4. Healthcare infrastructure

When a plan is embarked to bring a clinical trial to a specific site, it is critical for any sponsor to look at the infrastructure of that country as regard healthcare delivery (Table 5). Per Asian population comparison, the Philippines ranks fifth following that of China, India, Indonesia and Japan, but our birthrate is fast growing. Although we have a modest number of doctors, the number of hospitals, and corresponding hospital beds (i.e. healthcare infrastructure) may not be enough to service the entire population.

As of 2002 (Table 6) the physician density per 10,000 population, is about 12, but this should have changed drastically with the ever growing population, including that of the paramedical and support personnel. Interestingly, the pharmaceutical personnel density is only half of that of the physician density.

Table 5 Healthcare infrastructure in Asian region

Country	Population (in mn)	No. of Hospitals	Hospital beds	No. of Doctors
Australia	20.6	1,291	82,000	57,000
China	1,320	18,700	3,300,000	2,000,000
Hong Kong	7	40	31,937	8,700
India	1,097	7,300	684,000	780,000
Indonesia	222	1,200	133,200	45,000
Japan	127.7	106,468	1,800,000	270,371
Malaysia	26.6	346	50,540	18,250
NewZealand	4	158	24,000	9,000
Philippines	91	2,484	106,316	94,000
Singapore	4.4	29	11,545	5,747
South Korea	49	2,082	417,500	93,000
Taiwan	22.8	547	131,152	50,054
Thailand	63	1,300	135,000	19,000
Vietnam	83	833	136,000	50,100

(Biospectrumasia.com)

Table 6 Health workforce in the Philippines

Indicator	Value (year)
Dentistry personnel density (per 10,000 population)	6.00 (2002)
Number of dentistry personnel	43,220 (2002)
Number of nursing and midwifery personnel	480,910 (2002)
Number of other health service providers	90,788 (2000)
Number of Pharmaceutical personnel	46,360 (2002)
Number of Physicians	90,370 (2002)
Nursing and midwifery personnel density (per 10,000 population)	61.00 (2002)
Other health service providers density (per 10,000 population)	12.00 (2000)
Pharmaceutical personnel density (per 10,000 population)	6.00 (2002)
Physicians density (per 10,000 population)	12.00 (2002)

Source: http://www.who.int/countries/phl/en/

5. R&D expenditure/GDP (%): Asian countries

When one looks at the map of how a trial will move from the bench to the bedside (e.g. to clinical practice), what may create an impact is a translational research. Broadly defined, translational research provides a scientific link between laboratory research and human trials that potentially change healthcare in terms of diagnosis, and mainly treatment.

When one looks at the research and development (R&D) and the GDP percentage in Asian countries, Japan is at the helm (Fig. 7), and quite obviously, the Philippines is at the lower end, reflecting how much we value research at the present time and the attendant expenditures thereto. However, the trends are encouraging as we get enlisted more recently to multi-centric clinical trials.

6. Ethical & regulatory perspectives in clinical research in the Philippines

Ethical and regulatory agencies exist in our country. What used to be called BFAD or the Bureau of Food and Drug Administration, has been renamed as the Philippine FDA in 2009 (Table 7). Thus, the Philippine FDA now will look at the requirements for approval of clinical trials, monitoring release, and post-marketing surveillance once the drug has been released into the population.

Fig. 7 R&D expenditure / GDP (%) : Asian countries

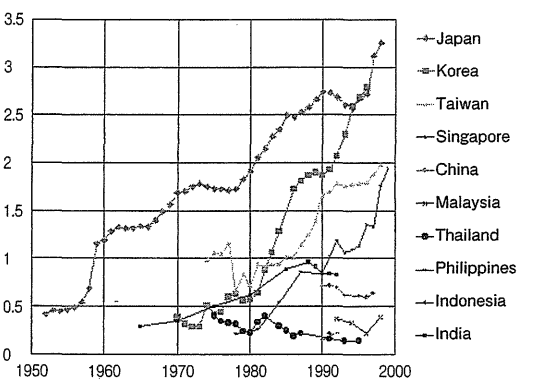


Table 7 FDA current regulations

- The BFAD was renamed into FDA by the power of the Republic Act 9711 which was signed into law in August 2009
  - — boosts the regulatory capacity of the FDA by mandating the establishment of adequate testing laboratories and field offices, upgrading its equipment and personnel, and authorizing the agency to retain income.
- AO No. 22 A.S. 1982: Guidelines for Research Involving Human Subjects
- BFAD Operation Manual on Drug Evaluation and Control
  - — Requirement for approval of Clinical Trial
  - — Requirements for products registered as Monitored Release prior to its approval for general use
    - Post Marketing Surveillance Studies

6.1 Philippine Council for Health Research and Development (PCHRD)

The PCHRD is the primary focal point of health research activities in the Philippines (Executive order No. 128), and it is an agency under the Department of Science and Technology. PCHRD organized the National Ethics Committee or the NEC in 1984. The NEC ensures that all health research and development proposals conform to ethical standards as set in the Philippine scenario. In addition, the NEC also promoted the formation of IRBs or Institutional Review Boards in different institutions (mainly hospitals) throughout the country.

Fifty percent of local research institutions actually have IRBs, and almost half of the 80 reported IRBs in the Philippines are in the National Capital Region, that is to say, Metro Manila (Table 8).

6.2 Institutional review board/ethics committee

The institutional review board safeguards the rights, safety and well-being of trial subjects. And in the Philippines, different institutions have different guidelines on clinical trials. But they all adhere to or they conform to the ICH-GCP guidelines. In the event that an institution participates in a clinical drug trial and an IRB is not existent locally, then that institution will have to utilize the NEC, which is actually housed in the National Institute of Health at the University of the Philippines General Hospital. To date, separate guidelines have been set for biomedical and behavioral researches in the country.

