＜質疑応答＞

野元　評価する時，一般には血液からコレステロールの値やバイオマーカーをみますが，神経系の病気の場合は実際にはinvestigatorの評価が基準になります．グローバルな治験をする時には評価者の差が大きくなりやすい可能性がありますが，現在，アジアの各国，欧米と比べて，国ごとの差はありますか．

水野　それはかなり少なくなってきていると思います．UPDRSが一番使われていますが，どの程度がⅡ度か，Ⅲ度の重症度かというinvestigatorを教育するビデオもでき，治験を始める前に皆で見て，同じ標準でつけようとしている．そうした改善はありますが，やはり人が行うことで変化はあると思います．ただ，nの大きい二重盲検治験になると，評価者の違いがあっても同様に両群に分けられるので，大きな問題にはなっていません．

*　　*　　*

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アジアにおける臨床試験の現状と課題：抗認知症薬

Current status and future perspectives in Asian clinical trials: Anti-dementia drugs

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はじめに

抗認知症薬，anti-dementia drugsに関して日本が加わったグローバルトライアルは，終了したものが1つ，現在進行形のものが4つほどありますが，Asian studyとして行われたもの，あるいは行われつつあるものはないと思います．東南アジアのいくつかの国でMCI (mild cognitive impairment) を持った人たちを対象としたトライアルが1つあると聞いていますが，まだ論文発表されていないと思います．ここではいくつかの課題を示したいと思います．

1．抗認知症薬トライアルの歴史的経緯

1990年に，抗認知症薬のトライアルを行う時に使用すべきcriteriaについてFDAが示しています (Table 1)．Dual Efficacy TrialsやDual Assessmentと言われるものですが，performance-based cognitive testを行い，認知機能，cognitive functionの変化を確かめることが1つ．もう1つは，その認知機能検査とは独立した評価，つまり別の評価者が行いますが，臨床的な状態像の変化を評価するよう示されたわけです．現在まで，少なくともsymptomatic treatmentに関してはこの基準が用いられています．

この基準に従った最初の大規模な抗認知症薬試験の論文は1992年で，*New England Journal of Medicine*にタクリン（商品名：コグネックス）という抗認知症薬，今はもう肝機能障害のためにほとんど使われませんが，Mount Sinai School of MedicineのKenneth L. Davisたちが行った試験の報告[*1]が初めてでした．その後同様の基準を使って，1998年にアメリカで塩酸ドネペジルの最初の報告[*2]がされています．その後にいくつかの薬が続くという状況になります．

Table 1　FDA guidelines for AD trials criteria for efficacy (1990)

◈ Dual Efficacy Trials:
Two independent outcome measures

- Improvement in cognitive function
  Performance-based cognitive instrument
  (e.g. ADAS cog.)
- Improvement must be clinically significant in global assessment (e.g. CIBIC (Clinician's Interview-Based Impression of Change), CIBIC plus, ADCS-CGIC)

*1 Davis KL, et al. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. The Tacrine Collaborative Study Group. *NEJM*. 1992；327(18)：1253-9.

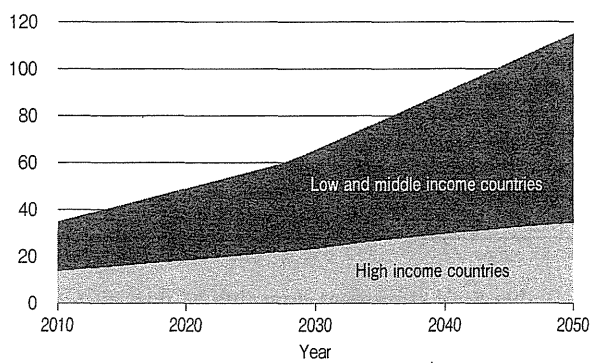
*2 Rogers SL, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology*. 1998；50：136-45.

ただ，このDual Assessmentは，抗認知症薬に比較的特異的な評価方法だと思います．このためにいくつかの利点もありますし，それから課題も出てきます．このリリースの後，1994年にIWG (International Working Group for Harmonization of Dementia Guidelines) をつくり，カナダ，アメリカ，イギリス，オーストラリア，日本の研究者・臨床医が加わり，symptomatic treatmentのプロトコルを作成・周知するグループをつくりました．医療経済的な指標やサプリメントも含めて*Alzheimer Disease & Associated Disorders*などに発表し，一定の貢献をできたと考えています．

一方，ADI (Alzheimer's Disease International) という国際的な学会が発表している*World Alzheimer Report*の2009年版の記事では，今後2050年に向けて，low and middle income countriesでは認知症の数が急激に増えていき，日本はhigh income countriesに入ることを示しています (Fig. 1)．

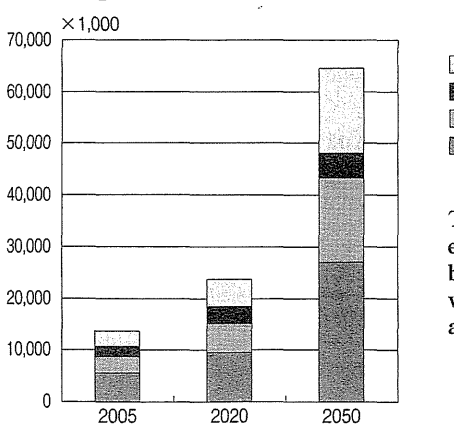
Fig. 2は2006年にADIが報告したレポートで，これから主に中国，インド，アジアの他地域，それから日本で，認知症がどのくらい増えていくかを示したものです．急激に増加するのは中国とインドが際立っています．こういう疫学的データからしても抗認知症薬を開発する上でAsian studyを行う意義は非常に高いと言えます．少なくとも十分なマーケットは存在するということです．

Fig. 1 The growth in numbers of persons with dementia (in million) in high income countries, and low and middle income countries



(*World Alzheimer Report* 2009, ADI)

Fig. 2 Total prevalence of dementia: China, India and other regional, 2005-2050



The dementia epidemic is certain especially in Asian countries because the number of people with dementia increase with aging population.

