Best Practices for ePRO Implementation in Clinical Trials

Moderated by:
Cindy Howry (YPrime)

Presented by:
Elisa Holzbaur (ALMAC) and
Serge Bodart (Biomedical Systems)

Presenter Biographies

Serge Bodart is currently based in Montreal, Canada. He has been involved in the ePRO business since 2000. Serge was a co-founder of SYMFO, a European-based ePRO provider. Prior to this, he served as an officer and helicopter pilot in the Belgian Army for 20 years. He now acts as the subject matter expert for eCOA Services at Biomedical Systems.

Serge has over 30 years of experience in project management. He holds a Master of Science in Telecommunications from the Polytechnic Division of the Royal Military Academy in Brussels, Belgium.

Elisa Holzbaur graduated with a Bachelor of Science degree in Cellular and Molecular Biology from Rider University and minors in Chemistry and Sales Management. In 2012, she joined Almac after working in Project Management, IVRS and ePRO Specialist roles at Covance, Merck, and Parexel.

Elisa earned her PMP certification from the Project Management Institute in 2006, is currently Manager of ePRO Services in the Clinical Technologies division of Almac and is based in North Carolina.

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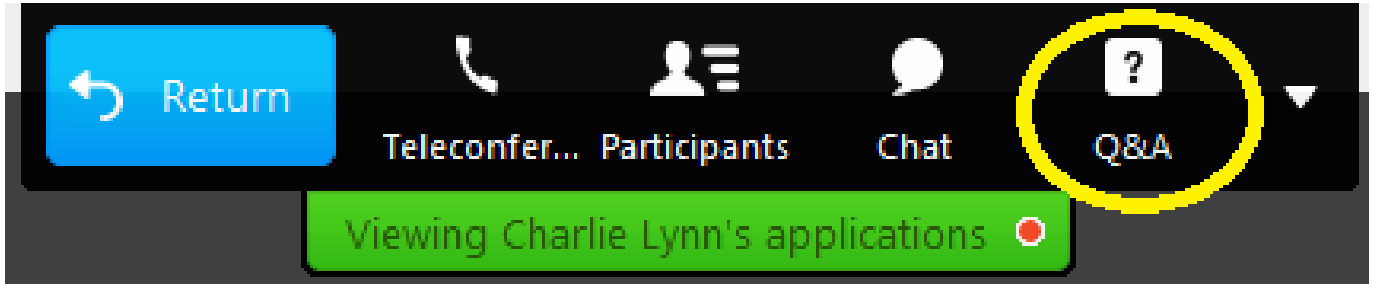

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ePRO Consortium

The Electronic Patient-Reported Outcome (ePRO) Consortium was established by the Critical Path Institute (C-Path) on April 1st, 2011.

Mission: To advance the science of clinical trial endpoint assessment by collaboratively supporting and conducting research, designing and delivering educational opportunities, and developing and disseminating best practice recommendations for electronic collection of clinical outcome data.

