

# Design and Implementation of a Comprehensive Data Flow for an Adaptive, Seamless Phase 2/3 Trial

Marcia Brackman, Data Scientist  
Eli Lilly and Company

The Eli Lilly logo, featuring the word "Lilly" in a red, cursive script font.

Answers That Matter.

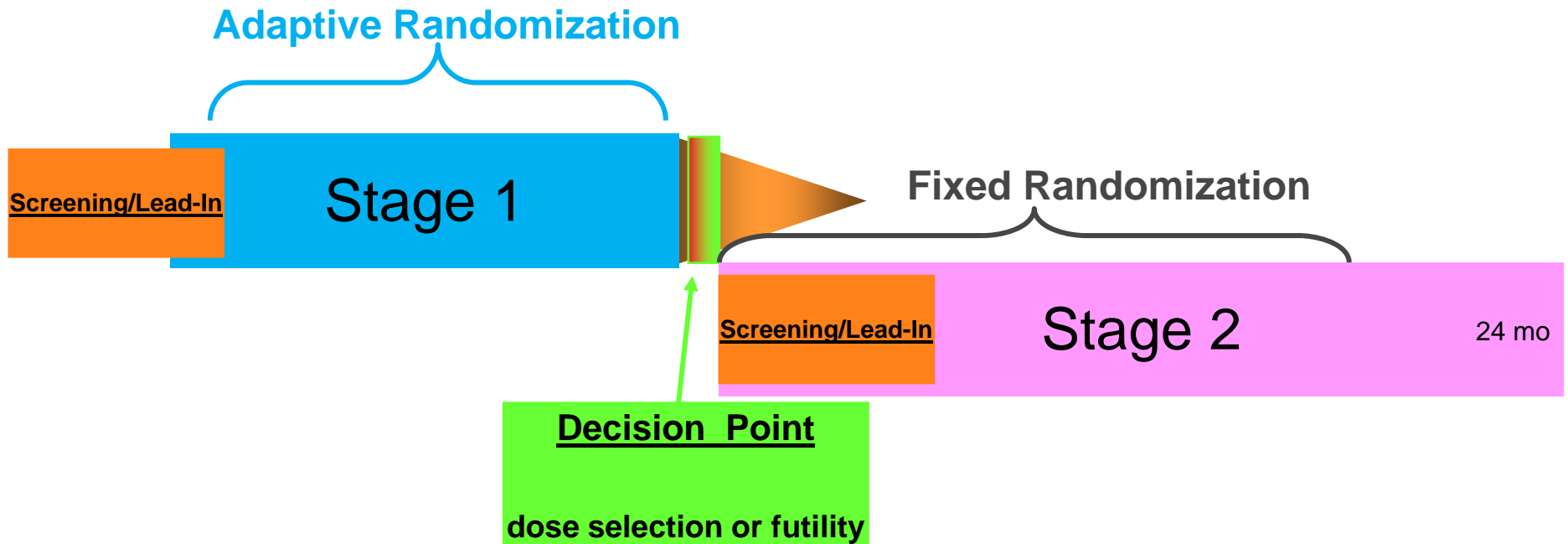
# What is an Adaptive Design?

- ▶ **Adaptive Design**: A clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the *validity* and *integrity* of the trial.
- ▶ **Adaptive BY Design**
  - Adaptation is a *design feature*, not a remedy for inadequate planning

# Opportunities: Right Patient, Right Dose, Right Time

- ▶ **More information sooner, with increased efficiency**
  - ▶ Reduce cycle time
    - Kill ineffective compounds earlier
  - ▶ Reduce late stage attrition rate (~ 50% across the industry)
    - Increase the probability of technical success
  - ▶ Take the right dose and population into Phase 3
    - Efficiently improve characterization of dose response
  - ▶ More winners to the market, faster
    - Shift toward more integrated approach to R&D
  - ▶ More informative registration package for the same or lower cost
- 
- ▶ **Optimize patient treatment within a trial**
  - ▶ Minimize patient exposure to ineffective or unsafe doses/treatment
  - ▶ Maximize patient exposure to effective and safe doses/treatment

