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Practical Considerations in Designing and Executing Early Phase Adaptive Trials: An Industry Perspective

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Overview

- Study conditions that do and do not favor adaptation
- Additional “costs” of conducting an adaptive design
- Case study #1: Dropping dose design
- Case study #2: Speed of enrollment
- Programmatic considerations when planning an adaptive design

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Flavors of Adaptive Design

- Stop for futility or success
- Drop or add a treatment group (drop inefficient arm, add new dose group)
- Combine phases of development (e.g. seamless Phase 2a-2b)
- Adaptive randomization
- Sample size re-estimation
- Predictive probability of Phase 3
- Patient enrichment

Conditions That Favor or Do Not Favor Adaptive Design

Favor

- Rapid turnaround of data from the sites to perform interim calculations (e.g., via EDC)
- Broad dose range to study (adaptive randomization increases efficiency of dose range finding study)
- Slow enrollment relative to readout of primary outcome measure
- Availability of biomarkers that are predictive of final outcome (allow longitudinal modeling)

Do not favor

- Fast enrollment relative to readout of primary outcome measure (e.g. disease modification of Alzheimer's)
- Complex drug packaging (blister packs in a multinational study)
- Heterogeneous study features over time

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What Do Adaptive Designs Buy Us?

- Increased efficiency
  - Maximizes the information value per resource unit
  - Increases the probability of subject allocation to more informative treatment groups
  - Allows early trial stopping when sufficient information is available (for futility or early success)
  - Allows more doses to be evaluated for a given total sample size
- Increased accuracy
  - Adaptive randomization results in more information (safety and efficacy) on the “winning” dose
  - More precise estimate of drug effect at Phase 2 increases probability of success of Phase 3

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What Do Adaptive Designs Cost Us?

Overall Consideration

- the potential benefits of an adaptive design should not be outweighed by the added scientific and operational complexity!

- Setup Time
  - Require more up-front discussion and simulation to determine the pre-planned adaptation algorithm
  - Trial simulations are necessary to investigate:
    - False positive and false negative decision rates
    - Statistical power
    - Adequate sample size
  - Operationalize the processes among multiple parties

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What Do Adaptive Designs Cost Us?

- External Spend
  - Drug manufacturing and drug supply management (e.g., larger number of doses than usual)
    - If multi-country, adds another layer to supply strategy, increasing inventory required and amount of unused/wasted drug
    - Implications for supply: bottles vs blister packs
  - Simulations and operationalization of adaptation may require external expertise/spend
  - IVRS (for adaptive randomization)

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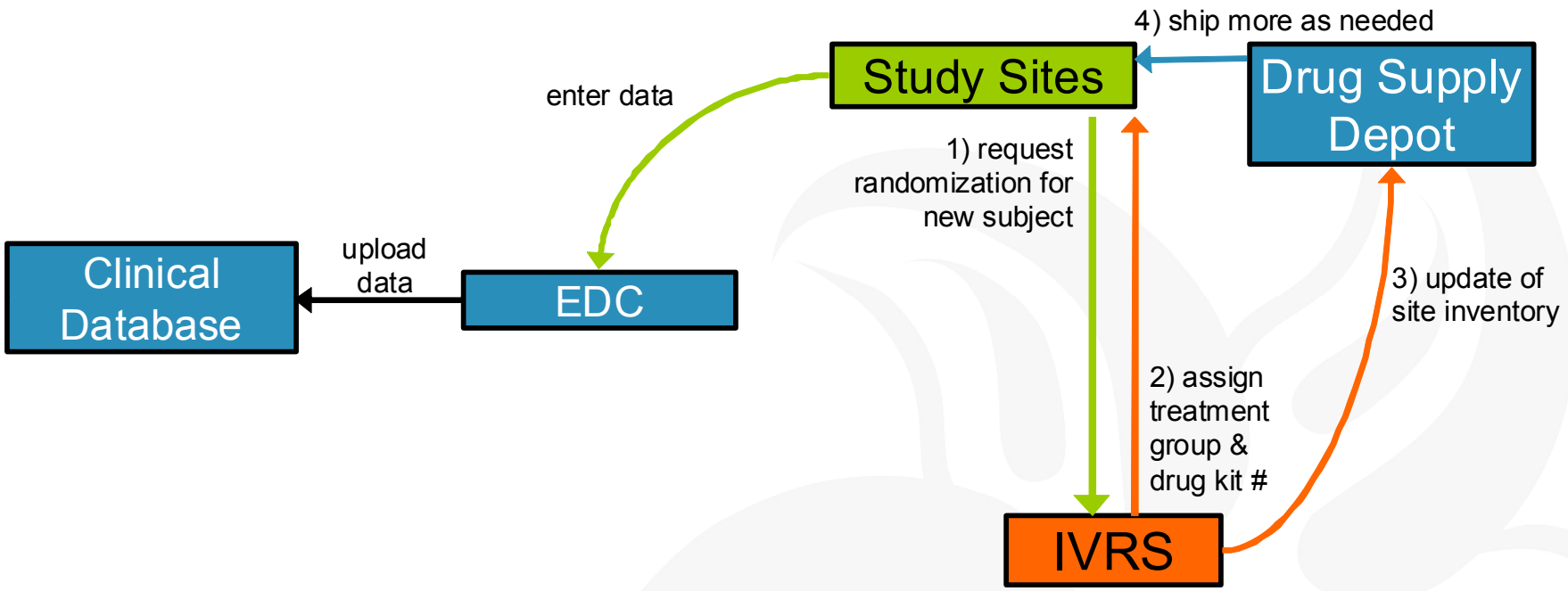
Information Flow: Operational Logistics for Traditional Study Design