ePRO Consortium Members

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ALMAC

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Webinar Objectives

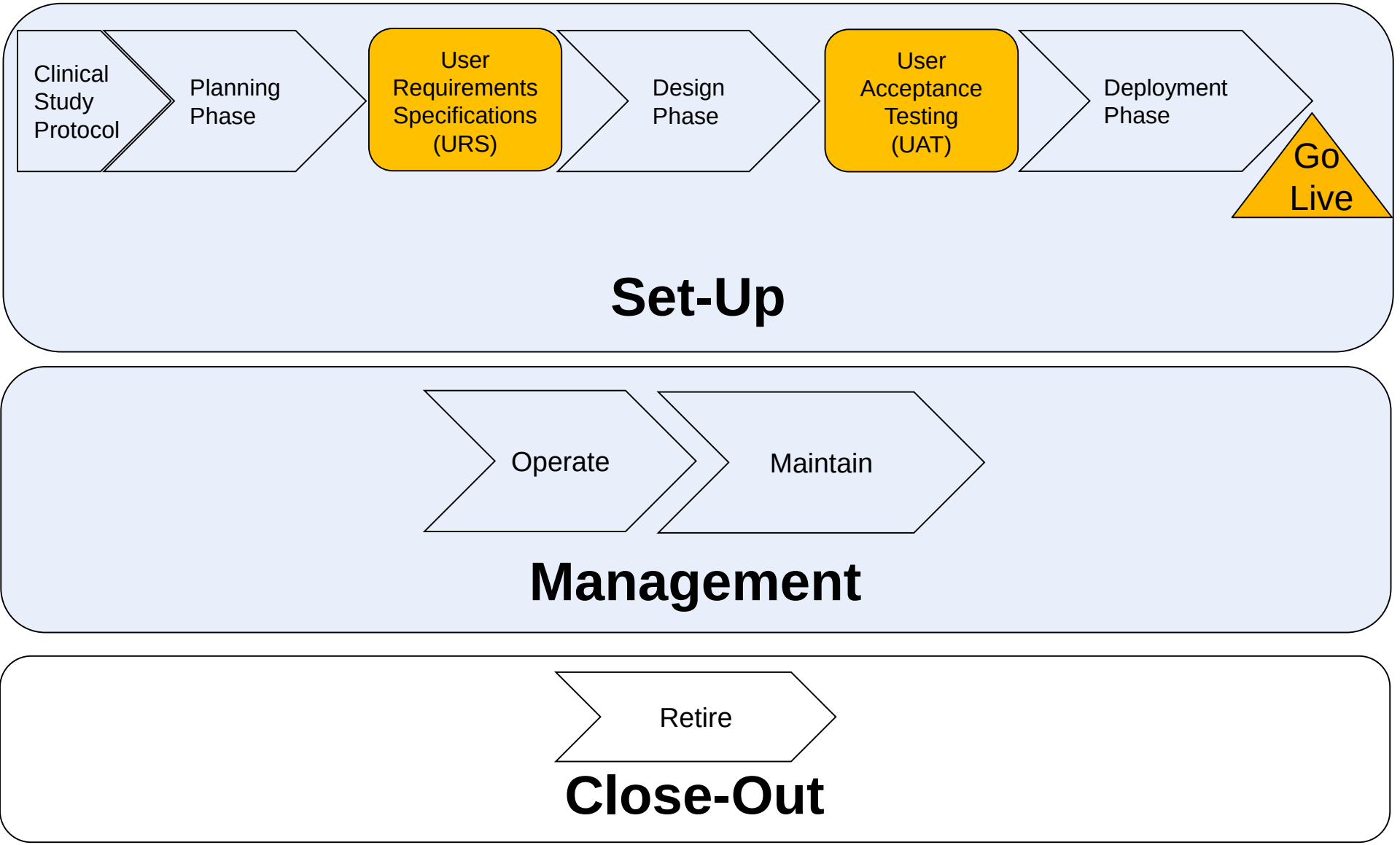
- ✓ Brief overview: Selecting the ePRO mode
- ✓ Review best practices related to the deployment of ePRO systems
- ✓ Identify key considerations for ePRO deployment in clinical trials