6.3 Submission of clinical trial to FDA

All trials in the Philippines are eventually submitted to the FDA, which is independent of the IRB. In effect, a sponsor who enlists a country site for a clinical trial will have to submit the dossier of the trial simultaneously to the national/local ethics committees and the FDA. A dossier includes the protocol, informed consent in English, and of course, individual ethics committees will also require translation to the local vernacular (Tagalog, Visaya, Ilocano, etc). Regulated fees may be required during the submission and evaluation process in the IRBs and FDA. A permission to import an investigational product is granted by another regulatory authority upon the approval of the clinical trial. Among others for instance, the Bureau of Quarantine regulates shipment of blood and similar products from outside of the Philippines.

Table 8 Ethical and regulatory perspectives

The *National Ethical Guidelines* cite a 2003-2004 survey indicating that only 50 percent of local research institutions have IERCs.
The same study found that almost half of the 80 reported IERCs in the Philippines are in the National Capital Region. (n3) According to PCHRD, researchers at institutions without their own IERCs should seek review from NEC or from other institutions. Both private and government researchers at institutions without IERCs have asked NEC, the National Institute of Health, the University of the Philippines and other institutions to review their proposals.

There are currently no formal national enforcement mechanisms in place for the *National Guidelines for Biomedical/Behavioral Research.*
Compliance is promoted primarily through "moral force." Individual IRECs may have their own enforcement mechanisms in place.

From the Harvard School of Public Health, Global Research Ethics Map

6.4 Regulatory approval system & timeframe

At par with our Asian counterparts, the general IRB regulatory approval system and timeframe, is about 2 to 4 months in the Philippines (Table 9). The said timeframe is independent from associated agency approval processes (e.g. the Bureau of Customs which regulates importation of investigational drugs and devices and equipment for research). Thus, the sponsors have to be aware that regulatory authorities exist in our country starting from the IRBs, the FDA, the quarantine office, and now the customs office. The list of items required by associated agencies to be submitted or satisfied by sponsors include tariff and duty rates, valuating rates, clearing imports, and so on, which entails quite a bureaucracy. The over-all regulatory approval process of clinical trials therefore, will span between 2 to 8 months from inception to final patient enrolment to the trial.

6.5 Issues and perspectives

There are a number of issues and perspectives that we can derive from the data that we have just presented. Among the challenges are: (1) Adherence to the new concepts and rules of the ICH-GCP standard application or implementation; (2) During clinical trial processes, monitoring and management remain challenging; (3) Institutional infrastructure may not yet be mature, including the shortage of experience, manpower and resources. What about the threats? These threats may include the variable and slow regulatory timelines and bureaucracy; the lack of regulatory guidelines; the indirect trade barriers/protectionism; the pricing controls; and the standard inspection system which may need to be robust.

7. Global trials vs. Asian trials

From the Asian R&D Fast Facts (2007-2008), cancer and cardiovascular diseases are on the top list, while, the unmet needs in the Philippines remain to be, lower respiratory tract infection, ischemic heart disease and tuberculosis.

It may be worthwhile to also look at the comparison of Asian trials in general versus that of the global trials. If you can see in Fig. 8, neurology is a measly 4.9 percent. If one were to derive data from a recent publication source (*Clinical Trial Magnifier*, Volume 1, 2008), the clinical trials in neurology globally is about 4.9 percent, and in Asia, about 3.4 percent. From the same source looking at the number of study sites and study protocols in

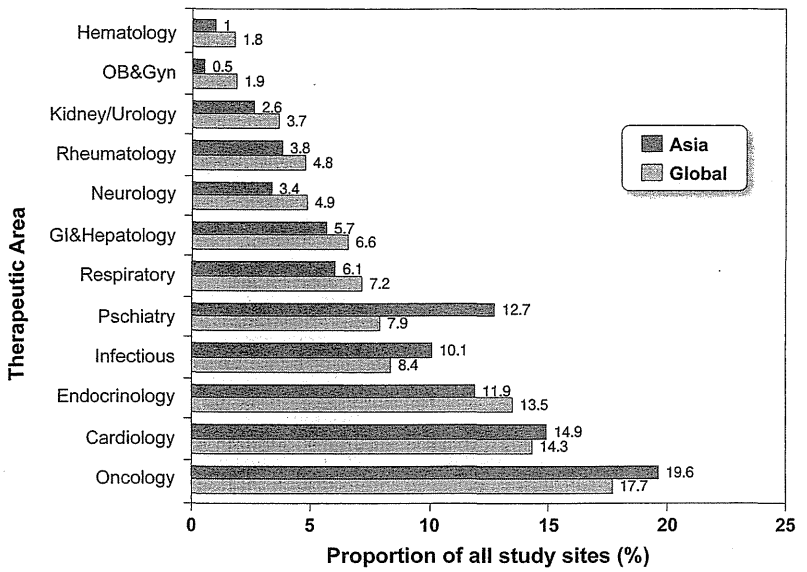
Table 9 Regulatory approval system & timeframe

Regulatory Considerations

Country	GCP Guidelines	Regulatory Authority	IRB Timeframe	Regulatory Timeframe	Est. Total Timeframe
Singapore	1998	CPA (HSA)	1－2 mths	1－2 mths	2－4 mths
Malaysia	1999	NPCB	1－2 mths	1－2 mths	2－4 mths
Thailand	1999	Thai FDA	2－3 mths	1－2 mths	3－5 mths
Philippines		BFAD	2－3 mths	3－4 mths	2－4 mths
Indonesia	2001	BOM	1－2 mths	1－2 mths	2－4 mths
India	2001	DCGI	1－2 mths	3－4 mths	4－6 mths
China	1999	SDA	1－2 mths	3－6 mths	4－8 mths
Hong Kong	1998	DOH	1－2 mths	1－2 mths	2－4 mths
Taiwan	1996	DOH	2－3 mths	2－3 mths	4－6 mths