# Case Study Design



**Stage 1:**

Time from study start to the Decision Point

**Decision Point:**

Time when dose(s) are selected for Stage 2 or the trial is stopped for futility

**Stage 2:**

Time from Decision Point to 24-month data lock

# Case Study Overview

- Adaptive, inferentially seamless, Phase 2/3 clinical trial design
- Multiple study drug dose arms plus active comparator and placebo arms
- Based on accumulating efficacy and safety parameters, dose assignment of patients will be optimized and exposure to ineffective or unsafe doses will be limited.
- After dose decision, study proceeds into the second stage by shifting from an adaptive to a fixed-randomization scheme for patients added in Stage 2.
- A Data Monitoring Committee (DMC) will monitor the adaptive algorithm during Stage 1 and oversee the safety of patients throughout the trial.
- An external vendor will perform the Bayesian analysis on a bi-weekly basis to provide updated randomization probabilities during Stage 1.
- An external vendor will prepare the DMC reports.

# Operational Aspects of Adaptive Design

- Design Documentation/Planning
- Enrollment Rate
- Data Management
- Data Flow
- Drug Management
- Randomization

# Design Documentation/Planning

- Adaptive trials require additional flexibility to account for their iterative nature and parallel processing
  - Document operating procedures well (protocol, Statistical Analysis Plan, DMC charter, simulation report, etc)
  - Document variances to operating procedures written for traditional designs
  - Maintain detailed “Issues and decisions” log
  - Assess company processes, systems, and expertise to identify the core work to keep “in house”; the work transfer to vendors; and the technology needed for successful execution
  - Develop communication plan to address predicted ramifications of the adaptation (i.e dropping dose arms at the decision point)
  - Create an ERB supplement describing how patients are adaptively allocated to the doses, how a dose decision will be reached, and the role of the DMC
  - Complete study development work in parallel (patient randomization system, data management platform, and study drug provision) – may require additional resources earlier in the process

# Enrollment Rate

- Rapid enrollment is not always optimal for adaptive design studies – need time to learn
- Simulations showed that the enrollment rate should be maintained between 5–8 patients per week
- Site selection
  - Selected sites with access to the appropriate patient population (over 50 sites in 6 countries)
- Investigators trained on the importance of controlling enrollment
- Sites restricted to number of patients they were contracted to enroll
- Enrollment was closely monitored using automated enrollment system and weekly faxes from sites giving screening and enrollment predictions

# Data Considerations

## Data Needs

- Define key data for adaptation and the data source(s)
- Determine how data will be collected and integrated for analysis
- Determine data format needs

## Frequency of Adaptation

- Plays a role in determining how to get the integrated key data for analysis

## Data Quality

- Balance data quality and timeliness to optimize decision making

# Data Considerations (cont.)

## Data Security

- Determine who needs access to 'unblinded' data
- Ensure data flow accounts for all security permissions so validity of the study is not compromised
- Secure and restrict access to adapting treatment lists or probabilities since these adjustments can be indicative of which dose(s) are favored

## Data Flow

- Determine who needs what data and when
- Document data flow risks and develop mitigation plans
- Fully test the data flow prior to study implementation
- Monitor progress to meet deliverables

**Document, Document, Document**  
Assure team alignment and understanding

# Key Data Needs

## ▶ Randomization Adaptations (Bayesian Analysis)

- Key blinded eCRF and lab data to vendor executing the response data analysis
- Treatment data to vendor
- Vendor runs analysis and sends updated randomization probabilities directly to Lilly's randomization system [Interactive Voice Response System (IVRS)]
- Vendor provides analysis output tables and figures to DMC for oversight of algorithm performance

## ▶ DMC Reporting

- Blinded data to DMC reporting
- Treatment data to vendor
- Vendor prepares and sends DMC report to the DMC members

Lilly study team cannot have access to any unblinded data.

