eCOA: How do we get better together?

Ninth Annual
Patient-Reported Outcome Consortium Workshop

April 25 – 26, 2018 ■ Silver Spring, MD

Disclaimer

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Session Outline and Objectives

- Understand challenges of current eCOA implementation
- Establish pathway for collaborative solutions to eCOA challenges

Session Participants

Moderator

- *Jean Paty, PhD* – Vice President, Consulting Services, Leading Patient Centered Endpoints Activities, QuintilesIMS

Presenters

- *Emily N. Smyth, PharmD* – Senior Research Scientist, Global Patient Outcomes and Real World Evidence, Eli Lilly and Company
- *Paul O'Donohoe* – Scientific Lead, eCOA and Mobile Health, Medidata
- *Kristina Lowe* – Vice President, Business Development, ERT
- *Katherine Zarzar* – Senior Manager, Patient-Centered Outcomes Research, Genentech, A Member of the Roche Group

Panelists

- *Robyn Carson, MPH* – Executive Director and Head, Patient-Centered Outcomes Research, Allergan
- *Katarina Halling, MSc* – Global Head Patient-Reported Outcomes, AstraZeneca
- *Sean Stanton* – Chief Executive Officer, Lifecore Solutions

Industry Landscape

- Approximately $500 MM will be spent on eCOA in 2018
- This means that approximately 1,000 -1,500 studies will be using eCOA this year alone
- The annual growth rate is 16% - very high for technology sector
- Yet, less than 1/4 of all possible studies incorporate eCOA
- The rapid growth has brought significant opportunities and challenges for us as an industry

eCOA Trajectory Mimics Other Technologies

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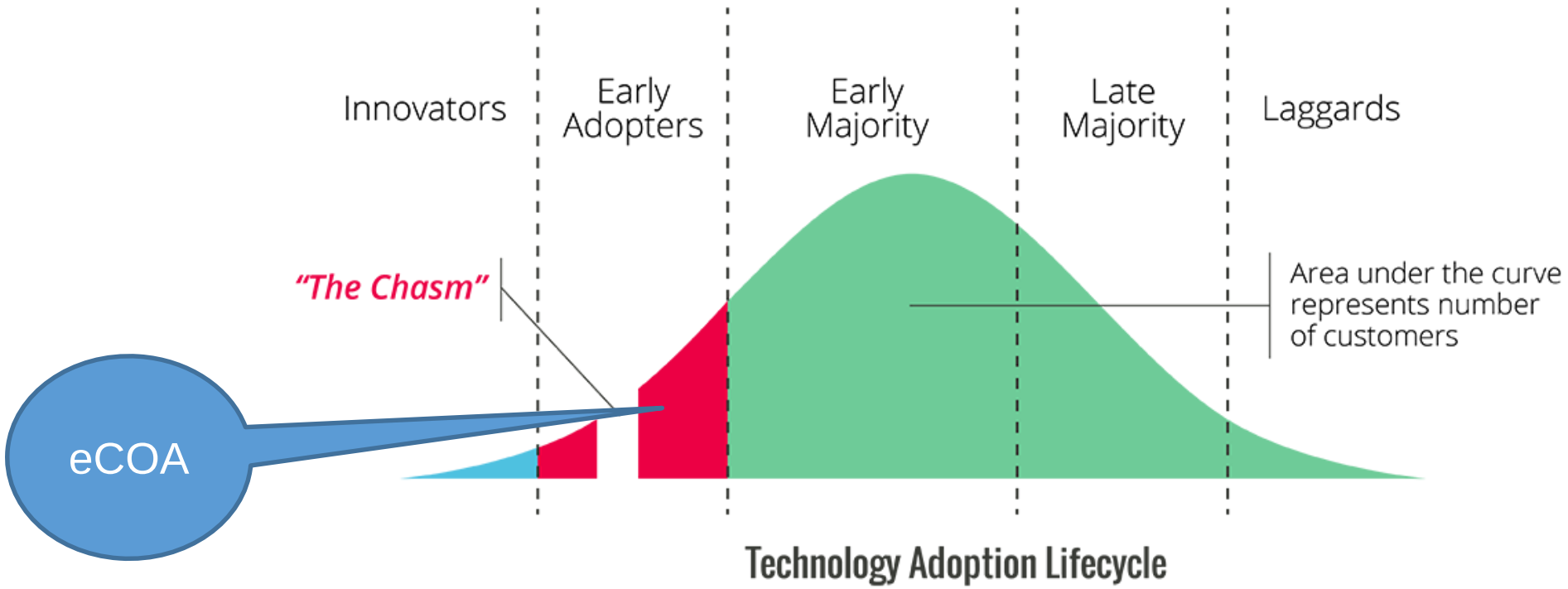
Crossing the Chasm: Technology Adoption Curve



Similarity to other technologies does not reduce pain

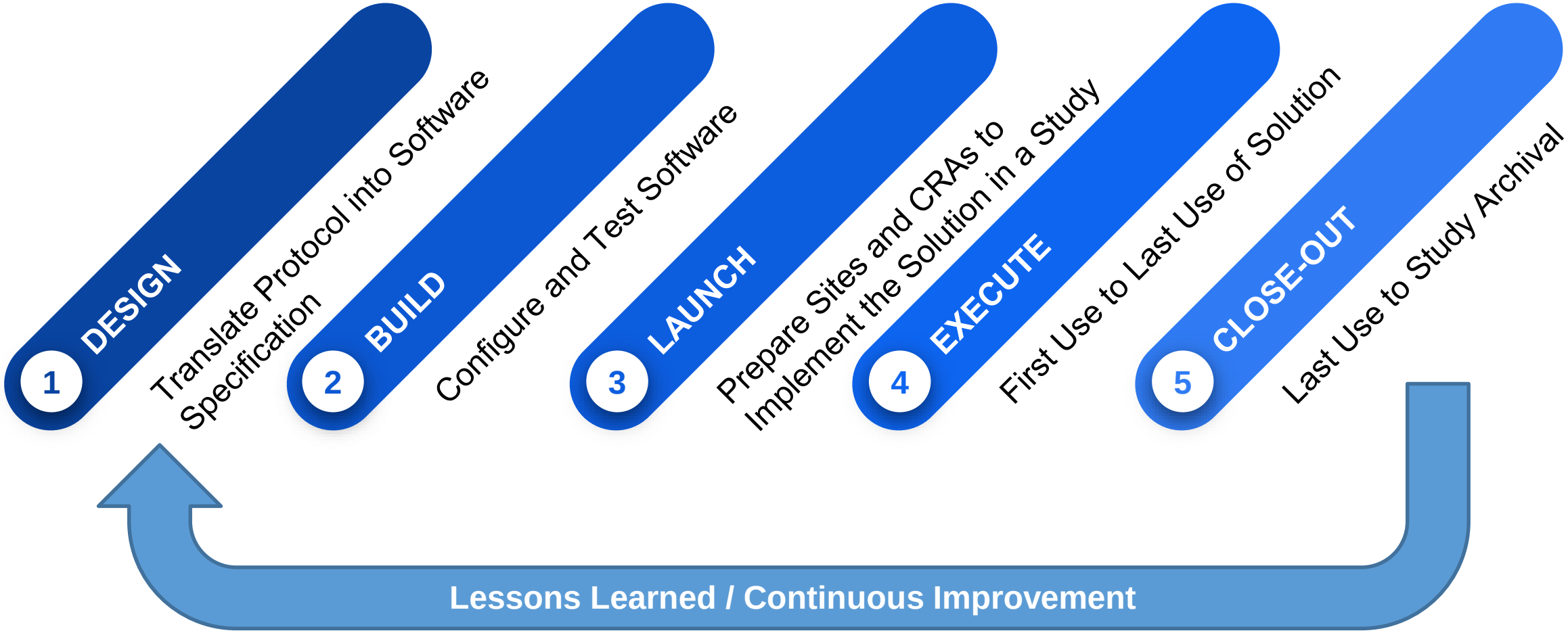
Image Source: https://ayogo.com/blog/crossing-the-chasm/

How do we get better together?