Selecting the ePRO mode

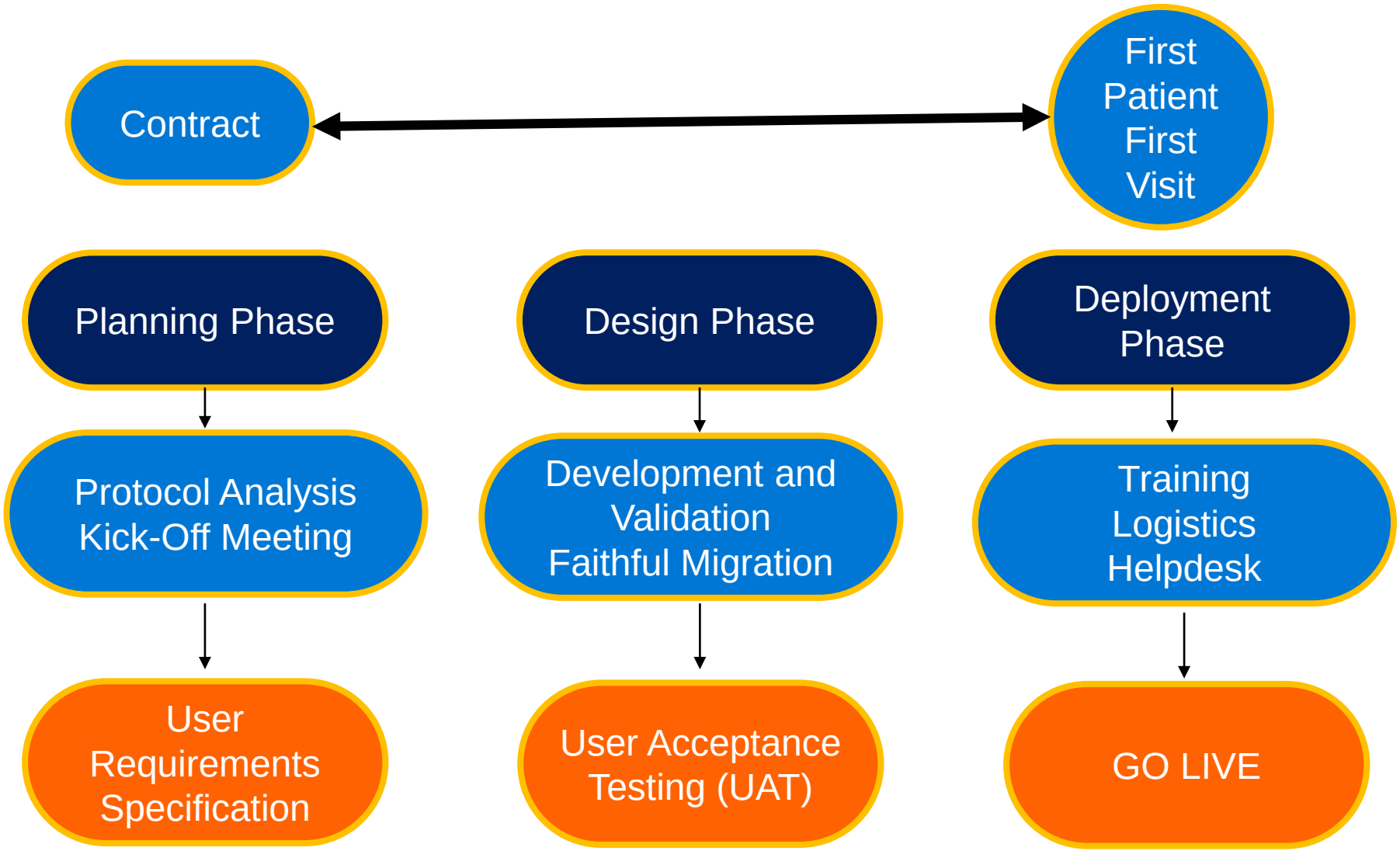
Appropriate ePRO mode selection should be based on different considerations:

- √ Patient characteristics
- √ Study design
- √ Study logistics
- √ Instrument characteristics

ePRO Development Life Cycle



Set-up


Contract
First Patient First Visit
Planning Phase
Protocol Analysis Kick-Off Meeting
User Requirements Specification
Design Phase
Development and Validation Faithful Migration
User Acceptance Testing (UAT)
Deployment Phase
Training Logistics Helpdesk
GO LIVE

Set-up – Planning Phase

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Study Protocol Analysis	
Analysis/Planning Item	**Considerations**
Electronic Patient-Reported Outcome (ePRO)	• Is the use of a diary described in the protocol? • What type of PRO measures is used in the trial? • Need for faithful migration
Number of Patients/Sites/ Timelines	• Cost impact • Training • Printed patient instructions quantity
Countries/Languages/Culture	• Translations • Linguistic validation
Endpoints	• Is it a primary, secondary or exploratory endpoint? • Migration/Equivalence
Assessments	• Field or site based • Frequency: daily, weekly, etc. • Schedule of assessment
Inclusion Exclusion Criteria	• Influence on alerting - reporting
Alerting	• Safety alerting • Entry of specific value or within a set range