# Data Management for Adaptive Analysis

## Bi-weekly adaptive analysis

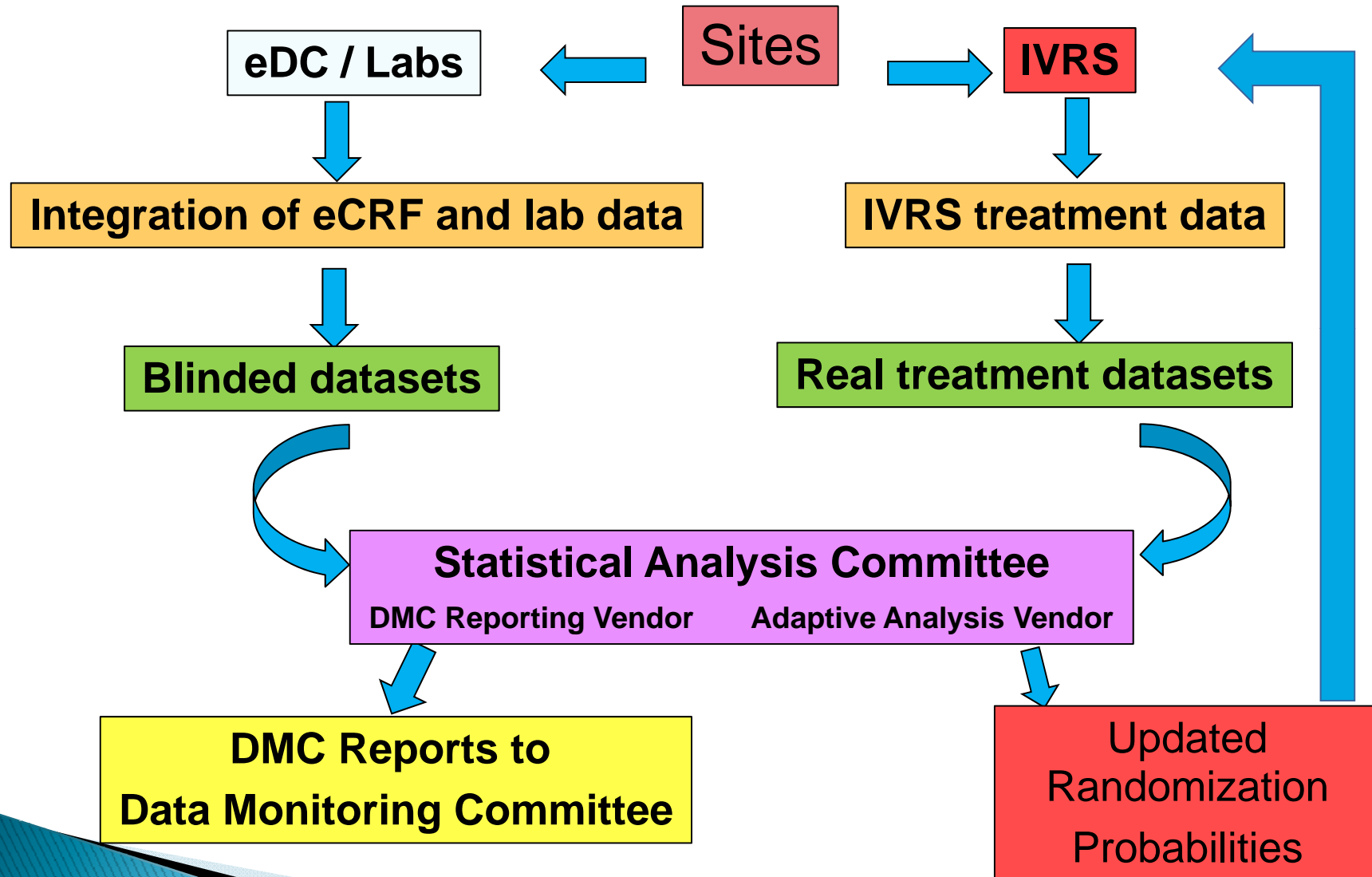
- Sites enter key response data into eCRFs within 48 hours of the patient visit
- Key response data reviewed, monitored, validated and subsequently queried (if necessary) to ensure the quality of the data is maintained
- More frequent data transfers from the central lab vendor are performed compared to a fixed trial
- Timely site resolution of queries about the data, such as missing values
- Timely integration of data from all sources (eCRF, lab, etc)

