Sponsor Infrastructure, Resources and Roles/Positions Needed to Support Successful Execution of ePRO/eCOA Strategies

Sue Vallow
GlaxoSmithKline

FIFTH ANNUAL
PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

April 29 - 30, 2014 ■ Silver Spring, MD

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Session Participants

Moderator

- *Sue Vallow, RPh, MBA, MA* – Senior Director, Patient Reported Outcomes, GlaxoSmithKline

Presenters

- *Kathryn Engstrom* - Data Scientist – Auto Immune, Eli Lilly and Company
- *Jonathan Helfgott, MS* – Associate Director for Risk Science (Acting), Office of Scientific Investigations, CDER, FDA
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Presentation to: PRO Consortium Workshop

Delivered by:

Jonathan S. Helfgott

Associate Director for Risk Science (Acting),

Office of Scientific Investigations, CDER, FDA

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- The contents of this presentation are my own, and do not necessarily reflect the views and/or policies of the Food and Drug Administration or its staff as per 21 CFR 10.85.

Outline

- Section I: FDA Requirements in Clinical Investigations
- Section II: Preparing for an FDA BIMO Inspection
- Section III: ePRO Case Examples

Section I: Overview of FDA's Regulatory Requirements for Clinical Investigations

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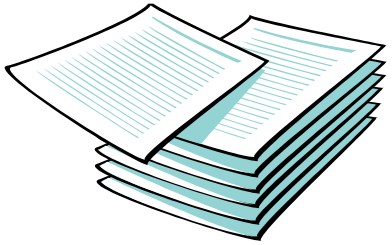
- FDA assesses compliance of Clinical Investigations through:
  - Regulatory requirements in 21 CFR Parts 11, 50, 56, 312, and 812; establishes the minimum threshold for compliance
  - Additional requirements established by the study specific protocol must also be followed as well as institutional policies

Section I: FDA Regulatory Requirements for INDs/IDEs

- All 21 CFR Part 312/812 regulations apply equally to both paper records and electronic records
  - 21 CFR Part 11



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- The use of computerized systems in clinical investigations does not exempt INDs/IDEs from any 21 CFR Part 312/812 regulatory requirement
- BIMO Sponsor/CRO Compliance Program Guidance Manual (CPGM)
  - Part III Inspectional, Section M, Electronic Records & Electronic Signatures

Section II: Common BIMO Deficiencies

Sponsor:

- Inadequate Monitoring
- Failure to secure investigator compliance
- Inadequate AE/UADE analysis and reporting
- Failure to obtain signed Investigator Agreement
- Failure to provide the Clinical Investigator with information necessary to conduct the investigation properly

Clinical Investigator:

- Failure to follow study protocol
- Failure to obtain Informed Consent
- Failure to document and report Adverse Events
- Failure to obtain IDE approval and IRB approval prior to initiating study
- Failure to maintain accurate, complete, and current records

Section III: ePRO Case Example #1

- PDA devices were issued to each subject and taken home to make daily reports
- The electronic information was transferred through the phone lines, to a server in Microsoft SQL format, when the PDA was docked each night
- After the last transfer of information, the ePRO data on the PDA was erased
- At the conclusion of the studies, the Sponsor sent archive CDs to all study sites in PDF format

ePRO Case Example #1 (Continued)

2 things could have been done differently:

1) The Clinical Investigator (CI) should have had access to each nightly transfer of data so that the CI can maintain source records on site as required by FDA

2) Sponsor should have had a process to demonstrate that accurate and complete data sets were able to be successfully transmitted from the PDA to the server

ePRO Case Example #1 (Continued)