Set-up – Planning Phase Example

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- **Asthma trial:** 600 screened patients, 400 randomized patients
- **Primary endpoint:** Change from baseline in weekly average of daily PEF over the treatment
- **Secondary endpoint**: Change from baseline in weekly average of the total daily asthma symptom score over the treatment
- **Exploratory endpoint:** Change from baseline in ACQ-6
- **Health economic variables**: EQ-5D-3L at all visits
- **First patient screened:** 01 Jan 2016
- **First patient randomized:** 01 Feb 2016
- **Duration:** 4 weeks screening, 3 months treatment
- **Recruitment:** 8 months
- **Inclusion criterion:** ACQ-6 score at randomization visit at least 1.5
- **Countries:** US only
- **Languages:** English and Spanish
- **Sites:** 20

Set-up – Planning Phase Example

Study Protocol Analysis	
Analysis/Planning Item	
PRO measure	Field diary to collect daily asthma symptoms, study and rescue medications Site: ACQ-6 (equivalence) EQ-5D-3L (faithful migration)
Number of patients/sites/timelines	600 screened, 20 sites Device only: smartphones/tablets needed
Countries/languages/culture	US – English, Spanish
Type of endpoint (measure)	Primary = PEF Secondary = daily symptoms Exploratory = ACQ-6
Assessments	Twice daily assessments for the field-based diary, site-based assessments for ACQ-6 and EQ-5D-3L
Inclusion criterion	ACQ-6 >= 1.5
Alerting	Alerts to the site for randomization criteria

Set-up – Planning Phase

Kick-Off Meeting (KOM)	
Important Item	**Considerations**
Face-to-face ideally and as soon as possible	• Critical to define roles and responsibilities of both sponsor and vendor
Draft/Review Communication Plan	• Roles and responsibilities • Biweekly meetings • Contact information
Define/Refine Requirements	• PRO tools, questionnaires (e.g., medication log, symptoms) • Migration requirements • Randomization report • Data load specification
Establish/Review Timelines	• Key milestone dates • IRB/ethics submission dates (if translations)

Examples of Provisioned Device Considerations
• Determine number of devices to be ordered

Set-up – Planning Phase

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User Requirements Specification (URS)
• ePRO workflow (questions, answers, branching logic) • Schedule of events and item completion window • Patient and site ID formats • Reporting (access, rights, content) • Randomization algorithms if any • Alerting (immediate alerting – e.g., suicide, safety alerts) • Data flow and data transfer specifications

