Multi-Regional Clinical Trials
: Operational Aspects
based on Korean Experience

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Objective of ICH

The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.
Drug Lag in Asian countries

Launch Drug Lag from Initial Country (2007)

Top sales 100 products in 2007 (10 were excluded due to old insufficient data),
MRCT (Multiregional clinical trial) can be one of solutions to reduce the drug lag

- Globalization of clinical trials is a reality.
- MRCT may cover different ethnic groups and different regions.
- MRCT may start simultaneously.
- Data from MRCT may be used for regulatory submission of different countries.
- Subset data from MRCT may be used as bridging data.

→ MRCT has opportunities/benefits and also challenges
Opportunities of MRCT

- Faster enrolment of subjects
- Usually cheaper with sites in emerging countries
- Trial sites in emerging countries have benefits
  - Access to innovative medicine
  - Development and training of staffs at sites
- Learn each other
- Improve quality
Challenges of MRCT

- From Government/Regulatory agency
- From the Investigator/Trial site perspective
- From the Patient perspective
- From the EC/IRB perspective
- From the Sponsor perspective
Other types of Challenges

- Different medical practice and local culture
- Different life style and diet
- Different concomitant diseases and medications
- Variation of regulatory and ethics approvals
- Relationship between investigators and subjects
- Central vs Local Lab
- Way of monitoring / Audit / Inspection
- Difficulty in supply chain and logistics
- Language
- ....
MRCT

- MRCT including emerging countries are challenging and rewarding
- Effort for decreasing differences and increasing similarities
- Better and careful panning with consideration of all related matters
- More frequent communication and close monitoring
- MRCT can be managed better with improving some of factors

→ Korean Case
A Korean case
: Changes in number of clinical trials in Korea

KFDA database

- Overall Number of Trials
- Multinational Trials


Number of Trials:
- Overall: 0, 5, 10, 17, 46, 61, 143, 136, 185, 218, 281, 400
- Multinational: 31, 33, 45, 55, 147, 216
Changes of Multinational clinical trials in Korea

2004 → 2008; 272.4% increment
- yearly 38.9% increase

- 2009 expectation 300
### Oncology Trials

#### Geographic locations of oncology trials initiated in 2004 and 2007.

**Source**: TrialTrove (accessed May 2006)

<table>
<thead>
<tr>
<th>Region</th>
<th>2004</th>
<th>2007</th>
<th>Difference</th>
<th>Percent change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America</strong></td>
<td>623</td>
<td>794</td>
<td>171</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Rest of World</strong></td>
<td>718</td>
<td>858</td>
<td>140</td>
<td>19%</td>
</tr>
<tr>
<td>Asia</td>
<td>86</td>
<td>129</td>
<td>43</td>
<td>50%</td>
</tr>
<tr>
<td>Australia</td>
<td>51</td>
<td>79</td>
<td>28</td>
<td>55%</td>
</tr>
<tr>
<td>South America</td>
<td>47</td>
<td>51</td>
<td>4</td>
<td>9%</td>
</tr>
<tr>
<td>Africa</td>
<td>23</td>
<td>26</td>
<td>3</td>
<td>13%</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>81</td>
<td>84</td>
<td>3</td>
<td>4%</td>
</tr>
<tr>
<td>New Zealand</td>
<td>13</td>
<td>9</td>
<td>-4</td>
<td>-31%</td>
</tr>
<tr>
<td>Middle East</td>
<td>28</td>
<td>23</td>
<td>-5</td>
<td>-18%</td>
</tr>
<tr>
<td>Latin America</td>
<td>33</td>
<td>23</td>
<td>-10</td>
<td>-30%</td>
</tr>
<tr>
<td>Western Europe</td>
<td>338</td>
<td>281</td>
<td>-57</td>
<td>-17%</td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>**</td>
</tr>
<tr>
<td>South Korea</td>
<td>18</td>
<td>48</td>
<td>30</td>
<td>167%</td>
</tr>
<tr>
<td>Philippines</td>
<td>4</td>
<td>10</td>
<td>6</td>
<td>150%</td>
</tr>
<tr>
<td>China</td>
<td>16</td>
<td>31</td>
<td>15</td>
<td>94%</td>
</tr>
<tr>
<td>Japan</td>
<td>23</td>
<td>39</td>
<td>16</td>
<td>70%</td>
</tr>
<tr>
<td>India</td>
<td>18</td>
<td>29</td>
<td>11</td>
<td>61%</td>
</tr>
<tr>
<td>Malaysia</td>
<td>5</td>
<td>8</td>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>Pakistan</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>50%</td>
</tr>
<tr>
<td>Singapore</td>
<td>18</td>
<td>25</td>
<td>7</td>
<td>39%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>22</td>
<td>29</td>
<td>7</td>
<td>32%</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>19</td>
<td>25</td>
<td>6</td>
<td>32%</td>
</tr>
<tr>
<td>Thailand</td>
<td>13</td>
<td>12</td>
<td>-1</td>
<td>-8%</td>
</tr>
</tbody>
</table>