- We will share common experiences in developing and implementing eCOA in trials
- The panel is comprised of sponsors, eCOA providers, and investigative site personnel
- We have spent a number of months discussing the real issues that face us in eCOA, and how we might address these together, collaboratively
- One major theme emerged and is the basis for much of the discussion today:

Misalignment of expectations among the eCOA stakeholders

Study Lifecycle



Design Phase

Emily Nash Smyth, PharmD – Senior Research Scientist, Global Patient Outcomes and Real World Evidence, Eli Lilly and Company

Paul O'Donohoe – Scientific Lead, eCOA and Mobile Health, Medidata

Design Definition and Goals

- Understand ***what*** you want to achieve in the study from a scientific perspective
  - Key questions per the clinical study protocol
  - Key objectives in the context of broader clinical development

- Define ***how*** you are going to achieve objectives from an operational perspective
  - Discuss and outline specification
  - Confirm countries and languages
    - Initiate/complete instrument licensing
  - Identify needs for specific study milestones
  - *Identify risks and rate limiters*

Design Phase
Key Issues Identified by Panel

1. Roles/responsibilities of sponsor and eCOA provider not clear
2. Sponsor unclear regarding what is being developed by eCOA provider because of lack of familiarity with process and "big picture," as well as method of reviewing screens
   - Can contribute to a potential lack of focus on critical functionality
3. Requests for back-up solutions – is it a necessity or distraction?

Focus Areas: Characterizing Roles/Responsibilities AND Need for Focus on Critical Functionality

Key Issue #1: Roles/Responsibilities Not Clear

Sponsor

- Therapeutic area
- Study protocol
  - Patient population/indication
  - Desired outcomes and desired patient compliance
- How (and at what point) the device will be implemented in the course of clinical care of the patient

eCOA Provider

- The eCOA system
- eCOA best practices
  - Basic workflows for data entry
  - Previous experience
    - Indication
    - Assessments

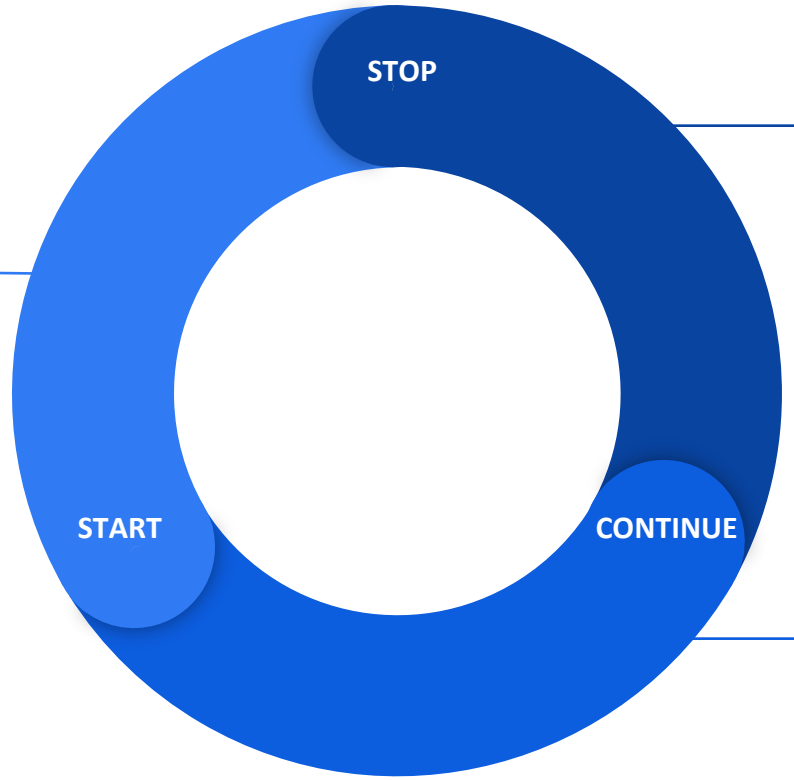
Key Issue #2: Complexity of Design

- Need to focus on key research questions, and functionality that is key to answering those questions – *Keep end user(s) in mind*
  - Significant operational and data integrity risk
  - Expectation for Sponsor:
    - Assessment schedule is as streamlined as possible to support necessary analyses and answer research question(s)
    - **Example 1**: Migraine study
  - Expectation for eCOA provider:
    - eCOA provider proposes most streamlined solution that is easily implementable by patient and site personnel
    - Value of utilizing standard screens
    - **Example 2:**
      - Ability to streamline verbiage
      - Fewest number of screens to accomplish goal

1. *Clear communication between Sponsor and eCOA provider is critical*
2. *Unnecessary complexity could have downstream ramifications including timeline delays for project, confusion by patient and/or site personnel, and need for data clarification forms*

DESIGN Summary

1. **Defining success;** clear communication is key as to what good looks like and what/when input is expected
2. **Greater insight into draft build** would help troubleshoot potential challenges in advance of User Acceptance Testing (UAT)
3. **Developing and implementing eCOA standards** to enable smoother UAT; less likelihood of unexpected results once software is released



1. **Making assumptions** that eCOA providers have all solutions - if intent of screens is unclear or if there are ideas for how screens can be further simplified, speak up

1. **Communicate so all team members understand**, and ensure that all appropriate team members are involved at the right time, so that specs can be appropriately built and are aligned with expectations on both sides

Build Phase

Paul O'Donohoe – Scientific Lead, eCOA and Mobile Health, Medidata

Emily N. Smyth, PharmD – Senior Research Scientist, Eli Lilly

Build Definition and Goals

- Translate the WHAT and HOW of Design Phase into fully functioning eCOA system
- Ensure hardware logistics are understood and in place
- Test the eCOA system to ensure it matches desired specification

Build Phase

Key Issues Identified by Panel

1. Miscommunication can lead to challenges:
   - Developing specifications to align with key research questions/needs
   - Programing of specifications according to plan
2. Review of associated documentation is onerous and cumbersome
3. Execution of User Acceptance Testing (UAT)
4. Is device equipped with appropriate software needed for implementation, and if not, what is the timeline?

