Recommended non-clinical studies before first-in-man trial

1) Safety pharmacology
2) Toxicokinetics and pharmacokinetics
3) Single dose toxicology (2 species)
4) Repeated dose toxicology (>2 weeks)
5) Genotoxixity
6) Carcinogenisity
7) Reproductive toxicology

Check points in human study
- consideration from tox findings-

Are there any non-invasive measures to detect the toxicological events in human?

Can the measure decrease risk of subjects? That is if we can get rid of toxicity before it turns to irreversible.

We should make every effort to avoid subjects' permanent dysfunction.

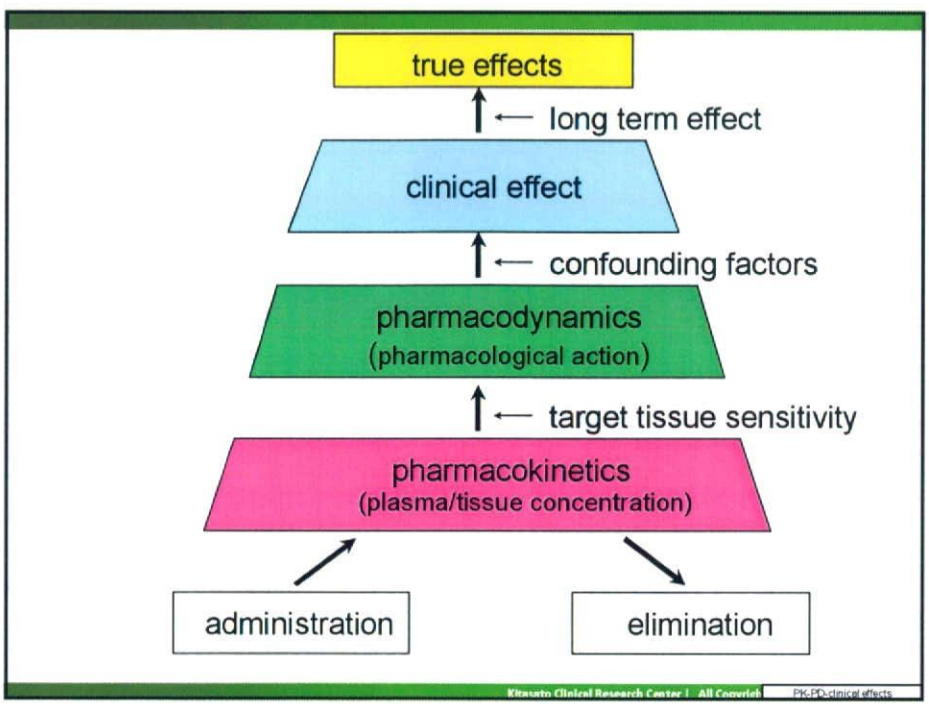
When QT prolongation is concerned

Exclude subjects with possible risks
Check family history of sudden death and LQT, serum electrolytes and ECG findings.

During studies, subjects should be monitored by telemetry and recorded by Holter ECG. Normal ECG assessment and blood chemistry are also needed.

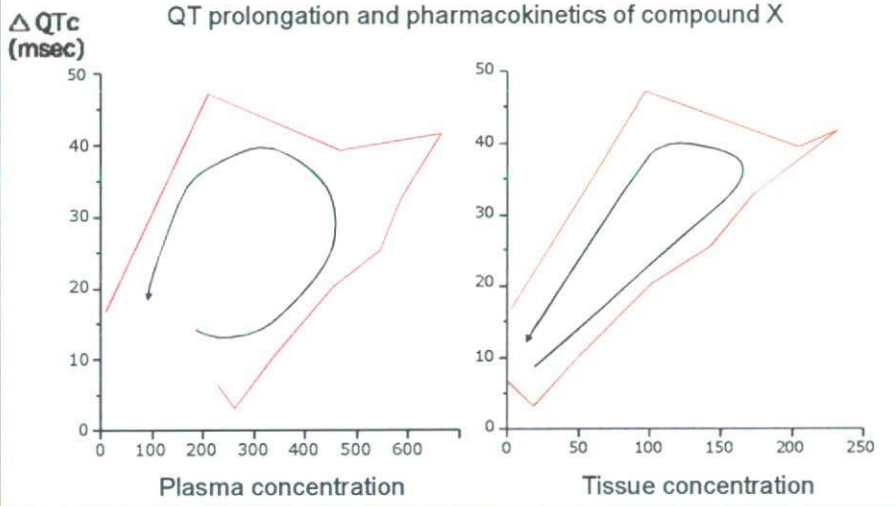
Note that QT prolongation is mainly caused by pharmacological action of drugs.

