Clinical Trials: Changes and Challenges

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JKK Consulting, LLC
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'The Future Ain’t What it Used to Be…'
Agenda

- Clinical trial landscape
- Regulatory changes
- Investigators and sites
- Conclusions

Clinical Trial Landscape
R&D Operating Conditions

- Productivity is highly variable and trending downward
- Cycle times are not getting shorter
- R&D spending continues to rise 9-10% annually
- Success rates have been nearly constant for 60 years with less than 1 in 5 drugs that enter clinical testing receiving regulatory approval
- 130,000 jobs have been eliminated since the end of 2008 with 12% coming directly out of R&D

Source: Ken Getz - Tufts

Cost per NME Rising Dramatically

- 19% of INDs make it to market; but only 1 in 6 newly launched drugs will recoup their total investment in R&D
- $120 billion in patent protected revenue at risk between 2013-2018
  - New drug approvals during the next three years will only replace 40% of these sales
- Branded drug competition has shortened market exclusivity to two years or less

Source: EvaluatePharma; PwC
Pharmaceutical Industry Productivity

(New Drug and Biologic Approvals by Year)

Source: FDA

Pipeline Activity and Growth
R&D Spending

$ Billions


Source: CenterWatch

Drug Development Durations

(Cycle Time in Years from IND Approval to NDA Approval)

Source: Tufts, CSDD, CenterWatch Analyses
**PDUFA Costs – 2014 (2013)**

- NDA: $2,169,100 (1,958,800)
- Establishment: $554,600 (526,500)
- Product fee: $104,060 (98,380)

**Drug Failures in Phase II-III**

Phase II failures 2008-2010:
- Efficacy: 51%
- Strategic: 25%
- Safety: 19%
- Pharmacokinetics / Bioavailability: 1%

Phase III failures 2007-2010:
- Efficacy: 66%
- Financial and/or Commercial: 7%
- Not Enough Data: 6%
- Efficacy vs. Placebo: 32%
  - As add-on therapy: 29%
  - Versus active control: 5%

*Nature Reviews Drug Discovery 10, 328-329 (May 2011)*
*Nature Reviews Drug Discovery 10, 87 (February 2011)*
Devices

- Concept to approval: 4 to 10 years
- Costs: $5 to $300 million, depending on complexity and regulatory requirements
- FDA approvals: about 40 unique devices per year (plus about 3000 510K clearances)

Issues

- Sponsor / CRO partnerships
- Globalization
- Complicated protocols
- Subject recruitment
- Investigators
- Site performance
- Compliance
Doubling Worldwide Pre-Clinical and Clinical Development Capacity

Source: Tufts CSDD analysis of Major Pharma and CRO headcount data. Number of US CROs in 15 geographic regions.

Disbursement of Clinical Trials Globally

Source: Tufts CSDD
## The Globalization Tradeoff

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<th>W. Europe</th>
<th>N. America</th>
<th>Emerging Regions</th>
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<tbody>
<tr>
<td>Time to Site Activation (months)</td>
<td>8.4</td>
<td>6.2</td>
<td>17.5</td>
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<tr>
<td>Enrollment Rates (per month)</td>
<td>9.5</td>
<td>10.6</td>
<td>21.1</td>
</tr>
<tr>
<td>Average # of Evaluable Patients</td>
<td>7.4</td>
<td>6.1</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Source: CenterWatch, 2011 (N= 236 Phase III global trials)

## Regulatory Changes

- New Regulations
- New Guidance
- Draft Guidance
Regulation

Informed Consent: a New Element

As of March 7, 2011, there is a new consent element:

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Regulation: Disqualification of a Clinical Investigator

- Extends clinical investigator disqualification to include all FDA-regulated investigational products
- An investigator determined by FDA to be ineligible to receive a particular investigational product is also ineligible to receive any FDA-regulated investigational product

(April 2012)
<table>
<thead>
<tr>
<th>New Guidance Documents - Final</th>
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<tr>
<td>IRB Continuing Review After Clinical Investigation Approval – Feb 2012</td>
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<tr>
<td>Exception from Informed Consent Requirements for Emergency Research – Mar 2011</td>
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<thead>
<tr>
<th>New Guidance Documents - Final</th>
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<tbody>
<tr>
<td>Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND (Guidance for Clinical Investigators, Sponsors, and IRBs) (Sept 2013)</td>
</tr>
<tr>
<td>Electronic Source Data in Clinical Investigations (Sept 2013)</td>
</tr>
</tbody>
</table>
Guidance Documents - Draft

- IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed (Nov 2012)

Dialogues on Diversifying Clinical Trials

Successful Strategies for Engaging Women and Minorities in Clinical Trials

The Society for Women’s Health Research
United States Food and Drug Administration Office of Women’s Health