Focus Area: Execution of User Acceptance Testing

Key Issue #3: UAT

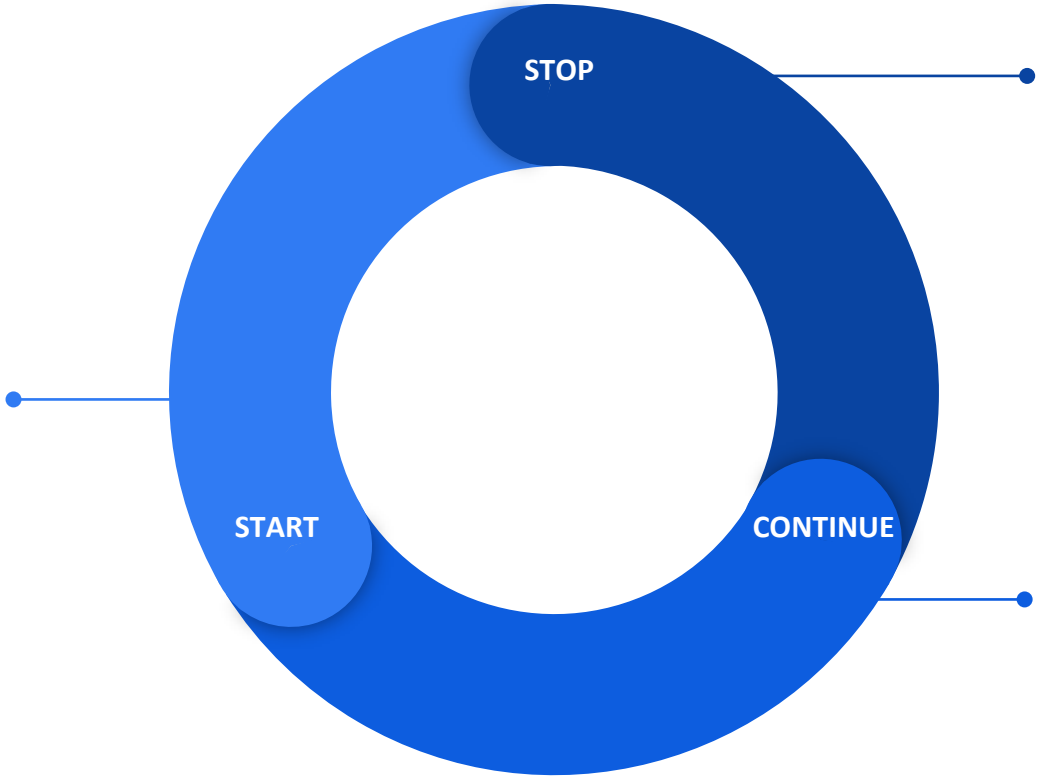
- What is involved in UAT?
  - Sponsor lacks expertise regarding process and responsibility
    - Unsure of how to design parameters, what to test
    - Vendors concerned about testing a system they built
  - Is UAT first time seeing the system?
    - Is there a better way of reviewing screens and draft builds?
  - UAT findings cause delay

UAT: Roles/Responsibilities

Sponsor	CRO (or party monitoring sites)	eCOA Provider
• Develop UAT script • Conduct UAT • Compile findings from UAT	• Sponsor UAT responsibilities can be outsourced to CRO	• Provide system and hardware to be tested • Provide guidance to eCOA naïve sponsors on the kinds of things they should be testing • Evaluate findings in terms of issues, bugs, and enhancements • Resolve issues and bugs in programming

BUILD Summary

1. **Asking questions** early in the process regarding key components of device, including timing of any necessary software updates to support capabilities
2. **Ensuring timely deployment** at site initiation visits



1. **Conducting UAT in a vacuum**; appropriate guidance should be given to set-up sponsor and eCOA provider for success

1. **Communicating** using language that all team members understand so that specs can be appropriately built and are aligned with expectations on both sides
   a. Asking questions to ensure intent of screens is clear
   b. Avoids downstream implications with UAT and potential delays with project

Launch Phase

Kristina Lowe – Vice President, Business Development, ERT

Katherine Zarzar – Senior Manager, Patient-Centered Outcomes Research, Genentech, A Member of the Roche Group

Launch Definition and Goals

- The eCOA solution is ready for release and it is time to prepare sites and CRAs to implement the solution in a clinical trial
- Equipment and materials are shipped
- An investigator meeting is often the first use of the solution for site/CRA training
- Alternative training methods are available from eCOA providers if an investigator meeting is not conducted
- Launch covers the entire site initiation period which can span many months for large, global trials

Launch Phase

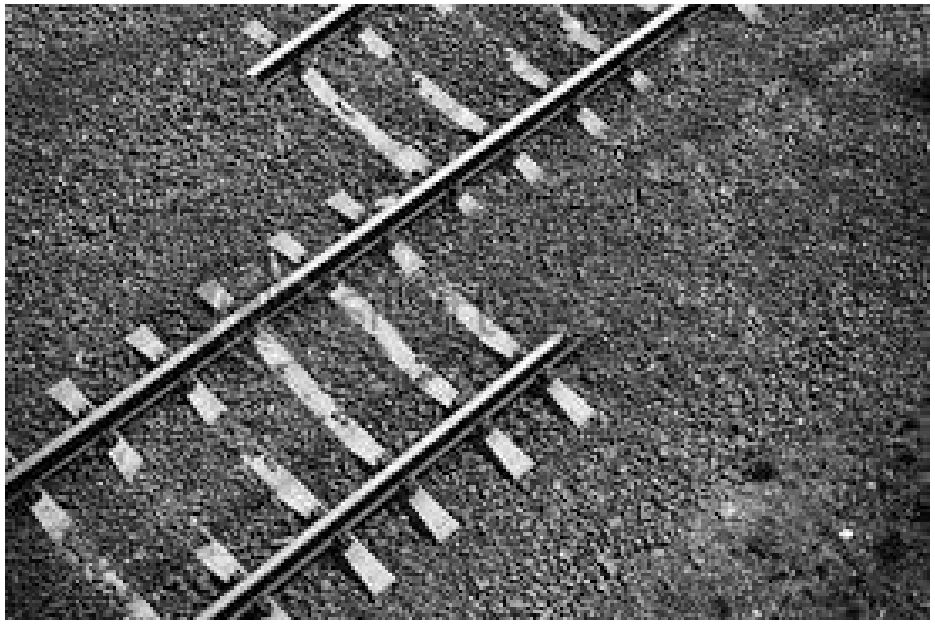
Key Issues Identified by Panel

1. Lack of Clear Logistics/Inventory Plan - How many devices should be at each site or at a local country hub?
2. Site Readiness - How are sites being supported to ensure their first interaction with devices is a success?
3. Timely support from eCOA provider when needed
   - What should the helpdesk do?
   - What should the project manager (PM) do?