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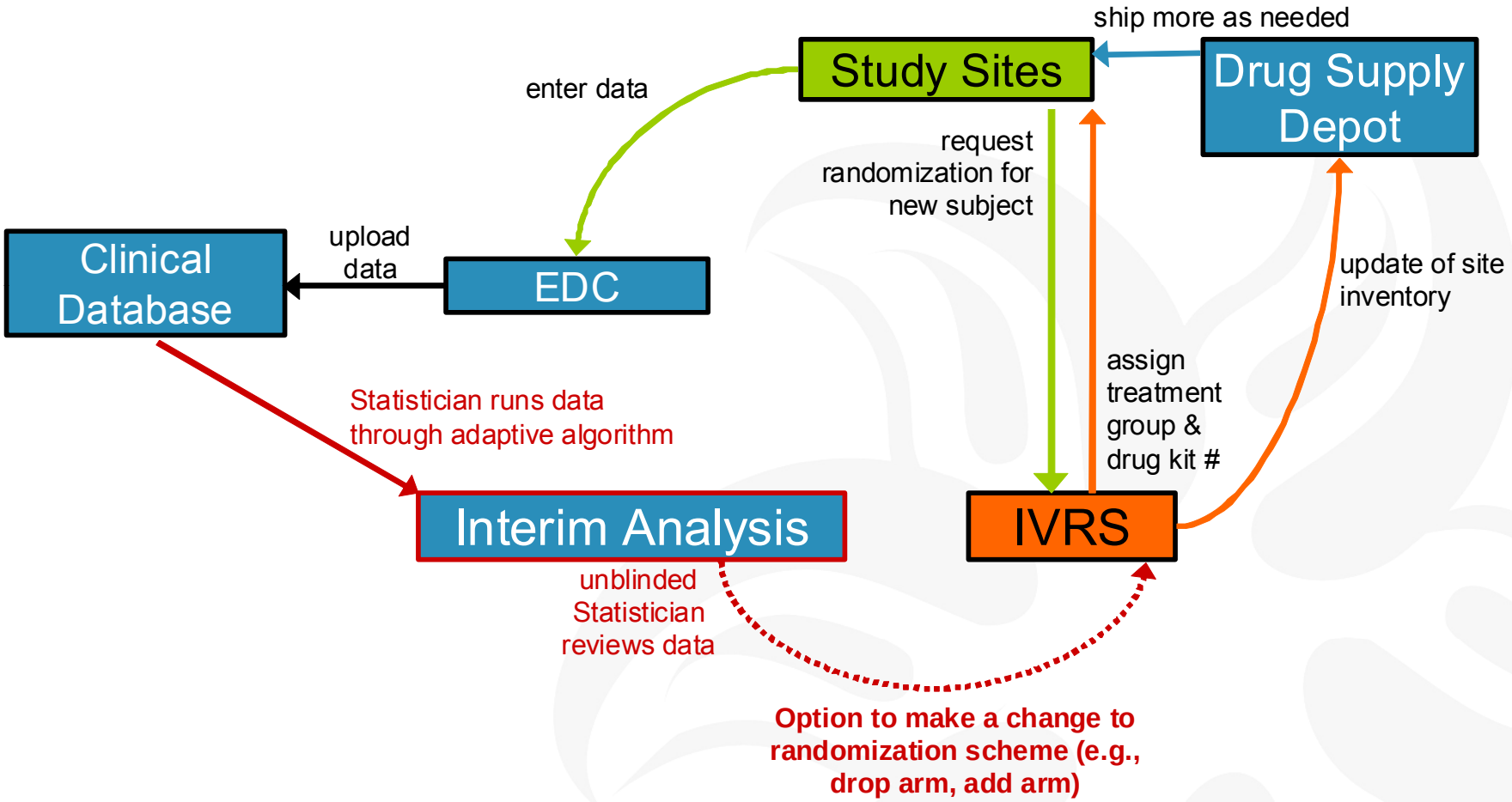
Information Flow: Operational Logistics for Adaptive Design (general)