 P120



 PK-PD-clinical effects

Hysteresis is not only for RR-QT but also for PK and QT

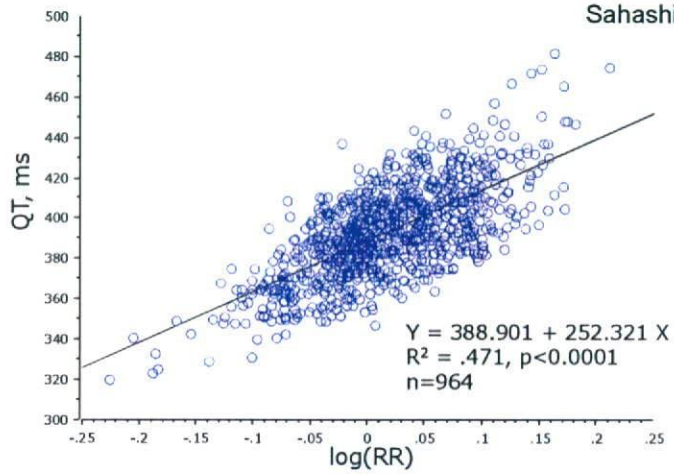


Single vs Multiple Dose Design

		Single Dose	Multiple doses
PK	half life short long elimination mainly renal others		metabolism active metabolite carry over effect
design		cross-over	parallel group
number	small	large	

RR-QT Relationship in Healthy Male Subjects
(964 readings from 103 subjects)

Sahashi et al., 2005



 P133

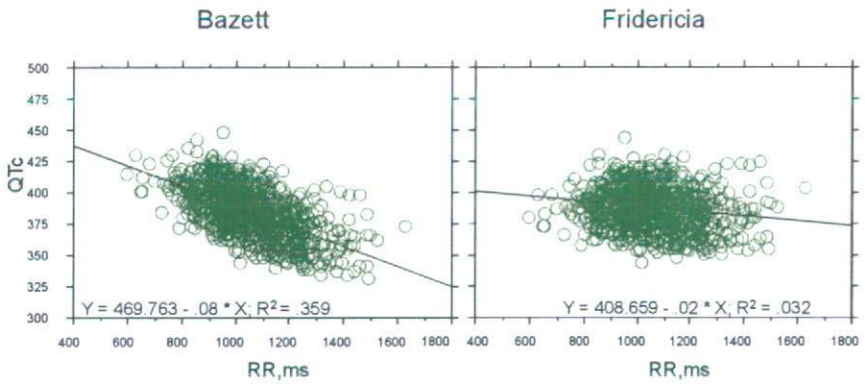
QT analysis

- Central measurement
- HR correction
  - Bazette, Fridericia, Framingam
  - Individual or group based correction
- Major problem is finding an appropriate correction method especially where the agent causes tachycardia.

 P134

Correction by Bazett is not enough. Correlation between RR and QTc

Sahashi et al., 2005



 P135

Limit values for QTc in categorical analyses

Absolute prolongation
- QTc interval >450 ms
- QTc interval >480 ms
- QTc interval >500 ms

Changes from baseline
- QTc interval increased from baseline >30 ms
- QTc interval increased from baseline >60 ms

 P136

Are there ethnic differences?

- Variants in LQT genes are more common in black population than in white.

  (Ackerman MJ 2003)

- Caucasians show larger QT prolongation by quinidine than Korean.

  (Shin JG, 2007)

- Common haplotypes of sodium channel exist among Asian population

  (Bezzina CR, 2006)

Repeating tQT is needed in Japan?

