The 2016 ICH E6(R2) Step 4 Addendum on Good Clinical Practice

Impact on CRO Operations

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What is “ICH;” Where Do They Fit In?

- **ICH is an Internationally-Recognized Voluntary Consensus Standards Organization**
- **Originally, International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (a.k.a. “ICH”)**
  - Founding in 1990
  - Regulatory Members
    - European Commission (EMA)
    - United States Food and Drug Administration (FDA)
    - Japan (MHLW and PMDA)
  - Founding Industry Members
    - EFPIA, JPMA, and PhRMA
Purpose of ICH

• Promote public health through harmonization that contributes to:
  – Avoiding unnecessary duplication of clinical trials and post-market evaluations
  – Development and manufacturing of new medications
  – Registration and supervision of new medicines
  – Reduction of unnecessary animal testing without compromising safety and effectiveness

• Accomplished through Technical Guidelines implemented by regulatory authorities
Current Status of ICH E6(R2) Step 4

- **Note recent ICH name change:**
  International *Council for Harmonisation*
  of Technical Requirements for Pharmaceuticals for Human Use

- The latest, “Step 4” version of E6(R2) is dated 09 November 2016
What is the “E6” Technical Guideline?

- “E” for “Efficacy,” Guideline number 6
- E6 for “Good Clinical Practice,” an international ethical and scientific quality standard for
  - Designing
  - Conducting
  - Recording, and
  - Reporting
  of trials that involve the participation of human subjects
- Guidance should be followed when generating clinical trial data intended for regulatory submission
Where Does GCP Come From?
ICH E6(R2) Step 4 GCP Update  May 19, 2017
Committees, representatives, hard work
ICH Guidelines

- Over 60 Guidelines published in areas of
  - “Q” for Quality
  - “S” for Safety
  - “E” for Efficacy
  - “M” for Multidisciplinary
- Expertise from industry + regulatory authorities
- Science-based, consensus driven
- Collaborative, commitment by regulators
- Common platform, tools, revision process
Looks like nobody got it right... again. "G.C.P." stands for "Good Clinical Practice"!
ICH Process for Changing E6(R1) GCP

- Original E6(R1) published and adopted in 1996
- Expert Working Group (EWG) organized in 2013
- Topic officially assigned in April 2014
- Step 1: Draft technical document by June 2015
- Step 2a: Refine document by June 2015
- Step 2b: Issue draft guideline by June 2015
- Step 3: Expert draft guideline in June 2016
- Expert Discussion finished in Lisbon, June 2016
- Formal ICH Assembly in Osaka, November 2016
- Step 4: Final R2 guideline issued November 2016
What’s the Point?

- Modernize ICH E6 GCP (not changed since 1996)
- Better enable innovative approaches to trial
  - Design
  - Management
  - Oversight
  - Conduct
  - Documentation
  - Reporting
- To ensure HSP and data quality
What happened: ICH E6(R1)→E6(R2)

- ICH using “Integrated Addendum” approach
- Published as changes to full-text with inserts
- Few deletions of earlier text; mostly additions
- Minor wording/phrase changes
- Step 2 published in U.S. Federal Register 29 Sep 2015
  - Comments from U.S. were due back by 30 Nov 2015
- Last comments were due back in January 2016
- The Step 4 version (09 Nov 2016) is final text
- For EU, Japan, US, Canada, & Switzerland, effective now
- FDA likely to “adopt” version as Guidance soon
I have **GOOD NEWS**!
For many CROs, ICH E6(R2) GCP changes are, *for the most part*, going to be pretty...
Why will E6(R2) be Easy for Most CROs?

- With exceptions, CROs already do these things
- We’ve been doing them for years (at Emmes)
- If not done it already, most know how
- We have experts at Emmes who have published, built tools & techniques implementing these items
- Looking at the details, you should not be surprised
- The “impact” of E6(R2) should be low on Emmes and most CROs conducting quality research

- OK, let’s look through the detailed list of changes...
Reviewing the R2 changes to ICH E6

Pull up your official copy of E6(R2) Step 4 directly from ICH:

Changes to Definitions in E6(R2)

- **Certified copies** [1.63]
  - Paper forms, verified by dated signature
  - Electronic files, copy generated by *validated process*

- **Monitoring Plans and Monitoring** [1.64 & 5.18.7]
  - You need a plan
  - *Frequent* mention of “centralized” monitoring is new, but not the concept of centralized monitoring (see later)

- **Monitoring Reports** [5.18.6(e)]
  - Include reports on centralized monitoring activities, not just on-site visits

- **Validation of Computerized Systems** [1.65]
  - Matches existing FDA guidance (from 2007); not new
Changes to GCP Principles

• Principal of “All Trial Information” being:  [2.10]
  – Recorded,
  – Handled, and
  – Stored

• To assure accurate  [2.13]
  – Reporting,
  – Interpretation and
  – Verification

• Applies to both paper and electronic records  [2.10]
Investigator Responsibilities

- Supervision of anyone delegated study tasks \[4.2.5\]
- Investigator must ensure any service provider \[4.2.6\]
  - Is qualified to perform duties assigned
  - Has implemented procedures to ensure integrity of
    o Tasks
    o Data generated
Investigator Responsibility Problems...

