

In Planning a Phase I study

Presumption

Little difference in free drug concentration and toxicity according to species



Most toxic reactions is predictable from multiple animal models.



Prepare as many observations and means as possible to minimize possible risks.

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) Genotoxicity
- 6) Carcinogenicity
- 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.

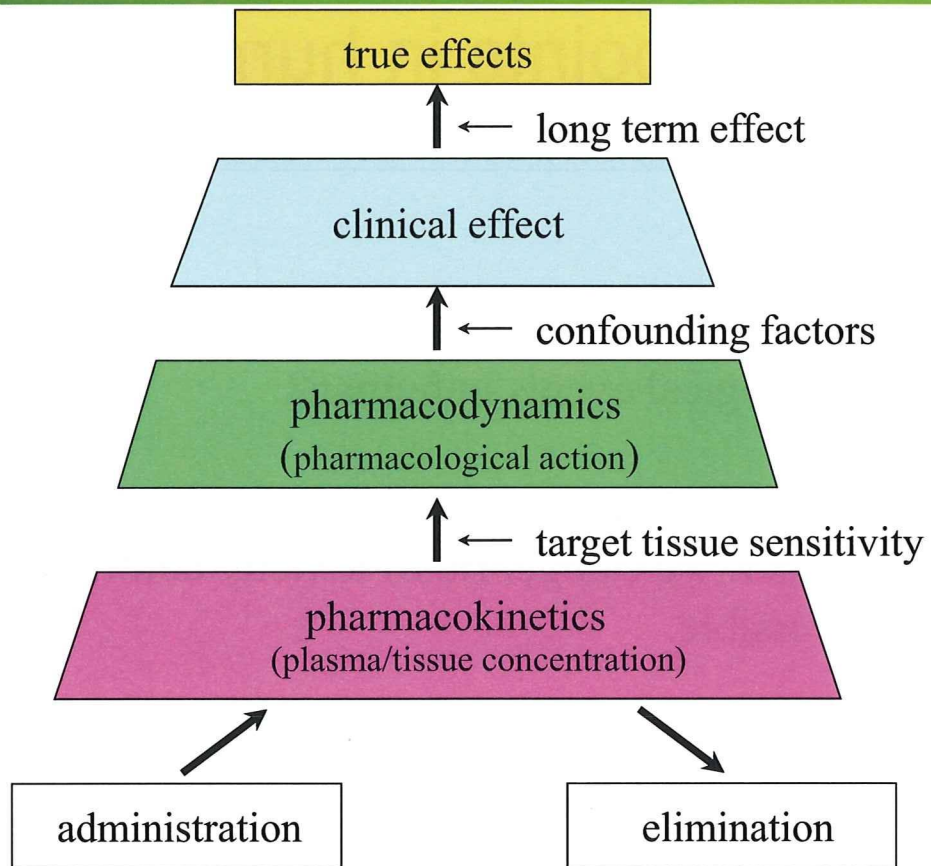
We should make every effort to avoid subjects' permanent dysfunction.