(Asia Pacific Members of ADI, 2006)

2. 認知機能検査に用いる評価基準

先ほど臨床的に意義のある変化を抗認知症薬の投与前後で確認できるかどうかが，Dual Assessmentとして確認されなければならないとお話しましたが，そのために最近用いられているinstrumentがADCS-CGIC (Alzheimer's Disease Cooperative Study Group-Clinical Global Impression of Change) で，USC (University of Southern California) の精神科のLon S. Schneider教授が1997年に発表したものです（Table 2）．これは7段階，著明改善から著明悪化までをclinical impressionでチェックするので，日本では非常に馴染み深いのではないでしょうか．介護者と本人との面接によって情報を得て，評価する方法をとります．こういうclinical impressionに基づいた評価でも，どのくらい評価者間に信頼性があるものか確認する必要があります．

Assessment Domains of ADCS-CGICはADCS-CGICに含まれる評価領域になります（Table 3）．General appearanceから始まって14番目のsocial functionまでありますが，これは領域がこう決められているだけで，具体的に質問のインストラクションは一切ありません（Table 4）．いわゆる評価者のクリニカルスキルに負うところが非常に大きくなります．

Table 2 ADCS-CGIC

Alzheimer's Disease Cooperative Study Group-Clinical Global Impression of Change (Schneider et al, 1997)

- Independent assessment of global change by the 7 point scale, compared with the baseline assessment
- Assessment based on the information from a primary carer and a person with dementia

Marked Improvement
Moderate Improvement
Minimal Improvement
No Change
Minimal Worsening
Moderate Worsening
Marked Worsening

Table 3 Assessment domains of ADCS-CGIC

1. General appearance
2. Arousal/attention/Alertness
3. Orientation
4. Memory
5. Language/Speech
6. Praxis
7. Judgment/Problem Solving/Insight
8. Content of thought
9. Hallucinations/Delusions
10. Behaviors/Mood
11. Sleep/Appetite
12. Neurological/Psychomotor activity
13. Basic/Instrumental activities of daily living
14. Social function

Table 4 ADCS-CGIC worksheet sample

Area: Relevant History	Probes: Recent clinical events? Illness?
Caregiver	
Patient	
Area: Observation	**Probes: Appearance, body movements, attitude**
Caregiver	
Patient	

3. 日本での治療評価の実例

Table 5は日本で行ったものですが，CIBIC-plus (Clinician's Interview-Based Impression of Change)，ADCS-CGICとほぼ似たものですが，それの信頼性を国内の研究者で確認しました．

ビデオテープを20本用意しました．抗認知症薬関係で実際に著明改善はなかなかないわけで，そのうち7本はsimulated patientsを使ってつくりました．残りの13本は実際の患者の前後の状態をビデオで記録したものです．20人の患者の前後ですからビデオ本数にすると40本になり，半年間のインターバルを置いてつくりました．それを11人の精神科医などエキスパートに協力してもらい，まったく独立して40組のビデオを7件法に従って評価をしたわけです．膨大な時間がかかりました．

その結果ですが，カッパ係数を用いて完全に一致した例は0.45になりました．Substantial agreementよりも低い，moderate agreementぐらいになるわけです．ただ，7件法ですが，1段階許容すると0.89まで上がります．0.89というとalmost perfect agreementのレベルまで達しますので，実際の臨床では十分だと思います．こういうスタディは日本とアメリカでは行われていますが，それ以外の国では行われていないという現状もあります．

4. Asian studyに問われる課題

Asian studyに関して，アジアの国々の中で臨床試験を行う上で，もう少しコミュニケーションを高めようという動きがあります．2007年にIWGのミーティングがフィリピンのマニラで行われた時に，ASAD (Asian Society Against Dementia)の立ち上げを行いました．その後，台湾の高雄，韓国のソウル，そして今年2010年はインドネシアのバリで行われました．インド，香港，中国，韓国，シンガポール，インドネシア，フィリピン，マレーシア，タイ，ベトナム，スリランカ，台湾，日本が参加しています．

この学会のミッションの1つは，アジアンプロトコルを考え，アウトカムメジャーに対してスキルを高めていこうということです．もう1つは，これらの国々は，ヘルスプロフェッショナルも含め，まだ認知症に対する認識が日本よりも低いため，それをさらに高めていこうというわけです．ASADに属する国々の中では，認知症はノーマルエイジングの一形態だと考えられているのが現状です．また，例えばインドでは，抗認知症薬が開発されたとしても，国民の大多数は他の病気になった時ですら医療機関にアクセスできないわけです．そういう現状の国もある．そういう意味で

Table 5 How reliable is the global assessment?

- Inter-rater reliability of CIBIC plus
- 20 video-taped mild AD patients (incl. 7 simulated pts.)
- 11 experts assessed 20 pts twice with 6 months interval.

	Improved				Worsened			
	Marked	Moderate	Minimal	No change	Minimal	Moderate	Marked	
Total	2	3	3	3	4	3	2	20

- Multiple rater kappa coefficient: **0.45**
  - Average proportion of complete agreement over all 55 pairs of 11 raters: 53.8%
- Multiple rater weighted kappa coefficient: **0.89** (disagreement of one grade is permitted)
  - Average proportion of agreement: 94.0%

(Homma et al. *Dement Geriatr Cogn Disord.* 2006 ; 21 : 97-103.)

は，ASADが行わなければいけないミッションも多岐にわたると思います．啓発的な活動がまず優先されるべきだと考えています．

Asian trialを行う上で考えなければいけない事柄を示します（Table 6）．1つは診断の問題．欧米間，日米間，日欧間で，いわゆる認知症，アルツハイマー病，血管性認知症，DLB（dementia with lewy bodies）等々の診断に関する試みは既に行われていますが，アジアの国々の中ではない．グローバルアセスメントに関するinter-rater agreementが，やはりアジアの国々の中ではまだないことです．特にプライマリーのアウトカムメジャーに関して，アジアの国々の中で使われた場合，そのequivalencyをどう確認するかという課題もあります．

それから，多くの認知機能検査では言語が使われていますが，その場合のethnic/cultural differencesをどう考えればいいのかという課題もあります．Linguistic validationと言えるかもしれません．日本，アメリカ，欧州のいくつかの国では，いわゆる言葉の属性に関するデータベースが既に整えられていますが，多くのアジアの国々ではまだデータベースは整備されていません．そうすると，使われる言葉，例えばfrequencyやfamiliarityやimageryをどう確認すればいいのか，予備的な研究が必要になってくると思います．

最後にethical issuesに含まれる課題ですが，少なくともアジアの国々でトライアルを行っていく時には，参加した国の人たちにも何らかのベネフィットがあるべきと考えます．仮に抗認知症薬と考え，果たして薬がその国で発売された時にどのくらいの人たちが使えるのかという問題です．インドだとおそらく8割の人は医療機関にアクセスさえできない，大部分の人は恩恵に浴することができないわけです．倫理的な側面に関する議論が十分にされていないと思います．2007年にそれに関する一文が*Lancet*に紹介されましたが[*3]，Asian studyを行う上での倫理的な側面に関して，一定のコンセンサスがさらに示されるべきだと思います．

＜質疑応答＞

座長（小林） 最後に示された診断のアグリーメントなど色々ありましたが，実際問題としてそれを統合する動きはありますか．

本間 一部にありますが，まだ本当に十分ではないと思います．

座長（小林） 患者が使えないというのは，政治的な問題など難しい問題があると思いますが，医師の中でできることもまだ行われていないということですか．

本間 このことに関する認識は少なくともあります．例えば，薬価の違いも大きな問題として取り上げられるべきだと思います．

Table 6 Issues which have to be considered for Asian trials

- Asian multi-national study on the diagnosis of dementia
- Inter-rater agreement study on outcome measures among Asian investigators
- How to confirm the equivalency of outcome measures used in each country?
- How to cope with ethnic/cultural differences in the verbal tasks?
  e.g. Is it possible to control the frequency, familiarity, image of words in the word recall/recognition tasks? In many Asian countries such database is not available. Strictly speaking, huge time-consuming study is needed before starting trials.
- Ethical issues

[*3] Epstein M. Clinical trials in the developing world. *Lancet.* 2007；369：1859.