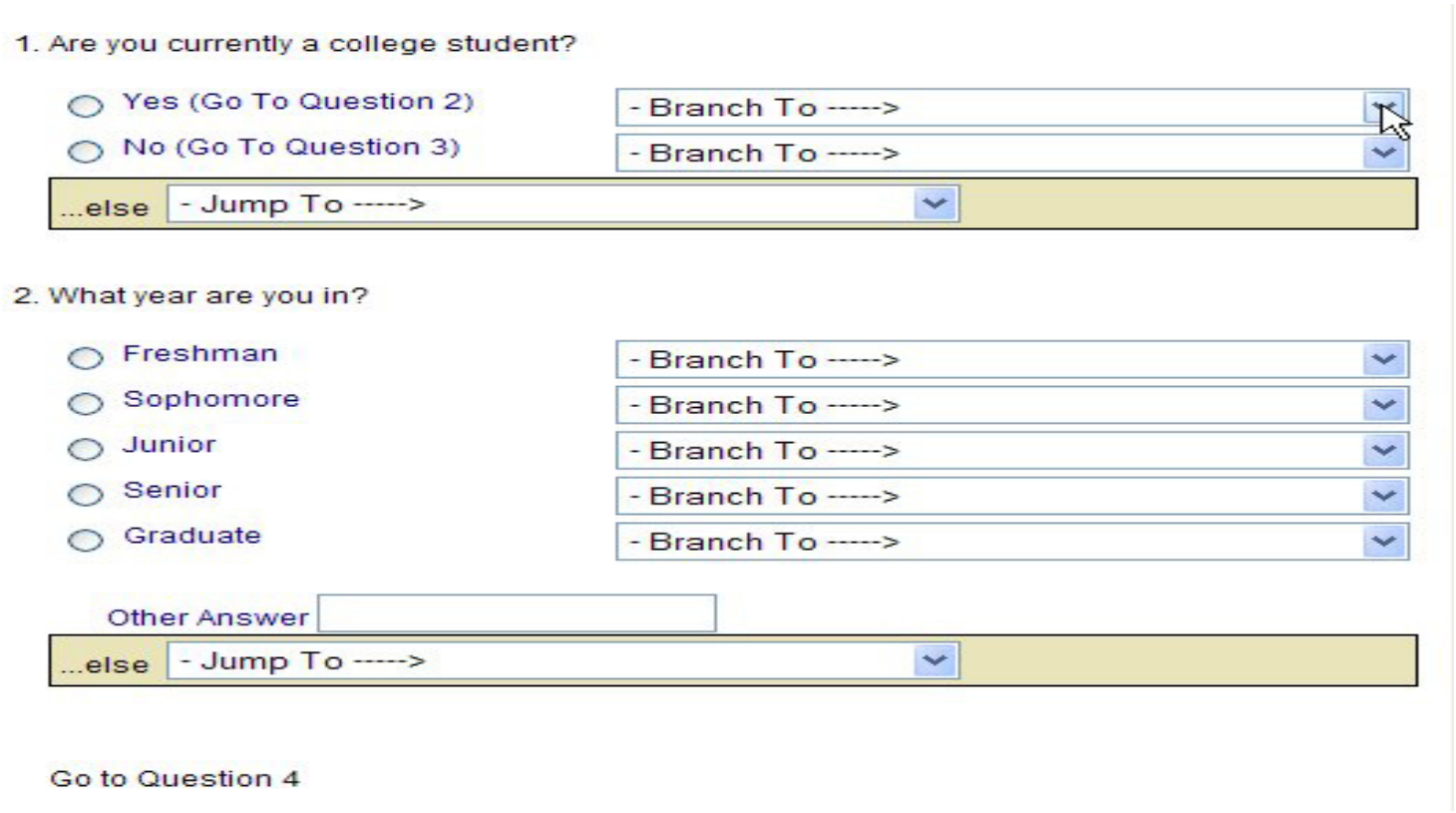
- Clinical Investigator was cited on the 483 for:
  - "Failure to maintain complete records" (21 CFR 312.62(b))
- Sponsor was cited on the 483 for:
  - "Failure to provide the Clinical Investigator with information necessary to conduct the investigation properly" (21 CFR 312.50)

ePRO Case Example #2: ePRO (*Direct Entry of Data*)

- A Questionnaire is used to collect clinical data, representing the study's primary endpoint, from Patients responding to a survey of questions on a Computer (ePRO)
- Certain responses to the questionnaire would "default" other downstream question responses, without notifying the Patient, allowing Patients to input values different from what was recorded by the system

ePRO Case Example #2:
(*Direct Entry of Data*)