- Admitting ethnic differences in drug-induced QT prolongation, repeating studies are not always necessary.
- Another approach such as bridging QT study (bQT) will be desired.

Global Clinical Trials in Japan

In 2005, global studies included Japan were only 6 trials.

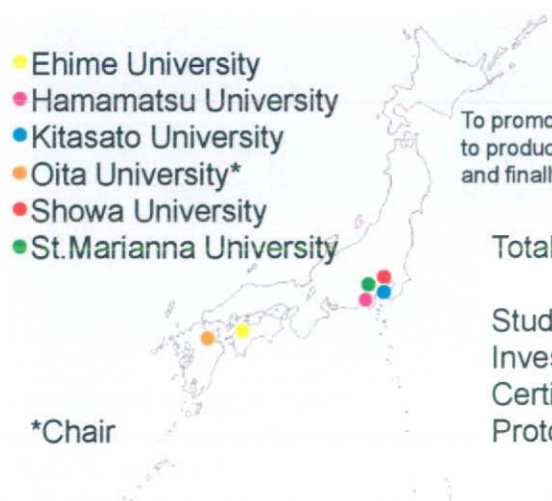
From 2007.4 to 2008.2, 35 notifications of global trials were accepted by PMDA.

Most of the studies are of oncology field and phase III trials by foreign companies.

J-CLIPNET

Japan Clinical Pharmacology Network for global trials

- Ehime University
- Hamamatsu University
- Kitasato University
- Oita University*
- Showa University
- St.Marianna University



*Chair

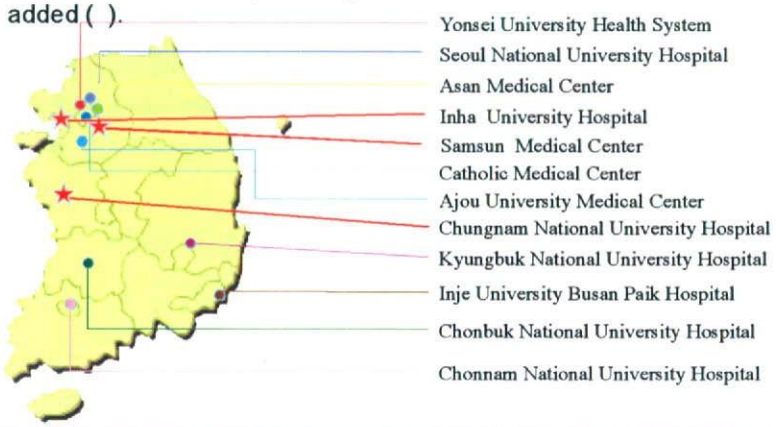
To promote international trials in Japan, to produce evidences for Asians, and finally to contribute to human welfa

Total Scale of J-CLIPNET

Study beds	93
Investigators	31
Certified CRC	
Protocols/yr	300

Regional Clinical Trial Centers in Korea

- 9 sites had been designated by MOHW, and 3 were ★ added ( ).



4th Korea-Japan Joint Symposium of Clinical Pharmacology and Therapeutics 2008

in 19th Annual Congress of the Korean Society for Clinical Pharmacology and Therapeutics / 2008 Annual Congress of the Korean Society of Pharmaceutical Medicine

Imperial Palace Hotel, Seoul, Korea
(http://www.imperialpalace.co.kr/)
November 13th ~ 14th, 2008

4th Korea-Japan Joint Symposium of Clinical Pharmacology and Therapeutics 2008

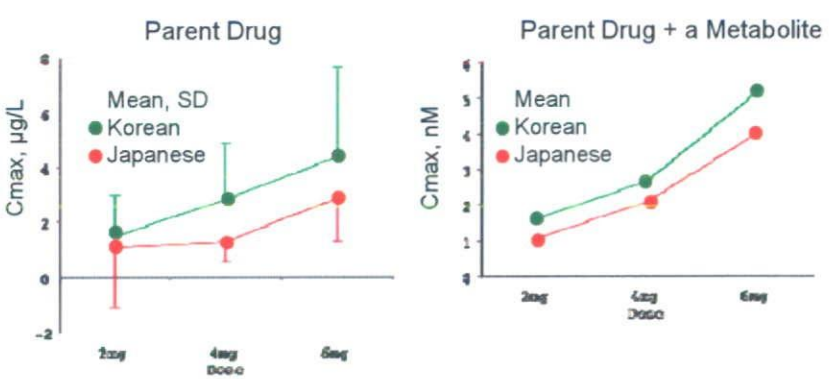
Constructing a Support Database for Asian Clinical Trials