Clinical trials in neurological disorders in Korea

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1. Global clinical trials

The contents of my presentation today include the current status of clinical trials in Korea, recent trials in neurology, and parameters used in trials for Alzheimer's dementia and Parkinson's disease. And finally I'll briefly cover the drug approval process in Korea.

South Korea is ranked as the 25th country in the world actively participating in global clinical trials. The increasing rate of global trial activities is fairly high. It's 18 percent per year.

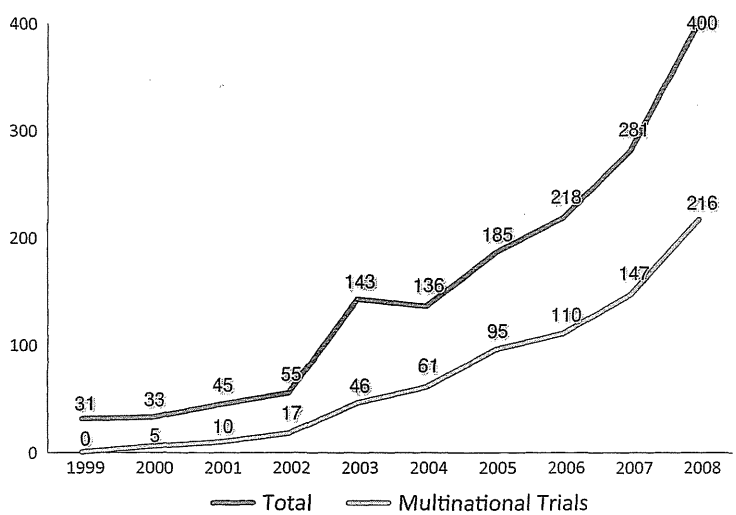
2. Clinical trials in Korea

The number of clinical trials performed in Korea has increased tremendously in the past 10 years (Fig. 1). The total number of clinical trials was 31 in 1999, but it increased to 400 in 2008. As for global trials, in 1999, there was no global trial performed in Korea; but in 2008, there were more than 200 global trials performed in the country.

2.1 Increase in early phase trials

In recent years also, there's an increasing trend

Fig. 1 Rapid growth in clinical trials



not only in Phase 3 trials, but also in early phase trials. From 2007 to 2008, there was a 37% increase in early Phase 1 or Phase 2 trials in Korea.

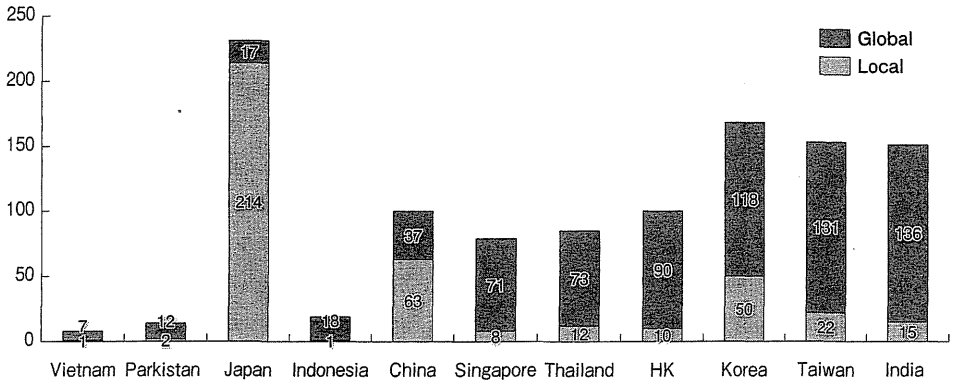
2.2 Domestic & global studies in Asia

According to data from the website www.clinicaltrials.gov, in 2006, Korea is the second most active country in Asia in terms of clinical trials, preceded by Japan. But if you look at this chart, majority of the trials conducted in Japan at that time were domestic trials, while those conducted in Korea comprised both of international and domestic trials. So it's a little balanced in Korea (Fig. 2).

2.3 Increasing trend of industry-funded studies

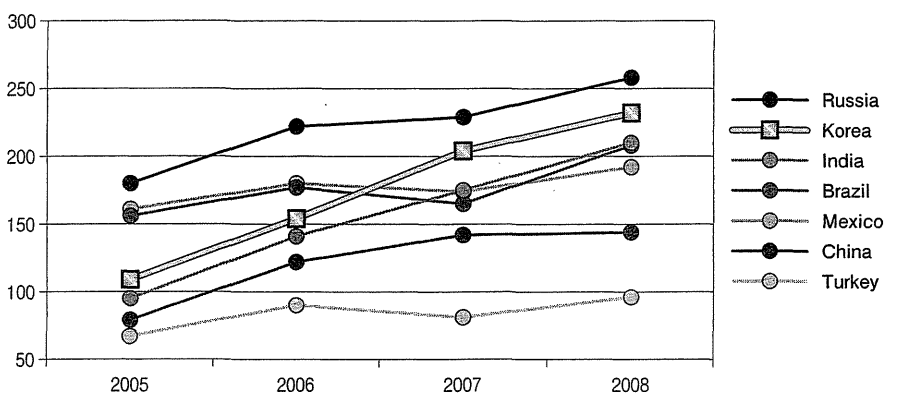
We also see an increasing trend in industry-funded studies among the emerging economies, such as Russia, Korea, India, Brazil, Mexico, China, and Turkey (ranking in 2008, Fig. 3). And in 2008, Korea was ranked second, preceded by Russia, in terms of the number of industry-funded studies.

Fig. 2 Domestic & global studies in Asia



Sources, Hong Kong Univ. CTC : www.clinicaltrials.gov (Oct 06)

Fig. 3 Number of industry-funded studies



Source: ClinicalTrials.gov, accessed 24 May, 2009

2.4 Trials by therapeutic areas

In terms of therapeutic areas, trials for cancer/oncology are the most frequently performed studies in Korea, followed by cardiovascular disease (Fig. 4). Neurology trials for CNS disorders are in third position, and these trials cover neurological diseases and also psychiatric diseases.