Set-up – Planning Phase

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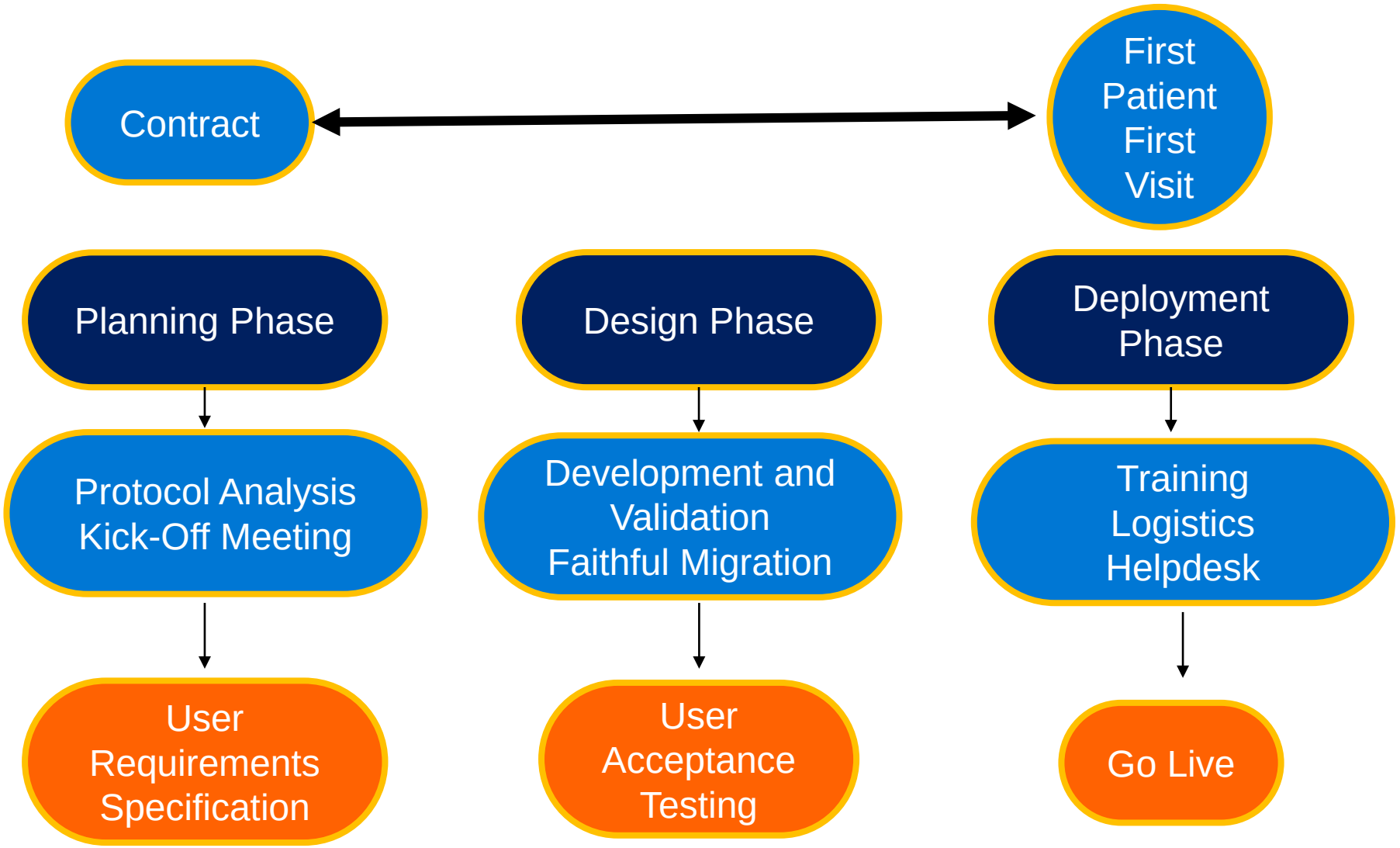
User Requirements Specification (URS)
Provisioned Device Considerations

- Device accessibility
- Training menu
- Investigator menu
- Alarms
- Data transmission
- Number and characteristics of devices, accessories (chargers, protection cases)

Set-up – Planning Phase

User Requirements Specification (URS) Phone/Web Considerations
• Integration with other functions of the phone/Web system (minimize site burden) • Call/Web flow (minimize patient/subject burden) • Translations – client review of recordings • Phone or text message reminder • Demonstration system

Set-up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Set-up - Design Phase

Design Phase	
Key Deliverables and Milestones	**Description**
Subject instruction documents	Patient user guides, diary cards
Site instruction documents	Site user guide
Translations/cultural adaptations	User guides, PRO measures (linguistic validation)
Submission packages for IRB/EC	User guides, screenshots, scripts
Software	Development and validation (Computer System Validation – CSV)
Reporting tool	Development and validation (CSV)
Faithful migration	Cognitive interviewing and usability testing

Set-up - Design Phase
Faithful migration

- A faithful migration is the development of alternative modes of data collection that do not bias responses.
- Migration process must ensure that there is no change in content and that subjects will interpret and respond the same way regardless of the mode.
- 3 levels of modification
  - MINOR: non-substantive changes to the instrument– Requires Cognitive Interview and Usability Testing
  - MODERATE: Changes in presentation or wording that can alter the interpretation – Requires Equivalence Testing and Usability Testing
  - SEVERE: Substantial changes in item responses or wording – Requires Full Psychometric Testing and Usability Testing.