Focus Areas: Site Readiness

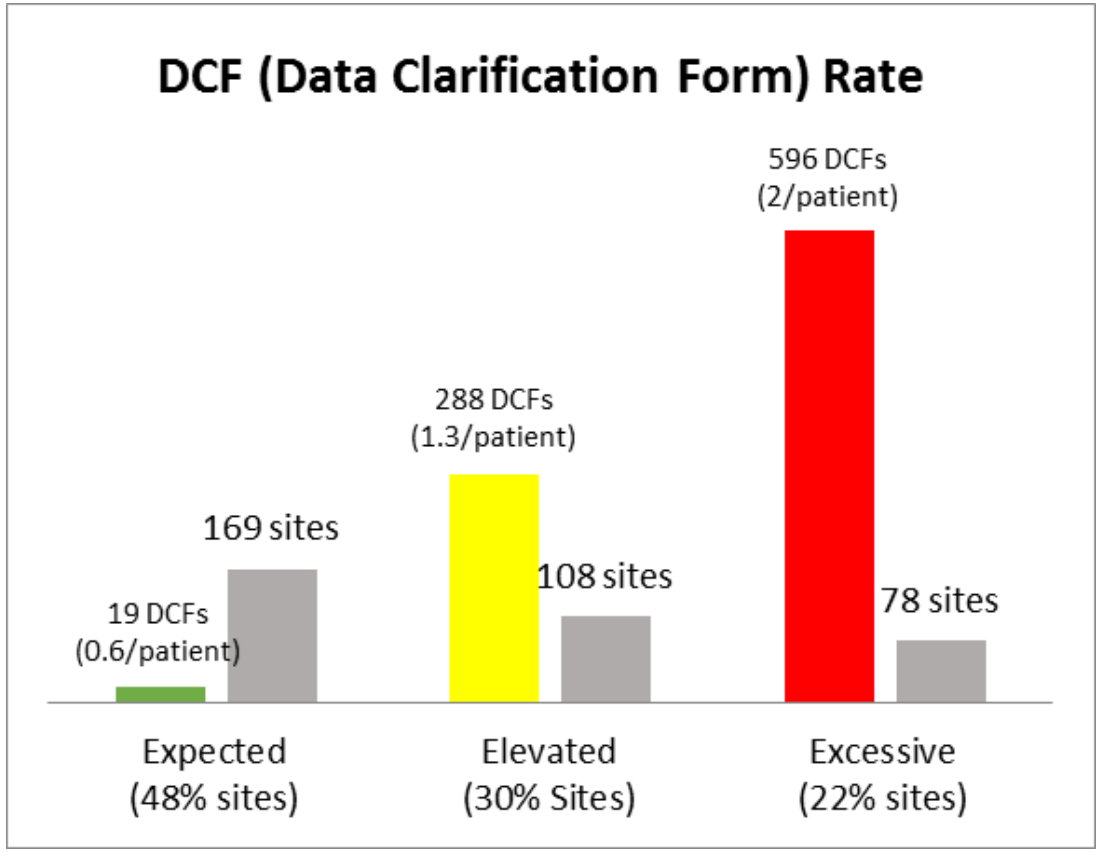
Key Issue #2: Site/CRA Readiness

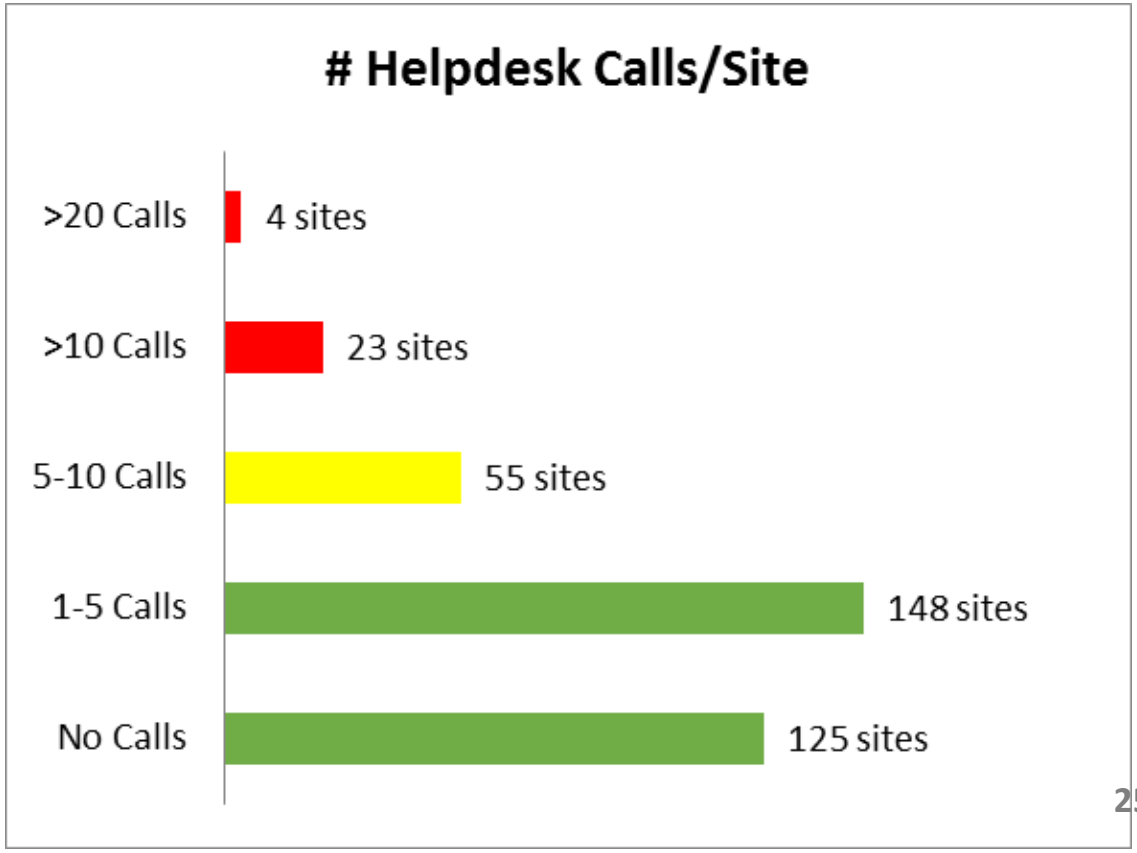
- Where do we observe the largest misaligned expectations during LAUNCH?
  - Sponsors, CROs, and eCOA providers make assumptions about who is responsible for preparing the site to successfully implement an eCOA solution
  - Site Readiness may be discussed early on (during bid-defense meeting or kick-off meeting), but is often overlooked to focus on Design Tasks
  - A Training Plan should be drafted after design is complete and finalized well in advance of UAT



Confident sites succeed, while unprepared sites struggle

Phase III Program, 355 Sites, 18 months into 4-year study. Sponsor believed the eCOA design and software were flawed. 48% of sites had expected DCR rates; 77% had low helpdesk call volumes and were performing very well with the system. Site Training was not well controlled, and many eLearning quizzes were never completed. Problem sites were targeted for re-training. Lesson learned around timely, mandatory training requirements *DURING LAUNCH* to avoid this situation in future studies.