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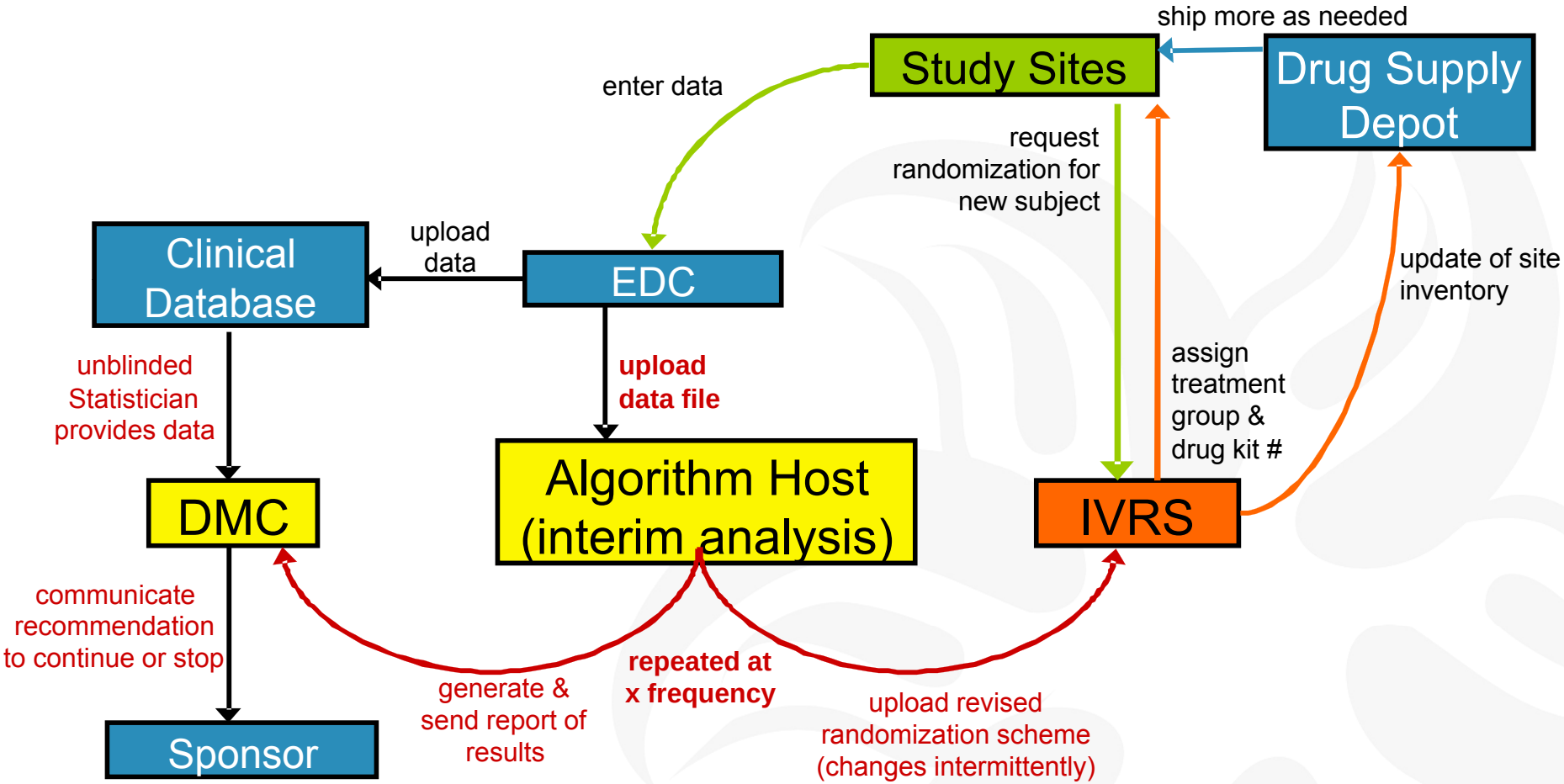
Information Flow: Operational Logistics for Adaptive Randomization Design