Set-up – Planning Phase

System Development Life Cycle (SDLC)*

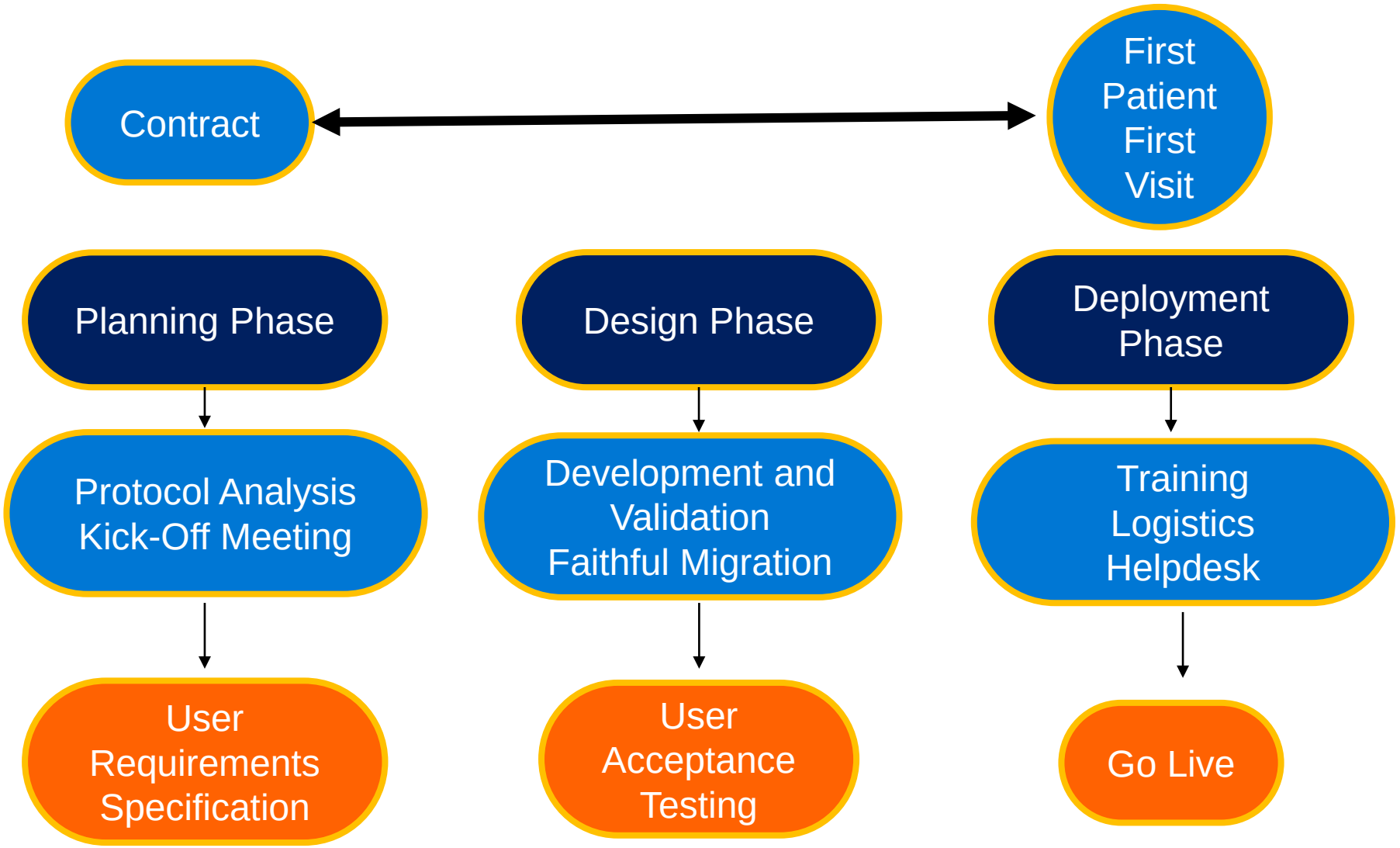
- *System requirements*
- *System design*: System design documentation to cover data collection and storage, Web portal and alerts, data transfer.
- *Coding – Tailoring – Software Development*: writing code or customizing modules of code already developed.
- *Testing by system provider*: described in Quality Test Plan (testing strategy, test scripts)
- *Traceability*: quality control so software meets user's needs
- *User acceptance testing*