Site/CRA Readiness: Roles/Responsibilities

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Sponsor

- Invest in proper training (not an area to trim down the budget)
- Develop Training Plan with eCOA provider (or designate this responsibility to CRO)
- Review/approve training materials
- Anticipate/expect retraining needs

CRO (or party monitoring sites)

- Ensure sites complete training materials and process
- Ensure site initiation visit includes eCOA set-up activities
- Ensure CRAs are prepared to actively utilize portal/eCOA reports to monitor site activity and retrain as needed

eCOA Provider

- Advise on recommended training plan based on patient population and site locations
- Develop training plan and materials during build phase and seek approval of all parties
- Identify for CRO/sponsor the sites/individuals that require training OR retraining

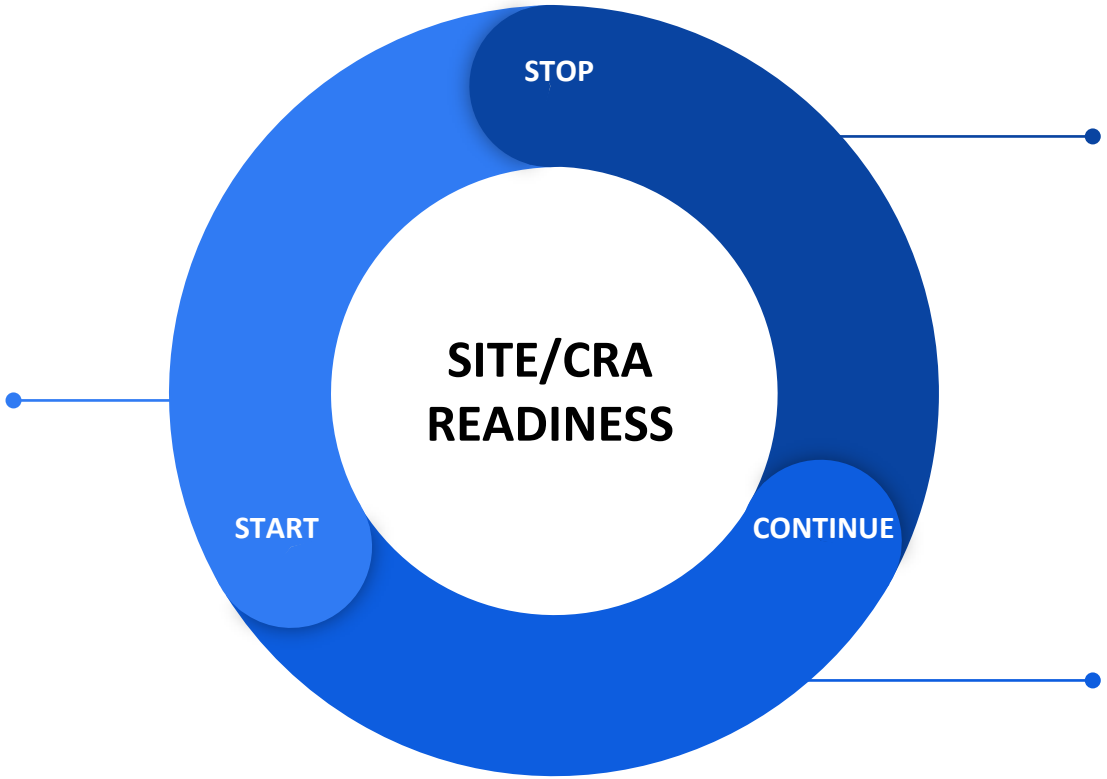
Site/CRA Readiness Objectives

- Develop a plan to confirm each site is prepared at the site initiation visit
  - Sites/CRAs are enthusiastic about using technology for the trial
  - Sites are confident to train a patient. CRAs are confident to train/retrain sites
  - Sites/CRAs understand their role in monitoring patient/site compliance
  - Utilize equipment checklist (e.g., sites charge equipment upon receiving shipment AND ensure equipment remains charged)
  - Sites have been provided device inventory in alignment with expected enrollment
  - Sites/CRAs are aware of lead-times and procedures for defective equipment replacement
  - Sites can transmit data successfully and reliably
  - Sites/CRAs understand how to use reports/portal
  - Sites/CRAs understand basic eCOA monitoring/troubleshooting activity (reset passwords, action/workaround for device not transmitting at home, monitoring of DCR / Help Desk calls by site for trends, etc.)
  - Sites understand where to go for support
  - Utilize eLearning to test for readiness

ePRO Consortium's manuscript titled "Training on the Use of Technology to Collect Patient-Reported Outcome Data Electronically in Clinical Trials: Best Practice Recommendations from the ePRO Consortium" submitted to *Therapeutic Innovation & Regulatory Science*, has been recommended for publication.

LAUNCH Summary

1. **Developing a Site Readiness Plan Early in the Process**
   A site readiness plan should be developed during the BUILD phase. Sponsor, CRO, and eCOA provider should contribute and approve plan
   a. Clear roles/responsibilities
   b. Clear timeline for site readiness activities



1. **Making Assumptions**
   Technology, like humans, is not perfect. Lack of a plan to ensure site readiness WILL cause downstream problems for sites and patients

1. **Questioning and Communicating Challenges**
   Use lessons learned to identify what's working and what's not working as you prepare future site readiness plans

Execute Phase

Kristina Lowe – Vice President, Business Development, ERT

Katherine Zarzar – Senior Manager, Patient-Centered Outcomes Research, Genentech, A Member of the Roche Group

Execute Definition and Goals

- The eCOA system is live and collecting data
- Includes enrollment of study subjects and all eCOA data collection during the trial
- Streamlined, effective deployment of the eCOA system
  - Sites and patients are able to activate devices successfully, and data are being collected and transmitted
  - Data are reviewed at regular intervals according to the data review plan outlined and agreed upon during the BUILD stage
  - Any issues identified are resolved quickly and efficiently

Execute Phase

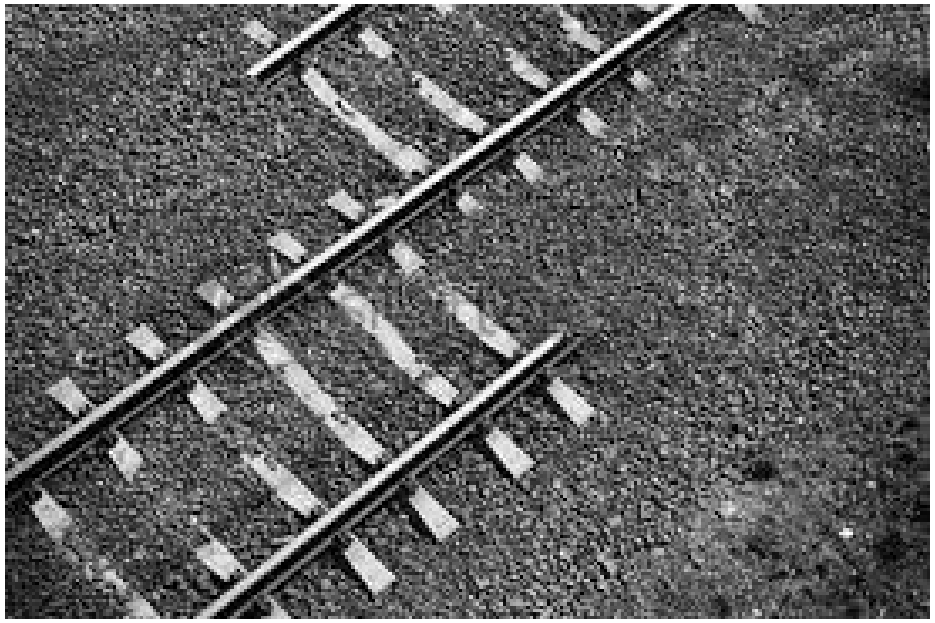
Key Issues Identified by Panel

1. Effective use of eCOA reports by sponsor, CRO, and eCOA provider
   - Who monitors eCOA data?
   - How do we define compliance?
   - What's the optimal way to assess site and/or subject compliance?
   - Clarity around roles/responsibilities
2. Unexpected Issues
   - eCOA provider is unable to supply devices (devices are no longer available from the manufacturer)
   - Devices displaying incorrect languages
   - Data sync failure, or data not transferring from devices
   - Data Management –
     - Incomplete or delayed data transfers
     - Who is responsible for ensuring a high-quality data-set? Misalignment of expectations of eCOA Provider and Sponsor, and late requests leads to challenges
   - Timely support from eCOA provider when needed
     - What should the helpdesk do?
     - What should the PM do?