2.5 Geographic distribution of multinational trials in Korea

Most of the clinical trials in Korea were performed in Seoul and Metro Seoul areas. Of the 1,130 trials conducted in the country, about 653 are carried out in Seoul and 141 are carried out in Metro Seoul areas. Other provinces have fairly low rate of clinical trials being conducted.

2.6 Most active Asian cities in clinical trials

Fig. 5 shows that Seoul is very active in conducting clinical trials and ranks in the top 50 of the most active Asian cities in terms of conducting multinational trials. Tokyo is rank 24. In Tokyo, majority of the clinical trials conducted are local trials.

2.7 Multinational trials in major hospitals in Korea

Most of the clinical trials in Korea are performed in major hospitals, especially in what we call the four major hospitals, including our hospital, the Yonsei University Hospital, Samsung Seoul Hospital, Asan Medical Center in Seoul, and the Seoul National University Hospital. These are all big hospitals with an average of 6,000 outpatients daily. My hospital, Yonsei University Hospital, has 1,245 doctors and 2,076 beds. Asan Medical Center has 1,180 doctors and 2,181 beds. Seoul National University Hospital has 1,126 doctors and 1,763 beds, and Samsung Medical Center has 820 doctors and 1,348 beds. These four major hospitals not only dominate the conduct of Phase 3 trials but also early phase trials, such as Phase 1 and 2, and Phase 4 trials as well.

As for sponsors of multinational trials, majority of the trials carried out in Korea are sponsored large multinational pharmaceutical companies such as GSK, Pfizer, Sanofi-Aventis, Janssen, Novartis, AstraZeneca. Some trials are conducted by CROs while a few others are investigator-initiated trials.

Fig. 4 Trials by therapeutic areas

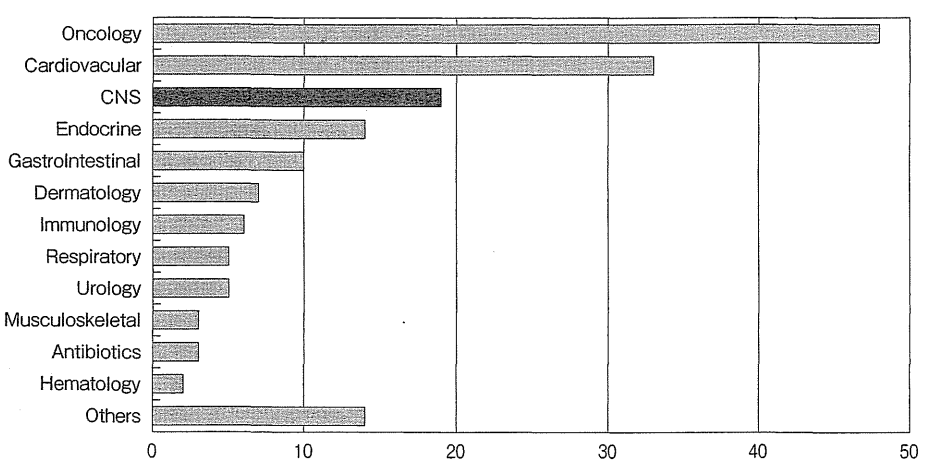
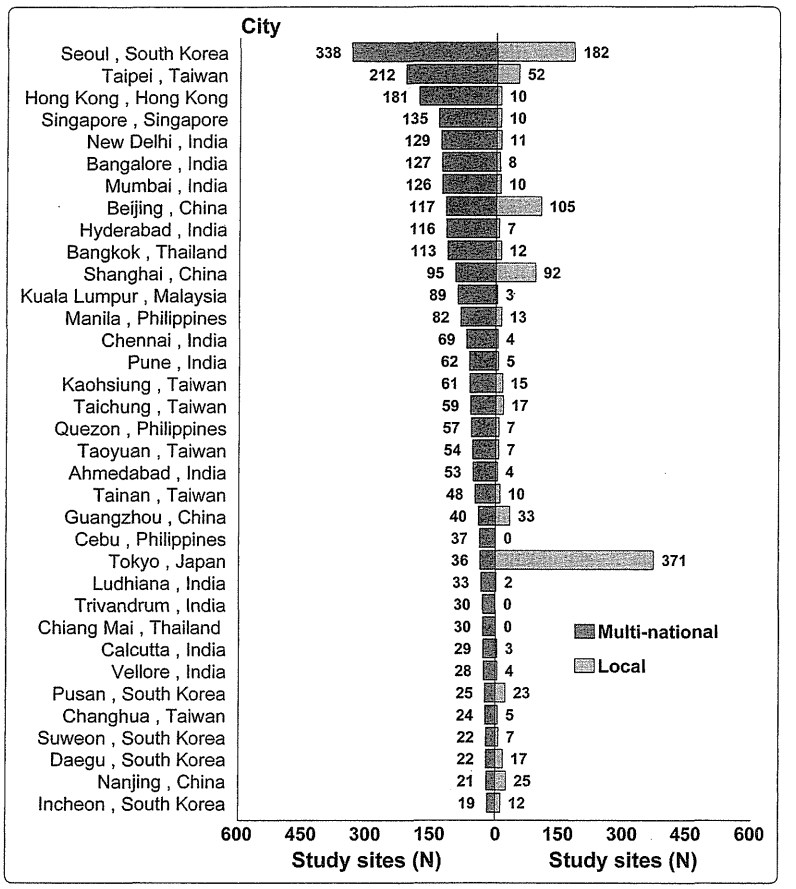


Fig. 5 Seoul: the most active city in clinical trials

The chart includes the number of study sites for both multi-nationally (ranking measure) and locally conducted industry sponsored clinical trials in the top 50 most active Asian cities.



Clinical Trial Magnifier. 2008 May ; 1(5). (www.ClinicalTrialMagnifier.com)

In terms of leading sponsors by types of trials, GSK and Pfizer are the leading companies performing clinical trials in Korea, and they carry out all kinds of studies – Phase 1, 2 and 3. My hospital is also involved in some Phase 1 trials by GSK, Janssen, and Wyeth and Pfizer.

3. Neurology trials in Korea (2005-2009/KFDA)

Now I'm going to talk about neurology trials which were performed in Korea from 2005 to 2009. We obtained data from the Korean FDA report. In 2005, nine (9) multicenter neurology trials were conducted according to the KFDA report, and these trials cover neuropathic pain, intracranial arterial stenosis, epilepsy, Alzheimer's dementia and stroke. In 2006, there were 8 trials conducted covering the areas of stroke, neuropathic pain, epilepsy, Alzheimer's dementia, restless leg syndrome, and myofascial pain. In 2007, we could see an increase in the number of trials conducted. In 2007, there were 15 clinical trials conducted in the areas of seizures, Parkinson's disease, epilepsy, Alzheimer's dementia, and blepharospasm. For the year 2008, there were 13 trials, mostly in the same fields of study. And in 2009, the same number of clinical trials, 13 trials, was conducted.