When QT prolongation is concerned

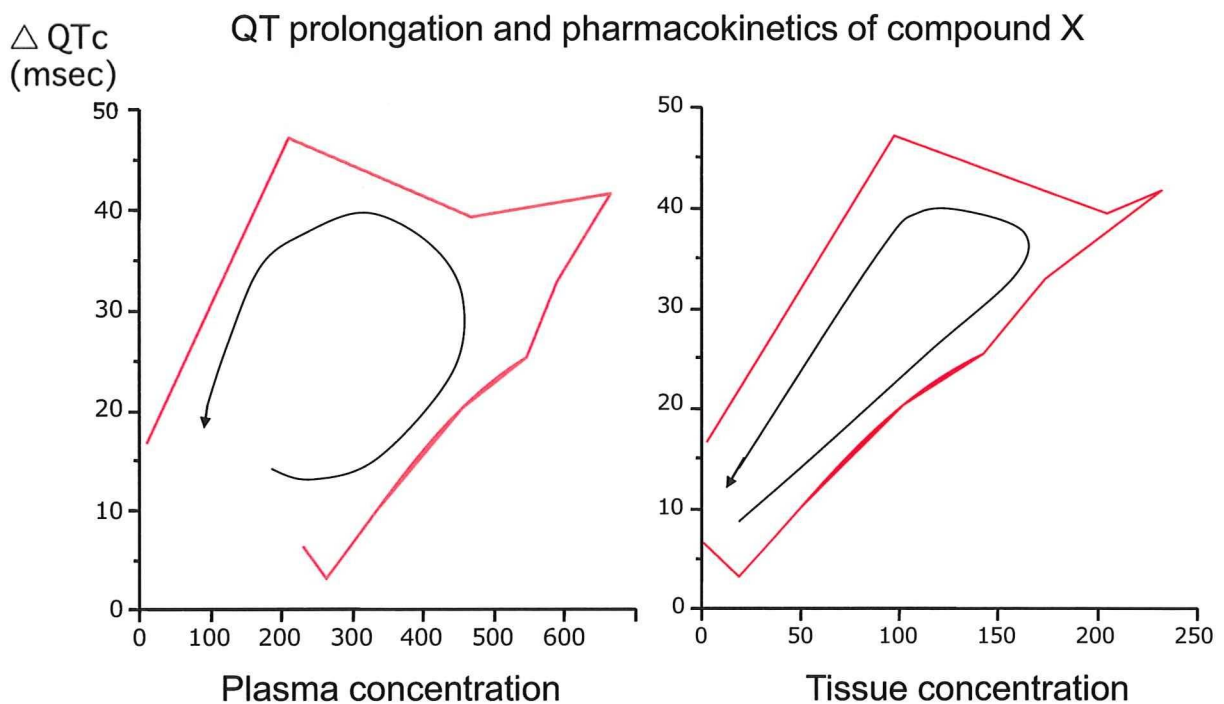
Exclude subjects with possible risks
Check family history of sudden death and LQT, serum electrolytes and ECG findings.

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.



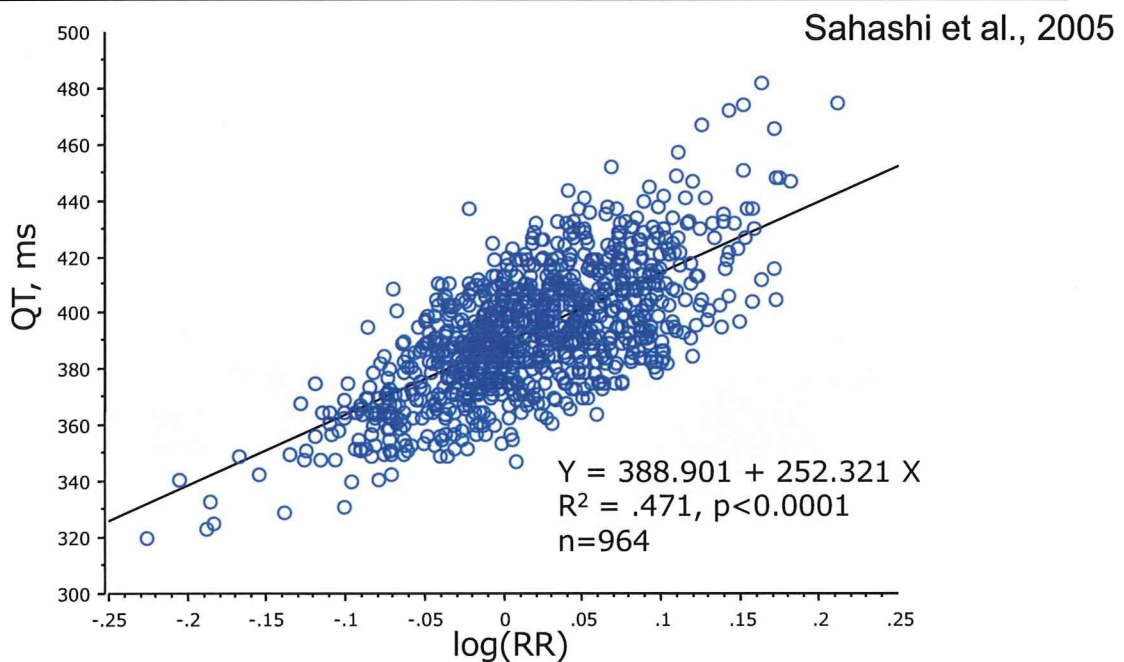
Hysteresis is not only for RR-QT but also for PK and QT