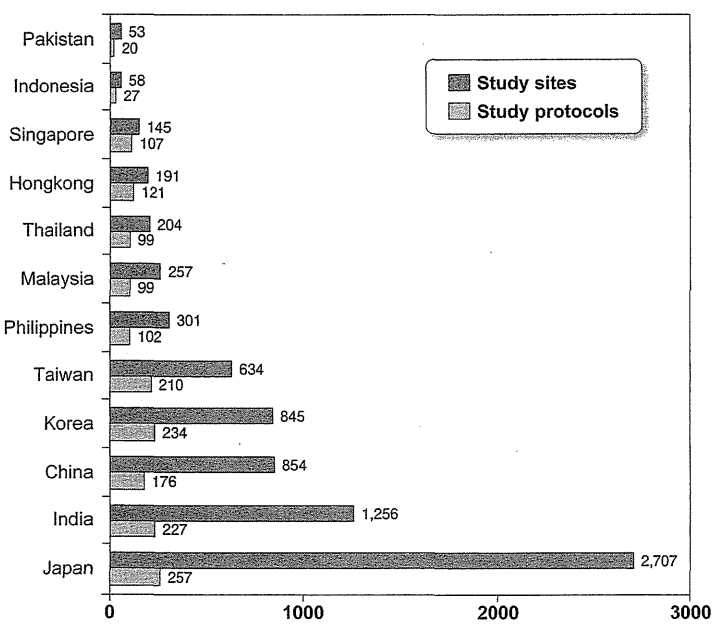
* The above average timeframes apply to pharmaceutical and biological products only

Fig. 8 Proportion of therapeutic areas among all sponsored clinical trials sites: Global vs. Asia



Source: *Clinical Trial Magnifier*. 2008 May ; 1(5).

Fig. 9 Number of study sites and study protocols in Asia per country



Source: *Clinical Trial Magnifier*. 2008 May ; 1(5).

Asia per country (Fig. 9), the Philippines has only about 301 study sites (6th place only) and about 102 protocols, compared to its Asian counterparts.

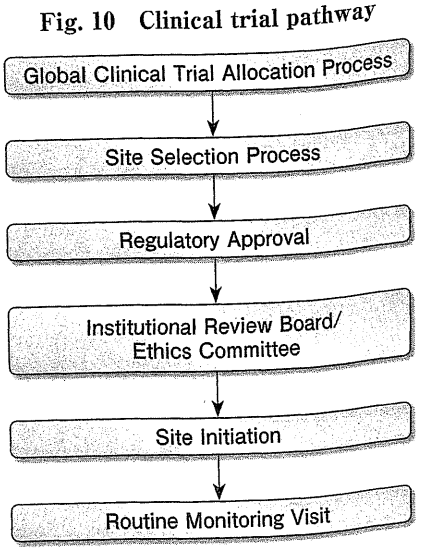
Now let's look at one example of a pharmaceutical company. They bring in about 300 protocols globally, or about 81.9 percent globally, and about 18.1 percent of the protocols are being brought to Asia. The most frequent neurological indications for these trials are stroke, epilepsy, movement disorders (Parkinson's disease and Dystonia), neuropathic pain, Alzheimer's disease, migraine and multiple sclerosis.

There are so many scales used in neurological studies, and I think these scales don't differ from those presented to by Professor Mizuno. These include UPDRS, PDQ39, PGI, CGI, VAS, MOS, HADS, BPRS, MMT, MAS.

8. Global clinical trial pathway

Fig. 10 is an illustration of what the pathway of a clinical trial should be. It starts with the global clinical trial allocation process, and then followed by what is referred to as the site selection process, then it goes through the tedious regulatory approval, then the review of IRBs, then the initiation of the trial, and then the monitoring of the trial through site visits.

Fig. 10 Clinical trial pathway



8.1 Global clinical trial allocation process

What constitutes an allocation process? This process looks at research program as regard protocol feasibility and even site feasibility. It is the pharmaceutical business unit that initiates the clinical trial feasibility process. The feasibility questionnaire will be forwarded to the clinical trial core countries. Criteria for country selection includes but not limited to productivity, market size, availability of subjects, disease prevalence of drug indication, regulatory and approval timelines and capability of the country in conducting a clinical trial.

8.2 Site selection process

What is the basis for the site selection process? It includes professional qualifications and experience to conduct the proposed study and this is done through review of the curriculum vitae, valid medical license, and experience. The individual, especially the principal investigator of that site, must have a certification from GCP or Good Clinical Practice certified doctor. If no training has been undertaken at the time of evaluation, training should be provided. Thus, a doctor need not continue participating in the trial, if there is no willingness to undergo GCP training. Similarly, there should be sufficient interest in the proposed investigation, including investing adequate time and resources to be devoted in the conduct of the study. In our own particular site for example at the Metropolitan Medical Center, we have a clinical research coordinator and sub-coordinators who really manage all these trials that we have been

engaging (12 trials to date). The most important and critical thing for us and within ethical standards (mandated by our local IRB) is we do not engage in trials that overlap or that conflict with other medications. Study site staff should have the appropriate qualifications and time to devote to the study, including a specific unit to conduct patient evaluations. In place also are study site facilities (e.g. laboratory/ancillary diagnostic in-hospital centers); access to study population; an understanding that there may be frequent monitoring; an understanding that the requirements on source documents have to be used during the study must fulfill and comply with all GCP requirements and standard.

8.3 Import license

Import license is very important especially if the study drug is not FDA approved, and it is necessary for the drug to be shipped to the Philippines. To secure import license for that drug, a copy to the FDA is needed, certificate of analysis, proforma invoice and import license. Approval usually takes from 1 to 6 months.

