Solutions for GCP Compliance Challenges

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IRB Brown Bag Session

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What are the GCP Compliance Challenges?

› Sources
  - OSI Metrics
  - FDA Warning Letters
  - Complaints by Sites/IRBs/Vendors
  - Sponsor Audit Observations
  - Monitoring Observations

What are the GCP Compliance Challenges?

› Size of the Organization/Staffing
› Investigator Oversight
› Qualifications and Experience of Site/CRO/IRB Staff
› Protocol Complexity
› Timelines, Milestones and Deliverables
› Regulations
› Culture
Inspections Overseen by OSI*
(CDER, FY 2005 - FY 2014)

- Postmarketing Adverse Drug Experience
- Risk Evaluation and Mitigation Strategy
- Good Laboratory Practice
- Bioequivalence
- Institutional Review Board/ Radiological Drug Research Committee
- Sponsor (GCP)
- Clinical Investigator

*Based on inspection start date – [OSI database as of January 20, 2015]
- IRB includes only CDER numbers – previously reported metrics may have used combined data across CDER, CBER and CDRH, Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
- Postmarketing Adverse Drug Event and Risk Evaluation and Mitigation Strategy inspection programs incorporated into OSI June 2011
**Bioresearch Monitoring Program Inspections* (CDER, FY 2014)**

*Based on inspection start date – [OSI database as of January 20, 2015]*

- IRB includes only CDER numbers – previously reported metrics may have combined data across CDER, CBER and CDRH

CDER numbers based on inspection start date – [OSI database as of January 20, 2015]
- CDRH numbers based on inspection end date, CBER numbers based on end date of classified inspections

**Clinical Investigator Inspections* (All Centers, FY 2014)**

*CDER numbers based on inspection start date – [OSI database as of January 20, 2015]*
- CDRH numbers based on inspection end date, CBER numbers based on end date of classified inspections

CDER 56%
- CBER 16%
- CDRH 28%

CDER 452
- CBER 131
- CDRH 220

Total 803
Clinical Investigator Inspections*
(CDER, FY 2005 – FY 2014)

*Based on inspection start date – [OSI database as of January 20, 2015]

Clinical Investigator Inspections Final Classification*
(FY 2014)

*Based on Letter Issue date; Includes OAI Untitled Letters, [OSI database as of January 20, 2015]
**International Clinical Investigator Inspections Final Class***
(CDER, FY 2014)

*Based on letter issue date; Includes OAI Untitled Letters. [OSI database as of January 20, 2015]*

- No Action Indicated: 62%
- Voluntary Action Indicated: 36%
- Official Action Indicated: 2%

116 Inspections

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**Frequency of Clinical Investigator-Related Deficiencies Based on Post-Inspection Correspondence Issued***
(CDER, FY 2014)

*Based on letter issue date; Inspections may have multiple deficiencies. [OSI database as of January 20, 2015]*

Note: this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed in FY2014.
Frequency of Clinical Investigator Related Deficiencies Based on Post-Inspectional Correspondence Issued: Official Action Indicated (OAI) Final classification*
(CDER, FY 2014)

- Protocol: 67%
- Records: 55%
- Submission of false information: 12%
- CI Supervision: 12%
- Drug Accountability: 9%

33 OAI Inspections

*Based on letter issue date. Inspections may have multiple deficiencies. Includes OAI untitled letters. [OSI database as of January 20, 2015]
Note that this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed in FY2014.

OSI Warning Letters*
(CDER, FY 2005 - FY 2014)

- Postmarketing Requirements
- Postmarketing Adverse Drug Experience
- Good Laboratory Practice
- Bioequivalence
- Institutional Review Board/ Radioactive Drug Research Committee
- Sponsor (GCP)
- Clinical Investigator

*As of June 2011, the Postmarketing Adverse Drug Event inspection program was incorporated into OSI
Includes Clinical Investigators, Sponsor/CRO/Sponsor-Investigator (GCP), IRB, BEQ, GCP, Adverse Drug Event (ADE) and Postmarketing Requirements (PMR) Warning Letters
PMR includes all required studies and clinical trials that are mandated by statute (e.g., section 505(o)(3) of FDCA, PRIEA, Animal Rule and 21 CFR 314 and 601 Subparts H and E, respectively.
During the 2nd quarter 2015, the FDA issued 173 warning letters (Apr 2015 – Jun 2015)
- April: 76
- May: 46
- June: 51

Of the 173 warning letters, 3 (2%) warning letters were issued in regard to GCP violations.