Focus Areas: Data Management and Monitoring eCOA Compliance

Key Issue #1: Data Management and Monitoring eCOA Compliance

- Where do we observe the largest misaligned expectations during EXECUTE?
  - Misalignment on what monitoring compliance means and what data management (DM) means
  - Sponsors expect eCOA providers to monitor data quality and to offer robust reporting mechanisms to enable their teams to monitor data quality
  - eCOA providers do not always have data management expertise and do not monitor data quality
  - eCOA provider reports are not always able to be reconciled with sponsor systems, which leads to inaccurate information being reported
  - Sites/CRAs do not understand their role in monitoring
  - Sponsors struggle to understand the different reports, as each vendor has different reporting functionality



Example Compliance Report

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Visit Name	Questionnaire Type	Number of Patient Months in Study	Number of Surveys Completed	Number of Surveys Marked as not done	Number of Surveys Missing Despite Visit in eCRF	Surveys Completed as % including eCRF	Surveys Completed as % excluding eCRF	Patient Activation Rate
Cycle 1 Day 1	EORTC QLQ-BR23	11907.02	799	40	57	89.17%	95.23%	0.89
Cycle 1 Day 1	EORTC QLQ-C30 V3	11908.07	828	27	42	92.31%	96.84%	0.92
Cycle 1 Day 1	EQ-5D-5L	11907.02	796	42	58	88.84%	94.99%	0.89
Cycle 2 Day 1	EORTC QLQ-BR23	11767.42	773	36	61	88.85%	95.55%	0.89
Cycle 2 Day 1	EORTC QLQ-C30 V3	11767.42	795	29	46	91.38%	96.48%	0.91
Cycle 2 Day 1	EQ-5D-5L	11767.42	768	37	65	88.28%	95.40%	0.88
Cycle 3 Day 1	EORTC QLQ-BR23	10798.03	673	30	51	89.26%	95.73%	0.89
Cycle 3 Day 1	EORTC QLQ-C30 V3	10804.27	691	21	43	91.52%	97.05%	0.92
Cycle 3 Day 1	EQ-5D-5L	10798.03	674	30	50	89.39%	95.74%	0.89
Cycle 4 Day 1	EORTC QLQ-BR23	10170.95	632	14	43	91.73%	97.83%	0.92
Cycle 4 Day 1	EORTC QLQ-C30 V3	10170.95	642	11	36	93.18%	98.32%	0.93
Cycle 4 Day 1	EQ-5D-5L	10170.95	632	15	42	91.73%	97.68%	0.92
Cycle 5 Day 1	EORTC QLQ-BR23	9211.5	548	16	39	90.88%	97.16%	0.91
Cycle 5 Day 1	EORTC QLQ-C30 V3	9211.5	552	14	37	91.54%	97.53%	0.92
Cycle 5 Day 1	EQ-5D-5L	9211.5	544	18	41	90.22%	96.80%	0.9
Cycle 6 Day 1	EORTC QLQ-BR23	8405.37	493	10	29	92.67%	98.01%	0.93
Cycle 6 Day 1	EORTC QLQ-C30 V3	8405.37	494	10	28	92.86%	98.02%	0.93
Cycle 6 Day 1	EQ-5D-5L	8405.37	491	11	30	92.29%	97.81%	0.92
Cycle 7 Day 1	EORTC QLQ-BR23	7084.68	402	4	31	91.99%	99.01%	0.92
Cycle 7 Day 1	EORTC QLQ-C30 V3	7084.68	404	3	30	92.45%	99.26%	0.92
Cycle 7 Day 1	EQ-5D-5L	7084.68	401	5	31	91.76%	98.77%	0.92
Cycle 8 Day 1	EORTC QLQ-BR23	6382.36	359	8	20	92.76%	97.82%	0.93
Cycle 8 Day 1	EORTC QLQ-C30 V3	6382.36	360	7	20	93.02%	98.09%	0.93
Cycle 8 Day 1	EQ-5D-5L	6382.36	359	8	20	92.76%	97.82%	0.93
Cycle 9 Day 1	EORTC QLQ-BR23	5462.37	297	11	20	90.55%	96.43%	0.91
Cycle 9 Day 1	EORTC QLQ-C30 V3	5462.37	299	9	20	91.16%	97.08%	0.91
Cycle 9 Day 1	EQ-5D-5L	5462.37	297	11	20	90.55%	96.43%	0.91

Example Compliance Report

Data Management and Compliance Monitoring: Roles/Responsibilities

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Sponsor

- Identify key sponsor contacts to be involved in data quality discussions with eCOA providers
- Outline realistic data quality and compliance expectations
- Develop study teams and monitors trained to review reports and take prompt action to address compliance concerns
- Reduce “firefighting” and frequent escalations, which create resource strain for both eCOA providers and sponsors

CRO (or party monitoring sites)

- Monitors should review reports to assess site needs
- Notify sponsor team of any issues, and if sites require retraining

eCOA Provider

- Provide DM contacts to liaise with sponsor DM team
- Play a greater role in risk-based monitoring and flagging issues that may require follow up from the sponsor or CRO team (e.g., site non-compliance, missed visit, missing data - eCOA providers can help confirm if data are truly missing, or if it is a data transfer issue)
- Provide reliable reports, which can be reconciled with sponsor EDC systems and train sponsor teams on how to use reports