8.4 Clinical trial agreement

As regard CTA (Clinical Trial Agreement), a question often raised, this is developed and executed based on the sponsor's policies and guidelines as well as local requirements. The monitoring team, headed by the Clinical Project Leader drafts, facilitates and participates in the review of the CTA. In our site, the CTA is ideally signed by the principal investigator with the director of the institution or the hospital. Thus, it involves a three-party signature process but in some occasions, the procedure may require a 2-way signature process between principal investigator and sponsor. In the latter instance, the local IRB head witnesses the document signing. In short, a direct agreement between the sponsor and the clinical trial investigator is not encouraged.

8.5 Site initiation

Once the trial has been approved, and the CTA has been signed, then the site initiation is started. The initiation is scheduled close to or when the site is ready to screen patients. It can be completed over multiple visits if deemed necessary by the Clinical Research Associate (CRA) or the Clinical Project Leader. Key topics that are recommended to be presented during the site initiation include: Overview or the characteristics of the compound; protocol background, rationale, study design and objectives; information about the study drug; protocol visits; Adverse events (AE) reporting; completion of Clinical research forms (CRFs); laboratory procedures; breaking of code; responsibilities of investigator; documentation; and filing and update of the ISF.

8.6 Routine monitoring visits

As regard progress of the trial, a monitoring team will oversee the study and site activities ensuring compliance with the protocol. Monitoring activities include onsite visits as well as regular contacts with the site staff. The frequency of visits will depend on the number of patients and complexity of the study. In this connection, other monitoring teams (e.g. US FDA, if involved) may also do site visits, especially if a site is having fast patient enrolment or increased AE profile, among other reasons.

Again going back to the clinical trial pathway, you have the global clinical trial allocation process, site selection process, regulatory approval, IRB, site initiation and routine monitoring visits. This is the same pathway that happens in the clinical trials from my country.

9. Concluding remarks

On the lighter side, Professor Nomoto also asked me to be in this meeting because he wanted me to share my thoughts about globalization in terms of clinical trials, and maybe even regionalization. My idea is these kinds of meetings are timely in thresh-ing out issues related to clinical trials in our part of the world. The impact is our having to be aware that more and more the Asian region becomes an important contributor in patient cohorts of multi-centric clinical trials. Thus, regulatory similarities and differences between countries are highlighted so as to learn from each other, and hopefully for-tify a regionalization research trend. After all, our patient physical traits appear to be similar, and we have the dire responsibility to improve and deliver quality health care. Perhaps, embarking and par-ticipating in translational research may not be a bad stepping up point.

9.1 Responsibility to patients

While ethical standards indicate that we protect the rights of patients and do no harm on them, especially those enrolled in clinical trials, there is also the other side. Participation in global/regional trials is just but one facet. We do have a responsi-bility to take part in the care of our patients indig-enous to our locale.

For example, DYT3 dystonia or X-linked dysto-nia-Parkinsonism of Panay (referred to as "Lubag" in the world literature) is only found in the Philippines and nowhere else. While there is no question in globalization of clinical trials as regard diseases like Parkinson's disease and the like, such may not be the approach in these indigenous dis-eases. Again, the budgetary constraints will come into play in conducting trials to such a few cohorts of patients, not even seen worldwide, as pharma-ceutical companies may not be interested to invest in this endeavor. DYT3 patients remain our respon-sibility and we have to matter in terms of manage-ment in this neurodegenerative disorder.

9.2 Movement disorder society of the Philippines

That is the reason why we formed the Movement Disorder Society of the Philippines, and we have now been officially affiliated with the MDS in 2009. Unfortunately, the government has not been pro-active in improving lives of these cohorts of DYT3 patients. We therefore developed a database for these patients, as we are now finding more and more reasons to go into deeper studies as regard therapy. It is our hope to embark on clinical trials in DYT3 using drugs already available in the mar-ket, or will be available in the future. Of course for obvious lack of resources, we had to collaborate with our friends. And for this matter, our Japanese colleagues were the first ones who mapped the pro-tein abnormality in DYT3 (TAF1), through the efforts of the laboratory of Kaji and Makino at Tokushima University.

<Q&A>

Q：I want to know your country's education for the principal investigator, especially on clinical trials. You mentioned GCP training, and in addi-tion to that, the education of clinical pharmacolo-gists or something like that. Please tell me about that.

Rosales：You asked about the educational back-ground. For the clinical investigators, certainly they have to have an M.D., a license to become a practicing medical doctor. There are PK studies actually and PD studies that are coming pari passu, by the way, with clinical trials. I am aware of the fact that we have trials that together also use PD

and PK trials simultaneously actually. In this regard, we have to have some certification from the Board of Pharmacy that these individuals who will be doing the PD-PK studies are certified pharmacists. As regard our support staff, the clinical research coordinator (CRC), for example, in my site I have only one dedicated person. However, I have 5 sub-CRCs and they are also GCP-certified. They undergo GCP training and certification. They have to have a certification which actually will only last for two years. The GCP certificate will expire in two years. So therefore after two years they have to undergo another GCP-training. These are the requirements. Now the CRC and support staff in my site, for example, are certified medical technologists, nurses and physical therapists. When I say certified, they shall have passed the certifying national board examinations in the Philippines, and this process will eventually lead to acquiring a license to practice the profession. The same shall hold true for clinical pharmacists. Then, the conduct of research will be an added training from the center these people will be employed at.

Chairman (Iwasaki) : You mentioned about the indogenous disease in your country. I think global clinical trials are not focused on such kind of diseases. So you have some frustration about this matter. Do you have some interaction with the pharmaceutical industry; to ask for some kind of collaborative research trial for finding good way to treat an indogenous disease?

Rosales : You were kindly referring to DYT3 or XDP, which is really a disease only seen in my country. Professor Mizuno is well aware of this disease as he himself had a chance to see some of these patients. We have now in our database about 400 patients. And every time I am given an opportunity to talk to an audience like this, I always try to sneak in a mention of this disease. The reason being that we really wanted to gather some support especially from the pharmaceutical industry to run some clinical trials for this disease, which is now a different situation, like you have a global trial going to different countries, but now we have an indogenous disease. Thus, we want to ask some pharmaceutical companies to engage in clinical trials targeting this disease because we have the database, we are ready and we are willing to enroll patients. In fact, after our last movement disorders meeting (November, 2009), one pharmaceutical company boldly committed to try their medications in XDP.