Yuji Kumagai[1,2], Leon Bax[2], Wang Guoqin[2]

1) Clinical Trial Center, Kitasato University East Hospital
2) Kitasato Clinical Research Center, Kitasato University

 P143

A Case of Drug with Differences in PK between Korean and Japanese



http://www.info.pmda.go.jp/shinyaku/g0604.html

 P144

A case of AEs in Korean and Japanese

-Is There Difference in Safety Profiles?-

In a Korea-Japan Clinical Trial for OAB, the pattern of AEs was apparently different.

	AE (%)	types of AE
Korea	48.0%	17
Japan	70.2%	54

Compliance of the drug was also different, and prevalence of those who took more than 75% was 100% in Japanese and 95.2% in Korean.

http://www.info.pmda.go.jp/shinyaku/g0604.html

A case of AEs in Korean and Japanese

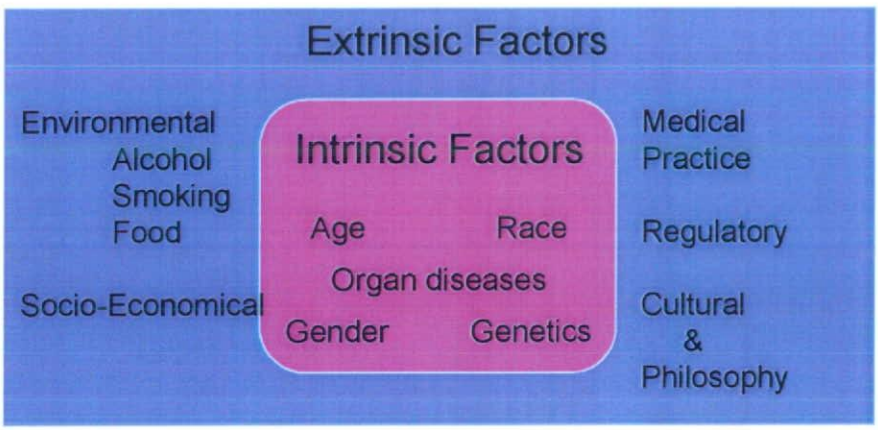
-Is There Difference in Safety Profiles?-

AEs found more than 5 % in a Korea-Japan trial of OAB

Korea	Japan
Dry mouth	Dry mouth
Abdominal pain	Headache
Dyspepsia	Abdominal pain
Voiding dysfunction	Constipation
Urinary retention	Diarrhea
	Abdominal fullness
	Thirst
	Somnolence
	Rhinitis
	Upper air tract inflammation
	Cystitis
	Voiding dysfunction
	Blurred vision

http://www.info.pmda.go.jp/shinyaku/g0604.html

Intrinsic and Extrinsic Factors in International Clinical Trials



 P147

Factors Related to Life Style

Food	Drug Absorption, Metabolism Diseases
Alcohol	Drug Metabolism, Diseases
Smoking	Drug Metabolism, Diseases
Socio-economy	Severity and Prevalence of Disease

 P148

Dosage Regimen

Dosage regimen may be different between countries, partly because of intrinsic differences. However, large differences are found within Asian countries probably due to regulatory, cultural and historical differences.

Point is not "dose" itself but "dose-response". Scientific approaches may exist to overcome for efficacy.

Ex) PK/PD analysis, biomarkers, PET study etc.

