

# Clinical Trial Capacity and New Drug Reviews Related to MRCTs in Taiwan

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# Outlines

- Clinical Trial Capacity in Taiwan
- New Drug Reviews in Taiwan
- MRCT: Regulators' Perspective in Taiwan

# Clinical Trial Capacity in Taiwan

1. General clinical trial environment in Taiwan
2. National Research Program for Biopharmaceuticals (NRPB) as an example
3. Clinical Trial Center in NTUH as an example

# Milestone of Clinical Trials Regulation in Taiwan

- 1996 Guidance for Industry: Good Clinical Practice
- 1998 GCP inspection started
- 1998 CDE established (non-governmental organization)
- 2003 Guidance of Institutional Review Board  
Organization & Operation
- 2003 Structure & Content of Clinical Study Reports
- 2005 Guidance of Good Clinical Practice (revision)
  
- Currently 17 official regulatory statutes (法規) for IND  
(investigatory new drug) announced by Ministry of Health and  
Welfare (MOHW)

# Clinical Trial Study Site & Investigators

- Clinical trial study site (for new drug investigations) must be qualified as teaching hospital by Ministry of Health and Welfare (MOHW)
- Total 131 study sites (hospitals) as of 2013
- Principle investigators (PIs) must be qualified
- Periodic accreditation of IRBs by MOHW
- Two study sites accredited by AAHRPP
- 23 IRBs was certificated by FERCAP

AAHRPP: Association for the Accreditation of Human Research Protection Program

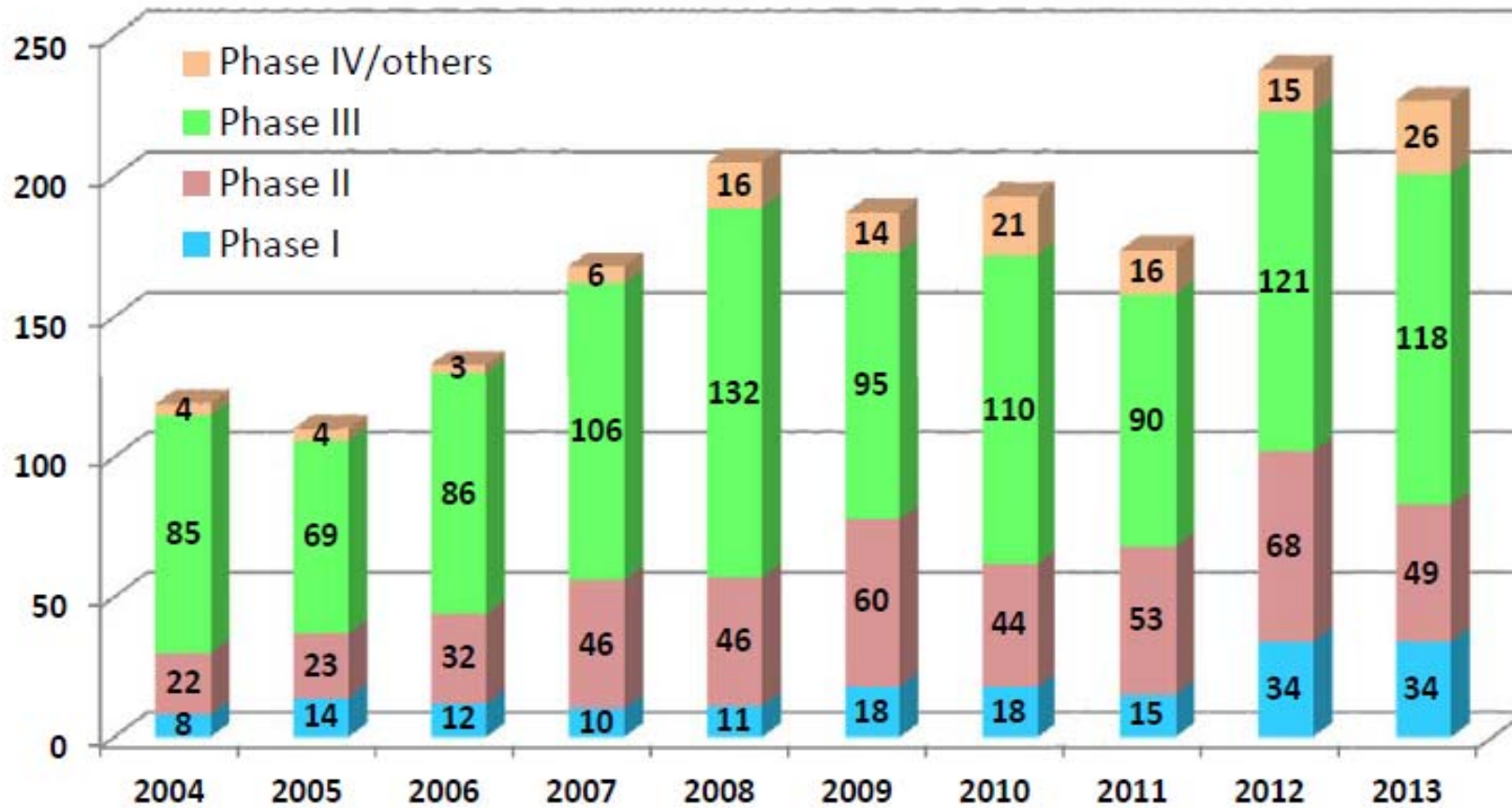
FERCAP: Forum for Ethical Review Committees in the Asian & Western Pacific Region