Prior to go-live for study, highly recommended to perform dry-run of information loop with dummy data to confirm proper operation

Startup Timeline & Extra Costs: Sample for Response-Adaptive Randomization

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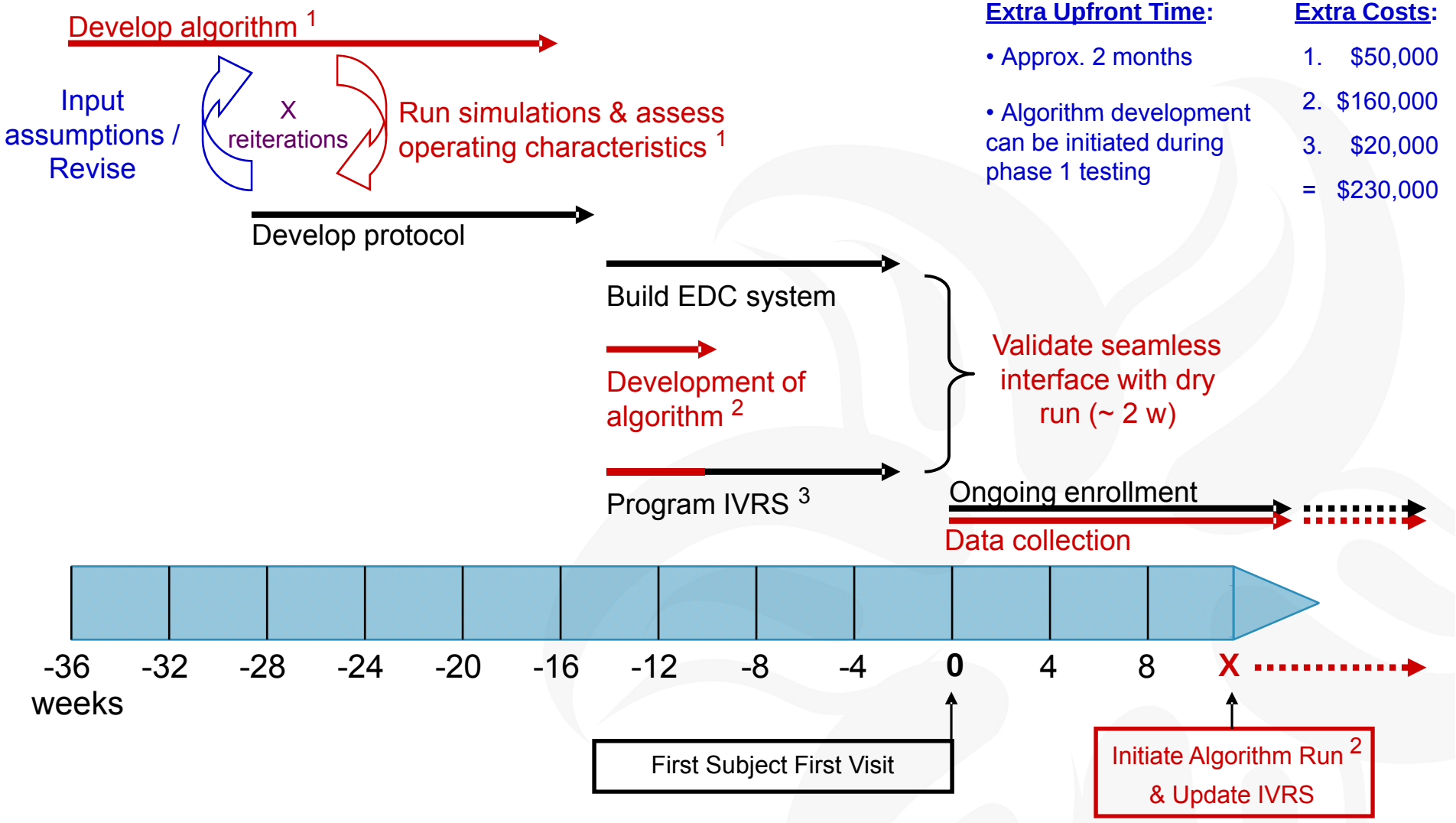

