Draft Guidance - Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics (Sep 2018) and (2) FDA Feedback received during Pre-IND meetings for JNJ-54175446 (Mar 2017) and JNJ-67864238 (May 2018)

[2] Prepared by Office of Hematology and Oncology Products, in cooperation with Oncology Center of Excellence and CBER

EU Heads of Medicines Agencies' Clinical Trials Facilitation Group (CTFG)
Recommendation paper on the initiation and conduct of complex clinical trials
12 February 2019 (*http://www.hma.eu/ctfg.html*)

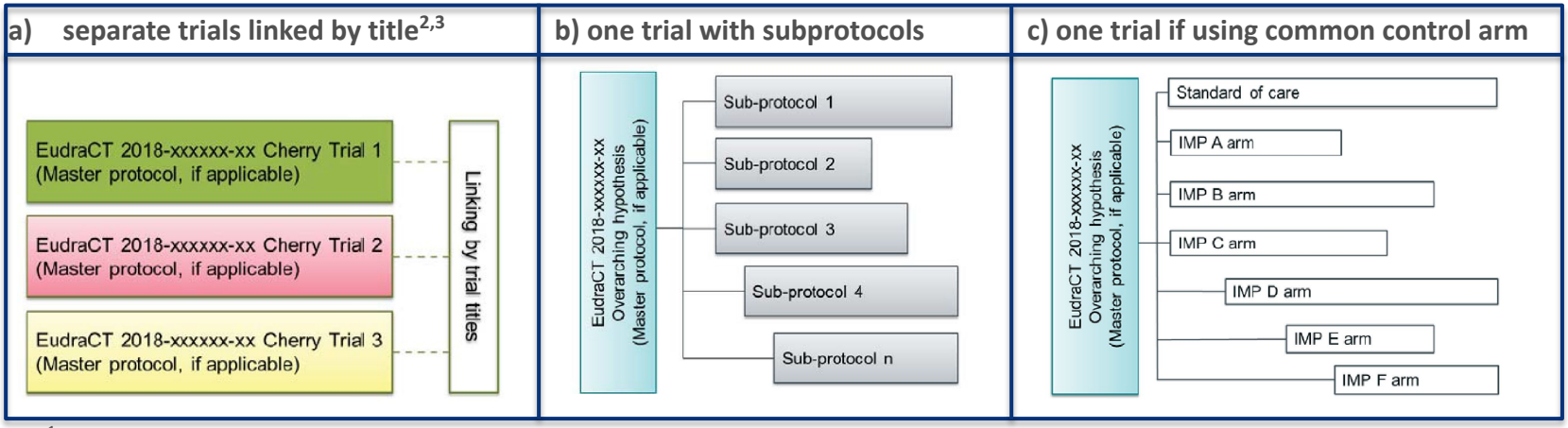
Complex Trials...

- have separate parts that could constitute individual clinical trials, e.g.,
  - sub-protocols (independent statistical analyses)
  - study arms (statistical analyses depend on other cohorts, e.g., control arm)
- are characterized by extensive *prospective* adaptations, e.g.,
  - addition of new IMPs and/or target populations
  - closure of sub-protocols based on futility or safety
- may have a common screening platform and/or a common operational framework, which may be described in a master protocol
- are generally considered appropriate primarily for phase I/II exploratory clinical trials