**Note**: Data may not be exhaustive.
Number of Studies in Asia
(09.2005-10.2007)

Number of protocols registered with ClinicalTrials.gov between Oct. 2005 and Sep. 2007

Source: Clinical Trial Magnifier Vol. 1:5 May 2008
www.ClinicalTrialMagnifier.com
Active Asian Cities in Clinical Trials

The top 10 most active Asian cities conducting industry sponsored clinical trials.

Source: Clinical Trial Magnifier Vol. 1:5 May 2008
www.ClinicalTrialMagnifier.com
Factors to increase MRCT in Korea

1. Strong government initiative
   - Government’s R&D strategy
   - Favorable regulatory environment
     • Changes in regulation in clinical trials
     • Parallel IND and IRB process
     • Reduced IND review period
   - KoNECT

2. Excellent sites and investigators

3. Qualified and well operating IRBs

4. Improving quality

5. Availability of CROs

6. Investment from sponsors

Continuous expansion of investment and creation of next-generation growth engines

### Pan-ministry policies

- **'83 legislated Genetic Engineering**
- **'94 Establishment of 1st phase BioTech2000**
- **'94 Establishment of 2nd phase BioTech**
- **Pursued next generation growth engine industries (bio new medicine · organs)**

### Aggressive R&D investment

[Chart showing investment increase by an annual average of 30% from '95 to '06]

- **'95:** 868
- **'99:** 1,608
- **'01:** 3,791
- **'03:** 5,302
- **'06:** 8,021

[Unit: KRW 100million]
Government’s R&D Strategy

National Technology Roadmap in Sept. 2002

- Clinical Trial Technology: capacity building

1. Developing Formal/Systematic Educational Programs
   - Clinical Investigators, Clinical Pharmacologist, Clinical Trial Pharmacist,
     CRA, CRC, IRB members, Regulatory personnel etc.

2. Establishing Center of Excellence for Clinical Trials

3. Standardization of IRB Operation, and Quality Assurance/Accreditation mechanism

4. Good Regulatory & Review Practices: based on sound regulatory sciences

5. Improving Global Communications

6. Improving Public Awareness
Government R&D Strategy

Presidential Committee on Healthcare Industry Innovation (醫療產業先進化委員會)
- Presidential Decree No. 156 (Aug. 2005.)
- chaired by prime minister
<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec 1987</td>
<td>KGCP established</td>
</tr>
<tr>
<td>Oct 1995</td>
<td>KGCP Enforced &amp; implemented</td>
</tr>
<tr>
<td>Jan 2000</td>
<td>Revision of KGCP in accordance with ICH-GCP</td>
</tr>
<tr>
<td>2001</td>
<td>Introduction of Bridging Study</td>
</tr>
<tr>
<td>Dec 2002</td>
<td>Separation of IND/NDA</td>
</tr>
</tbody>
</table>
Favorable Regulatory Environment in Clinical Trial

**IND Process**

Pre-IND Consultation → IND Submission → KFDA Review → IND Approval

- Protocol
- CMC
- Preclinical
- Clinical
- IB

**30 working days**

**Total approval timeline**: 30 days

**IRB Process**: parallel review with RA process

IRB Submission → IRB Committee → IRB Approval

- Protocol, ICF (Translated), CRF
- IB
- CV

**2-4 weeks**

**Contract With Hospital** → Study Initiation
Favorable Regulatory Environment in Clinical Trial

Reduced IND approval time

KFDA database
Korea National Enterprise for Clinical Trials (KoNECT)

2007. 12 – 6 years program

- **RCTC : 15 Regional Clinical trial centers**
  - 6 more CTC (2008, 2009)

- **Clinical Trials Professional Training Academy**
  - 12 Center of Excellence in Education & Training
  - Clinical Investigators, Clinical Pharmacologist (domestic/oversea)
  - CRA, CRC, CT Pharmacist
  - Pharmaceutical Medicine
  - Biostatistician, Pharmacovigilance, DB manager