Extra Upfront Time:

- Approx. 2 months
- Algorithm development can be initiated during phase 1 testing

Extra Costs:

1. $50,000
2. $160,000
3. $20,000

= $230,000

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Case Study: Dropping Dose Design

- 8-week, multicenter, parallel group study with 4 dose groups of an investigational drug, placebo and an active comparator in nervous system indication
- Primary efficacy variable:
  Mean change from baseline to final on a continuous random variable
- Sample size: total 275 subjects (55/arm)
- One Interim efficacy evaluation:
  When 125 subjects (approximately 25/arm) had completed the Week 6 visit (including early discontinued subjects)
- Interim analysis data set: use Week 6 data only
- Stopping criteria:
  If a monotonic dose-response relationship is observed AND there is < 20% likelihood that a dose has a > 0.5 point improvement over placebo

Case Study: Dropping Dose Design

Predictive probability that the p value for the treatment difference is < 0.05

	Dose 1	Dose 2	Dose 3	Act. Ctrl.
Pred [p-val.<0.05]	5.6%	0.6%	4.9%	16%
2nd look (4wk later)	3.1%	0.3%	4.9%	14%
3rd look (8 wk later)	1.6%	0.0%	5.0%	65%
Pred [Pr(D>0.5|data) >0.8]	1.7%	0.1%	1.7%	6.6%
2nd look (4wk later)	0.7%	0.0%	1.3%	4.6%
3rd look (8 wk later)	0.0%	0.0%	0.5%	30%
Final p-value (one-side)	0.554	0.887	0.457	0.031

Predictive probability that there is a >80% likelihood that the treatment difference is at least 0.5 points

Approximate number of subjects per arm in the interim analysis.

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Case Study: Dropping Dose Design

- **Example #1 learnings:**
  - Temporal heterogeneity of a trial can compromise the performance of an adaptive design
  - Selection of decision criteria for futility can have a large impact

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Case Study: After-the-fact Interim Analysis On a Completed Study

- An 8-week study with 4 dose groups of an investigational drug, placebo and an active comparator; parallel group design
- Planned sample size 45/arm → total sample size of 270
- Team considered a dropping-arm adaptive design, but the likelihood of fast enrollment led to the choice of traditional design
- Average enrollment rate over 5 months: 54/month
  - 45/month for the first three months
  - 68/month for the last two months
- The study showed that there was no treatment effect for any of the dose groups
- Retrospectively defined 3 interim evaluations:
  - 1st interim when 138 subjects (23/arm) finish Week 6 visit
  - 2nd and 3rd interims are one week apart due to fast enrollment speed
  - calculate Predictive Prob. of {final p-val ≤ 0.05} at each interim look
- Dropping arm criteria:

  Make dropping-arm decision for an investigational dose group if Predictive Probability of {final p-val ≤ 0.05} ≤ 0.15 for the group, *and* the active control achieves a predictive probability ≥ 60%