Single vs Multiple Dose Design

		Single Dose	Multiple doses
PK	half life short elimination others	long mainly renal	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)

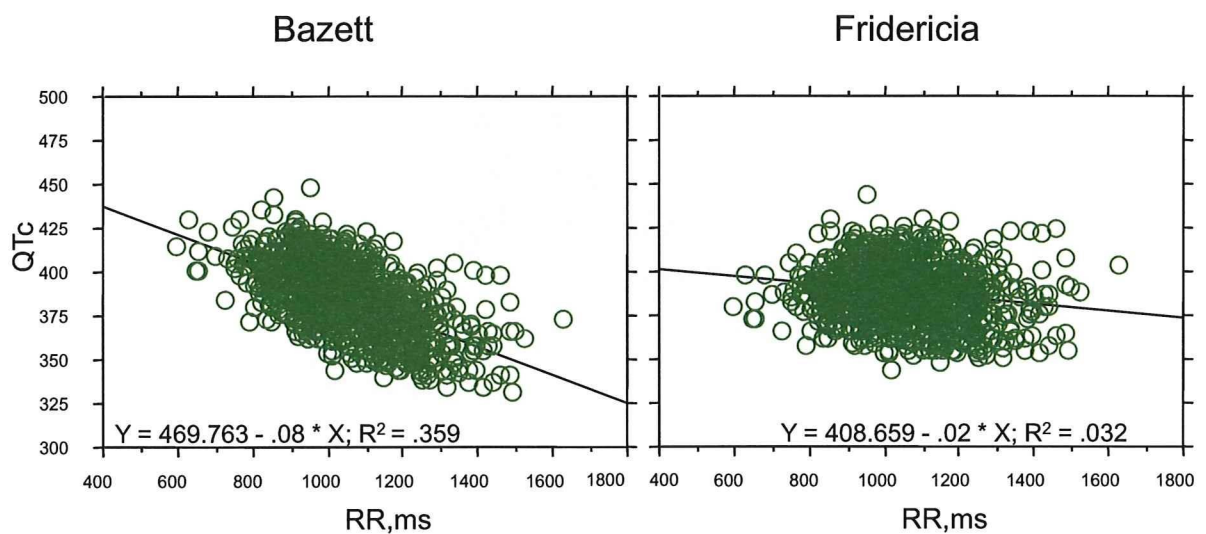


QT analysis

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

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

Sahashi et al., 2005



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

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

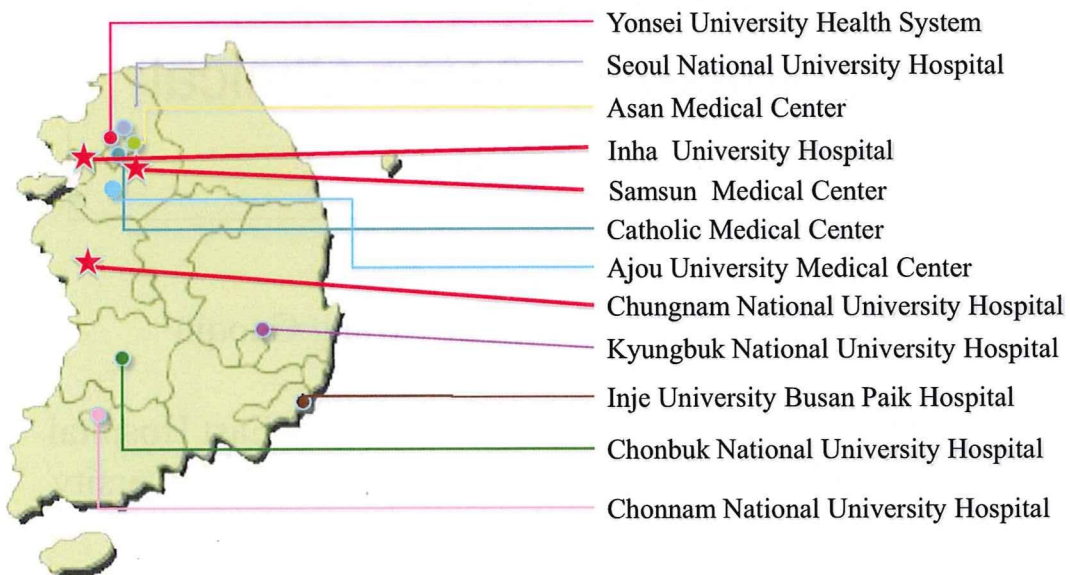
To promote international trials in Japan, to produce evidences for Asians, and finally to contribute to human welfare.

