Building Quality into Clinical Trials and Avoiding Common Pitfalls

Michael E. Marcarelli, PharmD
Director, Division of Bioresearch Monitoring
Office of Compliance
Center for Devices and Radiological Health
US Food and Drug Administration
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OVERVIEW

• FDA Bioresearch Monitoring (BIMO)
• Data and trends
• Lessons learned…
Bioresearch Monitoring

• Known as BIMO
• Mandated by Congress in 1976
• Agency-wide program
• Inspection-based
FDA BIMO INSPECTIONS

• Four (4) Areas of Focus
  – Sponsor/Monitor/Contract Research Organization
  – Clinical Investigator (CIs)
  – Institutional Review Board (IRB)
  – Non-clinical laboratory (GLP)
TWO UNIVERSAL GOALS

• Human Subject Protection

• High Quality Data
Scientific Misconduct

Percentage in survey of US based scientists who engaged in questionable research practices

- 15.5% Changed a study’s results to satisfy a funding source
- 15.3% Dropped data from analyses based upon a “gut feeling”
- 12.5% Overlooked other’s use of flawed/questionable data
- 10.8% Withheld research results
- 7.6% Circumventing minor rules protecting humans subjects

Source: Nature June 2005

n = 3247
CDRH BIMO Inspections
Fiscal Years 2000 - 2004
Global Industry Issues

- Failure to identify and/or address issues
- Failure to correct recurring issues
- Failure to provide an accountable company culture
- Maintaining an environment of conflict of interest
CDRH Sponsor Compliance Rates

NAI, VAI, OAI
## Sponsor Deficiencies Fiscal Years 1998 - 2004

<table>
<thead>
<tr>
<th>Category</th>
<th>FY 1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
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<tbody>
<tr>
<td>Inadequate monitoring</td>
<td>63%</td>
<td>65%</td>
<td>68%</td>
<td>65%</td>
<td>33%</td>
<td>37%</td>
<td>40%</td>
</tr>
<tr>
<td>Failure to secure investigator compliance</td>
<td>33%</td>
<td>27%</td>
<td>44%</td>
<td>27%</td>
<td>19%</td>
<td>24%</td>
<td>21%</td>
</tr>
<tr>
<td>Inadequate device accountability</td>
<td>17%</td>
<td>23%</td>
<td>28%</td>
<td>19%</td>
<td>7%</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>Obtain FDA/IRB approval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4%</td>
<td>18%</td>
<td>11%</td>
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Investigator Deficiencies
Fiscal Years 1998 - 2004

<table>
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<tr>
<th>Issue</th>
<th>FY 1998</th>
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<th>2002</th>
<th>2003</th>
<th>2004</th>
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</thead>
<tbody>
<tr>
<td>Failure to follow investigational plan/regs</td>
<td>32%</td>
<td>46%</td>
<td>47%</td>
<td>44%</td>
<td>44%</td>
<td>51%</td>
<td>54%</td>
</tr>
<tr>
<td>Protocol deviations</td>
<td>21%</td>
<td>8%</td>
<td>26%</td>
<td>40%</td>
<td>20%</td>
<td>38%</td>
<td>16%</td>
</tr>
<tr>
<td>Inadequate subject protection/IC</td>
<td>24%</td>
<td>19%</td>
<td>21%</td>
<td>28%</td>
<td>21%</td>
<td>21%</td>
<td>24%</td>
</tr>
<tr>
<td>Inadequate device accountability</td>
<td>17%</td>
<td>17%</td>
<td>21%</td>
<td>27%</td>
<td>26%</td>
<td>18%</td>
<td>14%</td>
</tr>
<tr>
<td>Lack of FDA &amp;/or IRB approval</td>
<td>11%</td>
<td>9%</td>
<td>11%</td>
<td>5%</td>
<td>8%</td>
<td>13%</td>
<td>13%</td>
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</table>
CDRH BIMO Complaints
(Credible Allegations of Research Misconduct)

