Current Status of Clinical Research in India

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Clininvent Research Pvt Ltd
The police called. We're taking you out of the clinical trial and putting you in a criminal trial.
In human affairs, political, social, economic and business it is pointless to try to predict the future, let alone to look ahead 75 years. But it is possible and fruitful to identify major events that have already happened, irrevocably, and that therefore will have predictable effects in the next decade or two. It is possible, in other words, to identify and prepare for the future that has already happened.

Peter Drucker 1998
India was ranked 2 in overall attractiveness based on patient pool / cost efficiency / regulatory conditions / relevant expertise / infrastructure / environment (AT Kearney 2007)
Lost Decade: Incredible India?

Good News is No News!

Parliament Questions

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Number of Industry Trials (Clintrials.gov)
Korea

- KoNECT, the South Korea National Enterprise for Clinical Trials
- 124 Korean FDA accredited sites
- Standardization and harmonization of IRBs
- FERCAP Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) recognized ECs 26
India – Big focus on Potential
Little Focus on Quality

- Large naïve population of patients
- Focus on speed and cost
- Lack of ethics committee oversight
- Lack of regulatory inspections
- Compensation – foot ball between all stakeholders!
ANYONE GOING SLOWER THAN YOU
YOU CALL AN IDIOT.
ANYONE GOING FASTER THAN
YOU, YOU CALL A MANIAC!
…..quality suffers from the focus on speed and on “hard deliverables.

Pierre Azoulay 2003
National Bureau Of Economic Research
# US FDA Marketing Applications 2008

<table>
<thead>
<tr>
<th>Trial Location</th>
<th>Number of Subjects</th>
<th>Number of Sites</th>
<th>Average Number of subjects per site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philippines</td>
<td>367</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>China</td>
<td>424</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>409</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Brazil</td>
<td>1863</td>
<td>187</td>
<td>10</td>
</tr>
<tr>
<td>Poland</td>
<td>1849</td>
<td>194</td>
<td>10</td>
</tr>
<tr>
<td>Russia</td>
<td>1226</td>
<td>141</td>
<td>9</td>
</tr>
<tr>
<td>South Africa</td>
<td>1140</td>
<td>130</td>
<td>9</td>
</tr>
<tr>
<td>India</td>
<td>384</td>
<td>49</td>
<td>8</td>
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<tr>
<td><strong>Foreign Countries</strong></td>
<td><strong>52820</strong></td>
<td><strong>6129</strong></td>
<td><strong>9</strong></td>
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<tr>
<td><strong>USA</strong></td>
<td><strong>40039</strong></td>
<td><strong>5098</strong></td>
<td><strong>8</strong></td>
</tr>
</tbody>
</table>
Recruitment Challenges

• Consent (Gitanjali 2003)
  – Only 30% of subjects are likely to give consent to participate in a trial

• Complex protocol impact (Getz 2008)
  – Screen to randomized dropped from 75% to 59%
  – Randomized to study completion dropped from 69% to 48%
Funnel of Patient Recruitment

Potential: 100
Consent: 30
Randomized: 18
Completed: 9
Privatization of Clinical Trials

Public Hospitals
- Academic Researcher
- Disinterest
- EC Bureaucracy

Private Hospitals
- Researcher / Trialist
- Practice vs Recruitment
- Budget

Private Clinics
- Trialist
- Experience
- EC
- Safety
Quality in India: Trickle Down Effect?

- Global trials for USFDA / EMA
- Indian trials for new Indian molecules
- Indian trials for local registration
GCP: Standard of Compliance

Compliance

Data Integrity

Human Protection

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New GCP: Choose Any Two?

Good

Cheap

Presto
Compliance Tug of War

Good Clinical Practice

Great Challenge to Current Practice
Evolution of Ethics and Regulatory Guidelines

- 1947 : Nuremberg code
- 1964 : Declaration of Helsinki
- 1979 : Belmont Report
- 1996 : ICH Guidelines
- 2000 : ICMR guidelines
- 2001 : Indian GCP guidelines
- 2005 : Revision of Schedule Y
- 2006 : Revision of ICMR Guidelines
- 2008 : Revision Declaration of Helsinki
- 2010 : GCP for ASU Medicines
- 2011-12 : CDSCO guidelines
"It's safe to come out - the auditors have gone."
India : US FDA Inspections