Total Scale of J-CLIPNET

Study beds	93
Investigators	31
Certified CRC	26
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

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

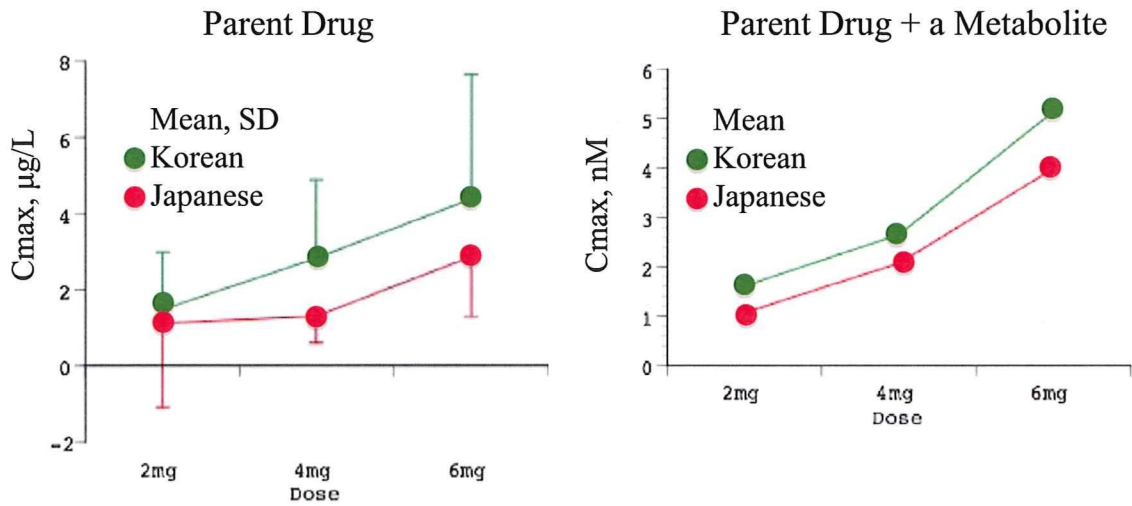
Constructing a Support Database for Asian Clinical Trials

Yuji Kumagai^{1,2}, Leon Bax², Wang Guoqin²

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

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



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

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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>

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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

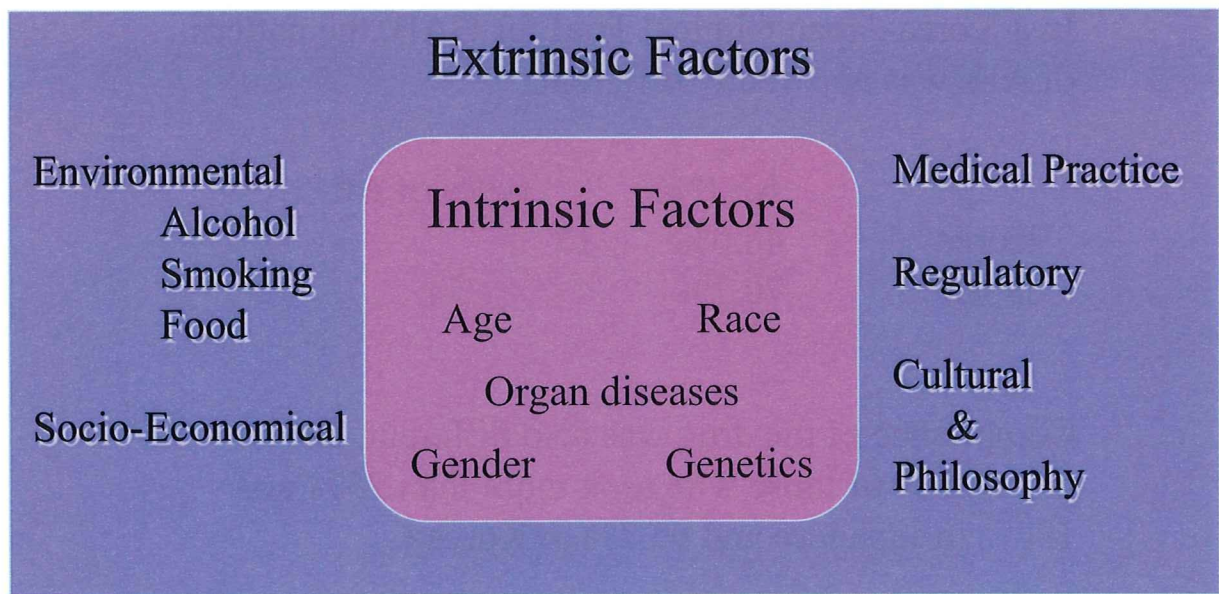
Korea	Japan
Dry mouth	Dry mouth
Abdominal pain	Headache
Dyspepsia	Abdominal pain
Voiding dysfunction	Constipation
Urinary retention	Diarrhea
	Abdominal fullness
	Thirst
	Somnolence
	Rhinitis
	Upper air tract inflammation
	Cystitis
	Voiding dysfunction
	Blurred vision