4. Summary of the trend

So in summary, during the period from 2005 to 2007, we can see an increase in the number of trials conducted in Korea in the year 2007, and the increase mostly comprised of Phase 3 trials. But in 2008 and 2009, there were some increase in early phase trials covering Phase 1 and Phase 2 (Fig. 6).

For disease indications, epilepsy and Alzheimer's dementia are the most frequently performed clinical studies in Korea followed by Parkinson's dementia and neuropathic pain. The study method is usually double-blind, placebo-controlled trials, and followed by double-blind, comparative study that compares test drug with other drugs (Fig. 7).

Fig. 6 Neurology trials registered in KFDA from 2005 to 2009-1

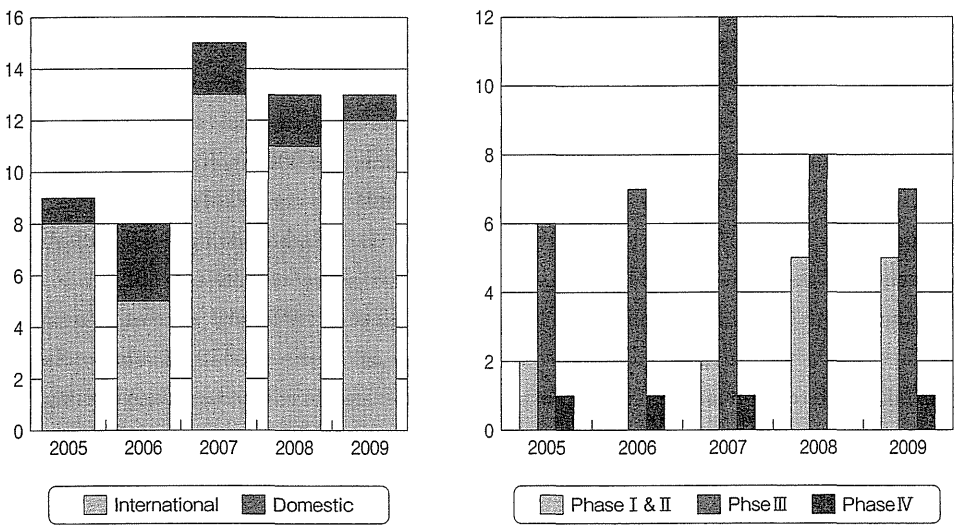
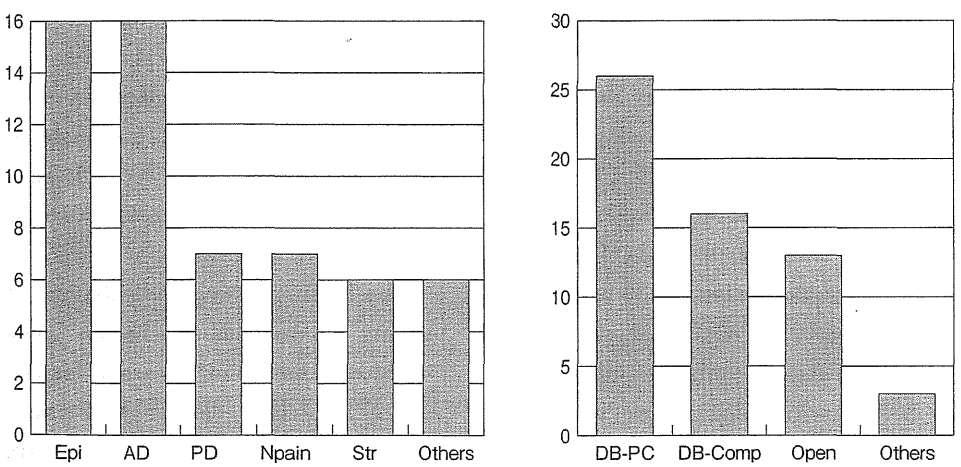


Fig. 7 Neurology trials registered in KFDA from 2005 to 2009-2



5. Participation in trials for dementia & PD

Now I'm going to discuss some of the trials for dementia and Parkinson's disease which I have participated in.

5.1 KD-501 study

The first trial that we participated in involves a compound called KD-501 which was developed by a domestic company. It is an herb extract. This study is a Phase 2 trial. It is a multicenter, double-blind, placebo-controlled, and parallel design trial performed in 10 centers. We plan to recruit 220 patients, with follow-up period of 12 weeks. The inclusion criteria are: (i) probable Alzheimer's disease, diagnosed by either DSM-IV or NINCDS-ADRDA criteria; (ii) the patient's MMSE score should be between 12 to 26, and the age should be from 50 to 85; (iii) and the patient should not be taking any AChE inhibitors or memantine at least for 3 months to be enrolled in this study. The primary outcome measure was ADAS-cog score change at 12 weeks of treatment, and secondary outcome measure was CDR, ADL, neuropsychiatric inventory and MMSE score.

5.2 LY450139

The other multinational global trial we are participating in is called LY450139 study. It is randomized, double-blind, placebo-controlled, parallel design trial, which is parallel designed for 64 weeks and then delay start designed to 84 weeks. It is multinational study involving a total of 1,100 patients. In Korea, we plan to include 80 patients, distributed to 10 patients per center. Inclusion criteria are probable Alzheimer's disease, diagnosed by NINCDS-ADRDA, with MMSE score of between 16 and 26. Primary outcome measure is the 11-item cognitive subscale of 14-item AD assessment scale (ADAS-Cog11). The other primary outcome measure is the 23-item Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL). Secondary outcome measures include biomarker, CDR, NPI, Dementia-Lite questionnaire, quality of life measures (including Euro-QoL-5D proxy), and MMSE.

5.3 LY2062430

Another study we are participating in is the so-called LY2062430. It is also similar designed study – randomized, double-blind, placebo-controlled, parallel design, with follow-up period of 80 weeks. It is a multinational study, and total number of patients is 1,000. In Korea, we plan to recruit 80 patients in 8 centers. Inclusion criteria are probable AD, diagnosed by NINCDS-ARDRA, with MMSE score of between 16 and 26 measured on initial visit. Primary outcome measures are the same as in the LY450139 study. Secondary outcomes measures are also very similar. But in this study we also measured the volumetric-based MRI. We used this MRI for secondary outcome measures.

5.4 Pramipexole ER

We also participated in trials for Parkinson's disease, the so-called Pramipexole ER (extended release) trials. This is a completed study. It was randomized, double-blind, placebo-controlled, three parallel group (ER, and IR (immediate release) and placebo-controlled) for 34 weeks. It was a multinational study, with total patient of 516. In Korea, it was originally planned to recruit 56 patients in 7 centers, but finally we enrolled 86 patients and 75 patients completed. Inclusion criteria are Parkinson's disease of 2 years or longer, and more than 2 hours daily "off" time. Primary outcome measure was UPDRS part 2 and part 3 score

change. Secondary outcome measure include (i) the percent "off" time and percent "on" time, (ii) proportion of patients with more than 20% improvement, (iii) CGI-I and PGI-I, (iv) levodopa dose, (v) quality of life measurements, and (vi) depression scale and sleep scale.

