A Case Study: Building a Research Program that Minimizes Legal Risk and Maximizes Compliance

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The Backdrop

- Common themes prevailed in AHCs
  - Clinical Research had questionable academic value
  - Variable appreciation for the distinction between clinical practice and clinical research
  - Variable appreciation for the rules of engagement
  - Compliance expectations were perceived by those in Academia to be lower than those expected in Pharma
  - Variable PI and staff expertise and limited resources
  - Limited investment in infrastructure to support the enterprise
What Changed?

- Clinical Trials a way to differentiate competition in the health care market place
- Early phase of drug development occurring in AHCs with greater frequency
- Rapid growth in investigator initiated research
  - Manufacturing occurring in academia
  - Increase in number and complexity of financial conflicts of interest
  - Increase in management of multisite clinical trials

Past V.s Present: A Model of Integration/Collaboration

[Diagram showing integration and collaboration between different sectors]
Strategic Plan: Potential for Innovation

- Foster Clinical Trials
- Establish a Penn Venture fund to support early stage research
- Provide ‘one stop shopping’ to faculty for discoveries and start-up companies

Academic Translational Research

Partner with the private sector

Translate discoveries into effective therapies, devices, products

Research and development alliances

Improve the human condition

The Challenges/ Disincentives

- Culture - limited incentive for faculty to engage
- Administrative burden perceived to be inexorable
- Cumbersome approval processes
- Variably trained support staff with limited longevity
- Limited ability of community to leverage existing resources
- Funding for the support structure
- Interface of IT support systems
Recommendations of External Review

- Centralizing clinical research support services

- Adopting a service model for all functions that support principal investigators

- Investing in IT infrastructure to facilitate access to information and provide support tools that enable clinical research

- Establish a leadership position with accountable authority and responsibility to work across the institution to optimize clinical research standards at Penn Medicine

Evolution of Central Resources
Engaged Leadership and Implemented Oversight

Penn’s Clinical Research Portfolio
**Continued growth in clinical trial volume and complexity**

**Growth in # of INDs**

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<table>
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<tr>
<th># of protocols with &gt; 1 site relying on Penn IRB</th>
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<td>1 - 5 sites</td>
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<td>6-10 sites</td>
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<tr>
<td>11-20 sites</td>
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<tr>
<td>20-30 sites</td>
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<th># of active studies with Penn serving as IRB of record for other sites</th>
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<tr>
<th>Total # of additional sites relying on Penn</th>
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**Awareness of the Risk Proposition**

- **Study Subject Harm**
- **Reputational Risk**
  - Patient harm
  - Ethical considerations
  - Conflict of Interest
  - Policy and regulatory compliance
- **Financial Liability**
  - Study subject, funding agency
Followed by

- An FDA inspection..........

Clinical trials are complex and highly regulated

Standards are set by federal (FDA, OHRP, NIH, CMS) or state regulations and institutional policies

Focus of Risk Mitigation

- Financial Fraud
- Privacy & confidentiality
- Data integrity
- Patient Safety
Enabling Compliant Research – a shared responsibility

Institutional commitment

Mitigating risk

Investigators

Research support staff

Technology

Facilitation & navigation

Education & Training

Study Design

Create Study Documents

Establish research team

IRB / other? Review

IRB Approval

Notification to Regulatory Authorities

Final Report

Follow up Visit Activity

Statistical Review

Data Management

Study Auditing

Study Initiation

End of Trial

Prospective review (QC)

Retrospective Review (QA)

Patient Enrollment

Study Monitoring

Investigator meeting

Site Initiation

Clinical Trial Lifecycle – Where does the risk exist?
Another External Assessment...

- Organization and oversight
- Infrastructure (IT, space, personnel, and training)
- Clinical Trial review and approval process
- Conflict of interest policies
- Define metrics for tracking compliance goals
- Assess the need for ongoing external input
- Recommend the frequency of reports to Trustees

Key Observations

- Drug manufacturing and management of investigational products
- Academic Faculty serving as regulatory sponsors
- Oversight of clinical trial conduct – Monitoring and Auditing
- Education and retention of a trained workforce
- Prospective reimbursement analysis and its compliance oversight
- Clinical Trials.gov reporting requirements
- Conflict of Interest
Key elements of an effective compliance program include

- Establish standards and procedures to prevent and detect noncompliance.
- Exercise effective compliance oversight via engagement of multiple levels of management, including the board of directors, senior management and compliance personnel; organization’s governing authority must be knowledgeable about the content and operation of the compliance program.
- Exercise due diligence to avoid delegation of authority to individuals with a history of behavior inconsistent with an effective compliance program.
- Communicate and educate employees on relevant standards and procedures and other aspects of the compliance program.
- Monitor and audit compliance programs, evaluate periodically for effectiveness, and have and publicize a system for employees and agents to report or seek guidance regarding noncompliance without fear of retaliation.
- Promote and consistently enforce the compliance program via incentives and disciplinary measures.
- Respond appropriately to noncompliance and take steps to avoid future noncompliance, including making any revisions to the compliance program.

Penn Medicine Compliance Program

Educating Research Professionals

CR 101
E learning Module
Access Training

Entry Level
CRC A

Early Career
CRC B/C

Mid Career
CRC C
Project Managers
Reg Affairs specialist

Masters
Reg Affairs

Clinical Trials Risk Mitigation: Recommendations

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<thead>
<tr>
<th>Standardization and Oversight</th>
<th>Status</th>
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<tr>
<td>• Institute formal scientific reviews in Departments</td>
<td>○</td>
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<tr>
<td>• Increase consistency and transparency in COI policies and process</td>
<td>○</td>
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<tr>
<td>• Standardize process and coordinate oversight across Penn Med hospitals</td>
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| Compliance                                                                                      |        |
| • Bring Investigational Drug Service into compliance with “Good Manufacturing Practices”     | ○      |
| • Expand research compliance program                                                           | ○      |
| • Centralize and audit prospective reimbursement analysis                                      | ○      |
| • Monitor compliance with clinicaltrials.gov                                                   | ○      |

| Training                                                                                       |        |
| • Mandate training for investigators, sponsors, monitors                                      | ○      |
| • Reduce coordinator turnover through career advancement and training                         | ○      |
Three years later.... Improving... not there yet

The End Game

- Create a culture conducive to clinical research
- Demonstrate regulation and facilitation can coexist
- Enable entrepreneurial activity
- Create a workforce of skilled clinical and translational investigators
- Attract sponsors and commercial partners
- Measure impact