Data Management and Compliance Monitoring: Objectives

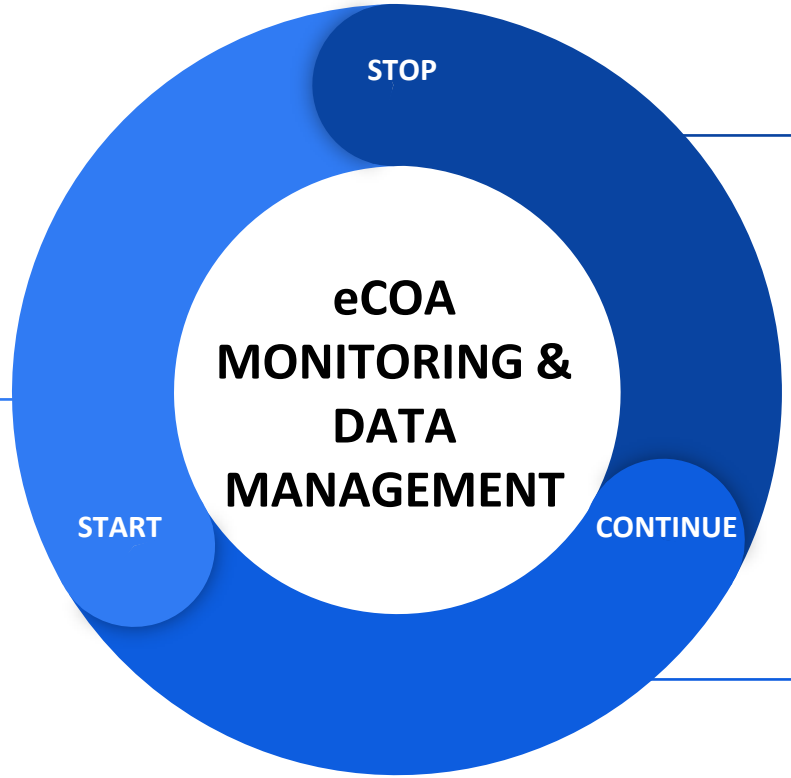
- Develop and document a plan for data management and compliance monitoring **early** (during the planning and design stage)
  - Align expectations on data quality and compliance requirements
  - Be realistic in outlining requirements - keep it simple, and focus on critical factors for study success
  - Clearly document roles/responsibilities of sponsor, CRO/monitors, and eCOA provider in monitoring compliance and ensuring the integrity of the data
  - Establish a clear action plan and communication pathway in case of non-compliance or data quality questions
  - Design an accurate reporting mechanism allowing visibility of site and subject compliance and overall data quality
    - Test the accuracy of the reports during UAT via test cases and test transfers
    - Ensure the report can be reconciled with relevant internal sponsor systems (e.g., a report designed internally within the sponsor organization or a vendor provisioned report that can be reconciled with sponsor systems)
  - Ensure the sponsor team and monitors are trained to review these reports to identify potential issues and cue corrective action
    - Missed baseline cues a call to the site, and action to rectify the issue (retraining, device replacement, etc.)
    - Missing data transfer from a patient take-home device cues a check-in with the patient

EXECUTE Summary

1. **Defining compliance in a standard way**
2. **Discussing expectations around compliance monitoring and data management requirements early**

a. Where applicable, link DM teams on sponsor side with DM counterparts on the CRO and eCOA provider side to align requirements

b. At a minimum, clearly outline compliance requirements and data management expectations in writing during study planning to ensure alignment between sponsor, CRO/monitors, and eCOA provider



1. **Outlining unrealistic goals**
2. **Passing compliance monitoring or DM to other parties**

a. Making assumptions

b. All parties involved (sponsor, CRO/monitors, and eCOA providers) have a role to play in monitoring compliance and data quality

1. **Having early conversations about data quality expectations**
2. **Collecting lessons learned and putting them into practice**

Close-Out Phase

Kristina Lowe – Vice President, Business Development, ERT

Katherine Zarzar – Senior Manager, Patient-Centered Outcomes Research, Genentech, A Member of the Roche Group

Close-Out Definition and Goals

- The last visit has been completed, and the eCOA system is no longer collecting new data
- The study is closing out, including final data transfers and database lock
- Data transfers occur on-time and according to specifications agreed upon during BUILD, enabling an efficient Close-Out and database lock

Close-Out Phase

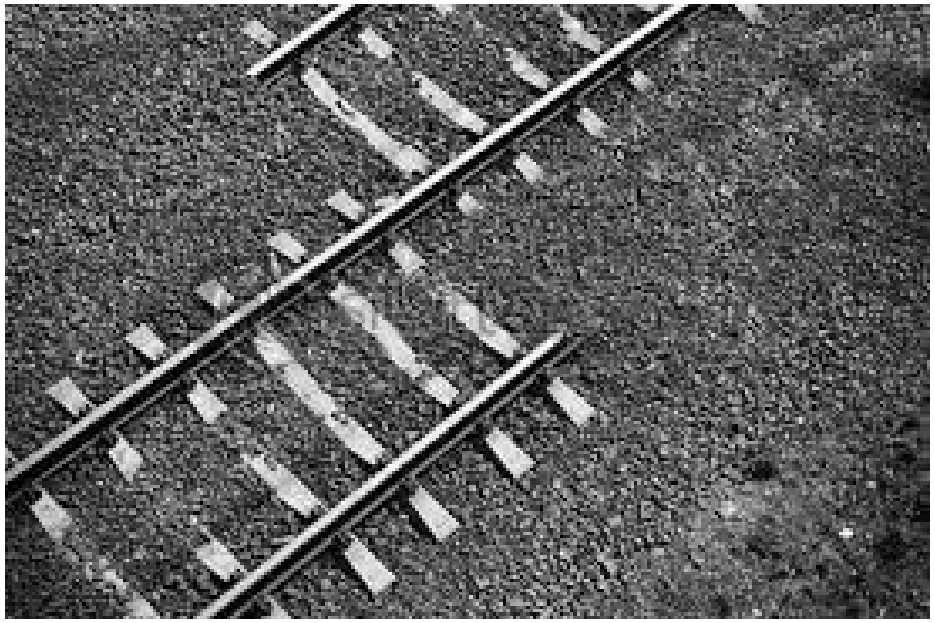
Key Issues Identified by Panel

1. Data Transfer Issues
   - Cleaning
   - Format
   - Security
   - Frequency
2. Data Lock Timelines
   - Agreement on what is being delivered and when
   - Need engagement of biostatistics and data management teams earlier in the process

Focus Area: Data Transfer

Key Issue #1: Data Transfers

- Where do we observe the largest misaligned expectations during Close-Out?
  - Misalignment on expectations for a “clean,” final data set
  - If data transfer requirements are not discussed early enough, eCOA providers may be unable to provide the requested outputs according to desired timelines
  - Late requests from sponsors and shifting timelines lead to significant challenges for the eCOA providers
  - Sponsors expect eCOA providers to review the dataset prior to transfer, and flag potential issues (e.g., missing data, duplicates)



Data Transfer: Roles/Responsibilities

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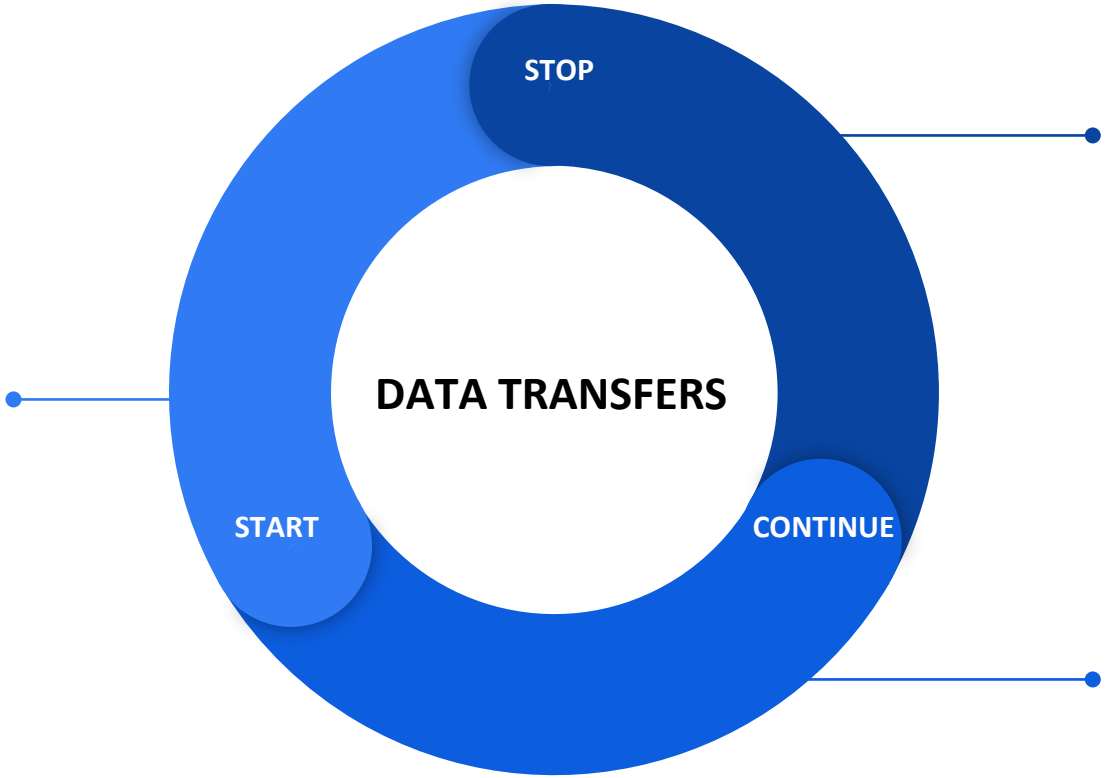
Sponsor	CRO (or party monitoring sites)	eCOA Provider
• Notify eCOA provider of data transfer specifications and requirements early (prior to system build) • Request a test transfer as part of UAT and update the system as needed to ensure appropriate specifications for the data transfer are established	• If coordinating the system build on behalf of the sponsor, ensure data transfer specifications are established according to sponsor requirements	• Work with sponsor team early to establish data transfer requirements, and provide test transfer data to ensure the system build is providing the necessary output • Ensure successful data transfer according to specification and at the agreed frequency