5.5 Safinamide

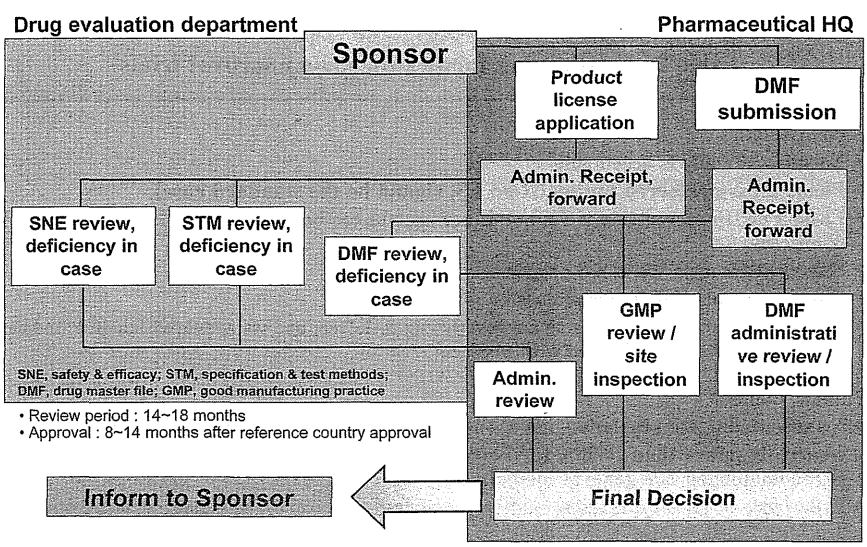
The other Parkinson's trial which is ongoing is so-called Safinamide. It is a randomized, double-blind, placebo-controlled, parallel design trial for 24 weeks. It is also a multinational study. Total patient is 480, and in Korea we are planning to recruit 40 patients in 4 centers. Inclusion criteria are Parkinson's disease with 5 or more years, levodopa responsive with dose between 4 to 10 times per day, and one and a half hours off-time per day. Primary outcome measure is daily "on" time measured by diary cards at 24 weeks. Secondary outcome measure include UPDRS Part II and Part III scores, dyskinesia rating scale score, CGI, daily off-time, change in LD dose, EQ 5D, PDQ-39.

6. Drug approval process in Korea

Now I will briefly cover the drug approval process in Korea. As you can see in Fig. 8, there are many aspects to be reviewed, and this include safety and efficacy, specification and test methods, drug master file and GMP review, site inspection, and things like that. The review period usually takes 14 to 18 months.

For drug registration in Korea (Table 1), the Korean FDA requires submission of quality pre-clinical data. Both pre-clinical and clinical data are required to be submitted. For clinical data, both the foreign approval and Korea data are required. For the foreign approval data, either FDA or EMEA or approval data from other leading countries is required in case it is an imported product. For Korean data, it is required that data should come from either participation in global studies or conduct of a local study. If it is participation in global studies, the sub-analysis in Korean population and comparison with general results are

Fig. 8 Drug approval process in Korea (by KFDA)



required. For conducting local studies, in case of regional or local study, the study design should be same or very similar to one of the global studies, or the so-called mother study, in order to show the comparable safety and efficacy in Koreans compared to Caucasians or other ethnic groups.

For drug approval trials, factors considered include study design and patient number (Table 2). For study design, Phase 3 trial is the preferred option. But Phase 1 or Phase 2 is also acceptable if Phase 1 or Phase 2 parameters can be linked to Phase 3 parameters, such as safety and efficacy. Study with many arms is not proper, and study to be included in global dossier is preferable. The comparator drug should be an approved drug in Korea. For the number of patients, there is no specified guideline in the regulation but the number should be sufficient to allow for descriptive analysis. Generally, more than 10 to 20 percent for Koreans per arm or more than 100 or 200 patients per study is recommended for general medicines. But the prevalence of target disease should be considered; so more prevalent disease usually requires enrollment of more patients.

Table 1 Requirements for drug registration in Korea (KFDA)

- Quality, Pre-clinical data
- Clinical data
  - Foreign approval (FDA, EMEA, or other leading countries), in case import products.
  - Korean data
    - Participate in global study
      - Sub-analysis for Korean populations and compare with the general results
    - Conduct local study
      - In case of regional or local study, the study design should be same / or very similar with one of global studies (called mother study), in order to show the comparable safety & efficacy in Korean compared to Caucasian.
      - In case Korean participated study is not included in global dossier, GCP inspection is needed during the NDA process, which may result in delay of the approval.

Table 2 Considering factors for drug approval trials

- Study design
  - Not-pivotal study is acceptable
  - **Phase III is preferred option (if no ES, should be the standard case)**
  - Phase I or II is acceptable if Ph I or II parameters can be linked to Ph III parameters (safety & efficacy)
  - Study with many arms is not proper
  - Study to be included in global dossier is preferable
  - Comparator drug(s) should be an approved drug in Korea, and its approved labeling (indication & posology) should be aligned with protocol
- Patient number
  - No specified in the regulation, but should be sufficient for descriptive analysis
  - **Generally, more than 10-20% for Korean per arm or more than 100-200 pts per study is recommended for general medicines**
  - Prevalence of target disease should be considered (more prevalent disease, more pts needed)

<Q&A>

Watanabe : I was very impressed to see your country's success in conducting clinical trials. I have two questions. How do you take ethnic difference in drug response into account when you start or when you plan to join global clinical trials? Do you need PKPD analysis before starting Phase 3 trials?

Sohn : In the trials that I participated in, as far as I understand, they do not perform any specific pharmacokinetic or pharmacodynamic studies especially for Korean people. I understand these are multinational studies which involve USA or European countries, also some Asian countries, something like that. But I'm not quite sure whether there are some trials performing that kind of aspects before going to Phase 3 trials. I have no idea. I have no information about that.

Watanabe : Second question is, what kind of incentives do you provide to investigators to encourage clinical trials? Do principal investigators have direct contract with the pharmaceutical industries?

Sohn : Actually there are, but I think we do not directly contact with pharmaceutical company. Instead we contact some CROs, clinical research organizations. They are the ones who contact the doctors, and whether they tested, whether they have some facilities, or whether they have enough patients to perform these studies. For incentives, actually I think there are two kinds of incentives which I could get from performing clinical trials. One, of course, is some economical support. The second one is, since the patients in my clinic are usually patients with Parkinson's disease and Alzheimer's dementia, although there are drugs available to treat symptoms of these diseases, there is no cure or there is treatment that's very effective. So by participating in clinical trials, it is kind of a new way I can provide care to the patient who will be involved in the study and they can get some benefits from new drugs.