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

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Intrinsic and Extrinsic Factors in International Clinical Trials



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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

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. 1999

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

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Endpoints

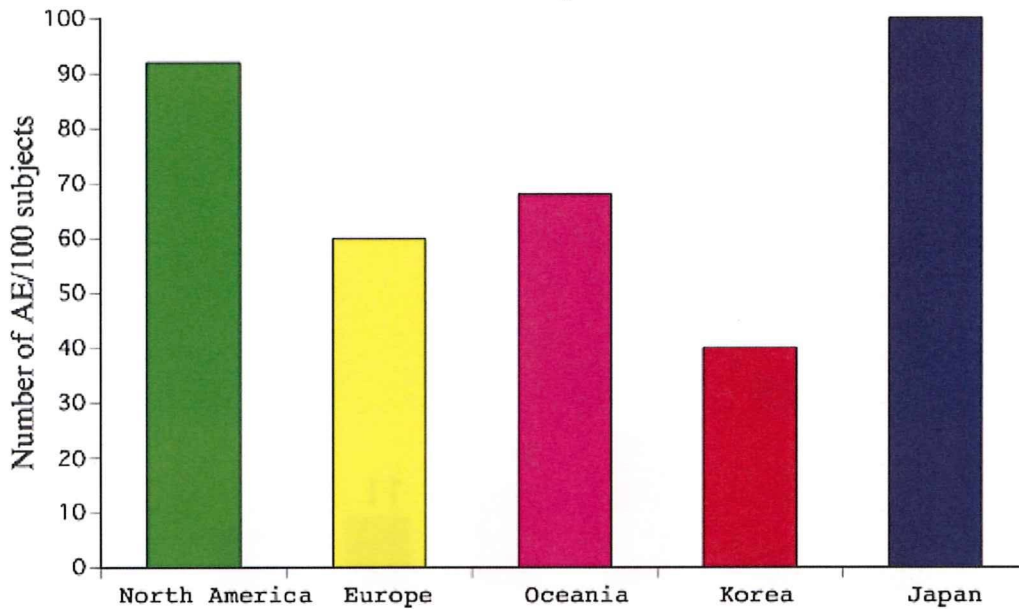
Selecting an endpoint is an essential matter in clinical trials, and a flexible approach is not appropriate.

A new study may be needed to validate the endpoint.

Standardization of assessment is also needed among investigators.