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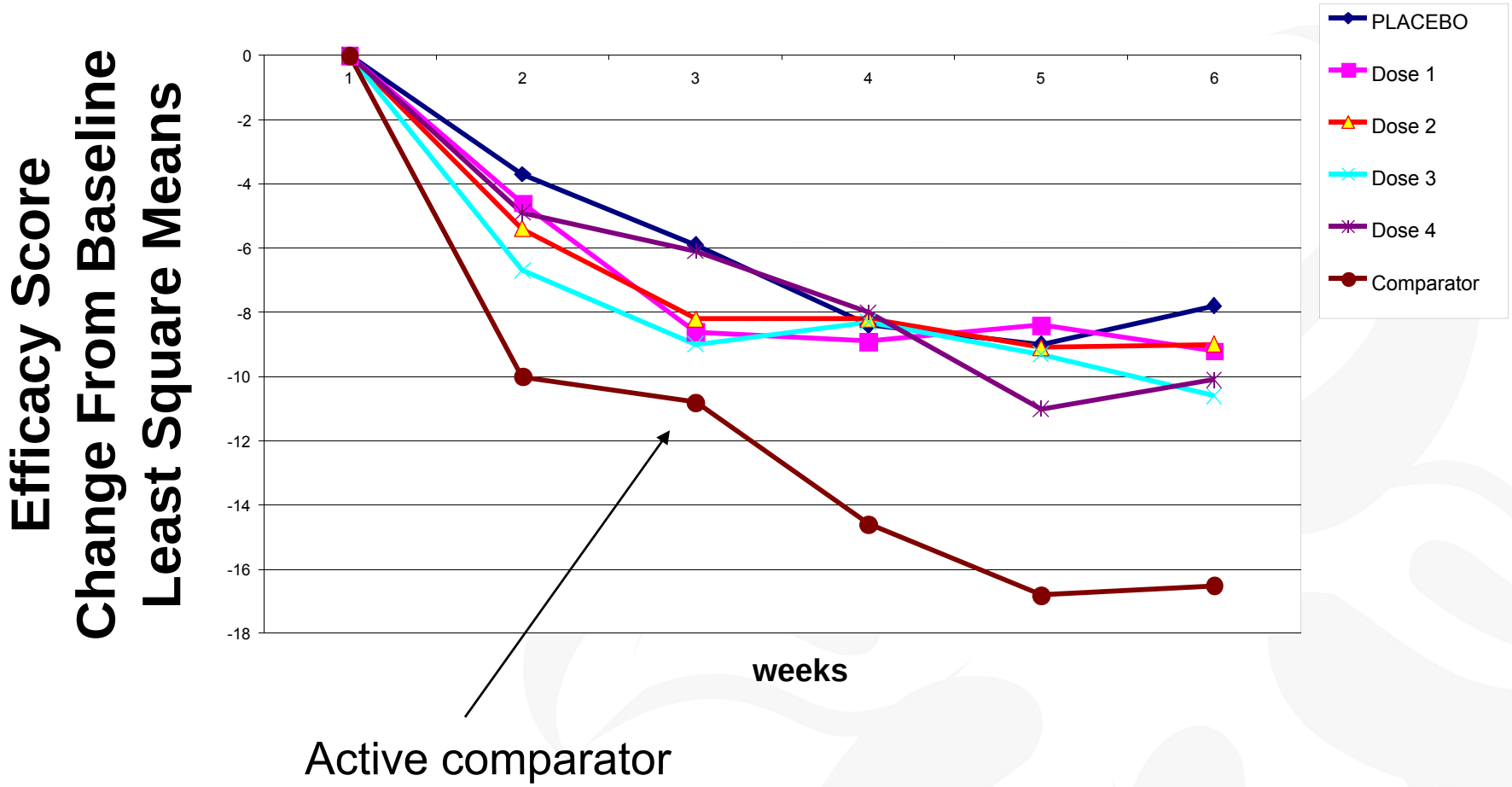
Study Drug Dose Groups Failed to Demonstrate Efficacy



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What If This Study Had Used A Dropping Arm Adaptive Design?

- We applied the following procedures to perform after-the-fact analyses on the interim data
- The first interim analysis used the data obtained at the time when half of the subjects finished Week 6 (~23/arm)
- Two more interim analyses followed weekly thereafter
- Dropping arm criterion:

  The predictive probability of

  {final p-value vs. placebo < 0.05} was less than 15%

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Results of the Retrospective Interim Analyses

Analysis	LSMEAN / Predictive Prob.	Placebo	Dose 1	Dose 2	Dose 3	Dose 4	Active Ctrl.
1st interim (23/arm)	LSMEAN	- 7.28	- 9.23	- 8.18	- 7.58	- 7.79	- 15.1
	Pred_prob [p-val<0.05]	/	22%	10%	6.9%	8.3%	96%
2nd interim (24/arm)	LSMEAN	- 7.38	- 8.87	- 7.93	- 7.60	- 7.82	- 15.3
	Pred_prob [p-val<0.05]	/	16%	7.4%	6.6%	7.9%	96%
3rd interim (25/arm)	LSMEAN	- 7.68	- 9.03	- 7.47	- 8.83	- 7.83	- 14.9
	Pred_prob [p-val<0.05]	/	14%	3.4%	12%	5.8%	93%
Final Analysis (45/arm)	LSMEAN	- 7.79	- 9.04	- 8.61	- 10.1	- 9.67	- 16.1
	Final p-value	/	0.311	0.373	0.177	0.231	<0.001