# Data Flow Development / Tools

If modifying your existing data flow for adaptive trial:

- ▶ Develop comprehensive process flow map and roles/responsibilities table
- ▶ Develop detailed timeline for each data flow step
- ▶ Develop a data flow risk mitigation plan
- ▶ Develop data flow communication plan
- ▶ Create comprehensive data extraction schedule for both randomization updates and DMC reporting
- ▶ Ensure that data flow will not compromise blinding
- ▶ Ensure entire data flow is extensively tested prior to implementation

# Data Flow



# Data Flow Design Risk Mitigation Plan Example

- Many vendors involved = numerous data handoffs
  - Mitigation: Minimize impact by setting up automated data transfers and utilizing SAS Drug Development (SDD) for data access.
- Bayesian analysis vendor requires data in custom format
  - Mitigation: Lilly prepares custom data files which are automatically routed to vendor bi-weekly.
- Determine how to get blinded integrated datasets and real treatment data to external DMC vendor
  - Mitigation: Establish vendor SDD accounts for a secure portion of SDD where vendor can prepare unblinded data sets and create the DMC reports. Carefully setup and test detailed folder structure and access rights.
- Unable to complete data extraction as scheduled
  - Mitigation: Immediately submit trouble ticket and study is on IT priority list

# Data Flow Implementation Risk Mitigation Plan Example (cont.)

- Issue with automated routers to send or receive data to/from vendors
  - Mitigation: Monitor and manually transfer data if necessary
- Issue with input file, so Bayesian analysis cannot be run
  - Mitigation: Extensive testing completed prior to actual update. Vendors will troubleshoot and address
- Treatment probabilities do not automatically upload into Lilly randomization system
  - Mitigation: Process was designed with quality checks to automatically reject file and initiate an investigation. Monitor and troubleshoot and manually upload if necessary.
- SDD folder structure permissions set up incorrectly
  - Mitigation: Extensively test prior to any unblinding

# Data Extraction Schedule – Example

DATE*	Central Lab data transfer	Data extraction	ADS/TFLs Created	ADS/TFL User Acceptance Testing	DMC Reporting Vendor
January 6, 2008	X	X			
January 13, 2008	X	X			
January 20, 2008	X	X			
January 27, 2008	X	X	X	X	
February 3, 2008	X	X			
February 10, 2008	X	X	X		
February 17, 2008	X	X			
February 24, 2008	X	X	X	X	X (blinded)
March 3, 2008	X	X			
March 10, 2008	X	X	X		
March 17, 2008	X	X			
March 24, 2008	X	X	X	X	X (blinded)
April 7, 2008	X	X			
April 14, 2008	X	X	X		
April 21, 2008	X	X			
April 28, 2008	X	X	X	X	X (unblinded)
May 5, 2008	X	X			
May 12, 2008	X	X	X		X (unblinded DMC Extract)
May 26, 2008 (1 <sup>st</sup> DMC Meeting)	X	X			

\*Illustrative example (not based on actual data)