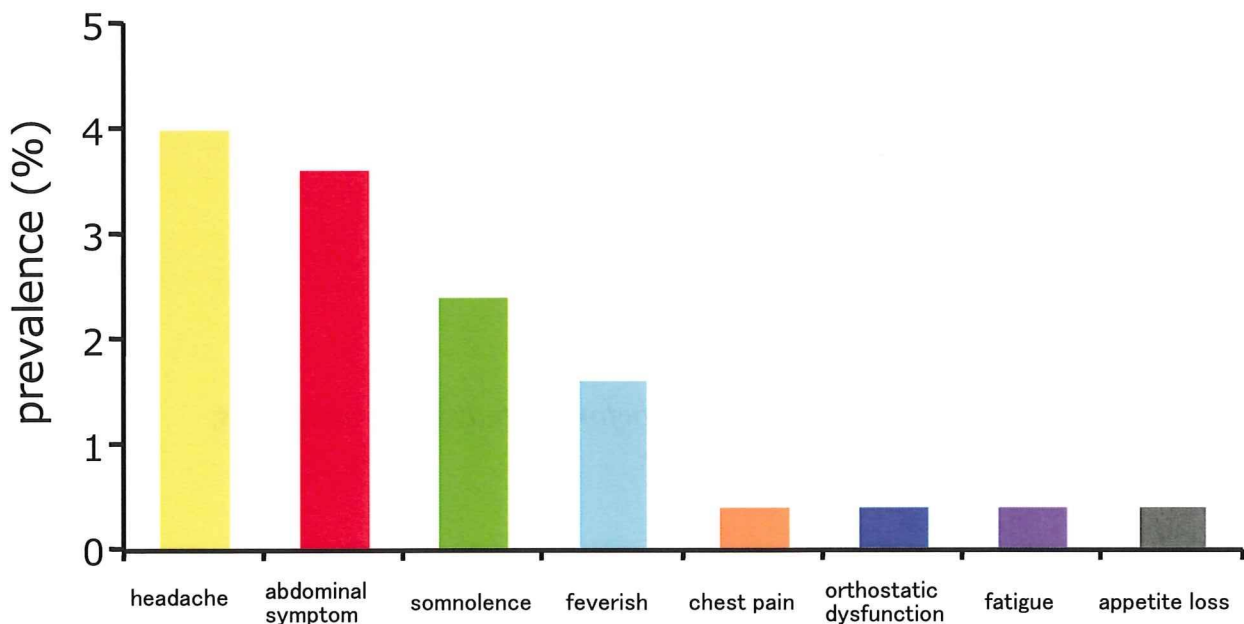
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Global distribution of AEs in placebo groups in studies of an agent affecting autonomic nervous system



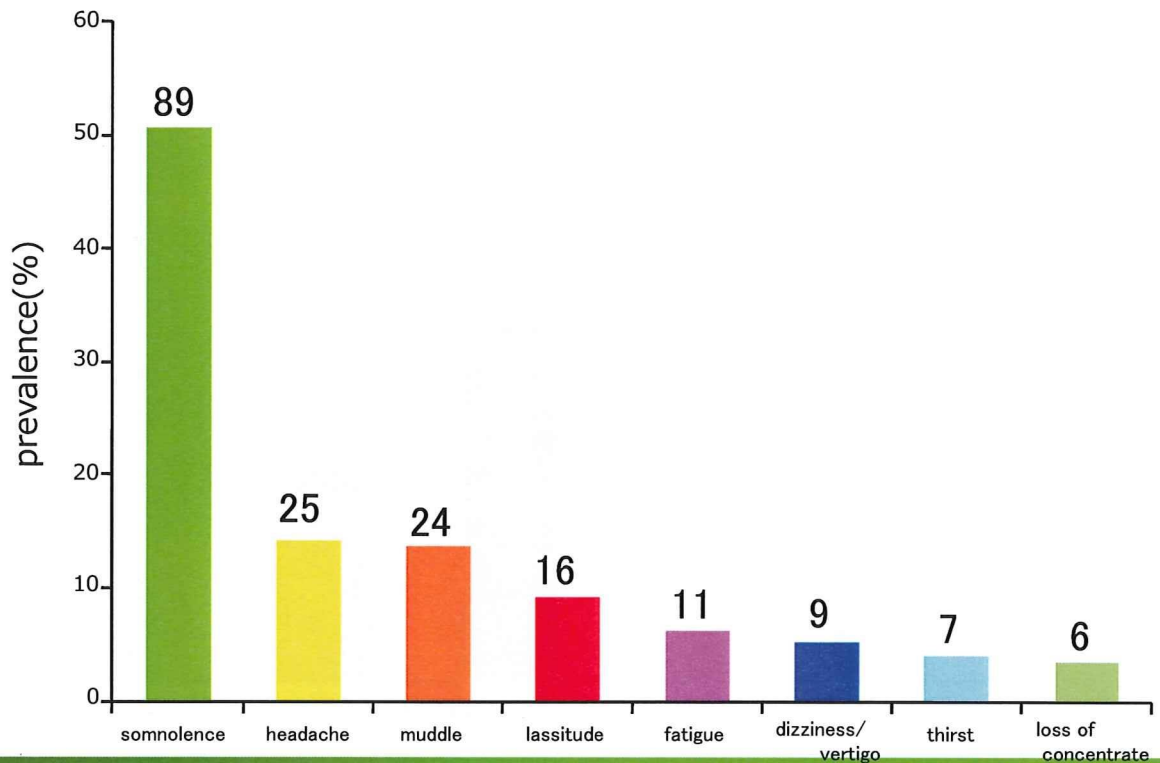
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Placebo related symptoms in the phase I studies of drugs of internal medicine, n=249