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用量の地域差について

Dosages and evidence on medicines in different countries, area or ethnics

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はじめに

国際共同治験のマネジメントの問題について様々に議論されてきていましたが，サイエンスの領域では第一に用量設定が問題になります．そこで今回，実際に使われている薬，臨床試験中の薬について，添付文書の情報，申請データ，および臨床試験中のものは発表されているデータに基づき，日本と欧米の用量について比較してみました．今回は，降圧薬，高脂血症治療薬，抗てんかん薬，パーキンソン病治療薬について取り上げてみます（Table 1）．

1. 降圧薬

降圧薬ではACE阻害薬，ARB（angiotensin receptor blockers），Ca antagonists，βブロッカーを取り上げます．

1.1 ACE阻害薬（Table 2）

エナラプリル，ペリンドプリル，カプトプリル，リシノプリル，いずれも日本と海外の両方でよく使われている薬を選択しました．エナラプリルは日本では5-10mgで，増減は約2倍までとされていますが，US/EUにおいては10-40mgが推奨用量として挙げられており，両者の差は2倍ないし4倍です．増減の増を20mgととると差は2倍くらいですが，一般的な推奨用量では4倍となります．ペリンドプリルは，日本が2-4mg，欧米では4-8mgで，これも約2倍の差です．カプトプリルの承認用量は，日本が37.5-75mg，場合によっては150mgまでとなっています．FDAでは50-150mgあるいは450mgまでとしており，これは日米で2倍ないし3倍の幅で用量が設定されています．リシノプリルは，日本では10-20mg，欧米では20-40mg

Table 1　Differences of dosage among area, countries or ethnics

1. Drugs for hypertension　降圧薬
2. Drugs for hyperlipidemia　高脂血症治療薬
3. Antiepileptics　抗てんかん薬
4. Drugs for Parkinson's disease
   パーキンソン病治療薬

Table 2　ACE inhibitors（ACE阻害薬）

	1日用量　mg/day		
	Japan	US/EU	
Enarapril レニベース®	5-10（増減）	10-40	×2-4
Perindopril コバシル®	2-4（-8）	4-8	×2
Captopril カプトリル®	37.5-75（-150）	50-150（-450）	×2-3
Lisinopril ゼストリル®	10-20（増減）	20-40（-80）	×2

あるいは80mgまでで，これも2倍くらいです．大体おしなべて日本と欧米の用量差は2倍くらいの範囲かと思います．

これらの推奨用量をグラフにしたものです(Fig. 1)．エナラプリルの幅が若干広いと思われますが，2倍ないし2倍強というのが大方の相違かと思います．

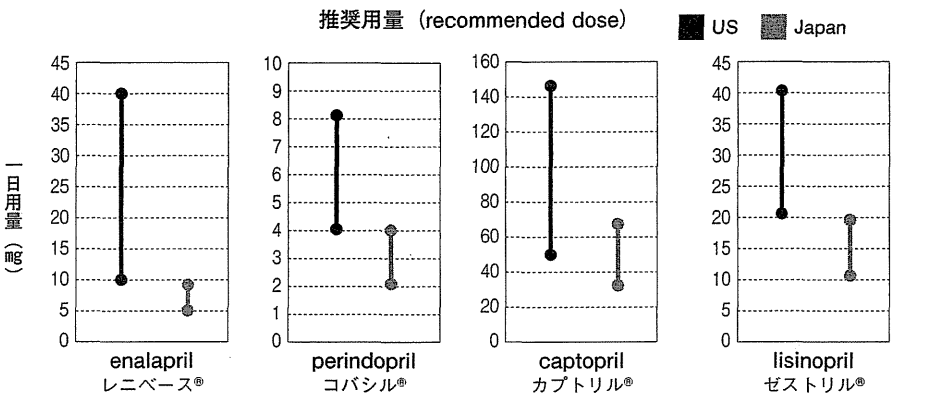
1.2 ARB (Table 3)

テルミサルタンは日本では40mgが基準で，これはFDAも40mgと，ほぼ同じに設定されています．カンデサルタンは，日本は4-8mg，US/EUは16mgあるいは32mgまでと，用量の設定に2倍の差があります．バルサルタンは，日本は40-80mgあるいは160mgで，欧米が80-160mgあるいは320mgまでと，約2倍の差です．オルメサルタンは，日本は10-20mg，欧米では20-40mgで，これも約2倍です．ロサルタンは，日本は25-50mgで，欧米は50mgと1ないし2倍ですが，ACE阻害薬に比べると若干差が小さく設定されていることになります．

1.3 Ca antagonists (Table 4)

アムロジピンは日本が2.5-5mg，欧米が5-10mgで，これはちょうど2倍に設定されています．ニカルジピンは日本が30-60mg，欧米では60-120mg

Fig. 1 Comparison of dosages of ACE inhibitors in Japan and US
(ACE阻害薬の推奨用量の比較)



添付文書 (insert package) より

Table 3 ARB (angiotensin receptor blockers)

	1日用量 mg/day		
	Japan	US/EU	
Telmisartan ミカルディス®	40 (-80)	40 (-80)	×1
Candesartan ブロプレス®	4-8 (-12)	16 (-32)	×2
Valsartan デイオバン®	40-80 (-160)	80-160 (320)	×2
Olmesartan オルメテック®	10-20 (-40)	20-40	×2
Losartan ニューロタン®	25-50 (-100)	50 (-100)	×1-2