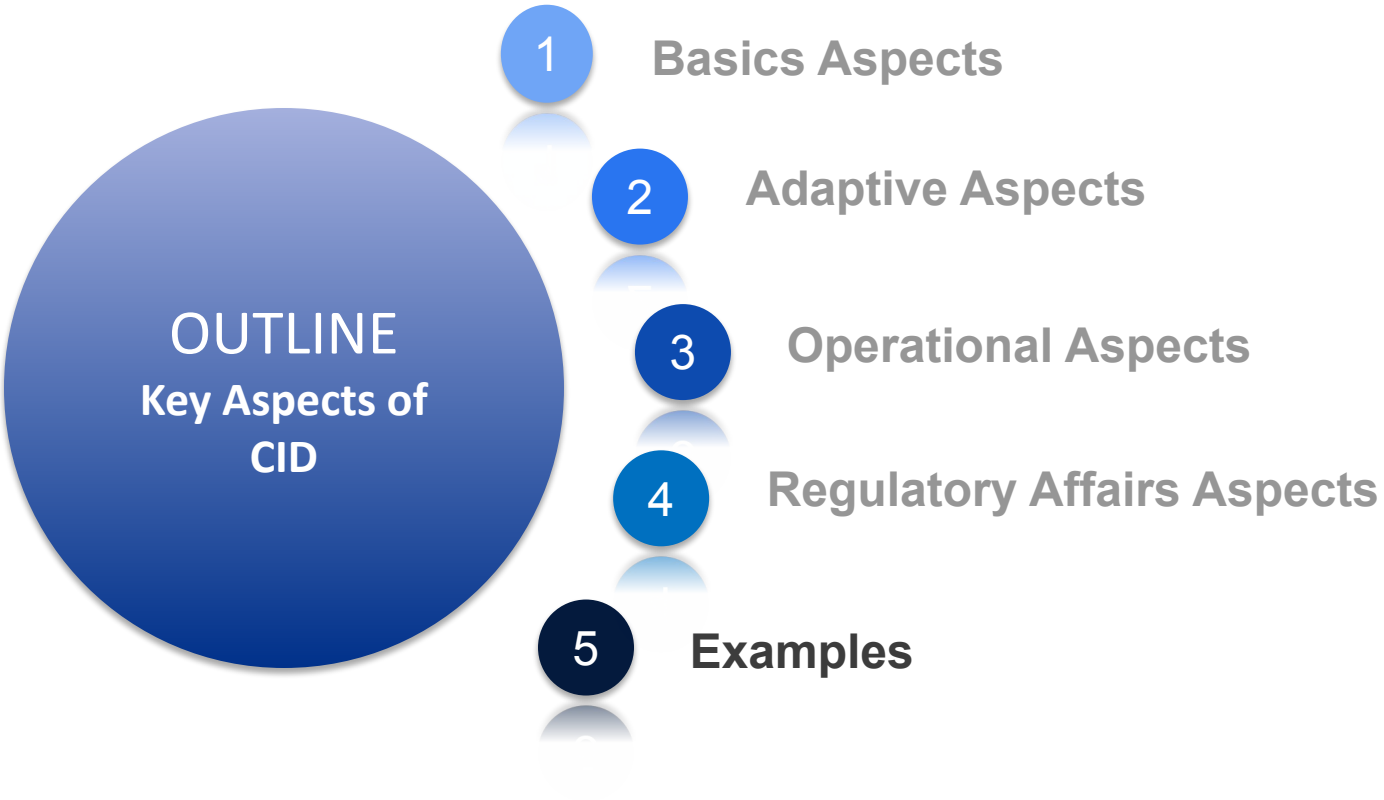
CTFG Key Recommendations

1. Clearly describe and justify design
2. Maintain scientific integrity
3. Ensure quality of trial conduct and optimize clinical feasibility
4. Ensure safety of trial subjects
5. Maintain data integrity
6. Reassess benefit-risk balance at critical steps throughout clinical trial
7. Validate companion diagnostics
8. Consider data transparency

Submission strategies[1]