Results: Dose 2, 3, and 4 would have been dropped at the first interim, and the entire study would have been stopped at the third interim

→ *Sample size saving **n=65***

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Case Study: After-the-fact Interim Analysis on a Completed Study

- **Example #2 learnings:**
  - Even rapidly enrolling studies can benefit from adaptations
  - Conduct simulations under a variety of study conditions to assess impact of adaptations

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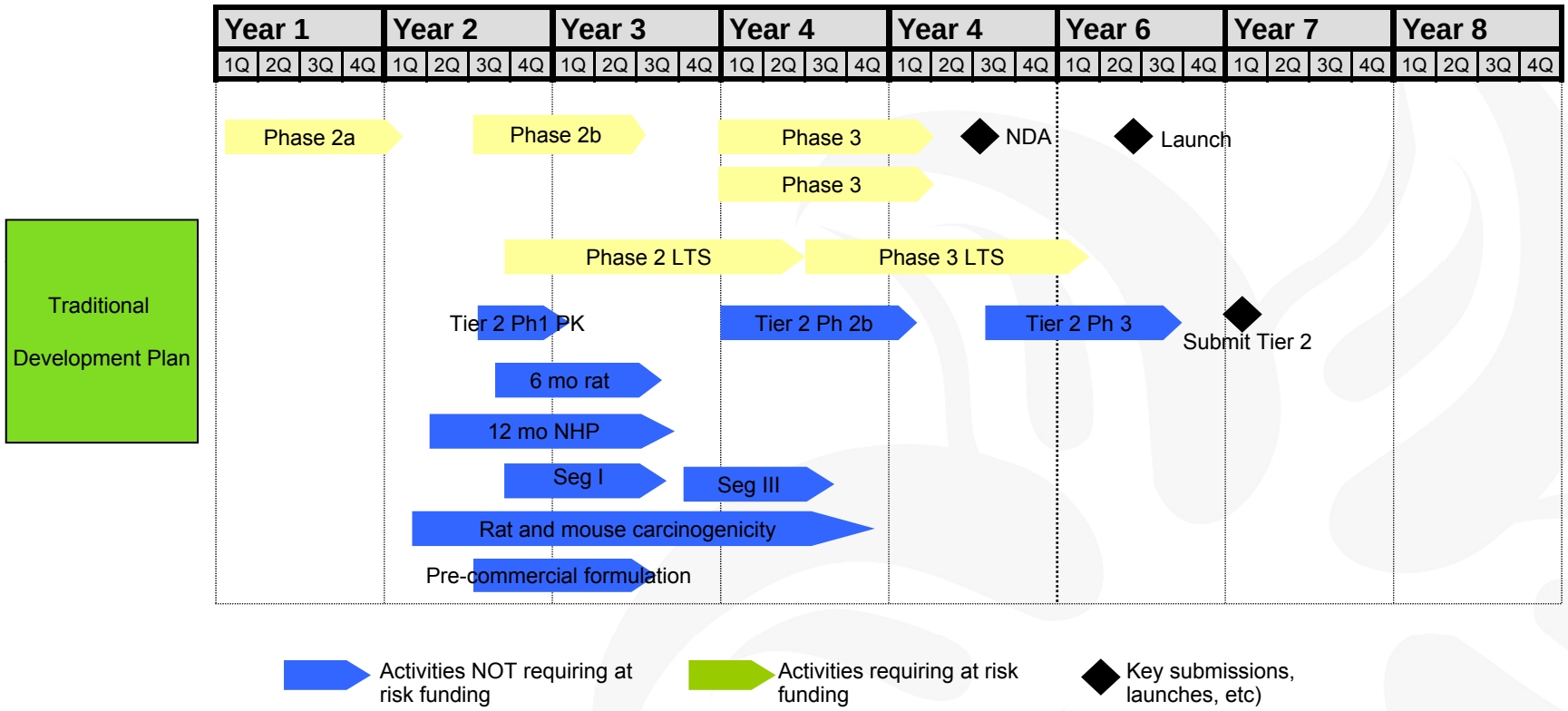
Programmatic Considerations When Planning an Adaptive Trial