But doctor, the protocol says not to...

Bah! I'm a scientist! I don't need a protocol!!
Investigator Records and Reports\[4.9.0\]

- Investigator to maintain adequate and accurate source & trial documents, which are “ALCOAC”:
  - Attributable
  - Legible
  - Contemporaneous
  - Original
  - Accurate
  - Complete (new addition to FDA’s traditional “ALCOA”)
Sponsor Responsibilities — Quality [5.0]

• Outlines need for Quality Management System
• Specifies Risk-Based Approach, including:
  – Critical Process and Data Identification
  – Risk Identification
  – Risk Evaluation
  – Risk Control
  – Risk Communication
  – Risk Review
  – Risk Reporting

“QMS” might be new to many people, and like ISO 9001:2015, is to be based on quality being proportionate to the inherent risk of the trial and the importance of the data being collected.
Sponsor Responsibilities

- Sponsor oversight of CROs & other vendors [5.2.2]
- Documented approvals of CRO duties [TORO] [5.2.2]
- Computerized systems must have SOPs for [5.5.3]
  - System setup, installation & use
  - System validation, functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning and decommissioning
  - Responsibilities for sponsor, investigators & others
  - Training must be provided to users
- Ensure data integrity; metadata with any changes
Risk-Based Monitoring Approach Emphasized

- Systematic but flexible “RBM”
- Utilize centralized (remote) monitoring
  - Routine review of data
  - Identify missing or inconsistent data, outliers
  - Unexpected lack of variability
  - Systematic issues
  - Potential manipulation or data integrity concerns
  - Statistical trends, ranges and consistency
  - Site and other performance metrics
  - Site selection for targeted on-site monitoring
More on Monitoring

- Monitoring Reports [5.18.6]
  - Sent in timely manner to Sponsor
  - Copied to others responsible for oversight
  - Review reports and do follow-up as indicated
  - Reports documented in adequate detail to verify compliance with the Monitoring Plan

- Monitoring Plan [5.18.7]
  - Tailored to HSP needs and data integrity risks
  - Describe strategy, responsibilities, methods & rationale
  - Attention to critical data and processes; training
  - Reference applicable policies & procedures
Monitoring and Noncompliance

- Noncompliance has to “significantly affect” or have “potential to significantly affect” HSP or data reliability to generate need for actions
- Noncompliance means sponsors should:
  - Take prompt action
  - Perform root cause analysis (RCA)
  - Implement corrective and preventive actions (CAPA)
  - If required by applicable law or regulation, inform regulatory authority(ies) when noncompliance is a serious breach of trial protocol or GCP
  - Potentially terminate trial site or even entire study
Essential Documents \([8.1]\)

- Sponsor and Investigator/Institution should:
  - Maintain record of storage location(s)

- Storage system should provide for:
  - Document identification
  - Document search
  - Document retrieval

- Default Essential Document list may be
  - Inadequate for a specific study; require supplements
  - Sponsor and Investigator/Institution must include supplemental files in their Trial Master File (TMF)
Essential Documents

- Moving from paper to electronic documents
- Preparing the “Trial Master File” (TMF)
- Requirements by most regulatory authorities for submissions in the ICH Electronic Common Technical Document (eCTD) format (ICH M4)
Essential Documents at Sites [8.1]

- Sponsor must assure that Investigator
  - Has control of and continuous access to CRF data reported to Sponsor
  - Sponsor should not have exclusive control of those data
- Whenever a copy replaces an original, it should be a Certified Copy
- Investigator/Institution should retain control of all Essential Documents they generate before, during and after the trial
Remember, it’s GCRP!
We’re done. Now, wasn’t that pretty ...
That was it! All of the ICH E6(R2) GCP changes in a nutshell.

Now, let’s get back to what we were already doing: not just Good Clinical Practice (GCP) since before 1996, but Good Clinical Research Practice (GCRP)!

Thanks! Q&A time now.