Table 4 Ca antagonists

	1日用量 mg/day		
	Japan	US/EU	
Amlodipine ノルバスク®	2.5-5 (増減)	5-10	×2
Nicardipine ペルジピン®	30-60	60-120	×2
Diltiazem ヘルベッサー®	100-200 (増減)	180-540	×2-2.5
Felodipine スプレンジール®	2.5-5 (-10)	2.5-5	×2
Nisoldipine バイミカード®	5-10	20-40 (-60)	×4-6

で，これも約2倍です．ジルチアゼムは100-200mg，欧米は若干差があり180-540mg，これはコントロールリリースの錠剤で1日量ですが，2倍から2.5倍くらいの差になっています．フェロディピンも約2倍くらいです．それからニソルジピンは差がありまして，日本は5-10mgというのが推奨用量になっています．欧米では20-40mg，場合によっては60mgまでという設定で，4-6倍とかなり大きな差があります．

1.4 βブロッカー (Table 5)

プロプラノロールは基準とされる薬の1つかと思いますが，日本は30-60mg，欧米が120-240mgあるいは640mgくらいまで，640mgを超えずに使ってほしいという記載になっています．用量差は4倍で，かなり大きな差があります．アテノロールはほぼ同じ用量設定になっています．これは1日1回ですが，メトプロロールは日本が60-120mg，欧米が100-450mgで約2倍差に設定されています．ビソプロロールですが，日本が5mg，欧米では5-10mgで，これも約2倍です．設定が同じというアテノロールもありますが，全体としては比較的大きな差がある設定といえるでしょう．

2. 高脂血症治療薬

次の高脂血症治療薬は開発において日本の寄与が非常に大きな分野です (Table 6)．プラバスタチンは日本が10mgで欧米が40mgです．10mgで効果が不十分な場合は20mgまで，欧米が80mgまでとなっており，4倍の差があります．各学会が治療ガイドラインを作成しますが，エビデンスとして用量に大きな差のある欧米の論文を使わざるを得ません．この分野は用量差がよく話題になります．アトルバスタチンが約1-4倍，これは10-20mgと原則として同じなのですが，有効ではない時に増量してもよい範囲は4倍までと，設定に大きな差があります．ロスバスタチンは日本2.5-5mgに対してUS/EUが5-20mgと，これは2倍の差があります．この薬は後で触れますが，民族差に初めて言及しています．ピタバスタチンは日本の1-2mgに対してUS/EUが2-4mgと，2倍になっています．シンバスタチンは日本が5-10mgという設定ですが，欧米では20-40mg，不十分な場合には80mgまでと設定されています．これは4倍から8倍という差になり，日本と欧米で用量設定に大きな差があります．

用量の民族差についてロスバスタチンは米国の添付文書では，アジア系では5mgを基準にという指示があります．一般には10mg，効かなければ20mgという記載です．今回みた中ではロスバスタチンが唯一民族差についてinsert packageで触れていました．

この時用いられた臨床試験の結果ですが，日本と北米とヨーロッパ（イタリア）でなされた開発

Table 5 β-blocker

	1日用量 mg/day		
	Japan	US/EU	
Propranolol インデラル®	30-60 (-120)	120-240 (-640)	×4
Atenolol テノーミン®	50 (-100)	50 (-100)	×1
Metoprolol セロケン®	60-120 (-240)	100-450	×2
Bisoprolol メインテート®	5 (増減)	5-10 (-20)	×2

Table 6 Drugs for hyperlipidemia (高脂血症治療薬 (スタチン系))

	1日用量 mg/day		
	Japan	US/EU	
Pravastatin メバロチン®	10 (-20)	40 (-80)	×4
Atorvastatin リピトール®	10-20 (-20)	10-20 (-80)	×1-4
Rosuvastatin クレストール®	2.5-5 (10, -20)	5-20 Asian people 5mg	×2
Pitavastatin ピポカ®	1-2 (-4)	2-4 With erythromycin 1mg	×2
Simvastatin リポバス®	5 (-10)	20-40 (-80)	×4-8

試験の結果をみてみました．その中で有害事象による脱落をみると日本の場合は1mg，2mg，4mgで各群20人を基準としており，2人，3人，3人と，だいたい10％から15％の方が有害事象のために脱落しています．

それに対して北米では5mgから10mg，20mg，40mg，80mgで，大きな用量差があります．各群40人で，脱落が0か1人で，80mgの群では1人も脱落していません．イタリアのデータをみると5mgと10mgで120人を基準にして脱落は2人と6人，2％から5％くらいでしょうか．北米でみますと0％から2％で，ヨーロッパが2％から5％，それに対して日本は10-15％，しかも日本で用いた用量は欧米の1割以下ということですから，明らかな差があるといえます．

こういうデータからAsian peopleは5mgという記載がされたのではないかと思いますが，臨床試験に基づく情報が添付文書に生かされた内容と思います．スタチン系薬物では2倍から4倍という用量差ですが，他にもそういう治療薬がありますので，ロスバタチンは1つのモデルとなる添付文書ではないかと思います．

3. 抗てんかん薬

次は抗てんかん薬です（Table 7）．ガバペンチン，トピラマート，ラモトリジン，これらは最近日本でも使えるようになった薬です．ガバペンチンの場合は日本が1,200-1,800mg，欧米が900-1,800mgで，ほぼ同じ設定で，上限は一応3,600mgまで，日本は2,400mgと若干差がありますが，体格差を考慮するとほぼ同じとみていいかと思います．トピラマートの場合は日本が200-400mg，欧米も200-400mgと同じですが，ただ不十分な時に増やしていい設定が日本の600mgに対して1,600mgと，約2倍の差があります．ラモトリジンは日本200-400mgに対して欧米200-500mgと，これは薬物の相互作用のある薬で，相互作用のない時の基準ですが，ほぼ同じに設定されています．カルバマゼピンはかなり前から使っている薬ですが，上限の基準は日本1,200mgに対し欧米1,600mgとなっています．体格差を考えると同じと思います．プリミドンはかなり古い薬ですが，日本では1,500mgくらいまでという添付文書になっていますが，FDAは250-1,000mgまで，どうしても無効なら2,000mgまでという記載になっており，推奨量が他の薬とは逆で，日本のほうが多くなっています．ただ実際使ってみると，忍容性に問題があり使いにくい薬です．この用量まで持っていくということは，よほど難治性の場合で患者を励まして使う用量になるかと思います．これについては欧米のほうが低く設定されているといえます．古い薬で見直しはなかなか難しいと思いますが，添付文書の用量に関しては少し考慮してもいいの