# Distribution of Study Sites

- 22 Medical Centers and 8 Centers of Excellence for Clinical Trials
  - Taiwan Clinical Trial Consortium (TCTC) in 12 TA such as Lung Cancer, Breast Cancer, GI and Helicobacter, Pediatric Infection, Oncology Phase I Trials...
  - Central-IRB with 7 Authorized Medical Centers
  - Clinical Trial Joint Review with 17 Hospitals
- 2 AAHRPP Accredited



# IND Number and Distribution



# National Research Program for Biopharmaceuticals (NRPB)

- Launched in 2011
- Objectives
  - (1) to develop a fully-integrated biopharmaceutical pipeline
  - (2) to set up an National-wide network
  - (3) to strengthen the biotech industry value
  - (4) to accelerate commercialization
  - (5) globalization of research output via international cooperation
  - (6) Establish platforms for translational medicine
- NRPB Clinical Trial Consortium (TCTC)  
Program Director: Dr. Pan-Chyr Yang



# NRPB Clinical Trial Consortium

 <p>肺癌臨床試驗聯盟 Lung Cancer Consortium</p>	 <p>胃腸疾病與幽門桿菌合作聯盟 Gastrointestinal Disease &amp; Helicobacter Consortium</p>	 <p>肝炎及肝癌臨床試驗聯盟 Liver Disease Consortium</p>
 <p>乳癌臨床試驗合作聯盟 Breast Cancer Consortium</p>	 <p>高血壓相關疾病聯盟 Hypertension &amp; Cardiac Disease Consortium</p>	 <p>慢性阻塞性肺病聯盟 Pulmonary Disease Consortium</p>
 <p>婦科癌症研究聯盟 GYN Oncology Consortium</p>	 <p>血脂和動脈粥樣硬化聯盟 Lipid and Atherosclerosis Consortium</p>	 <p>精神疾病臨床試驗聯盟 Mental Disorders Consortium</p>
 <p>癌症早期臨床試驗聯盟 Oncology Phase I Consortium</p>	 <p>小兒感染症聯盟 Pediatric Infectious Diseases Consortium</p>	 <p>成人感染症臨床試驗聯盟 Adult Infectious Diseases Consortium</p>
 <p>中風臨床試驗聯盟 Stroke Consortium</p>	 <p>腎臟疾病臨床試驗聯盟 Renal Diseases Consortium</p>	