Difference of Drug Usage for Psychotic inpatients between Japan and Hawaii

Anders et al. 199

Agent	Japan (%)	Hawaii(%)
Bromperidol	10	0
Chlorpromazine	60	6
Clozapine	0	18.1
Fluphenazine	3.3	9.6
Haloperidol	46.7	21.7
Levopromazine	23.3	0
Thioxetine	0	8.4
Timiperone	16.7	0

Endpoints

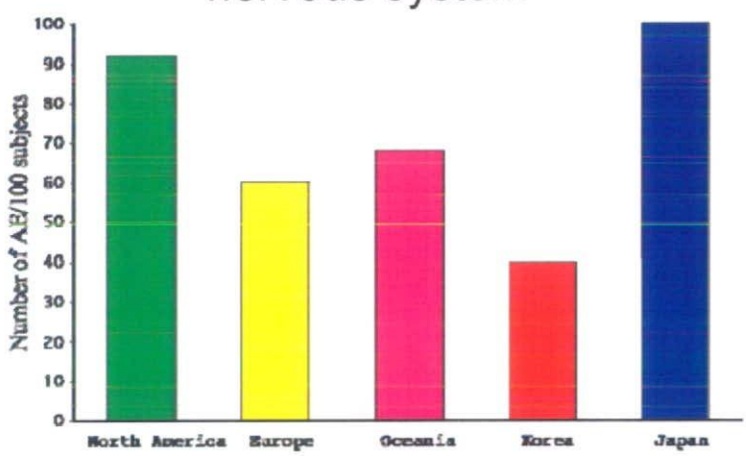
Selecting an endpoint is an essential matter in clinical trials, and a flexible approach is not appropriate.

A new study may be needed to validate the endpoint.

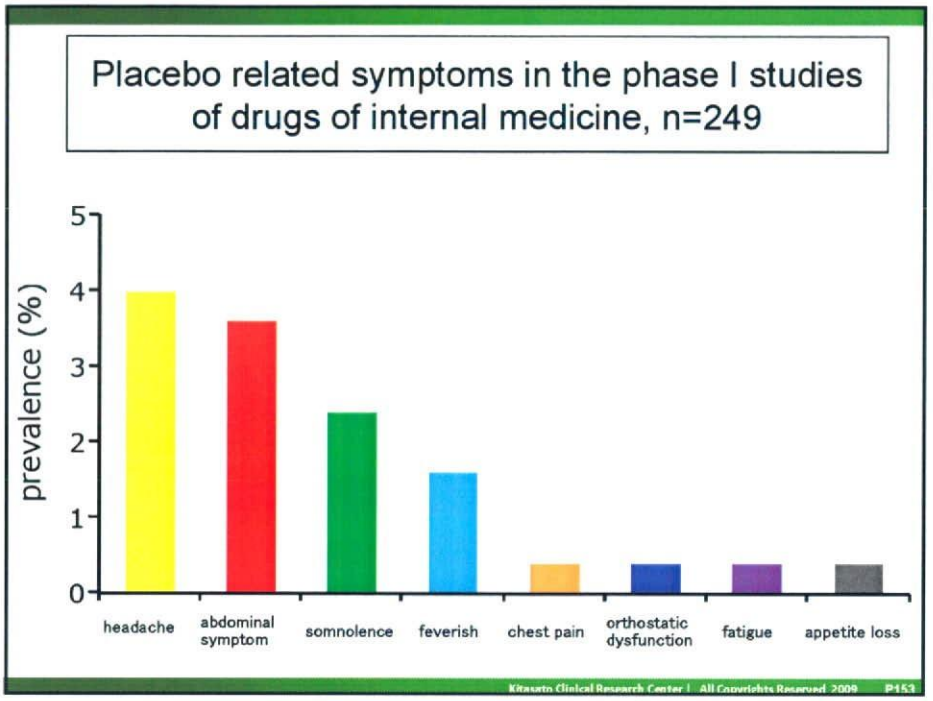
Standardization of assessment is also needed among investigators.