- The Sponsor should have designed the system to *block* Patient input of responses to the "defaulted" questions
- Poor human-factor considerations



Case Example #3: Integrating SAS
(*Training of Personnel*)

- A Sponsor was using computers for direct entry of clinical data by the Clinical Investigators, representing the study's primary endpoint
- The computer integrated a built-in Statistical Analysis Software (SAS) function to "analyze" all source data
- The SAS was "rounding up/down" certain inputted values as part of the "analysis"

Case Example #3: Integrating SAS

(*Training of Personnel*)

- These were critical clinical values that should not have been “rounded” but recorded as is
- The protocol for gathering and maintaining source data should ensure that the data is being captured accurately and not altered
- Source data needs to be separated from SAS analysis

Case Example #4: IVRS
(*Internal Security Safeguards*)

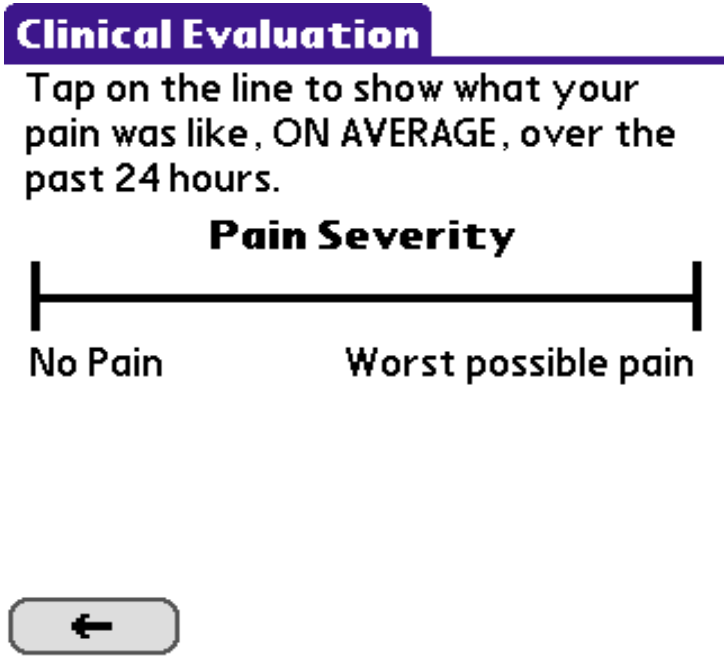
- An Interactive Voice Response System (IVRS) was used to collect clinical data, representing the study's primary endpoint, from Subjects responding to a survey of questions using a touch-tone telephone
- There are 3 requirements to access the IVRS:
  - Toll free number from International Country of Origin
  - 6 digit Patient Identifier (Uniquely Assigned for each patient)
  - 6 digit PIN (Patient's Birth-date)

Case Example #4: IVRS

(*Internal Security Safeguards*)

- What design feature of the IVRS could possibly lead to questionable data capture?
- The PIN # is not encrypted, since it is the Subject's birth-date, and the Sponsor had access to this information!
- The IVRS had minimal security features to prevent unauthorized access
- Password should have been protected!!!

Case Example #5 (ePRO in Israel)




יומן בוקר
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Conclusion

The intent of FDA's regulatory requirements and guidance is:

- Ensuring confidence in the reliability, quality, and integrity of electronic source data, source documentation, and the computerized systems used to collect and store that data
- Ensure that electronic records used in clinical investigations are accurate, complete, and current

Important FDA Regulations on Software/Computers/Electronic Records

- 21 CFR Part 11
- Predicate Rules in 21 CFR Parts 312 & 812
- 21 CFR Part 820.30(g): *Design Controls*
- 21 CFR Part 820.70(i): *Automated Processes*
- 21 CFR Part 58: Good Laboratory Practices

FDA Guidance Documents on Software/Computers/Electronic Records

- Part 11 Guidance on Electronic Records & Signatures:
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072322.pdf
- General Principles of Software Validation:
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085371.pdf
- Off-The-Shelf Software Use in Medical Devices:
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073779.pdf
- Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software:
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077823.pdf

FDA Guidance Documents on Software/Computers/Electronic Records (Cont...)

