Conducting Clinical Trials in China: Advantages and Challenges

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## Outline

### A few facts about China
- Population
- GDP growth

### TB in China
- Huge patient population

### Conducting Clinical Trials In China
- Challenges: language / regulatory
  - largest TB cases in the world
- MDR-TB in China

### Strategies
- Work closely with the government
- Culture and relationships
Beijing is the capital and Shanghai is the largest city
Population

China / Population

1.357 billion (2013)

- China: 1.357 billion
- India: 1.252 billion
- United States of America: 316.5 million
GDP Growth in China
Monthly Salary of a Retired Village Teacher in China (in USD) – an example
Tuberculosis – A Forgotten Plague

- The deadliest killer in human history
- By the beginning of the 19th century, tuberculosis had killed $\frac{1}{7}$ of all the people who’d ever lived.

- Captain of death
- Consumption
- Wasting disease
- Run in families
- Romantic disease
A Romantic Disease

- Pale
- Slender figure
- Rosy cheeks
- Big eyes
- Romantic sensibility
- Spread among intellectuals and artists.

ROMANTICIZING TUBERCULOSIS: POETRY, PROSE, OPERA, AND SOCIETY OF THE ROMANTIC ERA by Gabriela Gordon Martinez
https://digital.library.txstate.edu/bitstream/handle/10877/4661/MartinezGabriela.pdf?sequence=1

Figure 1: An image from Ladies Monthly Museum in September, 1825. It depicts the ideal slender, pale figure with rosy cheeks.
A Romantic Disease (1800-1882)

- Slender / Pale / Rosy cheeks
- Consumption / white plague / white death
- Associated with poetic and aesthetic qualities
- Associated with arts, music, and literature
- Until the cause of the disease was discovered
- From a mysterious disease to being an infectious disease

Eleanor Roosevelt
Vivien Leigh
Andrew Jackson
Jane Austen
2/3 of MDR TB cases in 3 Countries
Urban/rural Population Distribution

http://www.chinability.com/Population.htm
Urban and rural population of China from 2004 to 2014 (in million inhabitants)
The Largest Human Migration in the world

In 2015, an estimated 1.3 billion trips were made, while 325 million people travelled across China during the week of Spring Festival.

http://www.1421.consulting/2015/03/the-largest-human-migration/
Poverty Cycle

1. **TB**
2. **Poor**
3. **Cost for Treatment**

The cycle shows how TB can lead to poverty and increased costs for treatment, which can then exacerbate poverty.
TB is a Disease of Poverty

94% of TB cases and 98% of TB deaths occur in developing countries. Moreover, it often affects the poorest of the poor within those countries.
Tuberculosis in China

- In 2003, China accounted for 17% of the total global TB burden, making it the second most TB-prevalent country in the world after India (WHO, 2004).
- In 2005, the estimated incidence of TB in China was 100 per 100,000, and the prevalence was 208 per 100,000 (WHO, 2007b).
- More than 5% of all TB cases are multidrug-resistant, which is defined as being resistant to at least isoniazid and rifampin (WHO, 2007b).
- The TB prevalence in rural areas, where almost 80% of the population resides, is almost twice that in urban areas. Consequently, TB is one of the top 10 leading causes of death in rural China (X. Liu, 2004).
TB Hospital in ZhuHai City, China
Why High MDR-TB Rate in China?

- Inadequate use of TB medication in public hospitals
- Insufficient treatment supervision
- Ineffective drug management and a lack of infection control
- The availability of TB drugs without a prescription
- Ignorance
- Poverty
- Stigma
China’s Army of Graduates Struggles for Jobs

http://www.nytimes.com/2010/12/12/world/asia/12beijing.html?_r=1
### 2013 年估算结核病负担（WHO）
Estimated TB Burden in China (WHO, 2013)

<table>
<thead>
<tr>
<th></th>
<th>发病 Incidence</th>
<th>死亡 Death</th>
<th>患病（菌阳） Prevalence (Bact +)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>全球 (Global)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>人数 No.</td>
<td>8.60million</td>
<td>0.94</td>
<td>12million</td>
</tr>
<tr>
<td>率（1/10万） 1/100000</td>
<td>122</td>
<td>13</td>
<td>169</td>
</tr>
<tr>
<td><strong>中国 (China)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>人数 No.</td>
<td>1 million</td>
<td>44000</td>
<td>1.40million</td>
</tr>
<tr>
<td>率（1/10万） 1/100000</td>
<td>73</td>
<td>3.2</td>
<td>99</td>
</tr>
<tr>
<td>类别/Case category</td>
<td>耐多药率MDR-TB rate(%)</td>
<td>广泛耐药率XDR-TB rate(%)</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------------</td>
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</tr>
<tr>
<td>新病人/ New cases</td>
<td>5.71</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>复治病人/Retreatment cases</td>
<td>25.64</td>
<td>2.06</td>
<td></td>
</tr>
<tr>
<td>所有病人/All cases</td>
<td>8.32</td>
<td>0.68</td>
<td></td>
</tr>
</tbody>
</table>
Currently Recommended TB Treatment