[1] the examples provided are illustrations, not intended to be exhaustive, and other scenarios are possible
[2] required for first-in-human IMPs and for advanced therapy medicinal products (ATMPs) without an EU marketing authorization
[3] recommended where the potential IMPs or populations to be added are very poorly defined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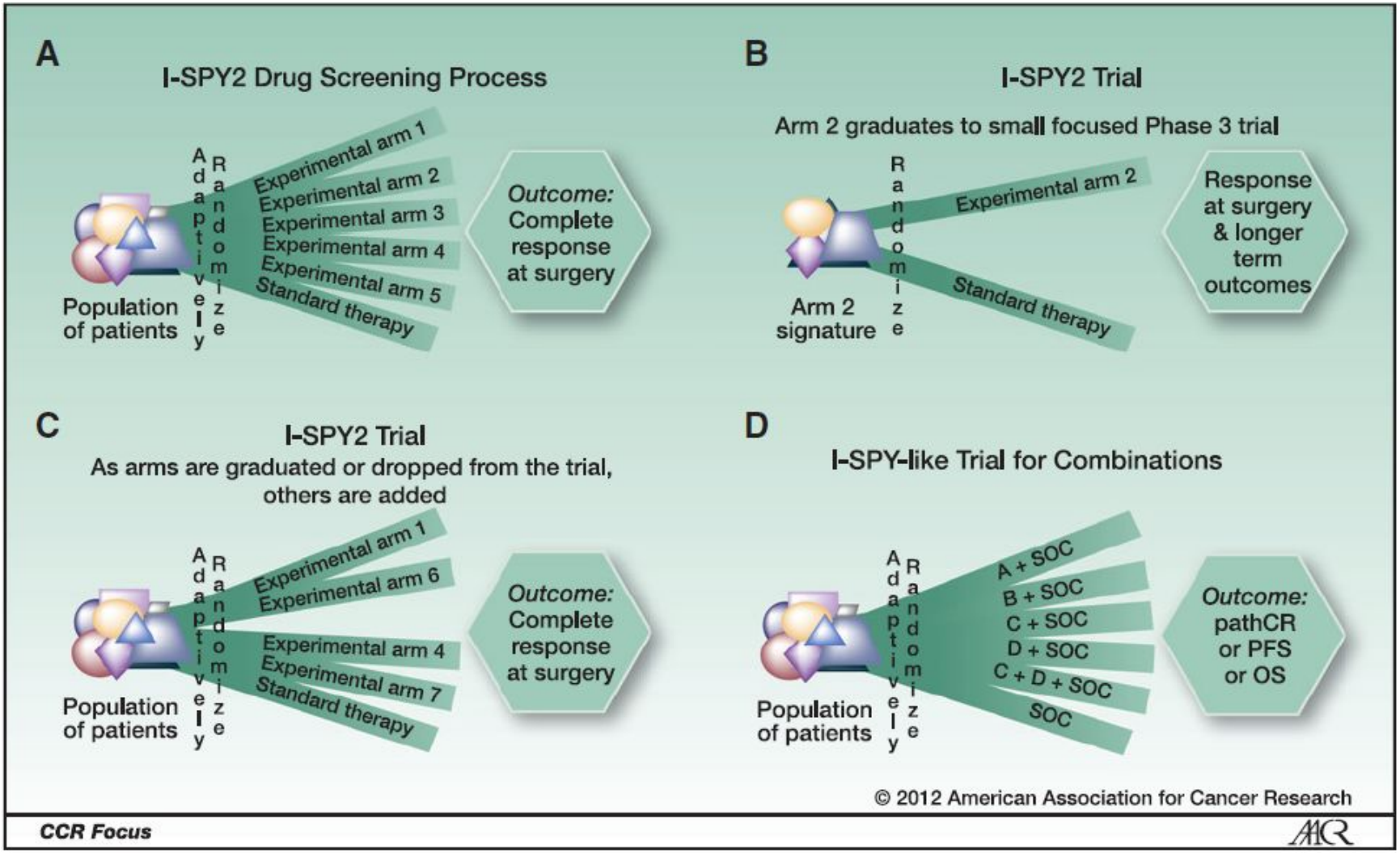
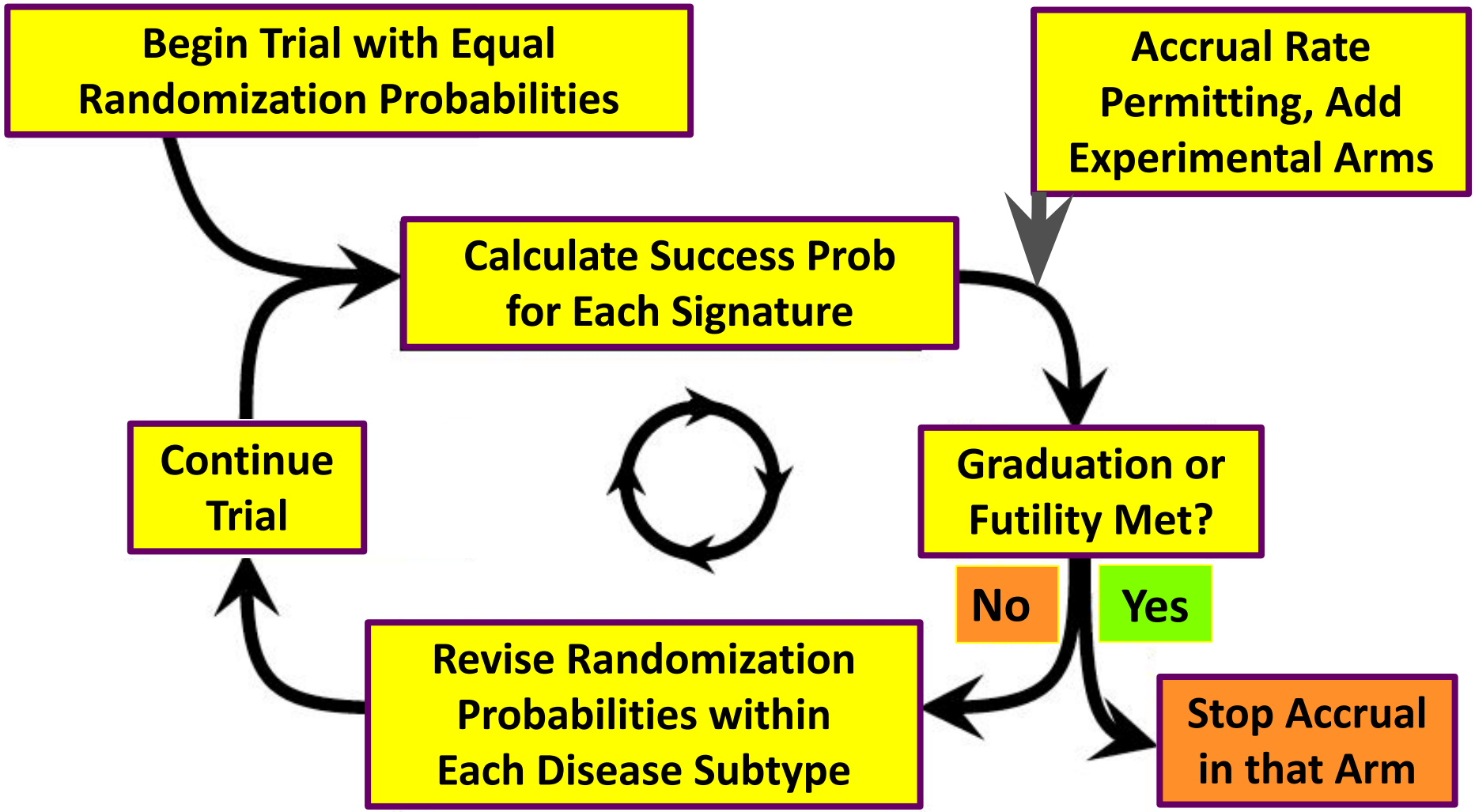
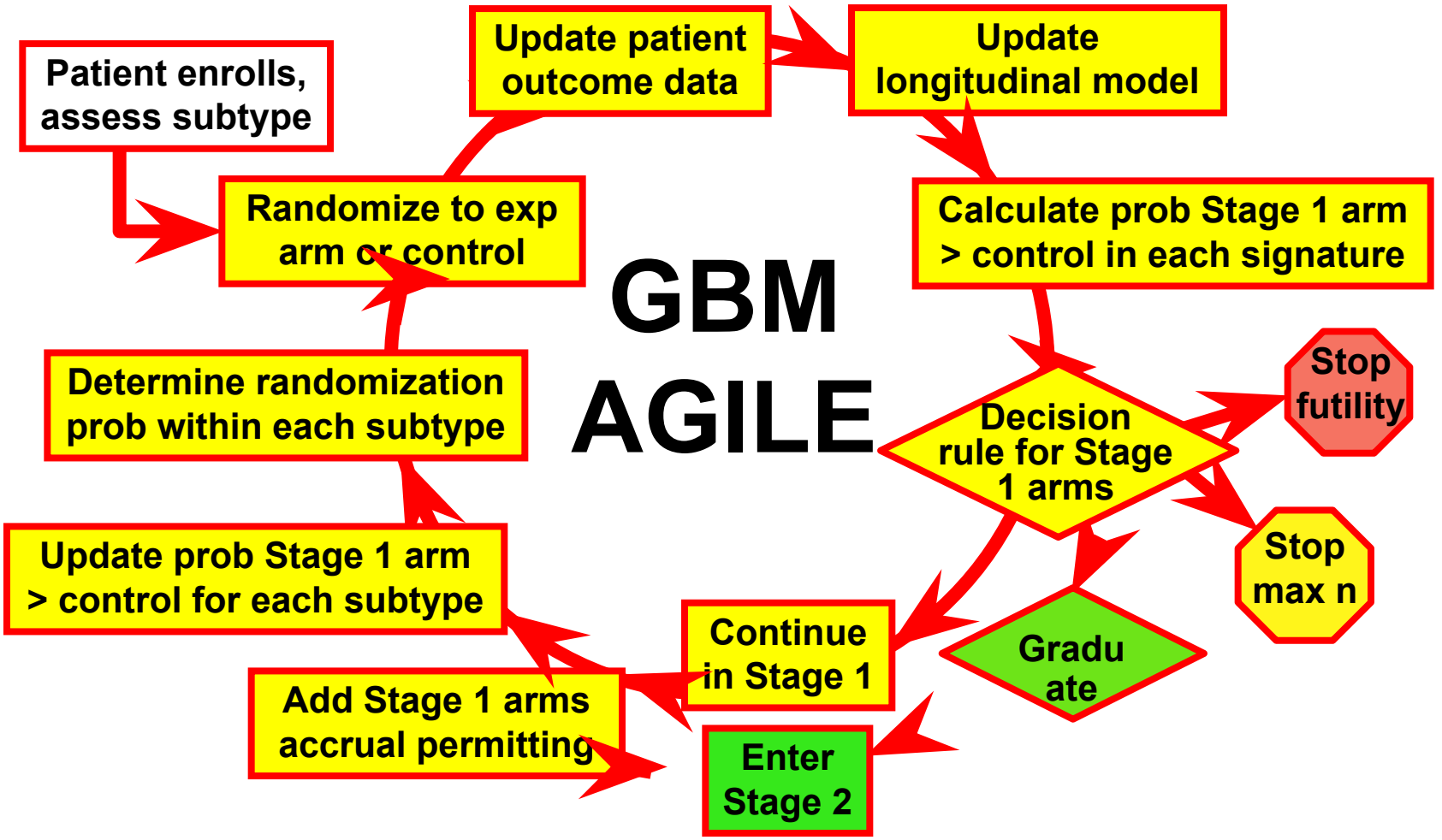
I-SPY2 Trial