ADS = Analysis Data Sets  
TFL = Table, Figure, Listing

# Data Flow Timeline – Example

Task Name	Duration	Start	Finish	Actual Finish	Predecessors	Successors
<b>Bayesian Analysis</b>	#####			NA		
Requirements Session	1 day?			NA		79,78FS+3 days
Requirements Approved	1 day?			NA	77FS+3 days	
Vendor develops and tests analysis program	1 day?			NA	77	80
Lilly approves program	1 day?			NA	79	81
Lilly transfers Fortran program to adaptive analysis vendor	1 day?			NA	80	82FS+9 wks
Adaptive analysis vendor completes Bayesian analysis software validation	1 day?			NA	81FS+9 wks	85,166FS+1.2 wks
Lilly sends example tab delimited EDS and IVRS treatment information to vendor	1 day?			NA		84
Vendor creates program to create data file for Bayesian analysis (from example tab delimited EDS/PEDS and IVRS treatment data files)	1 day?			NA	83	85,86
Lilly sends 'mock' .csv EDS/PEDS and IVR Test Data File (mock unblinding info) to vendor	1 day?			NA	164FS+1 wk,84,82	133SS
Test runs (until all issues resolved) of Bayesian Allocation Program and Bayesian Posterior Probability Tables using 'mock' data	1 day?			NA	164FS+1 wk,84	97FS+1 wk,87,167SS+1 wk
Test runs (until all issues resolved) of Bayesian Allocation Program and Bayesian Posterior Probability Tables using actual study data	1 day?			NA	86,152FS+6 wks,171SS+2 days	98
Vendor generates First Randomization Report	1 day?			NA	154FS+9.5 wks	171SS-12 wks
<b>Data Management Deliverables</b>	<b>129 days</b>			NA		
CRF approval	3 days			NA		
Annotated CRFs available	7 days			NA		
CRF Approval in Visit Structure	1 day			NA	15	91FS+3 wks
Edit Check Development and Data Validation Plan	2 wks			NA	90FS+3 wks	92
Database Specifications Agreement and Validation Methods Approval	1 day			NA	91	93
Requirements delivered and Vendor Set -up Time	3.5 wks			NA	92	94
Specifications Review Meeting (SRM)	0 days			NA	93	95,96
Edit Check approval	0 days			NA	94	
Database Build time	15 wks			NA	94,54	
Determine data needs for DM UAT to ensure UAT data can be used for AD programs and dataflow testing	3 wks			NA	86FS+1 wk	
Database User Acceptance Testing (UAT)	8 days			NA	171,87	
Database Go-Live	2 days			NA	154FS+9.5 wks	

\*Illustrative example (not based on actual data)

12-Nov-2010

# Data Flow and Drug Supply Touchpoints

- ▶ Assess drug supply as early as possible to optimize supply chain
  - More dosage strengths and greater quantities of drug available will likely be required
  - For seamless Phase 2/3, accelerated commercial formulation and/or a material bridging strategy may be needed
- ▶ Fully utilize randomization and drug forecasting system to ensure proper dosing is on-site prior to any patient visit
  - Ongoing trial simulations can help to reduce trial material requirements by allowing the creation of quantitative forecasts that take into account the effect of the adaptive algorithm in the randomization of patients

# Adaptive Randomization

- Develop the capability to change randomization schemes during the trial (to work under wide range of treatment scenarios) based on the key response data and study design needs
  - E.g. support burn in period assignments, adapt treatment allocation, transition to more traditional, blocked assignments, etc.
- Link or integrate the response data analysis to the process/system for executing the adaptive randomization in a standard format to avoid rework and disruption.
- Consider the up and downstream effect of any modifications made to one system or process in order to accommodate your adaptive design.
  - E.g. Needed a way to differentiate patients entering in Stage 1 vs. Stage 2, since our reporting database had never handled a multi-stage trial previously

# Summary

**A**utomate data flow process as much as possible

**D**ocument everything!

**A**nticipate potential issues and design mitigation plans

**P**lan, Plan, Plan

**T**est all aspects of data flow

**I**nvolve other functions earlier in study development

**V**endor oversight / communication is key

**E**nsure appropriate security measures are in place