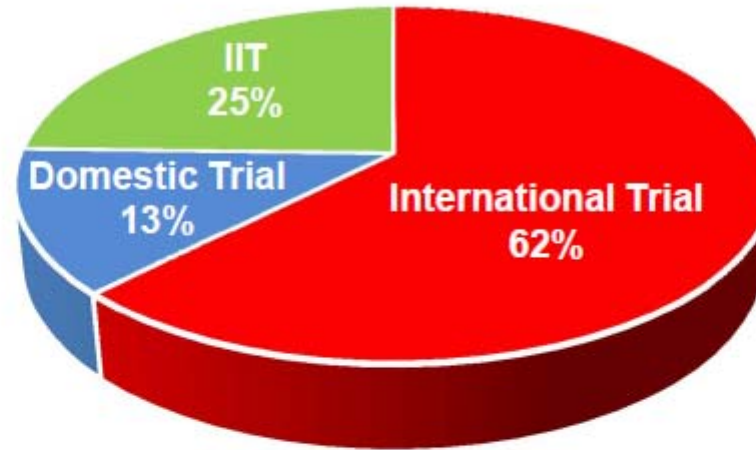
20 Medical Centers, 25,800 beds

# Clinical Trials Conducted by TCTC

Disease	Number of Trial				
	International	Domestic	IIT	Total	GC/AC*
Early Oncology	16	3	3	22	16
Lung Cancer	50	2	11	63	8
Hepatitis & Liver Cancer	19	7	4	30	2
Breast Cancer	29	1	6	36	6
Gynecologic Cancer	6	4	3	13	5
GI Diseases & H.P.	8	3	12	23	14
Hypertension-related	28	6	3	37	11
Hyperlipidemia	7	1	4	12	1
COPD	15	9	14	38	11
Pediatric Infectious Diseases	9	6	9	24	0
Mental Disorders	24	2	14	40	2
<b>Total</b>	<b>211</b>	<b>44</b>	<b>83</b>	<b>338</b>	<b>76</b>

\*GC/AC:Global Chaiman/Advisory Committee

# Clinical Trial Conducted by TCTC



Category of Trial	International	Domestic	IIT	Total
No. of Trial	211	44	83	338
%	62	13	25	100

- 76 Chairmanship or Steering Committee Membership in international trials

IIT: Investigator Initiated Trial

# Oncology Phase 1 Clinical Trial Consortium

- International: 12 trials
- Domestic: 2 trials
- As Advisory Board: 14 trials
- First-in-human: 6 trials
- First in new indication: 3 trials

# National Center of Excellence for Clinical Trials and Research - NTUH

- Established in 2005 at National Taiwan University Hospital (NTUH), abbreviated as CTC-NTUH
- Funded by Department of Health, Taiwan; 16 million USD (2005-2010)
- Goal & Scopes
  - (1) Clinical trials & research center (including phase I center)
  - (2) Translational research center
  - (3) Clinical trial training center
  - (4) Comparative cost effectiveness research center
  - (5) Cardiovascular center
  - (6) Helicobacter pylori research center
  - (7) Infectious disease center

# CTC - NTUH



<http://www.ntuh.gov.tw/en/NCTRC/default.aspx>

# Clinical Trials Done in CTC-NTUH, as of 2012

Clinical Trials	Sponsored	Investigator-Initiated
Phase I	38	5
Phase II	113	19
Phase III	248	10
Phase IV	38	73
Others	19	74
<b>Total</b> <b>637</b>	<b>456</b>	<b>181</b>

# NTUH as Center of Excellence for Clinical Trials in Asia-Pacific, as of 2012

- Leadership in 40 international clinical trials
  - (1) Chairmen of 14 trials
  - (2) Steering Committee members of 26 trials



# Oncology Research Team at CTC-NTUH

- **Liver cancer:** Prof. Andrew Ann-Lii Cheng & Pei-Jer Chen
- **GI Cancer:** Prof. Kun-Huei Yeh
- **Thoracic cancer:** Prof. James Chih-Hsin Yang, Pan-Chyr Yang and Jeffery Jong-Jen Yu
- **Urologic Cancer:** Prof. Yeong Shau Pu
- **Breast cancer:** Prof. Huang and Assis Prof. Yen-Shen Lu
- **Head & neck cancer:** Prof. Ruey-Long Hung
- **Hematologic malignancies:** Prof. Hwei-Fang Tien
- **Phase I:** Prof. Joshua Chia-Chi Lin

# Phase I Cancer Trials in Taiwan

- N=140 in [clinicaltrials.gov](http://clinicaltrials.gov)
- MK2206 (AKT inhibitor)
- TLC338 (liotecan)
- TKI258 (kinase inhibitor)
- AV299, ficluzumumab (HGF monoclonal antibody)
- NC6004 (nanoplatin)
- BIIB022 (HSP90 inhibitor)
- BI6727, volarsertib (PLK1 inhibitor)
- PEP02 (liposomal irinotecan)
- PR104 (pre-prodrug of an alkylator)
- XL880 (multi RTKI)
- LDE225 (selective smoothend inhibitor)
- etc.....

# Strengths of Clinical Trials in Taiwan

- Trained and experienced investigators
- Trained and experienced clinical trial experts and research nurse
- Good and uniform medical environment
- Concentrated patients pools
- Government support
- Mature ethics committees

# New Drug Reviews in Taiwan

# Key Steps of New Drug Review

- Two key steps – usually in parallel
  - 1) BSE submission and review
    - based on ICE E5
    - assessment of ethnic difference
    - grant waiver or request bridging studies
  - 2) NDA submission and review
- Integration of BSE and NDA review