Table 7　Antiepileptics（抗てんかん薬）

	1日用量　mg/day		
	Japan	US/EU	
Gabapentin ガバペン®	1,200-1,800 (-2,400)	900-1,800 (-2,400) (3,600)	×1-1.5
Topiramate トピナ®	200-400 (-600)	200-400 (-1,600)	×1-2
Lamotrigine ラミクタール®	200-400	200-500	×1
Carbamazepine テグレトール®	600 (-1,200)	800-1,200 (-1,600)	×1-1.5
Primidone プリミドン®	1,500 (-2,000)	250-1,000 (-2,000)	×0.7

ではないかという印象を持ちます．抗てんかん薬については日本と欧米ではあまり差のない設定がされているといってよいかと思います．

4. パーキンソン病治療薬

パーキンソン病治療薬についてですが，L-dopa，ドパミンアゴニスト，セレギリン，エンタカポン，アマンタジン，抗コリン薬，アデノシン受容体拮抗薬などが現在使われていますし，また開発されています．Table 8はアゴニストを比較したものですが，プラミペキソール，ロピニロールが比較的最近の薬です．ブロモクリプチンは20年以上前になるかと思います．ペルゴリド，カベルゴリンが10年強使用しています．プラミペキソールとロピニロールに関しては日本と欧米の用量差は1.5倍くらいまでと，ほぼ同じくらいの用量設定になっています．ブロモクリプチンは約4.5倍から5倍の用量設定です．ペルゴリド，カベルゴリン，これは最近用量が変更になっていますが，最初の用量を比較しますとペルゴリドが4倍，カベルゴリンは同じくらいの用量に設定されています．ドパミンアゴニストは，以前は用量にかなり差を設けていましたが，最近の治療薬は同じで，これは抗てんかん薬と同様に考えることができるのではないかと思います．

Table 9は開発治験のデータですが，エンタカポンの臨床試験を日本とアメリカでほぼ同じ条件で実施されたものを比較しています．L-dopaの用量ですが，日本が400mgで，この時の北米のデータが700mgくらいで倍近い差があります．エンタカポンの用量は日本が100mgと200mg，欧米が200mgとなっています．効果は若干欧米のほうが良かったとみられます．ただ100mgと200mgに関して日本は差がなかった．このことから現在は1回100mgを原則として200mgまで使用できるという基準になっています．

この時の有害事象ですが，効きすぎた場合に起こるdyskinesiaと呼んでいる有害事象をみますと，ほぼ差がありません．日本がプラセボ，100mg，200mgで，0%，7.8%，8.5%，欧米が0%から7%です．欧米は200mgでないと十分でないというので200mgに設定されています．日本は100mgと

Table 8 Dopamine agonists
（ドパミンアゴニスト）

	1日用量 mg/day		
	Japan	US/EU	
pramipexole	-4.5	-4.5 (-6)	×1.5
ropinirol	-15	-24	×1.5
bromocriptine	-22.5	-100	×4.5
pergolide	-1.25	-3 (-5)	×2.4 (4)
cabergoline	-3 (4)	-3 (-5)	×1

Table 9 L-dopa and entacapone

Area & Time	Japan 2006	Japan 2006	Japan 2006	US/EU 1998	US/EU 1998	
L-dopa (mg/day m±SD)	431 ±131	431 ±132	455 ±161	705 ±283	701 ±293	×2
ENT mg/day	0	100	200	0	200	
ON time hr time vs placebo	0.5 (0 hr)	1.4 **(0.9 hr)**	1.4 **(0.9 hr)**	9.2 (0 hr)	10.7 **(1.5 hr)**	
Dyskinesia % emerged	**13.3% (0)**	**21.2% (7.8)**	**22.8% (8.5)**	**1.2% (0)**	**8.2% (7)**	

200mgを比較していますが，両者で有害事象に関しても差がない，効果についても差がないことから100mgを基準とし，不十分な方の場合は200mgまで使うという，リーズナブルな用量設定になっています．

現在臨床試験中のアデノシンの拮抗薬についてですが，これは開発の途中ですが論文として，あるいは学会のデータとして発表されているものを用いています[*1~3]．用量が20mgと40mg，欧米では20mgと60mgだったものを比較しています．効果に関して有効時間はほぼ変わりなく，同じくらいの時間になっています．それに対してdyskinesia（有害事象）についてみると，日本と欧米を比べると若干欧米で多いのではないかと読むことができます．ただこれはベースとなる併用薬のL-dopaの用量が異なります．現在，日本では300mgの後半から400mgくらいが用いられていますが，FDAの添付文書をみると，L-dopaの基準を800mgとしていますので，臨床試験の結果と併せて考えても大体700-800mgというのが欧米での標準のL-dopaの用量と考えられます．そうすると，dyskinesiaで差がありますが，もととなるL-dopa用量に差があるので，その1つの表現と考えられます．パーキンソン病に関しては治療薬の用量，基準となるL-dopaの用量が倍になっています．このことからL-dopaの調整薬を用いる時には至適用量は差があると考えられるのではないかと思います．

Table 10 Differences of dosage among area, countries or ethnics
（地域における用量差について）

• 治療薬により地域別に低用量あるいは高用量の試験を行う．Clinical trials with broad dose range will be required in global trials.