September 22-23, 2011
Washington, DC

Society for Women’s Health Research
Food and Drug Administration
SITES and INVESTIGATORS

Patient Recruitment

<table>
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<tr>
<th>Year</th>
<th>Mean Number of PIs per Active IND</th>
<th>Mean Number of Patients per NDA</th>
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<tr>
<td>1997</td>
<td>5.7</td>
<td>5,582</td>
</tr>
<tr>
<td>1999</td>
<td>8.0</td>
<td>5,435</td>
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<tr>
<td>2001</td>
<td>9.2</td>
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<td>2003</td>
<td>8.5</td>
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<td>2005</td>
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<tr>
<td>2007</td>
<td>11.2</td>
<td>2,186</td>
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<tr>
<td>2009</td>
<td>12.4</td>
<td>2,094</td>
</tr>
<tr>
<td>2011</td>
<td>12.9</td>
<td>2,103</td>
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</table>

Sources: Tufts CSDD
Active Unique Investigators
Filing Form 1572s World Wide

Source: FDA's Bioresearch Monitoring Information System File (BMIS)

Increasing Proportion of Novice Clinical Investigators

Source: CenterWatch analysis of FDA's BMIS database; Note: Experienced investigators conducted at least one study in the prior year
Growing Proportion of Community-Based Principal Investigators

Investigator Turnover Rates by Region

Source: FDA's Bioresearch Monitoring Information System File (BMIS)

Source: CenterWatch 2011
Investigative Site Performance - Enrollment

<table>
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<tr>
<th>Enrollment Speed</th>
<th>Percent of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of actual enrollment timeline being less than or equal to planned enrollment timeline</td>
<td>46%</td>
</tr>
<tr>
<td>Incidence of actual enrollment timeline being between 100% and 200% of planned enrollment timeline</td>
<td>39%</td>
</tr>
<tr>
<td>Incidence of actual enrollment timelines exceeding 200% of planned timeline</td>
<td>15%</td>
</tr>
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</table>

Source: Tufts CSDD, 2011  N= 15,965 global sites

Questions

- Why aren’t enrollment targets being met?
  - Study fit

- Are studies getting more complicated and harder to do than they used to be?
The Evolving ‘Typical’ Phase III Protocol

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2012</th>
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<tbody>
<tr>
<td>Total Number of Endpoints</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Total Number of Procedures</td>
<td>106</td>
<td>167</td>
</tr>
<tr>
<td>Total Number of Eligibility Criteria</td>
<td>31</td>
<td>50</td>
</tr>
<tr>
<td>Median Study Duration in Days</td>
<td>140</td>
<td>175</td>
</tr>
<tr>
<td>Total Number of Countries</td>
<td>11</td>
<td>34</td>
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<tr>
<td>Total Number of Investigative Sites</td>
<td>124</td>
<td>196</td>
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<tr>
<td>Total Number of Patients Randomized</td>
<td>729</td>
<td>597</td>
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<tr>
<td>Median Number of CRF Pages per Protocol*</td>
<td>55</td>
<td>180</td>
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<tr>
<td>Total Number of Data Points Collected per Protocol*</td>
<td>N/A</td>
<td>929,203</td>
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</table>

Source: Tufts CSDD; *Medidata

Protocol Scope/Endpoint Creep

Endpoints

- Primary
- Key Secondary
- Supporting, Tertiary, Exploratory

- 2004: 1 Primary, 4 Key Secondary, 4 Supporting, Tertiary, Exploratory
- 2012: 1 Primary, 6 Key Secondary, 7 Supporting, Tertiary, Exploratory

Source: Tufts CSDD
## Trends in Protocol Complexity by Phase

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
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<tbody>
<tr>
<td><strong>2011 Unique Procedures (median)</strong></td>
<td>30.3</td>
<td>29.2</td>
<td>28.4</td>
<td>26.4</td>
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<tr>
<td>10-Year Growth</td>
<td>35.3%</td>
<td>58.8%</td>
<td>43.0%</td>
<td>46.3%</td>
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<tr>
<td><strong>2011 Total Procedures (median)</strong></td>
<td>191.6</td>
<td>192.1</td>
<td>146.6</td>
<td>96.1</td>
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<tr>
<td>10-Year Growth</td>
<td>32.4%</td>
<td>64.1%</td>
<td>56.6%</td>
<td>62.6%</td>
</tr>
<tr>
<td><strong>2011 Total Work Burden (median)</strong></td>
<td>50.9</td>
<td>56.6</td>
<td>42.0</td>
<td>28.1</td>
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<tr>
<td>10-Year Growth</td>
<td>48.4%</td>
<td>73.1%</td>
<td>55.6%</td>
<td>56.9%</td>
</tr>
</tbody>
</table>