A
I-SPY2 Drug Screening Process
Population of patients
Adaptively Randomize
Experimental arm 1
Experimental arm 2
Experimental arm 3
Experimental arm 4
Experimental arm 5
Standard therapy
Outcome: Complete response at surgery
B
I-SPY2 Trial
Arm 2 graduates to small focused Phase 3 trial
Arm 2 signature
Randomize
Experimental arm 2
Standard therapy
Response at surgery & longer term outcomes
C
I-SPY2 Trial
As arms are graduated or dropped from the trial, others are added
Population of patients
Adaptively Randomize
Experimental arm 1
Experimental arm 6
Experimental arm 4
Experimental arm 7
Standard therapy
Outcome: Complete response at surgery
D
I-SPY-like Trial for Combinations
Population of patients
Adaptively Randomize
A + SOC
B + SOC
C + SOC
D + SOC
C + D + SOC
SOC
Outcome: pathCR or PFS or OS
© 2012 American Association for Cancer Research
CCR Focus
AACR

I-SPY 2 Adaptive Process

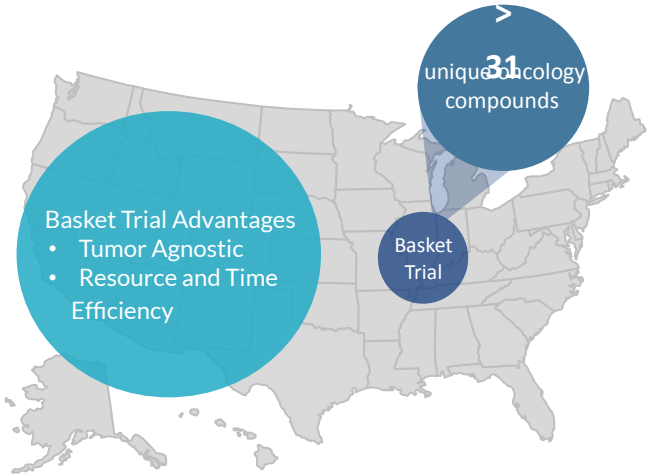


GMB AGILE: Seamless Integration from "Learn" to "Confirm"



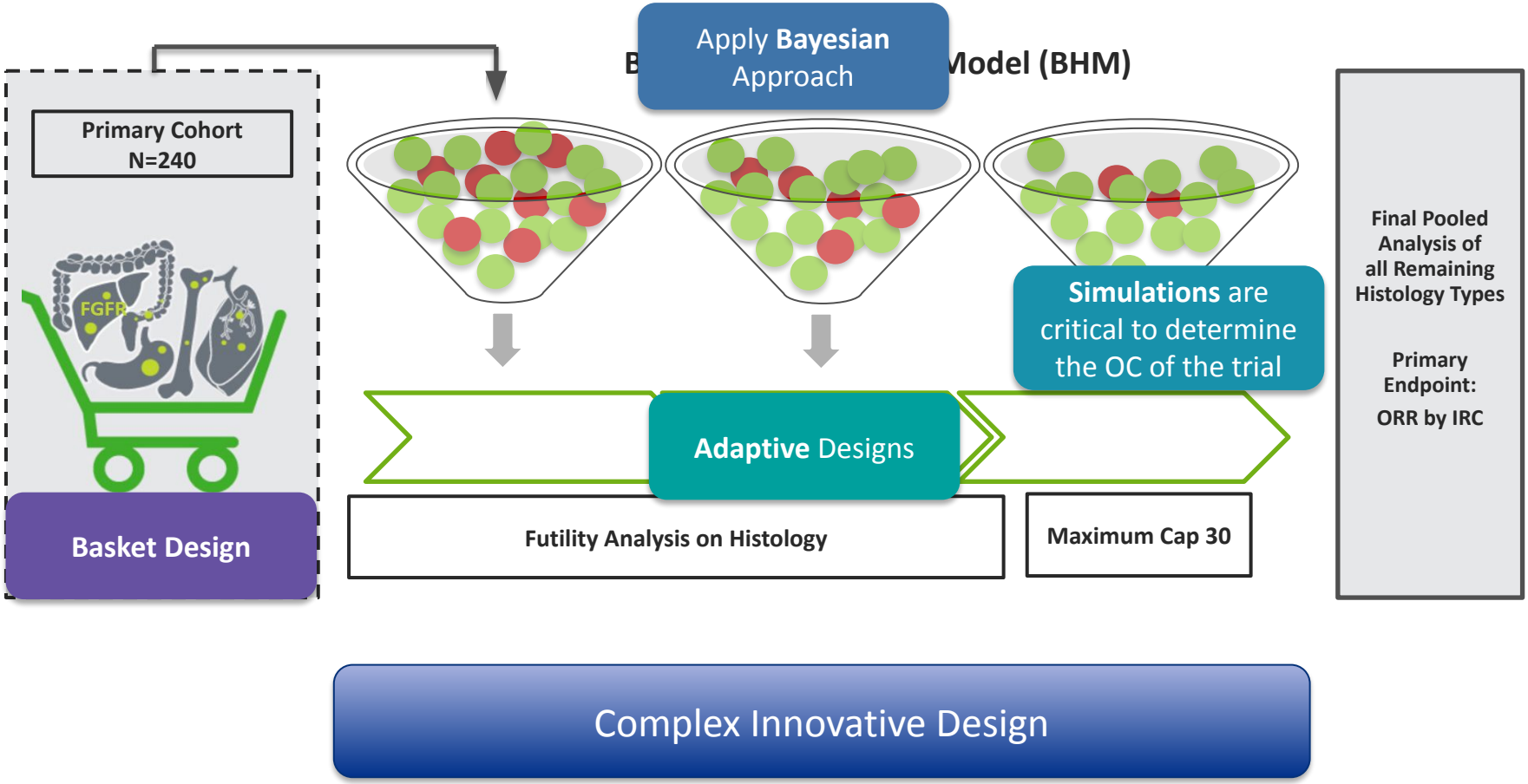
Janssen's First Tumor-Agnostic Bayesian Adaptive Basket Trial in Erdafitinib