*: Zbrozek A, Hebert J, Gogates G, et al. Validation of electronic systems to collect patient-reported outcome (PRO) data - Recommendations for clinical trial teams: Report of the ISPOR ePRO systems validation good research practices task force. *Value Health 2013:16:480-9.*

Set-up - Design Phase

Sponsor performs User Acceptance Testing (UAT)	
Process by which the clinical trial team determines if the system meets expectations and performs according to the system requirements documentation	
UAT environment needed (separate from production) **Diary content** **Branching logic** **Security (passwords, reset passwords)** **Translations** **Training and demonstration menus** **Reporting tool** **Alerts** **End to end testing** **Data transfer to sponsor**	
Provisioned Device Considerations	**Phone/Web Considerations**
• **Device configuration by sites**	• **Reminders messages**
• **Compliance features such as alarms**	• **Integrations**

Set-up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Set-up - Deployment Phase

<table>
<tr><th colspan="2">Deployment</th></tr>
<tr><th>Administrative Items</th><th>Considerations</th></tr>
<tr><td>List of participating sites and staff</td><td>• Study team including: sponsor, CRAs/monitors, project managers
• Site staff including: PI, study coordinator</td></tr>
<tr><th>Provisioned Device Considerations</th><th>Phone/Web Considerations</th></tr>
<tr><td colspan="2">Installation/Configuration Management: ensures ePRO deployment with the correct software version and local settings</td></tr>
<tr><td>• Logistics:
▪ Identify and order devices
▪ Test devices inspections
▪ Configure devices
▪ Consumables: cables, plugs, chargers (adapted to countries), protections/covers
▪ Shipping devices
▪ Customs issues: Israël, Argentina, South Korea, etc.
▪ Ship in advance to site initiation/FPFV</td><td>N/A</td></tr>
</table>

Set-up - Deployment Phase

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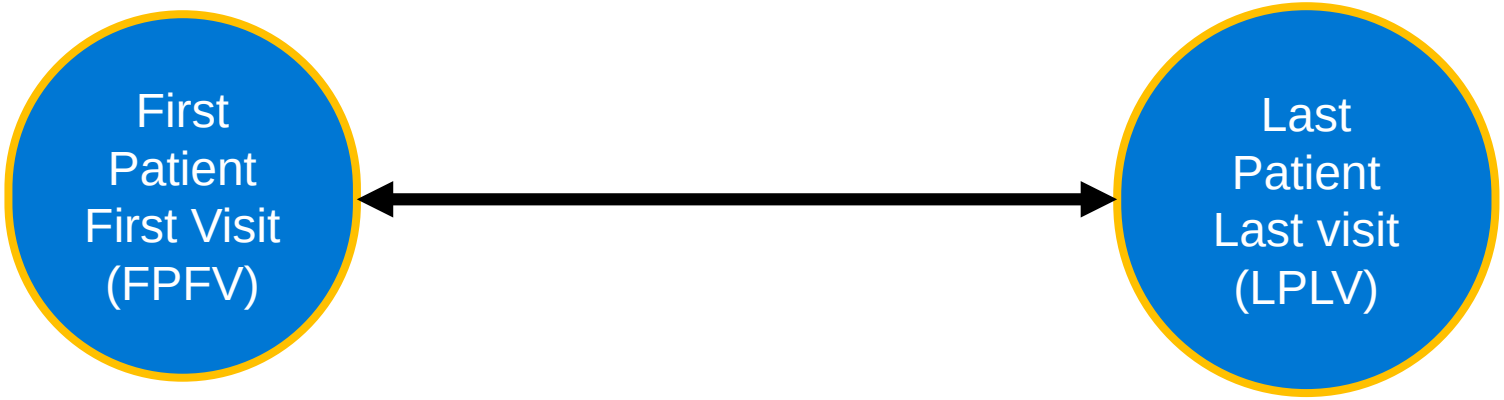
Training is key.	
Training Items	**Considerations**
Location	• Investigator meeting with hands-on practice • Refresher sessions • eLearning (when possible) • Documentation (Web-based)
Who to Train	• Site staff • CRA/Monitors • Patients/Subjects (local language)