Initial Phase
- INH
- RIF
- PZA
- EMB

Continuation Phase
- INH
- RIF

Extended If
- Cavity on CXR
- Culture positive
- at 2 months

Month: 1 2 3 4 5 6 7 8 9
No New TB Drugs Over the Last Few Decades

TB Drug Development Milestones:

1944 | Streptomycin
1949 | P-Aminosalicylic Acid
1952 | Isoniazid
1954 | Pyrazinamide
1955 | Cycloserine
1962 | Ethambutol
1963 | Rifampicin

“TB is the only disease where people can go hibernation for decades and wake up with no changes” – Margaret A. Hamburg
Tuberculosis: NIH and NIAID Funding

- NIH
  - $199M (FY2011 est.)

- NIAID
  - $157M (FY2011 est.)

$665,000 in 1985

Five Key Factors in Clinical Trials

- Infrastructure
- Regulatory conditions
- Patient Availability
- Cost-efficiency
- Expertise
Conducting Clinical Trials in China

- China has risen to be number 5 drug market across the world
- Almost all global companies have activities and operation centers in China
- Ranked to be the best place for clinical trials surpassed India despite regulatory barriers
- Domestic pharmaceutical companies grow rapidly (revenue from 10 million to 1 billion – government provides huge funding)
China 'most attractive' offshore clinical trial location
By Kirsty Barnes, 04-Jan-2007

- China topped a new list of the most attractive low-cost global locations to run clinical trials outside the US.
- China, despite its bureaucracy, government red tape and questions over intellectual property, has stolen the top spot from India who is seemingly more active in this arena and more in tune to the needs of the West.

China 'most attractive' offshore clinical trial location (2)
By Kirsty Barnes, 04-Jan-2007

- Clinical trials account for two thirds of the development cost for new drugs and off shoring to locations outside the US is becoming a common way to help pharma firms keep costs down by providing access to a new range of patients, aiding recruitment.

- India and Russia trailed China in the poll, with Brazil and Czech Republic following closely behind.
Why China being “most attractive” in clinical Trials?

• Largest urban patient population in the world
• Vast patient pool /recruitment rate high
• A huge network of hospitals with over 2.5 million doctors, nurses, and technicians
• Significantly lower salaries than their western counterparts
• Many more reasons -

Advantages Conducting Trials in China

1. Cost-effectiveness (1/2 or 1/3 cost of US)
2. Improved regulatory environment
3. Large patient population
4. Hospital (site) readiness
5. Experienced PIs
6. Rapid enrollment
7. Supportive team work / participants – physician relationships
8. Enthusiasm of participants
9. China is in great need of collaboration and cooperation from foreign countries
HPTN 058 Accrual Projections

A Phase III Randomized Controlled Trial to Evaluate the Efficacy of Drug Treatment in Prevention of HIV Infection and Death Among Opiate Dependent Injectors
HPTN 058 Accrual by County

Number of Participants

Country

China

Thailand

708

202

Generated Date: 12/27/2010
HPTN 058 Accrual by Site

Accrual by Site for Protocol HPTN 058 (10144)

No. of Participants

Sites

Generated Date: 12/27/2010
Dedications of Site Staff

- Work many hours per day – no vacations or holidays
- Leaders are highly involved and provide direct guidance
- Community support
Challenges Conducting Clinical Trials in China

1. Dose differences due to different ethnicity
2. Concurrent alternative medicines
3. Ethical committees
4. Regulatory barriers
5. Language Translation needed
6. Culture differences
7. Training/oversight/monitoring
Language Translation Needed

- Simultaneous translations for training and workshops
- Protocol translations
  - EAE manual
  - Grading table
  - All forms
  - Example of HPTN 058 (all translations done by the site PI in a very timely fashion)
# Regulatory Challenges

## Differences Between CFDA and FDA

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>CFDA</th>
<th>FDA</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>State Food and Drug Administration</td>
<td>Food and Drug Administration</td>
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</table>

