Managing an IRB for GCP Inspection / Audit

GCP Related Issues for IRB Management

or

“Areas for Improvement”

[GCP Findings from Audits and Inspections]

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Head, Clinical Quality Assurance, Asia Pacific, South Africa and India
Agenda

• Global IRB Findings (from Roche GCP Audits)
• CDER Inspections of IRBs in the US
• FDA Inspections in Asia Pacific - Roche Experience
• Criteria for FDA Acceptance of Foreign Non-IND Data
Global IRB Findings (1)

• Documents reviewed and / or approved not identified (by version / date etc.)
[ICH GCP 3.1.2 and 8.2.7]
  – So what was actually reviewed and approved ?
    Especially important for the ICF !

• Not all “written information” given to patients reviewed and approved [3.1.2 and 4.4.1]
  – So were the patients unduly influenced ?

• Payments / compensation to patients not reviewed and approved [3.1.2, 3.1.8 and 3.1.9]
  – Problems of coercion or undue influence ? – as above
Global IRB Findings (2)

• Qualification of PI inclusive CV not reviewed
  [3.1.2, 3.1.3 and 4.1.1]
  – How do we (surveyors / auditors / inspectors) know that the IRB knows
    this investigator?

• Submittance of e.g. Annual Reports not enforced –
  PI not reminded when “forgetting” to submit reports and / or no “penalty”
  [3.1.4 and 4.10.1]
  - Can the IRB perform an adequate “continuous review”? 

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Global IRB Findings (3)

• Inadequate composition [3.2.1]
  – Missing the non-scientific and / or independent member

• Or if part of IRB: not always present at meetings
  – Has the review been mainly scientific ?

• “Meetings” by email – not always Face to Face [3.2.3]
  – Has there been a possibility of free / unbiased discussions and deliberations ?
Global IRB Findings (4)

• Expedited review of approval procedure not specified [3.3.5]
  – How do we know who made a decision?

• Not timely in notifying decisions re. protocol amendment to the investigator [3.3.9]
  – Thus delaying implementation of any changes or updates of which had had the approval of the IRB

• Requirements & timelines for submitting ADRs / SAEs / SUSARs not specified [3.3.8 and 4.11.1]
  – How will the PI know what to submit when?
Global IRB Findings (5)

• Membership list does not always specify the period of the function [3.4]
  – How do we know that it is current?

• No written procedures! [3.2.2 and 3.3]

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• Observations that we can not put down as “findings” (no evidence or regulations)
  – “Rubber stamping” – no questions / comments at all
  – No follow-up or repercussion if late or no submissions of annual report, local SAEs etc
CDER Inspections of IRBs in the US
Classifications and Deficiencies for FY 2002-04 (and updates from 2006)

Personal communication for Dr. Johansen from

Good Clinical Practice Program

Office of Science and Health Coordination

Office of the Commissioner

U.S. Food and Drug Administration
FDA Recognizes the Importance of IRB Inspections to Implementing GCP

- FDA has inspected U.S. IRB’s since 1980
- FDA performs 250-300 IRB inspections per year from an inventory of approximately 1600
- 4-5% of inspections result in official action (OAI)
  - Required action is most typically a notification to FDA (15 days) of steps to come into compliance
  - In 3 cases (FY 99): Sanctions imposed
### Definitions of FDA Inspection Classifications

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAI</strong></td>
<td><strong>No Action Indicated</strong></td>
</tr>
<tr>
<td></td>
<td><em>(no significant findings)</em></td>
</tr>
<tr>
<td><strong>VAI</strong></td>
<td><strong>Voluntary Action Indicated</strong></td>
</tr>
<tr>
<td></td>
<td><em>(significant findings)</em></td>
</tr>
<tr>
<td><strong>OAI</strong></td>
<td><strong>Official Action Indicated</strong></td>
</tr>
<tr>
<td></td>
<td><em>(major / serious findings)</em></td>
</tr>
</tbody>
</table>
IRB Classifications
All Centers - FY’03

- NAI: 29%
- VAI: 63%
- OAI: 4%
- Pending: 4%

n = 317
IRB Deficiency Categories
FDA Inspections - CDER, FY 02-03

- Procedures: 34%
- Minutes: 17%
- Quorum: 15%
- Consent Form: 12%
- Cont Review: 8%
- Exp Review: 10%

n= 321
Common Deficiencies Found in Informed Consent Documents

- 50.25(a)(7) Identification of person to contact regarding research, rights and injury
- 50.25(a)(4) Incomplete description of alternative procedures
- 50.25(a)(5) Inadequate confidentiality statement
- 50.25(a)(1) Incomplete description of research procedures
- 50.25(a)(6) Incomplete description of compensation and treatment for research-related injury
IRB Classifications
FY 2004 – All Centers

NAI: 50%
VAI: 39%
OAI: 8%
Pending: 3%
n = 198
IRB Deficiencies
FY 2004

n = 133

CDER Assigned Inspections
IRB Inspections*- FY 2000 - 2006
Center for Drug Evaluation & Research

*Based on Inspection Start Date

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IRB Classifications
CDER Inspections – FY06

N = 109
IRB Deficiencies*
FY06: CDER

*Based on Letter Date

NAI: 57%
Records: 21%
Research Review: 15%
Operations: 15%
Expedited Review: 8%
ICD Elements: 6%
N=108

3/2/07

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US IRB’s: Observations as Symptoms

• Heightened Workload Pressures
  – Adverse event reports
  – Protocol amendments

• Limited Resources

• Limited Useful Feedback on Multi-Site Trials

• Limited Feedback on Problem Investigators

• IRB Membership
  – competing commitments; training
FDA Inspections in Asia Pacific (1)
Roche Experience

• X-country, November, 2004 (483 was issued)

“Failure to assure that an IRB, complying with applicable regulatory requirements, was responsible for the initial and continuing review and approval of a clinical study.

Specifically, the PI failed to ensure that there was at least an annual review of the clinical study performed by the Research Ethics Committee, IRB, on or prior to initial approval date of 1/24/02. The PI’s annual report dated 6/10/03 was approved by the Research Ethics Committee on 6/30/03”.
FDA Inspections in Asia Pacific (2)

• Y-country, December, 2004 (483 was issued)

“Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others (delay in months).”
Criteria for FDA Acceptance of Foreign Non-IND Data
(21 CFR 312.120 (updated as of 27 Oct, 2008) and 314.106)

• Ethics acceptable to the world community
• Protection equal or greater than the ICH-GCP (no ref to the DoH!)
• Trial well-designed and well-conducted
• Investigators qualified
• Trial approved by independent review committee
• Trial may be inspected*

(* only the clinical trial centre, no IRBs / IECs inspected outside of the US!)
THANK YOU