Note: For abbreviated process of NDA review, bridging study must be waived

# Materials Required for BSE Submission

- Complete Clinical Data Package (CCDP) -
  - PK/PD data
    - dose response data
    - clinical efficacy and safety data
    - Asian PK/PD data
- Bridging Data Package (BDP, critical)
- Self-Evaluation Checklist
  - 12 items of intrinsic/extrinsic factors of ethnic sensitivity (mostly from ICH E5)
- Review Team:
  - PK and Clinical reviewers, Project manager

# Bridging Data Evaluation

- Comparison of PK profiles between Caucasian & East Asian
- Subgroup analysis of East Asian population from global trials (MRCT)
- phase II dose-response data from East Asian (**very useful !**)
- Results of bridging study in East Asian
- East Asian phase III (confirmatory trial) data; beyond the scope of bridging study

# East Asian Population

- **East Asian Population:** Subjects from Taiwan or subjects, from other regions (countries), who can represent Taiwan population.
- Intrinsic & Extrinsic factors may also be considered if the East Asian subjects came from regions (countries) other than Taiwan.
- Examples of special concerns of extrinsic factors in Taiwan
  - (1) High incidence of tuberculosis (reactivation of TB)
  - (2) High prevalence of hepatitis B (and hepatitis C also)
  - (3) Anti-coagulant not routinely given after orthopedic surgery of lower limbs.\*

\*

1. Lee CH et al. *J Throm Haemost* 2012; 10:56-63
2. Lee CH et al. *J Throm Haemost* 2012; 8:1515-1523



# Key Points to Consider in NDA Review

## Clinical Aspects

- Dose-response (DR) results (phase II study)
  - prove of concepts; lack of DR trend → doubtful phase III results
  - appropriateness of target dose selection
- One or  $\geq 2$  confirmatory trials (pivotal studies)
- Selection of control group in RCT; recognition of single-arm study
- Justification of surrogate endpoint
- Consistency among primary endpoint and secondary endpoints
- Clinically meaningful efficacy results
- Adequacy of exposure (safety review): ICH guideline
- Important safety concerns (identified risk and signals)
- Requirement of risk management plan (RMP): rarely required
- Benefit/risk assessment

# Key Points to Consider in NDA Review

## Statistical Aspects

- Strict control of type I error for confirmatory trials (multiple arms, interim analysis, multiple endpoints to be claimed,.....)
- Appropriateness of randomization
- Appropriateness of important protocol amendments (timing, rationale...)
- Appropriateness of analytical methods and population
- Missing data handling (integrity of the clinical trial)
- Consistency of primary analysis with sensitivity analyses
- Whether bias existed when subjects excluded from primary analysis (ITT)
- Considering bias caused by premature discontinuation of subjects
- Balance of baseline demographics between treatment groups
- Rational of no-inferiority/equivalence margin for active-control studies

# Risk Management Plan (RMP)

- For some new drugs with important risk(s) which could be minimized by appropriate measures to achieve favorable benefit risk ratio
- Risk minimization measures if label warning is expected to be not adequate
- RMP Components: any combination of the followings
  - (1) Medication Guide (for patients)
  - (2) Communication Plan (for health care providers)
  - (3) Elements to Assure Safety Use (ETASU)
- Periodic reports of implementation of RMP are required.

# MRCT (Multi-Regional Clinical Trials) Regulators' Perspective in Taiwan

# Definition of MRCTs

- ICH E5, Q/A (R1), Q1 and Q11
  - (1) MRCT as a bridging study for a particular region
  - (2) Sufficient no. of subjects, adequate power to show likelihood
  - (3) Region: EU, Japan and US (according to Glossary of ICH E5, R1)
- In reality, many global trials were done in countries inside and outside ICH Regions.
- Scope of Regions
- Definitions of MRCT
  - (1) Narrow definition: Global trials done in  $> 1$  ICH Regions
  - (2) Broader definition: Global trials done in many countries inside and/or outside ICH Regions
- MRCT (or Multi-National Clinical Trials) in East Asian countries