Q : Just to answer that question that we just had, for the LY-compounds, we do have Japanese PK and PD data before, during the study, but not Korean data.

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Global clinical studies in Asia: Philippines side

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1. Growth of emerging market

The clinical trial industry in the Philippines is recently being looked at as somewhat dynamic, although we are not as dynamic as Korea would be. I think the impact should be seen in terms of the growth of emerging markets. It is obvious the Asian Pacific, in general, is quite a rapidly growing region (Fig. 1). Again there is a current shift in terms of clinical trials being conducted now and in the future, and that would be towards our region (Fig. 2).

Fig. 2　Current shift in geographical areas where clinical trials will be conducted

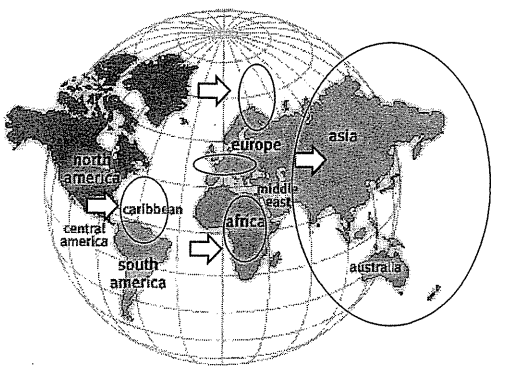
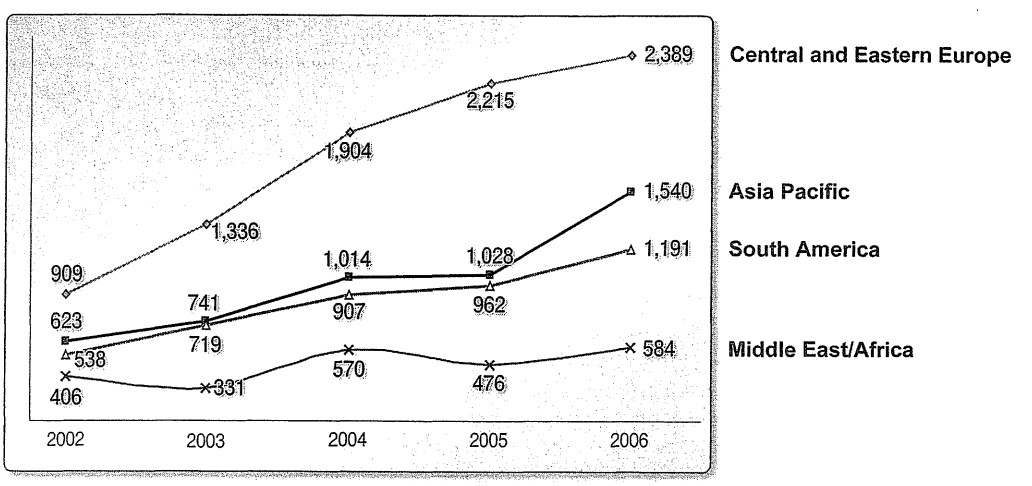


Fig. 1　Growth emerging market



CenterWatch 2007.

2. Economic impact of clinical trials

There is an economic impact of clinical trials (Table 1). For example in my country, a patient has to pay medications out of pocket, which means he pays the medications by himself. The insurance system is not robust; the insurance system is not good. So in terms of countries where there are insurance systems, maybe in terms of economic impact it becomes cheaper for the insurance company. In fact, as regard medications, the overall cost of treating clinical trial patients could be 17 percent less than patients getting standard treatment. So in clinical trials, and I think it could be true to some other countries as well, majority of the direct costs are shouldered by the pharmaceutical company. Now what are direct costs? Direct costs are the protocol-induced activities (Table 2).

3. Statistical indicators

Look at the situation in terms of statistical indicators (Table 3). The Philippines is now in the 12th spot in comparison to other countries in terms of population. Population growth rate is very high. The age structure though is at about 15 to 64 years of age.

3.1 Ten (10) leading causes of morbidity/mortality

When one looks at the morbidity or the 10 leading causes of death, number and rate per hundred

Table 1 Economic impact of clinical trials-1

- A study at The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute showed that in many cases it would be ***cheaper for the insurance provider*** to allow the patient to participate in a clinical trial. In one such trial, the research sponsor covered the chemotherapy charges, thereby saving the insurance provider over $100,000 over a typical 4 month treatment period.
- A study at Memorial Sloan-Kettering Cancer Center in New York City showed that the overall average cost of treating clinical trial patients was ***17% less*** than treating patients receiving standard care. (1)
- Karmanos Cancer Center in Detroit concluded in their study that costs for treating advanced lung cancer over a 6-month time period was on average $1,400 less for patients enrolled in a clinical trial. (2)

(1) Quirk J. Schrag D, Radzyner M, et al. *Proc Am Soc Clin Oncol.* 2000; 19: 433a. (abstr 1696).
(2) Bennett CL, Stinson TJ, Vogel V, et al. *J Clin Oncol.* 2000; 18: 2805-10

Table 2 Economic impact of clinical trials-2

- In the Philippines however majority of ***direct costs are shouldered by the sponsor,*** although no actual studies have been done yet to analyze the economic impact

What are Direct Costs?

Direct costs include costs of specific clinical procedures and costs of the research and administrative activities *required by the study protocol. These activities are often referred to as* ***"protocol-induced"*** activity, although the term properly includes also those clinical procedures mandated by the protocol and extending beyond standard care.

thousand in the Philippines (Table 4), what remains to be in the high end is respiratory infections. However, when one looks at mortality, the situation is that of the diseases of the heart, and if grouped together, vascular diseases.