<table>
<thead>
<tr>
<th>Focus</th>
<th>CFDA</th>
<th>FDA</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Generic drugs</td>
<td>New drug applications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major emphasis</th>
<th>CFDA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Importation of drugs and small scale of domestic development</td>
<td>All IND and NDA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regulatory approval relies on</th>
<th>CFDA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Existing data and clinical trial experience</td>
<td>Independent new data from new trials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Center of attention</th>
<th>CFDA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Manufacturing of drugs</td>
<td>Approval new drugs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IND review timeline</th>
<th>CFDA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Was one year – now 3 months</td>
<td>One -3 month</td>
</tr>
</tbody>
</table>

[http://www.medpace.com]
## CFDA Recent Improvement in Regulatory Environment

<table>
<thead>
<tr>
<th>Before</th>
<th>Now</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use SFDA guidelines</td>
<td>Adopting more and more ICH guidelines and FDA regulations</td>
</tr>
<tr>
<td>No pre-IND meetings</td>
<td>Many pre-IND meetings if requested</td>
</tr>
<tr>
<td>Less open to sponsors</td>
<td>More dialogs and meetings with sponsors; participate international meetings</td>
</tr>
<tr>
<td>Review takes long time</td>
<td>Faster turn-over time</td>
</tr>
<tr>
<td>No training events</td>
<td>Sponsored /cosponsored many workshops on GCP, GLP, ICH. GMP for the SFDA reviewers, principle investigators, CROs, and other staff</td>
</tr>
</tbody>
</table>

http://www.medpace.com
CFDA New Initiatives

- Adopts ICH and FDA guidelines with the increase of western companies
- Accepts pre-meetings and consolations
- Participating international meetings such as DIA and AAPS
- Science-based approaches
- Trainings / workshops to promote ICH, GMP, GLP, and GCP
FDA Inspections of China sites and CROs

- In 2009, FDA inspected three pre-clinical CROs and one bioanalytical lab. All were satisfactory.
- In 2009, FDA conducted eight clinical site inspections. All were satisfactory.
- Conclusion: clinical sites in China are capable to conduct GCP standard and reinforce it by US FDA or EMEA.
WHO Reports in 2008:

World-wide per year:
- 9 million new TB cases (Incidence rate 100/100,000 and prevalence rate 208/100,000 in China)
- 500,000 new MDR-TB (or ~5% new cases)
- 40,000 XDR-TB

WHO Releases Report on Global Scale of Drug-Resistant TB
[Feb 27, 2008]
What Has Chinese Government do to Fight TB?

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991–2000</td>
<td>The Second National Tuberculosis Program, implemented that set new national targets for TB control and increased directly observed treatment short-course (DOTS) coverage in urban and rural areas (Zhao et al., 2003)</td>
</tr>
<tr>
<td>2003–2004</td>
<td>Chinese government committed to meeting global targets for TB diagnosis and treatment by the end of 2005 (WHO, 2005b)</td>
</tr>
<tr>
<td>End of 2005</td>
<td>China reached the global targets of 70% case detection and 85% treatment success (WHO, 2007b).</td>
</tr>
</tbody>
</table>
Bill Gates Joins China's TB Control Efforts

Chen Zhu
Chinese Health Minister

Bill Gates
Bill & Melinda Gates Foundation
China is a "perfect laboratory" for large-scale testing of new tools and delivery techniques to fight TB because of “its skill, its scale, its TB burden, its love of innovation and its political commitment to public health.”

Bill Gates, Beijing, April 1, 2009

http://news.xinhuanet.com/english/2009-04/01/content_11113696.htm
Gates Foundation Provided 33 Million US Dollars to:

**Introduce** new diagnostics and new drugs, patient monitoring strategies and new approaches to help patients complete treatment
Officials from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, and from China’s Henan Provincial Bureau of Health will meet in Zhengzhou, China, on April 29 to sign an implementation arrangement intended to foster research on tuberculosis, including clinical research on new treatments for multidrug-resistant tuberculosis (MDR TB). The Henan Provincial Bureau of Health and the NIAID plan to develop jointly a collaborative TB research program at the Henan Provincial Chest Hospital.
NIAID TB Project in China

**Study**

- Tuberculosis in China

**Objectives**

- To improve TB diagnosis and testing by determining the number and proportion of patients admitted with suspected TB who actually have TB (definite or probable).
- To assess the prevalence of non-tuberculosis bacteria among patients with presumed TB

**Location**

- Henan Provincial Chest Hospital (estimate enrollment 210)
China TB Clinical Trials Consortium (CTCTC)

• Members: Hospitals that are CFDA certified or in the process of being certified TB clinical and research institutions.