Data Transfer: Objectives

- Identify Data Transfer requirements and specifications **early**
  - Align expectations of sponsor and eCOA provider on data transfer requirements at the start
    - This should include both the data transfer specifications and a discussion on how involved in reviewing the data the eCOA provider will be (e.g., will they review the data set and flag duplicates before sending it?)
  - Document agreed-upon specifications, and test these specifications via test transfers during UAT
  - Ensure direct lines of communication between sponsor data transfer experts and eCOA provider experts to enable efficient alignment and resolution when challenges arise
  - Outline clear communication pathways for each study team and agree upon response/query resolution timelines, in case of questions during final data transfer stages
  - When possible, standardize at the organization level, or at a minimum the program or study level

CLOSE-OUT Summary

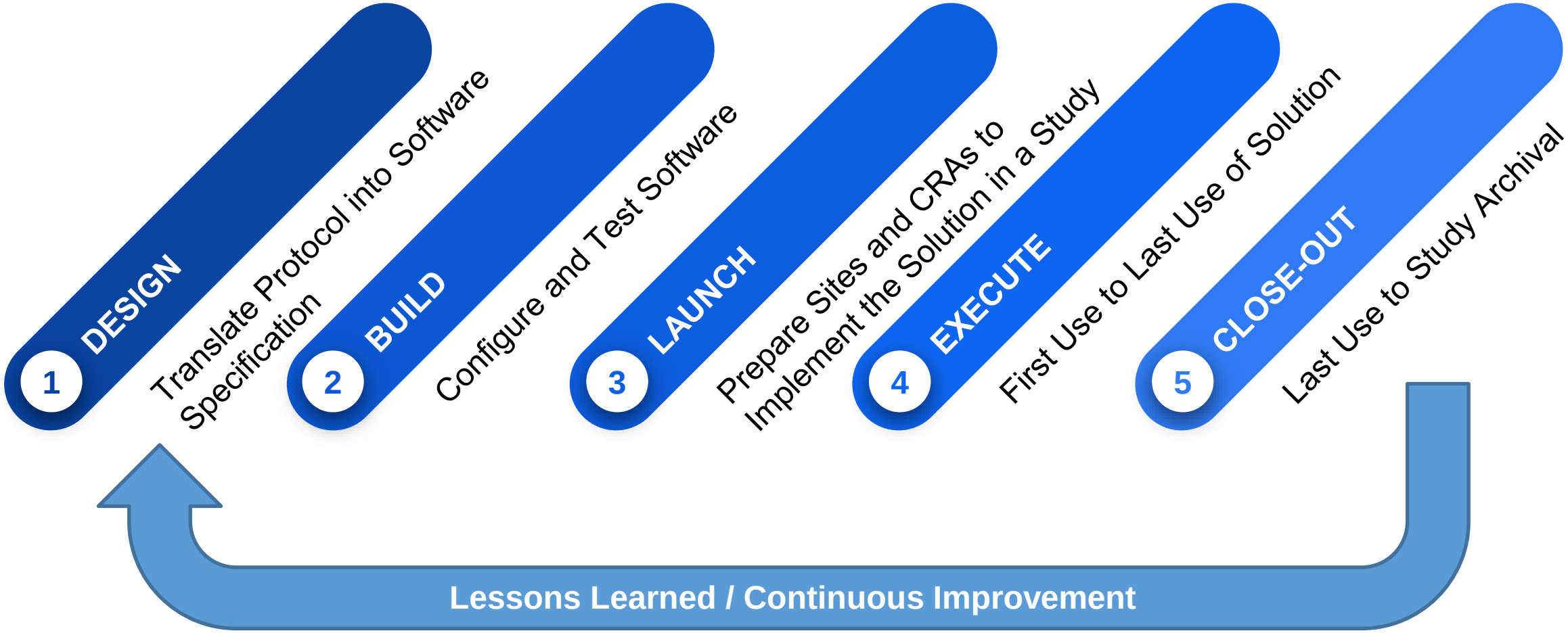
1. Planning the data transfer requirements and testing these requirements during planning, system design, and build
2. Encouraging the development of standards whenever possible



1. Only discussing the data transfer specifications during close-out

1. Expanding communication pathways and partnerships between eCOA providers and sponsors to enable open dialogue

Study Lifecycle



Summary

- We have misaligned expectations among the key stakeholders: sponsor (or agent/CRO), eCOA provider, and site
- Establishing and specifying clear roles and responsibilities for all stakeholders is a critical step for success
- Issues will occur: the criticality of the issue and its effective resolution relies on collaboration
  - Clearly define what you want to achieve and how you want to achieve it
  - Build the system to achieve that
  - Clearly define roles and responsibilities
  - Nice to haves vs. need to haves

eCOA is here: we can succeed if work together

Panel Discussion and Q & A

Moderator

- *Jean Paty, PhD* – Vice President, Consulting Services, Leading Patient Centered Endpoints Activities, QuintilesIMS

Presenters

- *Emily N. Smyth, PharmD* – Senior Research Scientist, Global Patient Outcomes and Real World Evidence, Eli Lilly and Company
- *Paul O'Donohoe* – Scientific Lead, eCOA and Mobile Health, Medidata
- *Kristina Lowe* – Vice President, Business Development, ERT
- *Katherine Zarzar* – Senior Manager, Patient-Centered Outcomes Research, Genentech, A Member of the Roche Group

Panelists

- *Robyn Carson, MPH* – Executive Director Patient-Centered Outcomes Research, Global Evidence & Value Development, Allergan
- *Katarina Halling, MSc* – Global Head Patient-Reported Outcomes, AstraZeneca
- *Sean Stanton* – Chief Executive Officer, Lifecore Solutions