- Guidance on Electronic Source Data in Clinical Investigations:
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf

Computerized Systems Used in Clinical Investigations:

  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf

- *Specific Concerns When Using Electronic Patient Reported Outcomes (ePRO)*:
  - *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071975.pdf*
- Guidance on Mobile Medical Applications:
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf

Sponsor Roles, Infrastructure Needed to Support Successful ePRO/eCOA Implementation: *Data Management Perspective*

Kathryn Engstrom

Eli Lilly and Company

Case Examples

	Indication 1	Indication 2	Indication 3	Indication 4
Compound A	ePRO Paper[1]	ePRO Paper[1]		
Compound B	ePRO eCOA		Paper[2]	ePRO eCOA
Compound C	ePRO eCOA eDiary		ePRO eCOA	ePRO eCOA

ePRO completed at site visit.
eCOA completed by assessor during patient visit.

Use of paper:
1 – Copyright owner of 1 assessment would not approve for electronic presentation
2 – Timeline between funding and FPV too short

Lessons Learned

- Protocol language
  - Vague wording in protocols around requirement for collection on devices can lead to misinterpretation by sites.
  - If you expect PROs to be collected at the beginning of a visit, prior to other procedures and assessments, call it out: during site selection

Lessons Learned

- Passwords
  - Patient and site user passwords are required to have clear attribution of each data point.
  - Understand how these will be created, stored, reset if forgotten.
    - Note that most devices do not have non-English keypads
    - Long intervals between visits increases likelihood of forgotten passwords
  - Site users must have access to be declared enrollment ready

Lessons Learned

- Device redundancy
  - Access to a real-time back-up is a necessity.
    - Replacements can be overnight shipped at best
    - % of device failure claims as reason for missing data at sites with one device vs. multiple is significantly higher
    - Sites may resort to paper assessments and then transcribe them into device.

Lessons Learned

- Data accessibility to sites, CRAs, sponsor
  - Sites are required to maintain complete records, therefore if using eSource they must have comprehensive views of unblinded data.
    - Consider the readability format of these presentations and the burden of accessing.
  - CRAs need views which allow them to easily check site compliance.
  - Sponsors need views which allow them to perform study-level oversight.
  - The vendors don't know what you need.

Lessons Learned

- Crazy things site will try to do:
  - Double collection of PROs at a visit as means of self-correcting for patient number entry error.
  - Requesting change to date/time stamp
  - Requesting changes to patient reported data (especially when an entry or discontinuation criteria).
  - Collect on paper (copies of screen shots submitted to ERB, from own clinical practice, downloaded from internet) and transcribe to eSource.