• Purpose: To bring together best national TB medical facilities and serve as an international platform for TB clinical trials on prevention, treatment, and diagnosis strategies.
CTCTC Leadership Groups

- **Chair:** Xu Shaofa
- **Vice Chair:** Li Liang (executive)
- **Secretariat:** Liu Yuhong, Jiang Xiaoying, clinical trial focal person from each of member hospitals
Beijing Chest Hospital, Capital Medical University
Beijing TB & Thoracic Tumor Research Institute
Clinical Center on Tuberculosis, China CDC (CCTB)
WHO Collaborating Centre for Research and Training on TB
Beijing Chest Hospital
Chengdu Public Health Clinical Center
Shanghai Pulmonary Hospital
Shandong Chest Hospital
The Map of 16 CTCTC Member Hospitals

Complete Sites List

<table>
<thead>
<tr>
<th>Sites assessed in 1st round</th>
<th>Sites assessed in 2nd round</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Beijing Chest Hospital, Beijing</td>
<td></td>
</tr>
<tr>
<td>2  Tianjin Chest (Haihe) Hospital, Tianjin</td>
<td></td>
</tr>
<tr>
<td>3  Shandong Provincial Chest Hospital, Jinan</td>
<td></td>
</tr>
<tr>
<td>4  Shanghai Chest Hospital, Shanghai</td>
<td></td>
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<tr>
<td>5  Shanghai Public Health Clinical Center, Shanghai</td>
<td></td>
</tr>
<tr>
<td>6  Chongqing Tuberculosis Institute, Chongqing</td>
<td></td>
</tr>
<tr>
<td>7  Changsha Central Hospital, Changsha</td>
<td></td>
</tr>
<tr>
<td>8  Chengdu Infectious Disease Hospital, Chengdu</td>
<td></td>
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<tr>
<td>9  Shenzhen Donghu Hospital, Shenzhen</td>
<td></td>
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<tr>
<td>10 Guangzhou Chest Hospital, Guangzhou</td>
<td></td>
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<tr>
<td>11 Wuhan Tuberculosis Institute, Wuhan</td>
<td></td>
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<tr>
<td>12 Shenyang Chest Hospital, Shenyang</td>
<td></td>
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<tr>
<td>13 Fuzhou Pulmonary Hospital, Fuzhou</td>
<td></td>
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<tr>
<td>14 Xinxiang No. 1 People’s Hospital, Xinxiang</td>
<td></td>
</tr>
<tr>
<td>15 Zhenjiang No. 3 People’s Hospital, Zhenjiang</td>
<td></td>
</tr>
<tr>
<td>16 Shanxi Provincial Tuberculosis Institute, Xi’an</td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of Dr. Liang Li (Sep. 2015)
Anthony S. Fauci - March 24, 2011

“I look forward to a future when US-China leadership in combating TB, through concrete projects such as our joint research partnership in Henan, makes significant, transformative advances in the diagnosis, treatment, and management of TB worldwide.”
“I am in the process of exploring the possibility… of utilizing our HIV/AIDS clinical trials networks for the implementation of similar clinical trials capacities for TB as well as other infectious diseases.”

--- Pacific Health Summit, June 17, 2009
DAIDS/NIAID TB Clinical Research Team
Countries with NIAID HIV/AIDS Clinical Research Sites

~600 sites in 49 countries

February 2012
Joint Effort Combating TB
GCP Training in Beijing, 2009
GCP Training in Beijing, 2009
Take Home Message

- China has the large patient population
- High quality, low cost, and quick turn-over clinical trials can be conducted in China
- Extensive trainings and oversight maybe needed
- China is a great opportunity for CT, but many challenges exit.

Effective communication is the key for success
CMA and NIH jointly organized a workshop “Building a Partnership for Clinical Research Programs for TB” in April 15, 2011
President Obama Calls for Comprehensive Global Health Strategy

“Too many still die from diseases that shouldn’t kill them.”
-Ghanaian Parliament Address, July 2009

“We cannot wall ourselves off from the world and hope for the best, nor ignore the public health challenges beyond our borders. . . The world is interconnected, and that demands an integrated approach to global health.”
-Global Health Initiative Statement, May 2009

President Barack Obama at NIH, September 2009
Pudong in Shanghai