Source: Tufts CSDD

## The Impact of Protocol Complexity (In the Literature)

- Higher levels of study design complexity associated with poorer data quality and analysis *(Friedman et al. 2010; Nahm et al. 2008)*

- More procedures associated with higher incidence of unused data in the NDA submission *(Abrams et al. 2009)*

- More complex study designs are associated with lower levels of physician participation and referral rates *(Ross et al. 2004)*

- High study volunteer drop out rates are associated with complex protocol designs *(Andersen et al., 2009)*
Tufts CSDD Studies on the Impact of Complexity on Study Performance
(All TAs, Phases II-III)

| Study volunteer screen to completion rate | -50% |
| Time from Protocol Ready to FPFV (median) | +12% |
| Time from Protocol Ready to LPLV (median) | +73% |
| Number of Amendments | +68% |

Source: Tufts CSDD

And another ‘difficulty’ factor...

Standards for clinical care of patients ≠ Standards for FDA regulated research
The Clinical Investigator

- An individual who actually conducts a study (i.e. under whose immediate direction the drug is dispensed to a subject.)

- In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.

[21 CFR 312.3]
Sponsor-Investigator

- An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.
- The term does not include any person other than an individual.
- The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

[21 CFR 312.3]

Who’s in charge at the study site?

- Good News: Clinical investigators are in charge
- Bad News: Clinical investigators are in charge and held accountable

FDA regulations permit sponsors to delegate their responsibilities to Contract Research Organizations (CROs) but do not permit clinical investigators to delegate their general responsibilities to CROs or site management organizations, subinvestigators, or study staff.
Investigator Responsibility

Regulations are designed to:

- Ensure the quality and integrity of data collected in clinical trials
- Ensure that the rights, safety and welfare of research participants are protected

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that:

- The data and reported results are credible and accurate.
- The rights, integrity, and confidentiality of trial subjects are protected.
STATEMENT OF INVESTIGATOR

1. NAME AND ADDRESS OF INVESTIGATOR:

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION INCLUDING A STATEMENT OF QUALIFICATIONS:

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED:

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY:

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEWING AND APPROVAL OF THE STUDY:

6. NAMES OF THE INDIVIDUALS (e.g., research nurses, residents, assistants who will be assisting the investigator in the conduct of the investigation):

7. NAME AND CODE NUMBER (IF ANY) OF THE PROTOCOLS IN THE AID FOR THE STUDIES TO BE CONDUCTED BY THE INVESTIGATOR:

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:


   1. Complete all sections. Attach a separate page of additional space if needed.
   2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
   3. Attach protocol outline as described in Section 8.
   4. Sign and date below.

   INSTRUCTIONS FOR COMPLETING FORM FDA 1572 STATEMENT OF INVESTIGATOR:

   10. SIGNATURE OF INVESTIGATOR:

   WARNING: A false or forged signature is a criminal offense. U.S.C. Title 18, Sec. 1001.
Commitments on the 1572

- **Personally** conduct or supervise investigation.
- Follow protocol.
- Ensure all persons assisting is study are informed of their obligations.
- Inform subjects that drugs are being used for investigational purposes.
- Ensure informed consent (21 CFR Part 50) and IRB review, approval and reporting (21 CFR Part 56).
- Report to sponsor adverse events (21 CFR 312.64).
- Maintain adequate and accurate records and make them available for inspection in accordance with 21 CFR 312.68.
- Ensure initial and continuing review by an IRB and report all changes to research and unanticipated problems involving risks to subjects, not make any changes without IRB approval except where necessary to eliminate immediate hazards.
- Comply with other requirements in 21 CFR 312.

1572

- The 1572 Statement of Investigator form is a legal contract with the FDA.
- It must be filled out correctly and followed.
FDA INSPECTIONS

FDA Bioresearch Monitoring Program

- Inspections of clinical investigators, sponsors, IRBs, GLP facilities and Bioequivalence studies
  - Investigator shall permit the FDA to have access to, and copy and verify any records or reports made by the investigator (312.68)
- Types of inspection
  - Data validation in support of new drug application
  - For cause (complaint)
  - Surveillance
### 2012 Inspections

<table>
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<tr>
<th>Center</th>
<th>Investigator / Site</th>
<th>IRB</th>
<th>Sponsor / Monitor</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBER (Biologics)</td>
<td>93</td>
<td>14</td>
<td>4</td>
<td>111</td>
</tr>
<tr>
<td>CDER (Drugs)</td>
<td>383</td>
<td>88</td>
<td>57</td>
<td>528</td>
</tr>
<tr>
<td>CDRH (Devices)</td>
<td>194</td>
<td>56</td>
<td>44</td>
<td>294</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>670</strong></td>
<td><strong>158</strong></td>
<td><strong>105</strong></td>
<td><strong>933</strong></td>
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### BIMO Inspections Completed FY 2012