- Total 41
  - NAI 23 (56%)
  - VAI 18 (44%)
    - Failure to obtain and/or document subject consent
    - Inadequate drug accountability
    - Failure to follow investigational plan
    - Inadequate and inaccurate records
    - Failure to notify IRB of changes, failure to submit progress reports
1. Consent forms and the actual implementation of the consent process during the study.
2. Method of monitoring the adverse events and the serious adverse events and remedial measures for such events.
3. Inclusion of vulnerable tribal population group.
4. Blurring of distinction between National Immunization Program and study.
5. Insurance coverage for the study participants.
6. Free supply of vaccine by the manufacturer and the statement in the consent forms that “you will not be charged for your daughter to receive the vaccine” that could be considered to be convert inducement and indirect coercion.
CDSCO : Inspection Findings (2)

• Consent
  – non-maintenance of original Informed Consent Form
  – discrepancies

• EC approval
  – discrepancies
  – decision making process
  – quorum of the Ethics Committee not as per Sch Y no lay person / legal expert present
CDSCO : Inspection Findings (3)

- Serious adverse events
  - non-payment of compensation
  - non-reporting of serious adverse events
- Case Record Form
  - non-maintenance of original CRF
  - irregularities in transcribing data from original source documents
- Monitoring discrepancies
- Trial in unapproved indication
THINK GLOBALLY,
ACT LOCALLY,
PANIC INTERNALLY
Recent Regulatory Reaction

- Parliament
- Press
- PIL

Regulatory Authority

Guidance / Office orders
Penal action threat
Regulatory Reaction

• New Drug Approval Committees
• Compensation *Come What May You Pay*
• Registration of EC
• Committees
  – Supervision Of Clinical Trials Of NCEs
    • Apex committee
    • Technical committee
  – Formulation of policies and SOPs for approval of new drugs, clinical trials, banning of drugs and FDCs
    • Expert committees
• Inspections
New Drug Approval Committee

• Mandate to conduct
  – In-depth evaluation of non-clinical and clinical data on the investigational product
  – Review of risk: benefit to the patient
  – Assessment of unmet medical need in India
  – Innovation vis-à-vis existing therapy

• Process inefficient and time consuming

New Delay Approval Committee
Clinical Trials Approved in India

<table>
<thead>
<tr>
<th>Year</th>
<th>number of applications</th>
<th>permissions granted</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>492</td>
<td>488</td>
</tr>
<tr>
<td>2010</td>
<td>546</td>
<td>529</td>
</tr>
<tr>
<td>2011</td>
<td>306</td>
<td>283</td>
</tr>
<tr>
<td>2012</td>
<td>480</td>
<td>253</td>
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</table>
Current Concerns

<table>
<thead>
<tr>
<th>Concern</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory approval</td>
<td>Delays and uncertainties</td>
</tr>
<tr>
<td>Compensation rules</td>
<td>Irrational and stringent</td>
</tr>
<tr>
<td>Registration of EC</td>
<td>Disapproval of some ECs</td>
</tr>
<tr>
<td>Clinical trial sites</td>
<td>Disapproval of private sites</td>
</tr>
<tr>
<td>Inspection process</td>
<td>Quality and Transparency</td>
</tr>
<tr>
<td>Expert committee</td>
<td>New policies / procedures</td>
</tr>
</tbody>
</table>
Current Status of Clinical Trials

- Quality
- Cost
- Speed

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Status Quo to Quotable Status

- **Quality**
  - Accreditation of all stakeholders
  - EC oversight and monitoring at site
  - Regulatory inspections

- **Speed**
  - Efficient NDAC process
  - Time bound regulatory approvals

- **Cost**
  - Rational compensation guidance
Paradigm Shift

Training

Registration

Accreditation

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Accreditation Approach

Policy
- Principle
- Process
- People
- Performance

Institute
Ethics Committee
Investigator
Research Staff
Although the public holds positive attitudes about the general importance of clinical research, the same cannot be said for public trust in the professionals who oversee, manage and support research. Distrust in clinical research professionals and those organizations responsible for ensuring patient safety, has increased dramatically.

Dr Ken Getz Monitor Sep 2008
The Communication Gap

- Public largely receiving a one-sided education about clinical trials
- Medical professionals / Academia not active in public awareness
- Industry avoids media out of fear
- Government silent spectator
Communication

Stakeholders
- Government / Academia / Industry

Media
- Television / Print / Electronic

Message
- Value and need for clinical trials
- Regulatory mechanisms for human subject protection
Future … depends on Us

There are three types of people in this world:
those who make things happen,
those who watch things happen and
those who wonder what happened.
- Mary Kay Ash