RAGNAR



The enrollment is based on molecular screening for FGFR Gene Alterations regardless of tumor types.

Tumor-Agnostic Bayesian Adaptive Basket Trial



FDA Guidance for Industry (2020). Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products.

Conclusions from RAGNAR Study

Basket Trials with Complex Innovative Designs allow:

- To answer **multiple study objectives** by testing several hypotheses
- To reach conclusions as **quickly** and as **efficiently** as possible
- To address the small sample size per histology by **borrowing information across tumor types** for improved power
- More **precise futility stopping**
- **Efficient** sample size allocation

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References

1. *Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both.* Woodcock J. and LaVange LM, NEJM, 2017, 377: 62-70
2. *The brave new world of clinical cancer research: adaptive biomarker-driven trials integrating clinical practice with clinical research.* Berry DA. Mol Oncol 2015; 9: 951-959
3. *The platform trial: an efficient strategy for evaluating multiple treatments*. Berry, Scott M., Jason T. Connor, and Roger J. Lewis. *JAMA* 313.16 (2015): 1619-1620.
4. *Innovations in Breast Cancer Drug Development – Next Generation Oncology Trials* Statistical Considerations in Designing Master Protocols , Lisa M. LaVange, Raji Sridhara, OTS/CDER/FDA Breast Cancer Workshop , Bethesda Oct. 21, 2014
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6. R Herbst et al, Design of a Disease Specific Master Protocol, Conference on Clinical Cancer Research, Nov 2012
7. R. Herbst, E Rubin, L LaVange et al, Design of a disease-specific master protocol conceference on Clinical Cancer Research, Nov 2012: http://www.focr.org/sites/default/files/CCCR12MasterProtocol.pdf
8. Addressing unmet needs through Master Protocols, at http://www.swog.org/Visitors/Fall14GpMtg/TM/Addressing-unmet-needs-through-Master-Protocols.pdf
9. http://www.partneringforcures.org/assets/Uploads/Innovators/FriendsCancerResearch.pdf

Thank you

VDragali@its.jnj.com

Julius Caesar Bustamante – *Pajaros*
Artwork from Healing Arts Initiative, a nonprofit organization that inspires healing, growth and learning through access to the arts for the culturally underserved.

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