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Placebo related symptoms in the phase I studies of psychiatric drugs, n=175



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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.

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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.

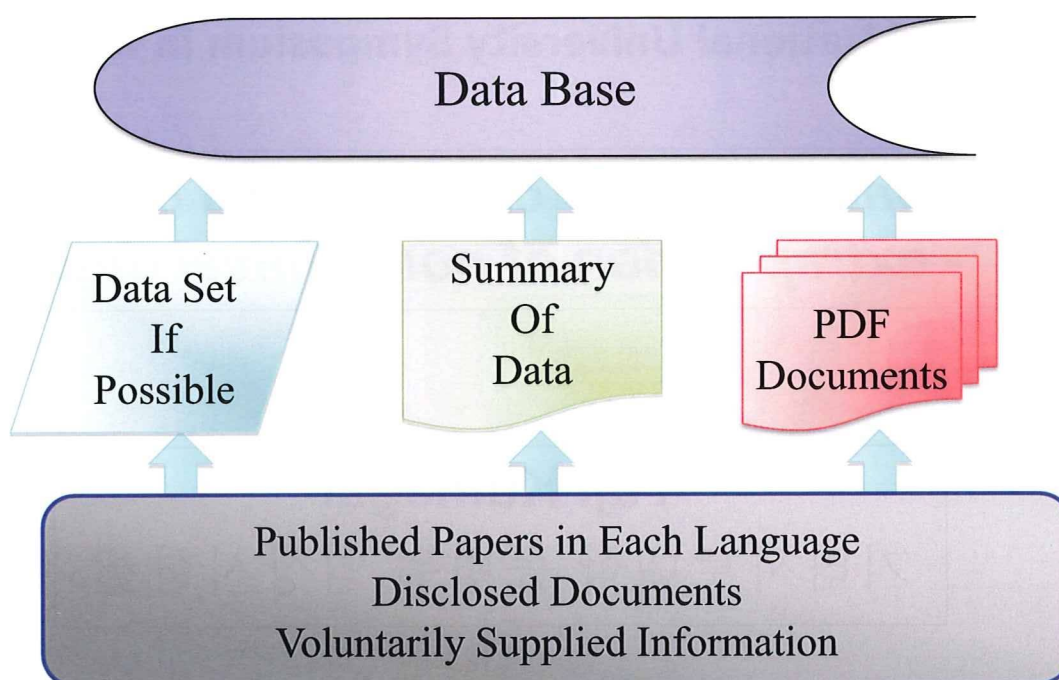
We propose
Constructing a Support
Database for Asian Clinical
Trials.

The Asian Drug Development Database
(AD³)

Type of Data

- Subject Characteristics
(Vital signs, Laboratory Data, Life Style, etc.)
 - Pharmacokinetic data
 - Pharmacodynamic data
 - Biomarkers
 - Endpoints
 - Adverse Events
 - Pharmacoepidemiology
(Medical Practice, Dose, Standard Therapy, etc.)
- Preferably in one PC.