Support	
Items	**Considerations**
Tech Support	• Organize (e.g., global projects) • Train support team on protocol specific aspects

Management


First
Patient
First Visit
(FPFV)
Last
Patient
Last visit
(LPLV)

Management

User Support	
Item	
Tech support	• Resolve site queries
Retraining	• As needed • E.g. Review help desk trends

Provisioned Device Considerations	Phone/Web Considerations
• Initial deployment and study close-out are labor intensive periods	• Print and ship patient user documents (e.g., diary card, instruction sheet)
• Shipments arrived at sites – tracking mechanism needed	
• Device configuration (patient IDs)	
• PIN codes	
• Reuse of devices	
• Replace broken devices	
• Need for consumables (e.g., batteries, plugs)	
• Sites with high recruitment rates – equipment swap	

Management

Project Management and Tracking	
Important Item	**Considerations**
Proactive project management	• Review reports • Monitor alerts

Track and monitor compliance	• Particularly important if data used to support endpoints
	• Regularly review ePRO compliance
	  • Subject/Patient, site, country and study levels
	• Determine plan to prevent future missing data
	  • Follow up with sites where non-compliance is high
	  • Talk with sites where non-compliance is low

Tools for additional training/ information distribution	• Monthly newsletter • Group meetings and information sharing forums for study sites

Management

Project Management	
Important Item	**Considerations**

Mid-trial changes	• Update requirements documents
	• Re-programming
	• Re-validation (including regression testing when needed)
	• UAT
	• Consider possible implications:
	  • User document updates
	  • Re-translation
	  • Submit updated patient facing information to IRB/EC
	  • Retraining of study team, sites, patients/subjects and support staff

Mid-trial data sets	• E.g. for interim analysis
Last Patient Last Visit (LPLV)	• Last event registered • Prevent access to project

Close-out

Close-Out

Close-Out Activities	
Item	**Considerations**
Copy of data to investigators	• Primary source data • Investigator is responsible for providing in the event of an audit • Non-editable format
Data load	Final transfer to sponsor
Archival	System decommissioned

Provisioned Device Considerations	Phone/Web Considerations
Decommissioning: data completion, device returns, documentation and notifications.	
• All data transmitted	• Database locked
• Block data flow	
• Devices returned	

Wrap-up

- Deploying ePRO systems globally is a complex process
- What you need to succeed:
  - Flexible and reliable technology
  - Good design
  - Training is critically important
  - Data transfer
  - Reporting tool
  - Proactive project management

Questions?

http://c-path.org/programs/epro

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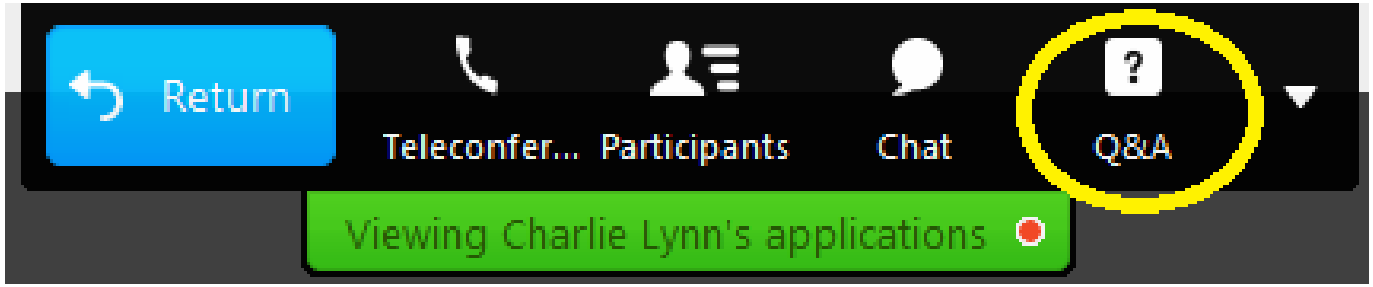

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Thank you for attending ePRO Consortium Webinar 4

Best Practices for

ePRO Implementation in Clinical Trials