 P151

Global distribution of AEs in placebo groups in studies of an agent affecting autonomic nervous system



 P152


Placebo related symptoms in the phase I studies of drugs of internal medicine, n=249
prevalence (%)
5
4
3
2
1
0
headache
abdominal symptom
somnolence
feverish
chest pain
orthostatic dysfunction
fatigue
appetite loss
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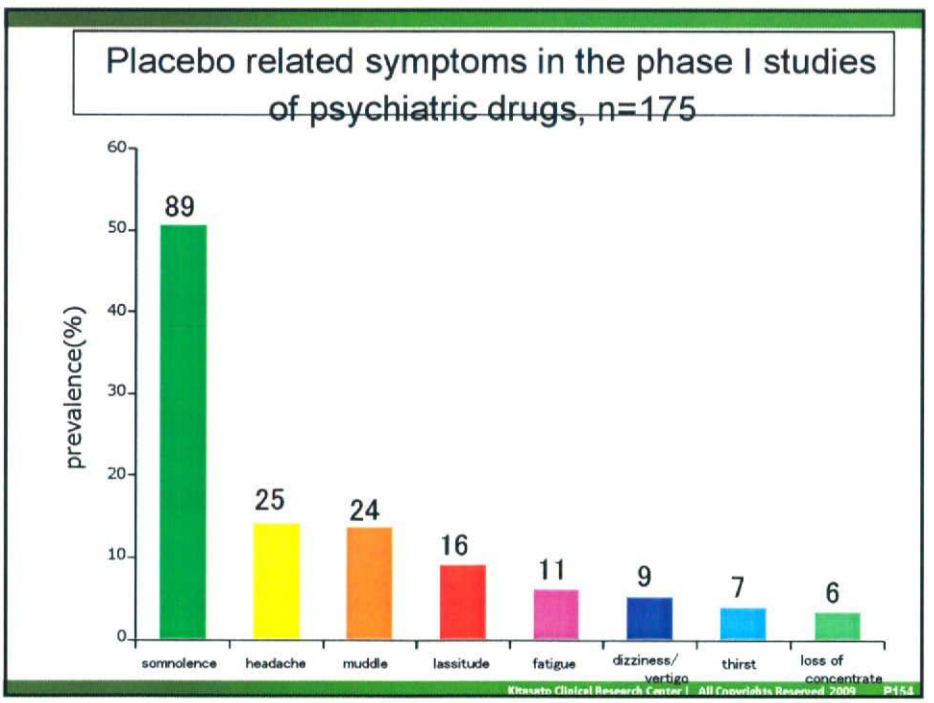
Placebo related symptoms in the phase I studies of psychiatric drugs, n=175
prevalence(%)
60
50
40
30
20
10
0
89
25
24
16
11
9
7
6
somnolence
headache
muddle
lassitude
fatigue
dizziness/ vertigo
thirst
loss of concentrate
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Point to Consider in Asian Trials - Adverse Event -

Picking up of AE

Different attitude of investigator
Different request from DM (and authority?)

Terminology of AE

Adherence to MedDRA is not preferred.
It will decrease quantity of information.

Assessment of causality and severity

Consensus should be formed before a study by investigators, the sponsor, and the authority.

Point to Consider in Asian Trials - Laboratory Test -

Validation of measurement

International certification such as CAP is not popular in Japan.

Difference in unit and reference limit

Accept difference?
Use central laboratory?

Interpretation of deviated value

Pick up every deviation as an AE? ---- Japanese way
Leave allowance to each investigators judgment?

Possible Measures for Extrinsic Factors

Procedures for clinical trials can be standardized,
but we can't standardize life styles.

Accepting differences as they are, we should accumulate background data for a ongoing trial and for coming trials even in a domestic practice.

Knowing cultures of the counterpart regions is the most important.

We propose Constructing a Support Database for Asian Clinical Trials.