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<th>Center</th>
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<tr>
<td>CBER</td>
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<td>14</td>
<td>4</td>
<td>4</td>
<td>115</td>
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<tr>
<td>CDER*</td>
<td>383</td>
<td>88</td>
<td>57</td>
<td>36</td>
<td>564</td>
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<tr>
<td>CDRH</td>
<td>194</td>
<td>56</td>
<td>44</td>
<td>11</td>
<td>305</td>
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<td>CFSAN**</td>
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<tr>
<td>CVM</td>
<td>27</td>
<td>na</td>
<td>4</td>
<td>9</td>
<td>40</td>
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<tr>
<td><strong>All Centers</strong></td>
<td><strong>697</strong></td>
<td><strong>158</strong></td>
<td><strong>109</strong></td>
<td><strong>60</strong></td>
<td><strong>1024</strong></td>
</tr>
</tbody>
</table>
**Most Common CI Deficiencies**

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – including informed consent issues
Most common IRB deficiencies

- Inadequate initial and/or continuing review
- Inadequate SOPs
- Inadequate membership rosters
- Inadequate meeting minutes
- Quorum issues
- Inadequate communication with CI/institution

Specific to devices – lack of or incorrect SR/NSR determination

Most Common Sponsor/Monitor Deficiencies

- Inadequate monitoring
- Failure to bring investigators into compliance
- Inadequate accountability for the investigational product
- Failure to obtain FDA and/or IRB approval prior to study initiation
Warning Letter Excerpt

- You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].
- You failed to conduct the studies or ensure that they were conducted according to the signed investigator statement and the investigational plan, and to protect the rights, safety, and welfare of the subjects under your care [21 CFR 312.60].
- You failed to report promptly to the IRB all changes in the research activity [21 CFR 312.66].
- You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60].

- You failed to personally conduct or adequately supervise the clinical investigations [21 CFR 312.60].
- You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
- You did not return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59.

Warning Letters
9/28/12, 5/14/13, 6/5/13, 6/12/13

- You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
- You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation.
- You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60, 21 CFR 50.20].
- You failed to assure that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 was responsible for the initial and continuing review and approval of the proposed clinical study [21 CFR 312.66].
Recently found…

- Blind person consent
- Poor storage of study documents
- Coercive recruitment practices
- Absent investigator
- Investigator conflict of interest
- Lack of supervision, knowledge
- Where did the site go?

Common mistakes –

- Risk factors for non-compliance
  - Poor supervision and training of study staff
  - Insufficient investigator involvement in study conduct
  - Inappropriate delegation of study tasks to unqualified persons
  - Failure to adequate protect study subjects
  - Overworked investigator and study staff (e.g., too many subjects, complex study with large data collection, too many concurrent studies)
How can clinical investigators ensure high quality data and subject safety?

- Build quality into conduct of the study.
- Create systems that limit opportunity for errors.
- Standardize systems and formats were possible, use validated instruments and definitions.
- Check CRFs and consents against each change in the protocol.
- Insist on training and then test it (dry runs).
- Have a disaster plan, e.g. back ups if key study staff leave or site experiences flood or disaster.

- Select qualified staff and ensure adequate training and supervision.
- Ensure staff are not performing tasks they are not qualified to do (e.g. assessing eligibility, performing physical exams, assessing AEs).
- Ensure oversight of subinvestigators and study staff.
• Fully understand scope of responsibilities.
• Ensure protocol is consistent with the best interests of subjects and allows adequate monitoring for subject safety.
• Assess ability to comply with:
  □ Protocol visits
  □ Laboratory testing
  □ Electronic systems for data capture, archiving, and transmission to sponsor.
  □ Maintaining records, drug accountability, inspections by FDA

• Implement a system to detect and correct errors in real time.
• Pay attention to monitoring and data queries and respond promptly.
• Have an audit trail of changes to make clear what was changed, who changed it, and why it was changed.
• Evaluate need for system wide corrections and training.
• SOPs – have them and use them
SUMMING UP…

Key Messages

- Clinical trials are increasingly more complicated and more difficult to do.
- Clinical investigators play a critical role in ensuring high quality studies.
  - Good care of patients is not the same as Good Clinical Practices (GCP) in research.
  - Ensure that all staff have a clear understanding of responsibilities under FDA regulations.
  - Think about and follow 1572 responsibilities.
Key Messages

- At stake is public confidence and participation in clinical trials
  -- and ultimately --
- The availability of safe and effective products

‘If you don’t know where you’re going, you might wind up someplace else!’