<table>
<thead>
<tr>
<th>Year</th>
<th>FY01</th>
<th>FY02</th>
<th>FY03</th>
<th>FY04</th>
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<td></td>
<td>9</td>
<td>15</td>
<td>41</td>
<td>41</td>
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</tbody>
</table>
CDRH BIMO COMPLIANCE RATES
(FY04: All Inspections vs. Complaints)

133% higher OAI rate in complaint follow-ups
Characteristics of Successful Firms

- Committed
- Responsive to public
- Use Risk Management
- Utilize Quality Systems
- Emphasize the basics
Winner of the "Not My Job" Award - ADOT
Litchfield Park, AZ 85
Responsiveness to Public

- Subject safety first = TRUST
- Respect for all subjects
- Info to subjects
- Understandable, transparent system
  - COIs, IRBs watching individuals, FDA running trials
- Ensure ethical conduct
- Rapid resolution and recognitions of problems – trial risk; subjects expect rapid assistance
Risk Management

• Greater risk gets greater attention
  – Safety monitoring, HSP, e-recordkeeping, pediatric subjects
  – Routine operations vs. serious adverse event reporting; more control needed in certain areas
  – Education enhanced websites & LDL
Quality Systems

• Difficult to inspect quality in (e.g., auditing)
• Quality must be built in
  – Systems approach
• Consistency (e.g., automation & standardization)
• Implement in a stepwise fashion
  – Build upon what exists
  – Focus first on areas of greatest pain and risk
  – Develop a sustainable program and culture
Emphasize the Basics

• Research subject protection measures
• Data quality?
  – Fitness for use
  – Meets customers needs
• What will FDA look at?
  – ALCOA
    » Attributable
    » Legible
    » Contemporaneous
    » Original
    » Accurate
Emphasize the Basics (cont)

• Less can be more….
  – Ex. 80 page IC; monitoring every data point

• Documentation vs paperwork
  – Who is it for and why?
  – Lack of understanding of the regs
  – Value to some not others
  – Fear (of what or why?)
SUGGESTIONS FOR A SUCCESSFUL STUDY

• Select qualified investigators
• Obtain investigator feedback on protocol requirements
• Provide adequate training up front
  – Stress importance of informed consent process
• Ensure adequate monitoring
• Bring investigators into compliance
QUALIFIED INVESTIGATORS

• Skills & experience appropriate for the device & its specific use in the study

• Adequate time, staff, equipment, & access to any specialized equipment required

• Knowledge of applicable regulations
PROTOCOL FEEDBACK

*When planning a study – consult potential investigators and others!*

• Inclusion/exclusion criteria appropriate & not unnecessarily restrictive
• Timing of procedures clinically appropriate
• Testing, initially & at follow-up visits, appropriate to the study endpoints
• Only essential data collected – errors estimated at 3%

INTERACTIONS UP FRONT CAN AVOID COSTLY PROTOCOL VIOLATIONS
TRAINING

Before study & when essential staff replaced

- Specific study expectations
- Procedures unique to the device or its use in the study
- Regulatory requirements
- Clinician versus Investigator
- Importance of the informed consent process
INFORMED CONSENT PROCESS

Well-informed participants:
- Understand study requirements up front
- Are less likely to drop out due to unexpected procedures
- Are more likely to be compliant with essential details
- Will promote confidence in research process
MONITORING

• Early & frequent enough for specific study
  – Early – ensures sites ready
  – Frequent – catches problems & noncompliance before repetitive
• Systemic issues can be corrected before study integrity is jeopardized
• Regular data audits avoid numerous queries & late database cleanup
• Training opportunities for new &/or non-compliant study staff or amended protocol
COMPLIANCE

• Predetermined strategy for obtaining
• Expeditious sponsor review of monitoring reports
• Immediate actions to correct noncompliance
• Where applicable, device shipments halted until evidence of compliance
• If all else fails, site’s participation in study terminated
To improve this picture, sponsors and institutions should:

• Seek training for their staffs
• Provide training for investigators
• Correct issues before they jeopardize submissions
• Focus company culture on good ethics and research practices
• Avoid potential conflicts of interest
CONTACT INFORMATION

mwm@cdrh.fda.gov

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring (HFZ-310)
2098 Gaither Road
Rockville, MD 20850