Table 3 Statistical indicators

STATISTICAL INDICATORS	
POPULATION	97,976,603 (#12 spot in comparison to other countries)
POPULATION GROWTH RATE	1.957% (#61 spot in comparison to other countries)
AGE STRUCTURE	
0-14 years	35.2%
15- 64 years	60.6%
65 years and up	4.1%
MEDIAN AGE	22.5
SEX RATIO	
At birth	1.05 male(s)/female
Under 15 years	1.04 male(s)/female
15-64 years	1 male/female
65 years and up	0.76 male/female
Total population	1 male/female

SOURCE: https://www.cia.gov/library/publications/the-world-factbook/geos/rp.html

Table 4 Mortality: Ten leading causes

Number and rate/100,000 Population Philippines
5-Year Average (2000-2004) & 2005

Cause	5 Year Average (2000-2004)		2005*	
	Number	Rate	No.	Rate
1. Diseases of the Heart	66,412	83.3	77,060	90.4
2. Diseases of the Vascular system	50,886	63.9	54,372	63.8
3. Malignant Neoplasm	38,578	48.4	41,697	48.9
4. Pneumonia	32,989	41.4	36,510	42.8
5. Accidents	33,455	42.0	33,327	39.1
6. Tuberculosis, all forms	27,211	34.2	26,588	31.2
7. Chronic lower respiratory diseases	18,015	22.6	20,951	24.6
8. Diabetes Mellitus	13,584	17.0	18,441	21.6
9. Certain conditions originating in the perinatal period	14,477	18.2	12,368	14.5
10. Nephritis, nephrotic syndrome and nephrosis	9,166	11.5	11,056	3.6

Note: Excludes ill-defined and unknown causes of mortality
(R00-R99) n=23,235
Last Update: June 29, 2009

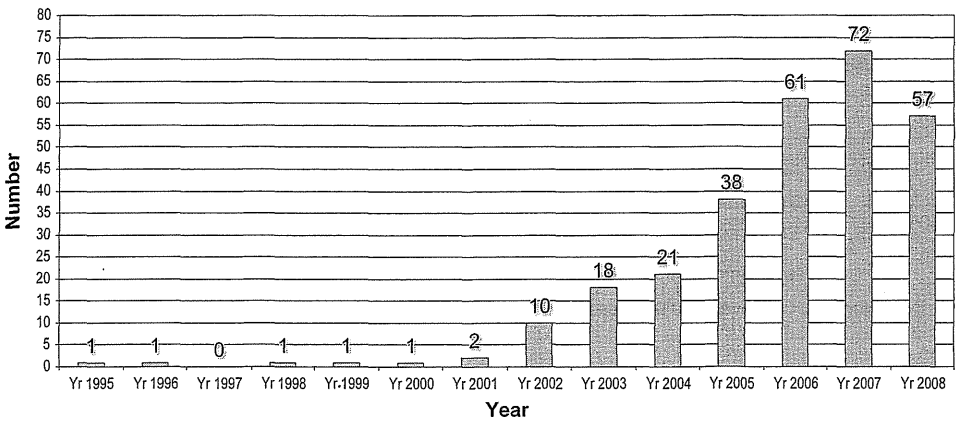
3.2 Data from ClinicalTrials.gov on CTs in the Philippines

Looking at some data acquired from the website ClinicalTrials.gov (Fig. 3), the number of clinical trials at the start of the year is increasing this time; similar to what is being shown in Korea.

As far as the number of clinical trials by phase (Fig. 4), majority are in Phase 3 trials, which is quite different from Korea. It appears Korea has more of the Phase 2 trials, but they also have a large part coming from Phase 3. Interestingly, the Philippines have a large number of Phase 4 clinical trials (42.14%), a phase largely hinged on post-marketing surveillance and potentially new indications or adverse drug effects.

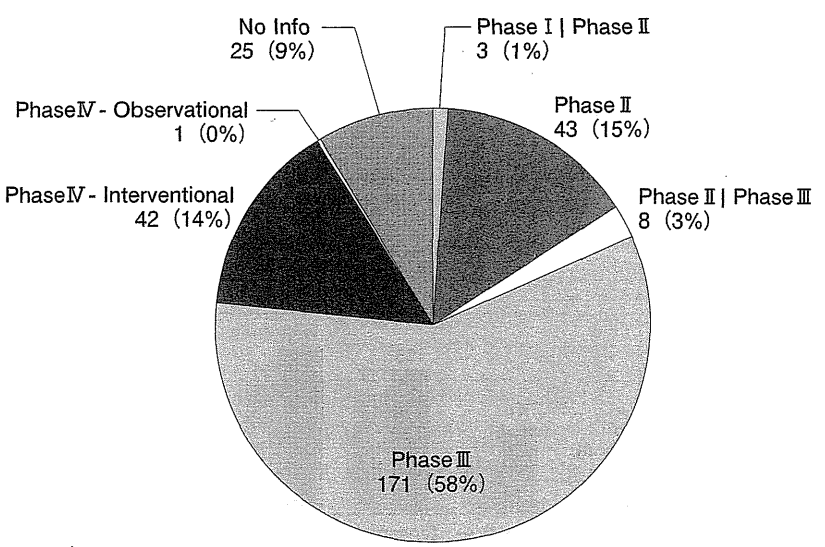
Towards the therapeutic areas (Fig. 5), neurological and psychiatric diseases have grown tremendously, really quite big nowadays, compared to

Fig. 3 Number of trials based on start year



From: www.clinicaltrials.gov

Fig. 4 Distribution of clinical trials by phases



the other therapeutic areas.

In terms of clinical trials registration in Asia for the period 2008 and 2009, it is clear that the Philippines part really pale compared to other countries (Fig. 6).

Again in the Philippines, if one looks at another data source, such as the database CiteLine, Phase 3 clinical trials dominate by far.

Fig. 5 Distribution of clinical trials by therapeutic area

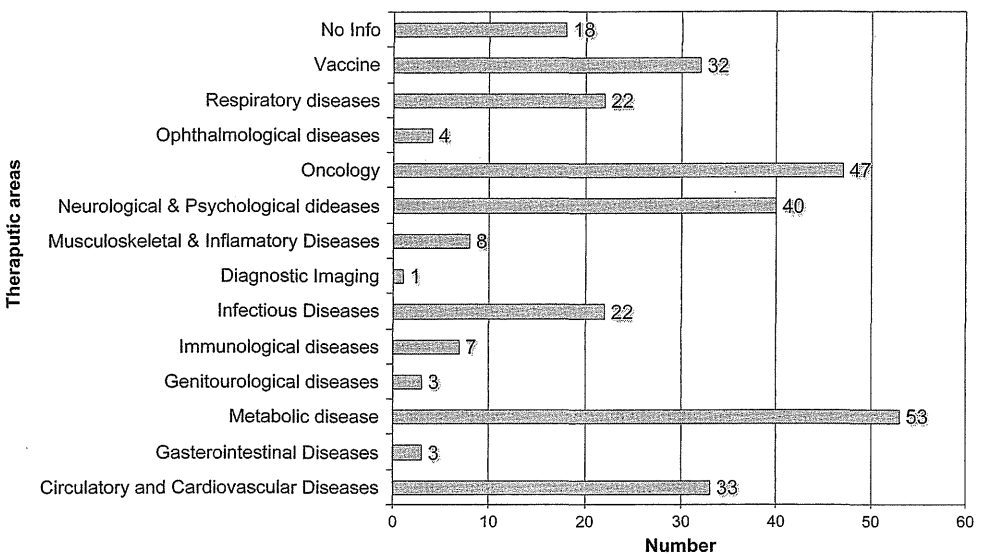


Fig. 6 Clinical trials registered at www.clinicaltrials.gov