As of 26 July 2015, the web page had uploaded warning letters dated through 30 June 2015.

2Q2015 FDA Warning Letter Review

Taken from FDA’s website:
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/

Regulatory violations coded under 21 CFR Parts 50, 54, 56, 312, 314, 320, 812, and 814.
- These regulatory sections of the CFR encompass what is generally regarded as Good Clinical Practices (GCP).
2Q2015 FDA Warning Letter Review

The observations noted by the FDA:

Sponsor GCP Inspection

- 1. **Failure to submit an IND for the conduct of clinical investigations with an investigational new drug that is subject to 21 CFR 312.2(a) [21 CFR 312.20(a), (b) and 312.40(a), (b)].**
- 2. **Failure to ensure proper monitoring of the clinical investigations [21 CFR 312.50; 312.56(a)].**

Clinical Investigator GCP Inspection

- You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

2Q2015 FDA Warning Letter Review

The observations noted by the FDA:

Clinical Investigator GCP Inspection

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].
What does the FDA Expect?

› Take action immediately!
› Address the observations noted in the warning letter
› Provide specifics that can be verified at a later date
› The solution should correct the issue and prevent recurrence.

What does the FDA Expect?

*Taken from warning letters on the FDA’s website*...

*Your written response is inadequate because you did not include a copy of your proposed monitoring plans. As a result, we are unable to determine whether your plans appear sufficient to prevent similar violations in the future. In addition, please note that a sponsor may transfer its obligation to monitor to a contract research organization only, and any such transfer of obligations must be described in writing (21 CFR 312.52).*
What does the FDA Expect?

Taken from warning letters on the FDA’s website.

Your response is inadequate because you have not provided sufficient details about your corrective action plan. You have not provided adequate documentation of your efforts to address subject noncompliance (e.g., phone calls, oral reminders during the following clinical visit) in the source records. Without those details in the records, we are unable to determine whether your corrective action plan is adequate to prevent similar violations in the future.

What does the FDA Expect?

Taken from warning letters on the FDA’s website.

Your response is inadequate because you did not provide sufficient information to enable us to evaluate the adequacy of your corrective action plan for use in any future clinical research that you may conduct. It is unclear how adding a “clinical trials link” to your site’s EMR will ensure that protocol requirements will be met for studies conducted at your site. You did not provide any details of a corrective action plan to prevent similar violations from occurring in the future, nor have you provided sufficient details regarding your plan to implement additional measures and procedures to address the inspection findings. Without these details, we are unable to determine whether your corrective action plan appears sufficient to prevent similar violations in the future.
Solutions to GCP Compliance

a. Seek clarification from the Sponsor
b. Read and review the FDA’s warning letters
c. Conduct an investigation
d. Document and collect data
   - What are the best metrics?
e. Listen to your staff
f. Attend the protocol feasibility discussions
   - Does this work for your site?
g. Track and Monitor protocol deviations and violations
h. Institute QC/review practices
i. Train your staff (early and often)

The Solution: ACT

› As soon as you become aware of the issue/problem
› Consider the patients, customers and stakeholders
› Consider the risk associated with the issue/problem
› Seek long-term solutions that address the root cause of the issue

Assess / Audit
- Conduct independent audits
- Perform internal assessments

Collaborate/Correct
- Consult specialists
- Implement Corrective and Preventive Actions

Transfer Knowledge
- Share learnings
- Training sessions to reinforce
GCP Compliance Checklist

ACT!
Take Action!
Act now! ACT often!
Corrective Action!
Preventive Action!

GCP Compliance Checklist - ACT

1. **Assessment / Audit**
2. **Collaborate / Root Cause / Corrective Action / Preventive Action**
3. **Transfer Learnings / Training**
Thank You!

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