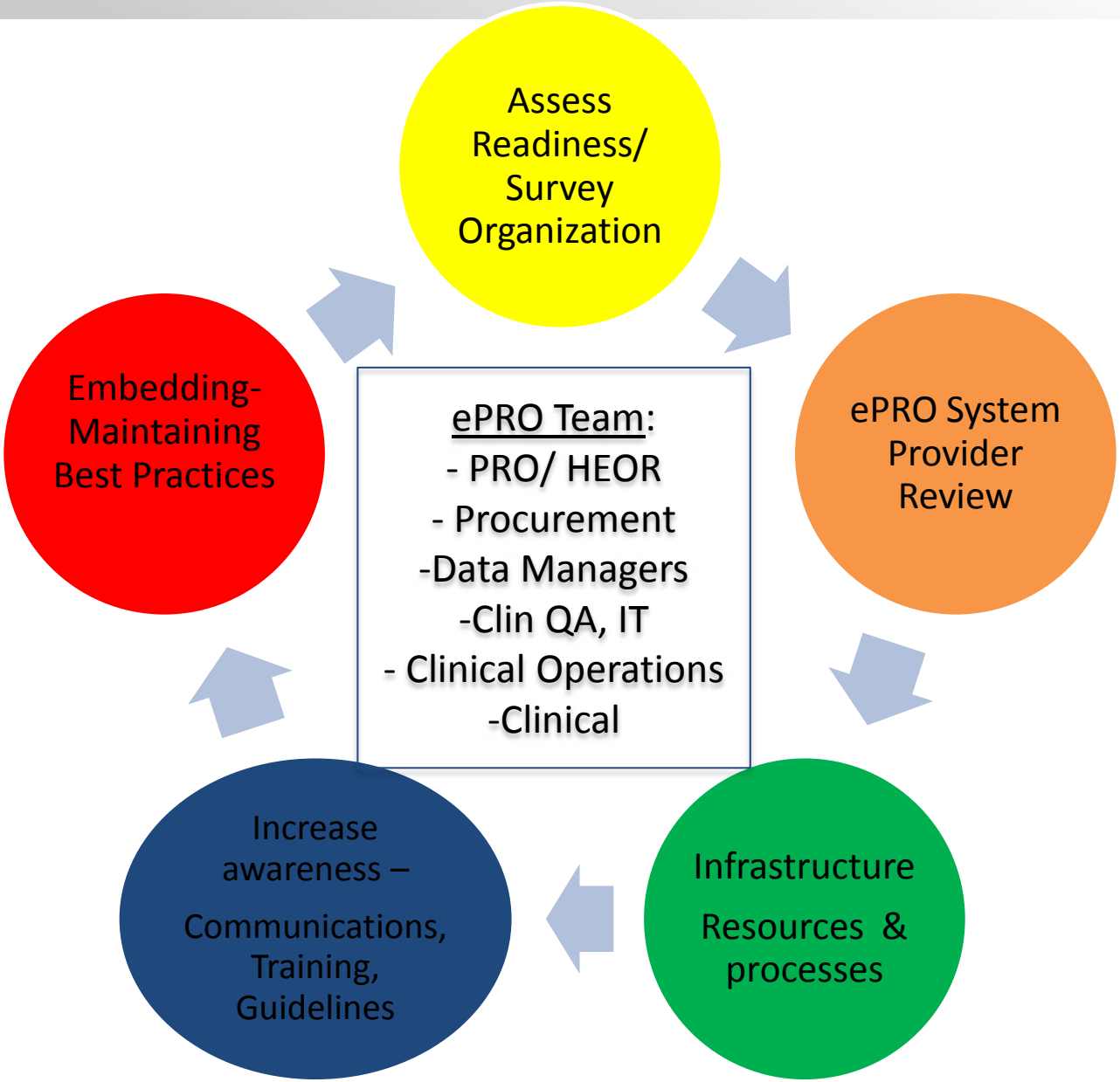
Sponsor Roles, Infrastructure Needed to Support Successful ePRO/eCOA Implementation: *Sponsor Perspective*