The Asian Drug Development Database (AD^3)

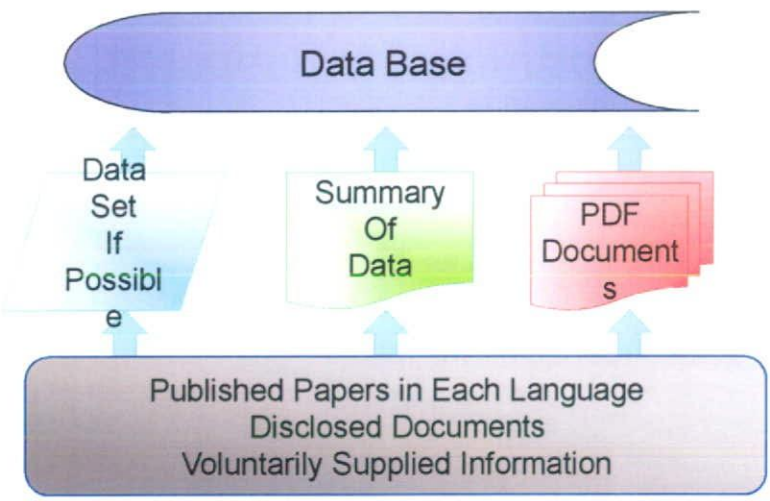
Type of Data

- Subject Characteristics
  (Vital signs, Laboratory Data, Life Style, etc.)
- Pharmacokinetic data
- Pharmacodynamic data
- Biomarkers
- Endpoints
- Adverse Events

Preferably in one PC.

- Pharmacoepidemiology
  (Medical Practice, Dose, Standard Therapy, etc.)

Collecting Data



What can be done by AD3?

- PK parameters of compound X?
  - PDF files of papers concerning PK
  - Summary data in HV (Data set, if available)

Ethnicity	Disease	Age	Gender	number	Cmax	AUC	CL
Korean	HV	20-30	M	8	***	***	**
Japanese	HV	22-38	M	10	***	***	**
Japanese	CRF	42-72	M&F	6	***	***	**

- Registered dose and actual dose of compound

Ethnicity	Registered Dose	Actual Dose (95%CI)
Korea	10-20mg	9.0 (7.1-125)
China	10-20mg	NA
Japan	5-10mg	8.2 (5.5-10.0)

 P181

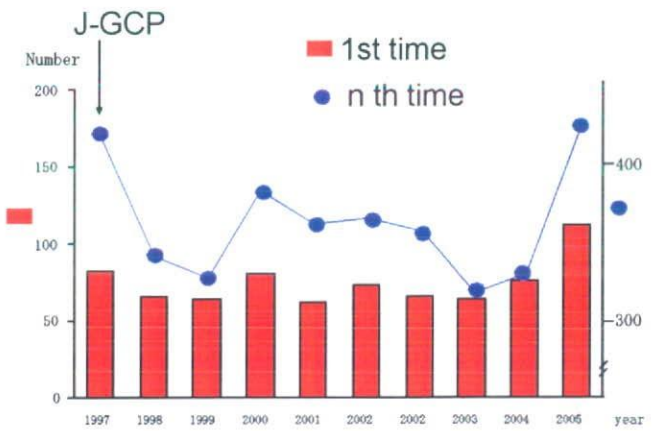
1st Charles River Laboratories and Institute of Laboratory Animal Resources Seoul National University Symposium in Korea

Designing of early clinical trials in Japan - extrapolation of non-clinical data

Yuji Kumagai
기타사토대학 동병원 임상시험센터

 P182

Number of Notification of Clinical Trial to PMDA



Type of Clinical Trials

- Pharmacokinetic Study

Analogy with Growth

First In Human Trial → Birth

- Dose-response Study
  - Phase II trial → Character building
- Confirmatory Study
  - Phase III trial → Adult

To Secure Subject's Safety

Careful checks of non-clinical data

Choose appropriate safety margin
in setting starting and max dose

Selection of subjects (HV or patient)

Detect early signals of human toxicity

Expert investigators and clinic environment

Safety of Phase I study

Monro & Metha

3 review of Phase I study (n =93.399, 29.162, 27.424)
Adverse reaction 1-3 %
Transient functional dysfuntion 109 (0.073%)

Kumagai et al, 2006

JACIC's survey in 97,987 healthy volunteers
Serious adverse events 49 cases
(Side effects 23 cases)
Shock, allergic reaction, cramp, liver dysfunction etc.