Sequential Phase 2a followed by Phase 2b allows delaying start of multiple preclinical studies and formulation development with substantial de-risking of investment

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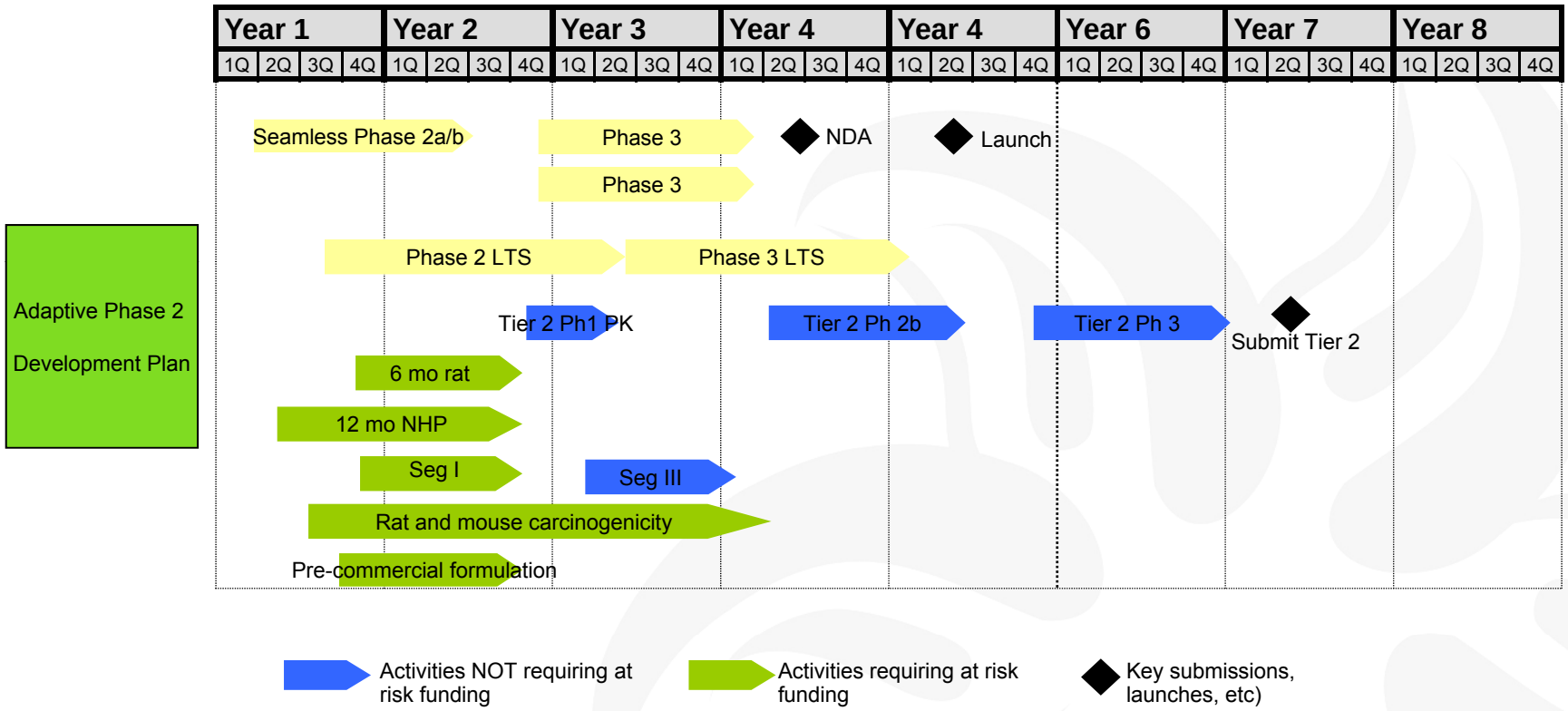

Seamless Phase 2a/2b can advance NDA by 1 year but requires starting multiple preclinical studies and formulation development prior to achieving POC.