Sue Vallow

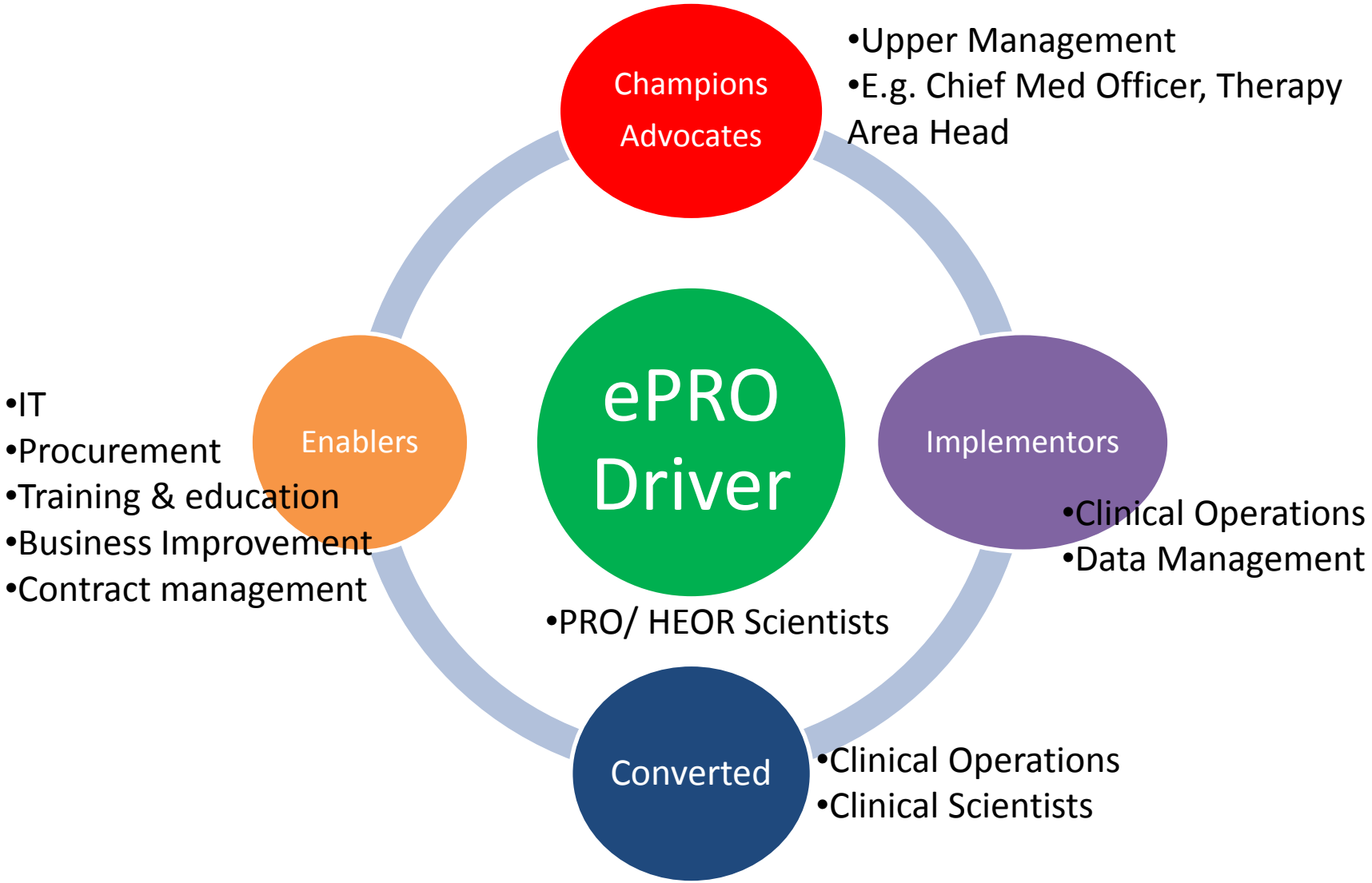
Driving ePRO Success

- Initiating an ePRO strategy
- Roles important to make this successful
- Study-level roles
- Maintaining ePRO as a way of life

Initiating ePRO in Pharma



Roles Important for Initiating ePRO



Critical Roles during ePRO Study Implementation

PRO/ HEOR Scientist

Project Management

ePRO Manager / Super Users

Clinical Lead

Clinical Operations Manager

Data Management

Monitoring

Maintaining ePRO Strategy at Sponsor

- Make part of PRO strategy
  - Need for PRO person / HO specialist driving
- Dedicated ePRO manager/ team
  - Helping to train for future when all can implement
  - SWAT / Super users to help teams in mean time
- Budget planning at program not study level
  - Build in costs of ePRO and triggers in planning process
- ePRO System Provider communications
  - Governance structures, sharing learnings, etc

Summary

- Key regulatory issues, audit findings and data management issues point to critical roles at sponsor level needed for managing ePRO
- Informed ePRO strategy planning – with right roles involved - helps to make ePRO implementation successful

References

- D. Eek, et al. “How to Implement an ePRO Strategy: A Best Practices Guide.” May 2013. PHT.
- M. Briggs, et al. “Embracing an ePRO Adoption Initiative: A Checklist of Best Practices to Make the Move from Paper to Paperless PRO.” Presentation at CBI PRO Conference, May 2010

Discussion and/or Questions?

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