- **New innovative technology development & Propagation**
  - 10 -15 Centers of Excellence in new technology
  - 6 major technologies related critical path.
2. Excellent sites and Investigators

Seoul National Uni. Hospital (SNUH)
Younsei Uni. Medical Center (YUMC)
Samsung Medical Center (SMC)
Asan Medical Center (AMC)

<table>
<thead>
<tr>
<th></th>
<th>Licensed Beds</th>
<th>Outpatients /day</th>
<th>Doctors</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNUH</td>
<td>1763</td>
<td>5663</td>
<td>1126 (Faculty 336)</td>
</tr>
<tr>
<td>YUMC</td>
<td>1841</td>
<td>5076</td>
<td>883 (Faculty 428)</td>
</tr>
<tr>
<td>SMC</td>
<td>1348</td>
<td>5520</td>
<td>820</td>
</tr>
<tr>
<td>AMC</td>
<td>2181</td>
<td>6633</td>
<td>1180 (Faculty 305)</td>
</tr>
</tbody>
</table>
Clinical Trial Center at sites

Regional Clinical Trial Center Network Program
- KMHW: spreading state of art environments

- 2004 – 2 centers
- 2005 – 4 centers
- 2006 – 3 centers
- 2008 – 6 centers
3. Qualified & Well-Operating IRBs

KAIRB (Korean Association of IRBs)

- Established in March 2002 to organize IRB education, enhance review capacities, and foster IRB networking.
- Published *Guidelines for Establishing and Operating IRBs* in Korean: February 2003
- Annual workshops for IRB members.

Some clinical trial centers achieved the accreditation by AAHRPP (Association for the Accreditation of Human Research Protection Program) / WHO FERCAP (Forum for Ethical Review Committee in Asia and the Western Pacific Region)
4. High quality of clinical trials

: Guideline for Designation of Institutions for Clinical Study

Purpose

To assure the quality of clinical study and site

Standard

- Appropriate facilities and equipments
- Resource pool to support clinical studies
- Activities of IRB
- Education program of GCP
- Structures and activities to manage clinical studies
## Qualified Institutional Pool

### Previous:

<table>
<thead>
<tr>
<th>Class</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>32</td>
<td>85</td>
<td>107</td>
</tr>
<tr>
<td>Dental Hospital</td>
<td>1</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>33</strong></td>
<td><strong>91</strong></td>
<td><strong>113</strong></td>
</tr>
</tbody>
</table>

Number of accredited hospitals

**Current:** No classification depending on the phase

Qualified Institution are increased to 127 as of Oct. 2008
Educational course for clinical trial Professions by KoNECT

- Catholic U
- Samsung Medical Center
- Yonsei U
- Seoul National U
- 6 University Hospitals
  - Kyungbuk National U
  - Inje U Busan Paik H
  - Kyunghee U
- Clinical Pharmacologists
- Clinical Investigators
- Pharmaceutical Medicine
- Pharmacoepidemiology/Biostatistics/DB management
- Trial Pharmacists
- Clinical Research Coordinators
- Clinical Research Associates(CRA)
- International Collaboration
- Fellowship Program in foreign/Domestic Institution (2008. 10 -)

- total 19 programs; 900 trainees/year
5. Availability of CROs

Domestic CRO

C & R Research

Medihelpline
IBioPharm (Preclinical)
ADMKorea

Global/Regional CRO

Quintiles
CMIC
ICON
PPD
COVANCE
pharm net

Apex
Novortec
Paraxel
Choice Pharma
6. Investment from sponsors

- Clinical Trial Investment US $10 MIL. for 3 years in SNUH
- Clinical Trial Investment US $20Mil. for 3 years
- R&D Investment US$ 26 MIL. for 3 years
- MOU between AZ and Ministry of Health & Welfare (05 April 2006)

Clinical Study Investment US $ 19 MIL. In 2006

Total Clinical Trials : 216
New progress

- CTN will be implemented
- Mutual recognition between IRBs
  → Central IRB
- Medical reviewers in KFDA
- NE Asian Tripartite Health Ministers Meetings
In Summary

- MRCT is for globalization of clinical trials and for ICH.
- Drug lag in Asia can be reduced by MRCT.
- With collaboration of stakeholders we can have better environment of MRCT.
- More progress will be made for facilitating MRCT in Korea.
Thank you for your attention!