# Review and Assessment of MRCTs

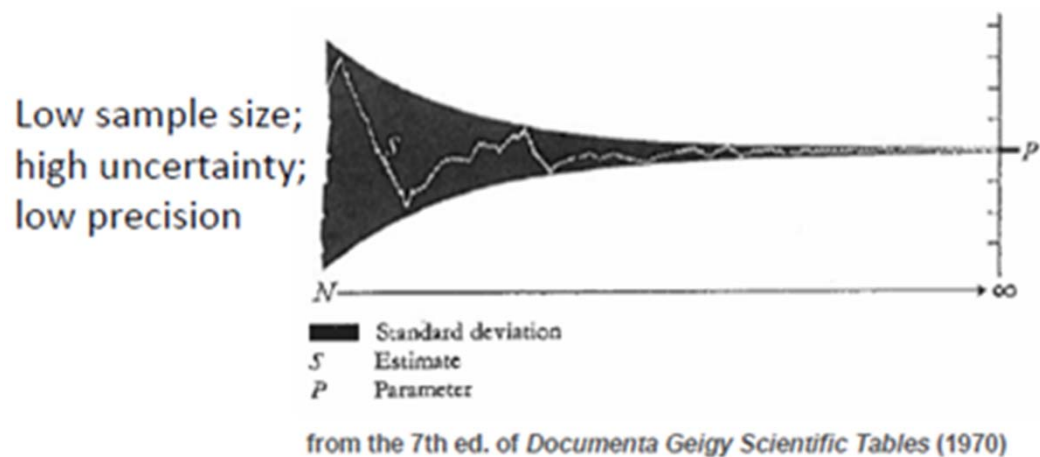
- MRCT: Global trial, usually phase III, using the same protocol (i.e. same dose) for all countries (regions) participated
- Review and assessment of MRCTs in Taiwan
  - (1) In BSE: trends of efficacy and safety in East Asian subgroup
  - (2) In NDA: efficacy and safety in overall population
  - (3) Successful overall results → Trends in East Asian subgroup
- In BSE, subgroup analysis by pooling of all East Asian subjects may be required if there are more than one MRCTs

# Limitations of MRCTs in Terms of Ethnic Difference

- Important ethnic difference must be excluded
- To justify target dose (if only one target dose in MRCTs)
  - (1) Similar PK profile between East Asians and Caucasians (or global population)
  - (2) Similar trends of dose-response between East Asians and Caucasians (or global population) *More Persuasive!*
- Sample size is calculated for overall population, not powerful for a certain subgroup analysis (e.g. for a certain country)
- Difficulty to interpret subgroup analysis if subgroup sample size is too small

# Limitation of Subgroup Analysis in MRCTs

- Variation of point estimate and 95% CI when sample size is small



- Baseline characteristics might be unbalanced between treatment groups in subgroup analysis; post-hoc adjustment of important covariates may be necessary.



# Academic Researches for the Methodology of MRCT

- Mostly researches of statistical methods
  - (1) Y-H Chen et al. *J of Biopharmaceutical Statistics* 2009; 19:900-915
  - (2) H Quan et al. *Stat in Med.* 2014; 33:2191-2205
  - (3) H Quan et al. *Drug Information J.* 2010; 44:617-632
  - (4) S-H Jung et al. *J of Biopharmaceutical Statistics* 2012; 22(2):312-328
  - (5) *J of Biopharmaceutical Statistics* 2012; 22(5) **Special Issues: Bridging & MRCTs**
- Clinical/PK/PD issues might be considered in addition to statistical methodologies
- New ICH Guideline, E17, is being drafted:
  - General principle on planning/designing MRCTs**
  - (1) Final concept paper published in May 2014
  - (2) Expert Working Group (EWG) will be established in 2Q 2014
  - (3) <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>

# Defining Region of MRCTs

- ICH regions might be not applicable in reality for MRCTs.
- ICH E5 Q & A principles might not be applicable for small countries
- Region  $\neq$  Country in most cases
- Definition of region should take into consideration of geographic boundaries and intrinsic/extrinsic factors.
- If important ethnic difference between East Asians and Caucasian is identified in PK/PD and dose-finding study, a **Multi-National** Clinical Trials done in East Asian Region (countries sharing similar intrinsic & extrinsic factors) may be a strategy for new drug development.

# Cooperation between Taiwan & Japan

- Sharing data of sponsor initiated early phase clinical trials (especially in oncology field) done in Taiwan, to avoid duplication and to facilitate new drug development
- For new drugs with significant/uncertain ethnic difference between East Asian and Caucasian, **Multi-National Clinical Trials** (phase III or II) done in East Asian countries (e.g. Japan, Taiwan.....) where intrinsic/extrinsic factors are similar may be one of the strategy of new drug development.

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Prof. Pan-Chyr Yang is currently President of National Taiwan University.

Prof. James Chih-Hsin Yang is currently Professor of Graduate Institute of Oncology; Director of Department of Medical research and Deputy Director of Department of Oncology in National Taiwan University Hospital & College of Medicine.

# THANKS FOR YOUR ATTENTION

ご清聴 ありがとうございます

Some viewpoints in this presentation may be subjective to change due to complexity of new drug reviews, policy of regulatory authority and evolution of sciences.