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	C _{max}	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 X

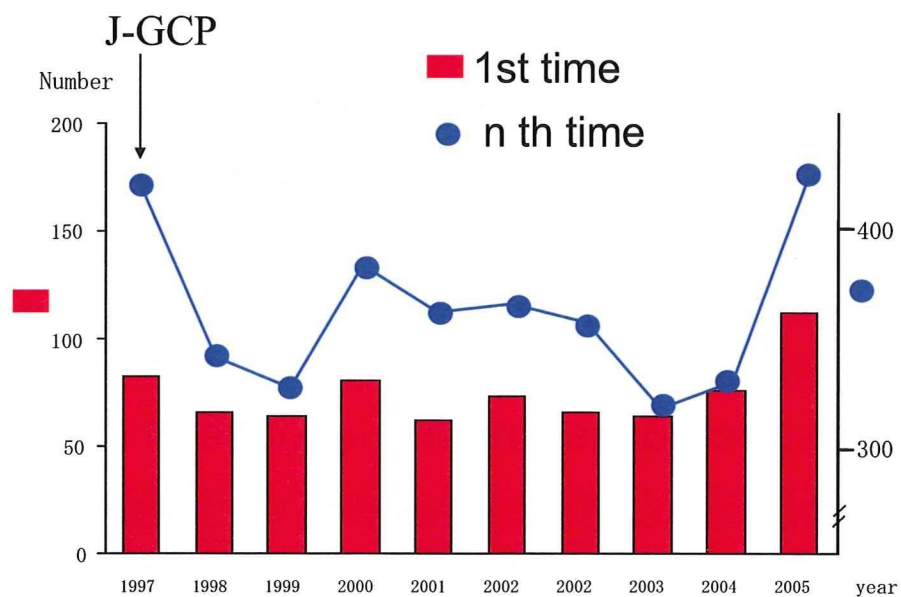
Ethnicity	Registered Dose	Actual Dose (95%CI)
Korea	10-20mg	9.0 (7.1-125)
China	10-20mg	NA
Japan	5-10mg	8.2 (5.5-10.0)

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

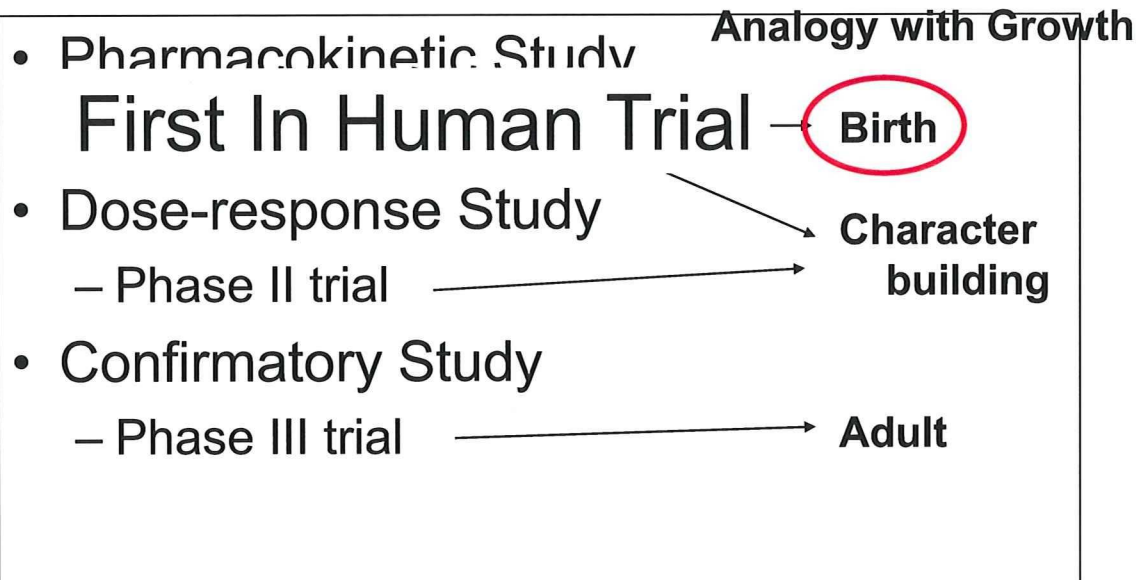
***Designing of early clinical trials in Japan
- extrapolation of non-clinical data***

Yuji Kumagai
기타사토대학 동병원 임상시험센터

Number of Notification of Clinical Trial to PMDA



Type of Clinical Trials



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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

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