Clinical Research in Japan:
From Academic Research Organization

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Clinical research-supporting infrastructure at academia

Keio’s experience so far

General issues & challenges
Clinical research support at academia
Planning & conducting clinical research to meet global standard

- Increasing complexity
- Stricter regulations and guidelines to abide by
- Multifaceted functions & expertise required: so far very limited availability
  - Trial design & protocol drafting
  - Biostatistical considerations
  - Operational aspects: contract, budget management, enrollment, monitoring,
  - Data management: CRF, data capturing etc.
  - Informed consent
Setting up a research support organisation

3-year MHLW grant to implement clinical research infrastructure

Clinical investigators

Supporting staffs

- Administrative assistants
- Data managers
- Biostatisticians
- Research coordinators/research nurses
More support required for Japanese investigators

Clinical investigators at Japanese academia:

- Atrocious clinical duty
- Very limited availability for research, basic or clinical
- Higher education for clinical research: almost nonexistent until fairly recently
  - Trial design, protocol drafting, power calculation, case report form, data management, regulations, informed consent, medical writing etc.
- Clinical research coordinators: mostly preoccupied with industry-sponsored trials
Clinical research support at Keio

• Before a study initiates:
  − Consultation for study design, sample size estimation, ethical consideration
  − Protocol drafting
  − CRF design
  − Liaise with industry to prepare contract etc

• During the study:
  − Data management
  − Allocation, study drug and sample delivery
  − Enrollment support by research nurses
  − Adverse event reporting

• After the study
  − Frozen data → statistical analysis
**N of clinical trials at Keio (ongoing + new)**

(1) Industry-sponsored clinical trials for NDA

<table>
<thead>
<tr>
<th>Year</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>119</td>
<td>120</td>
<td>122</td>
<td>126</td>
<td>117</td>
</tr>
</tbody>
</table>

(2) Investigator-initiated clinical research

<table>
<thead>
<tr>
<th>Year</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>74</td>
<td>142</td>
<td>167</td>
<td>196</td>
<td>170</td>
<td>187</td>
<td>215</td>
</tr>
</tbody>
</table>
Ongoing support for Inv.-initiated trials at Keio

1. Long-term comparative trial for antihypertensive agents (122/230 pts enrolled):
2. A comparative trial on chronic hepatitis
3. Endoscopic biopsy trial for inflammatory bowel disease
4. Post-operative trial on Crohn’s disease
5. Comparative trials on relapse ovarian cancer: contract clinical trial
6. Comparative trial on functional dyspepsia
7. Steroid-induced osteoporosis
8. Pulmonary hypertension associated with autoimmune diseases
9. Comparative oncology trial on non-small cell lung cancer
10. Comparative trial on the effect of a new rehabilitation programme for ambulatory disability
11. Trial on dose-reduction of antipsychotic agents for schizophrenia
12. Chemotherapy trial for oesophageal carcinoma
13. Comparative chemotherapy trial for colorectal cancer
14. Observational study on gastrointestinal complication by low-dose aspirin after MI/stroke
15. Comparative chemotherapy trial for ovarian cancer
16. Multinational trial to assess diagnostic reliability of new radiological procedure (40 pts to be enrolled at Keio)
17. Trial to assess diagnostic reliability for HPV infection
18. Comparative trial on metastatic brain tumor (operation plus irradiation)

(as of August 2009)
## Operational improvement in sponsored clinical trials

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>New global trials (total new sponsored trials)</td>
<td>1 (42)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Acceptance of English documents, inspections</td>
<td>None</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Acceptance of documents by mail</td>
<td>Only partial</td>
<td>Always accepted</td>
</tr>
<tr>
<td>Application ~ IRB approval</td>
<td>Min. 60 days</td>
<td>Min 8 days</td>
</tr>
<tr>
<td></td>
<td>(CRA visit: 4 times)</td>
<td>(Visit: once)</td>
</tr>
<tr>
<td>IRB approval ~ Test drug delivery</td>
<td>Min. 7 days</td>
<td>Min. 0 day</td>
</tr>
<tr>
<td>Drug delivery ~ First Pt In</td>
<td>43 (331 ~ 0)</td>
<td>25 (338 ~ 0)</td>
</tr>
<tr>
<td>Average study budget per Pt</td>
<td>Ca 1.83MM JPY</td>
<td>Ca 1.35MM JPY</td>
</tr>
<tr>
<td>Incentive towards patients in trial</td>
<td>None</td>
<td>Priority in checking out</td>
</tr>
<tr>
<td>EDC usage in sponsored trials</td>
<td>7%</td>
<td>19%</td>
</tr>
<tr>
<td>CRC support for investigator initiated trials</td>
<td>None</td>
<td>Available</td>
</tr>
</tbody>
</table>
## Inv.-initiated study vs sponsored trials: a significant disparity

<table>
<thead>
<tr>
<th></th>
<th>Inv.-initiated Study</th>
<th>Sponsored pre-NDA trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall objective</td>
<td>Directly related to clinical questions</td>
<td>More driven by market needs</td>
</tr>
<tr>
<td>Likely targeted disease</td>
<td>Severe, Tx-resistant rare disease, smaller pt population</td>
<td>Common disease with large pt population preferred</td>
</tr>
<tr>
<td>Financial background</td>
<td>Often underfinanced</td>
<td>Sufficient in-house budget</td>
</tr>
<tr>
<td></td>
<td>• Public research grant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Private research grant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Donation</td>
<td></td>
</tr>
<tr>
<td>Academic quality</td>
<td>• Varied</td>
<td>• Rigorously examined by in-house experts, regulatory agency, academicians</td>
</tr>
<tr>
<td></td>
<td>• Dependent upon in-house experience</td>
<td></td>
</tr>
<tr>
<td>Operational quality</td>
<td>Varied</td>
<td>Established</td>
</tr>
<tr>
<td>Regulation</td>
<td>MHLW guideline (2009)</td>
<td>Pharm. affiars law, GCP</td>
</tr>
<tr>
<td>Manpower, infrastructure</td>
<td>• Improvement under way</td>
<td>• Well-established</td>
</tr>
<tr>
<td></td>
<td>• Still insufficient</td>
<td>• Outsourced when necessary</td>
</tr>
</tbody>
</table>
## How to finance clinical research

Global-standard complex trials: more costly, requires better funding

<table>
<thead>
<tr>
<th>Source</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Governmental research funding</td>
<td>• Little COI</td>
<td>• Usage tightly restricted</td>
</tr>
<tr>
<td>(MHLW, MEXT)</td>
<td></td>
<td>• Cannot cover expenses over fiscal years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Highly competitive</td>
</tr>
<tr>
<td>Donation</td>
<td>• Flexible utilization</td>
<td>• Transparency questionable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Difficult to manage COI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unknown breakdown</td>
</tr>
<tr>
<td>Contract</td>
<td>• Transparent</td>
<td>• Limited precedents in Japan</td>
</tr>
<tr>
<td></td>
<td>• Equal partnership</td>
<td>• Mixed views within industry</td>
</tr>
<tr>
<td></td>
<td>• Clear break-down</td>
<td></td>
</tr>
</tbody>
</table>
Establishing research contracts with industry

- Better funding source for academia
  - More transparent collaboration, with COI better managed
- Suitable to estimate, in a pilot fashion, efficacy not tested by industry but recognised clinically
  - e.g. Malignancy with limited patient population
    - Testing drugs hard to develop for limited sales forecast
- Indispensable to acquire true-to-life clinical data on approved drugs
University of Minnesota Research Services Organization

- Established in 1997 to improve efficiency & invite industry-sponsored trials
- Major objectives: to improve and boost
  1. IRB activities
     - 600 protocols reviewed per annum as of 2008
     - 23 IRB admin staffs to support weekly IRB (35 members to rotate)
  2. Industry-sponsored clinical trials
  3. NIH-funded, investigator-initiated clinical research
- Initial contact to Site ready: 6~9M → within 3M
- Major activities
  1. Clinical trial support: CRC, regulatory affairs, administrative assistance: 60~100 protocols per annum
  2. Higher education for CRCs
  3. Establishment of a shared drive containing trial-related documents and materials to improve accessibility
- Running cost
  - 1/3~1/4: payment from industry for trial assistance (contract)
  - The rest: from within University
Issues and Challenges: summary

Clinical research supporting functions: crucial

- How to finance
  - Internally (intramural)
  - Externally (extramural)
    - Governmental grants
    - Research contract from industry
    - Outsourcing clinical research to academic research organisation: much more cost-effective than CROs

- How to appoint, train & develop appropriate staffs
  - Better exchange in between academia, industry and government needed
A fundamental challenge

**How to justify more investment in clinical research?**

- More resources into clinical research is needed
- Japanese health care system as a whole faces grave shortage in resources