5. 地域における用量差について
(Table 10)

治療薬によっては地域別に低用量あるいは高用量の試験が必要になります．グローバル試験では用量を設定する時に同じプロトコルで行うことが必要です．その際，用量幅を広げればいいのですが，用量に幅があるとプロトコルは複雑になり，経費も掛かります．多くの薬では2倍に，例えば1，2，4をみる場合に1，2，4，8とか，0.5，1，2，4とか1つ追加することにより，大体はカバーできると考えられます．高脂血症の場合はかなり幅を広くとらざるを得ないということがありますが，実際にグローバル試験を行う時は用量幅を1つとることにより，グローバル試験における用量設定ができると思います．

＜質疑応答＞

水野　最初の降圧薬であれほど維持量が違うとは知らずに驚きました．あの維持量は何かの根拠があって決めたのか，適当に決めたのか，その辺はいかがでしょうか．かなり古い薬物なので，適当に決めたものもあるのではないかと思います．

野元　当然，Phase Ⅰで安全性をみて，Phase Ⅱで用量に対する効果をみて決めます．その時に，効果のみられる用量と，βブロッカーの場合にはかなり徐脈になるので，その忍容量とのバランスで用量が決められたと思います．

Ca拮抗剤でしたら顔のhotnessなどが有害事象

*1 Mizuno Y, et al. Clinical efficacy of istradefylline (KW-6002) in Parkinson's disease: a randomized, controlled study. *Mov Disord.* 2010；25：1437-43.
*2 Hauser RA, et al. Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. *Mov Disord.* 2008；23：2177-85.
*3 LeWitt PA, et al. Adenosine A2A receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). *Ann Neurol.* 2008；63：295-302.

として起こりますので，そのようなバランスから決められたと思います．以前と現在では，どの用量までカバーするか．ある量で6割の人が効果を得られているが，用量を上げると7割の方まで改善が得られるますので，より良い効果を得るために用量が上がってきているという面はあると思います．

実際には診療の現場で効果をみながら用量を上げますので，現場の認識が高く，薬を使うコンセプトが広がってくれると，かなり高い用量まで持って行けるのではないかと思います．

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Medication use in Caucasian patients attending the Royal Adelaide Hospital Parkinson's Disease Clinic

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Introduction

I will be discussing the medical management of patients with Parkinson's disease (PD), not only in my institution, the Royal Adelaide Hospital, but in Australia more broadly. And I want to touch on the issue of potential racial differences that might influence the medication response and even the adverse effect profile of these medications.

I will discuss several issues in my talk. I will address the potential effects of race on medication response in PD. I will also discuss several other issues: how the government regulates medications in Australia, prescribing practices in the Royal Adelaide Hospital PD clinic and, finally, the potential role that genetic and cultural factors may play in the efficacy and side effect profile of anti-parkinsonian medications.

1. Ethnicity and PD trials

There is very little data on how ethnicity affects response to Parkinson's medications; certainly very little data from studies done in English-speaking countries. A recent paper in Parkinsonism and Related Disorders looked at minority enrolment in Parkinson's disease clinical trials from the United States (Table 1). These authors looked at all United States clinical trials in Parkinson's disease from

Table 1 Ethnicity and PD trials: There is little data!

Minority enrollment in Parkinson's disease clinical trials
Myra G. Schneider, Christopher J. Swearingen, Lisa M. Shulman, Jian Ye, Mona Baumgarten, Barbara C. Tilley
Parkinsonism and Related Disorders. 2009 ; 15 : 258-62.

- US clinical trials in PD from 1985-2007
- Case reports, reviews and methodological papers excluded
- 239 publications
- 41 (17%) reported ethnicity of subjects
  — 8% of subjects were non-Caucasian

1985 to 2007. They excluded from their analysis case reports, reviews and methodological papers, and looked at more large-scale clinical trials. They had 239 publications in their paper, and in only 41 (17%) of the studies was ethnicity of subjects even reported. In the studies where ethnicity was reported, only 8 percent of the subjects were non-Caucasian. The logical conclusion from this is that the American literature tells us very little about the response to anti-Parkinsonian medications in patients of non-Caucasian background.

1.1 Treatment guidelines: One size may not fit all

For this reason, even the most masterful of clinical guidelines papers, such as this recent paper on the management of Parkinson's disease by Olanow, Stern and Sethi, draws its data largely (when recommending drug dosages and drug selection) from data in white patients studied in English-speaking countries. However, these recommendations may not necessarily be applicable to patients of all ethnic backgrounds.

As some of the earlier speakers have mentioned, there is much better data about the potential impact of ethnicity on response to cardiovascular medications. Other speakers talked about the difference between Asian and non-Asian subjects in the risk of intra-cerebral hemorrhage in anti-platelet drug studies.

1.2 Ethnicity and response to BP medication

Similarly there is quite robust data showing that patients of different racial origins respond differently to anti-hypertensive medications. In the 1982 Veterans Administration Cooperative Study, a massive United States study looking at cardiovascular disease, thiazide diuretics were more effective in black patients, whereas beta-blockers were more effective in white patients. Differences between races in response to cardiovascular medicines extend to adverse effects. There is, for example, a higher risk of angioedema in black patients on certain types of anti-hypertensive medication. And it is reported that the risk of cough from angiotensin converting enzyme inhibitors is higher in Asian than in Caucasian patients. I was very interested to hear in Professor Nomoto's talk about the lower doses of ACE-inhibitors * that are recommended in the Japanese population than in United States and U.K. It is recognized that polymorphisms in genes of the renin angiotensin system underlie some of the differences in blood pressure response to angiotensin converting enzyme inhibitors. It is tempting to presume that that fact may also apply in the Japanese situation; that the differences in response may be from pharmacogenetic differences in the renin angiotensin system.

2. Pharmacogenetics and movement disorders

Well, what information do we have concerning pharmacogenetic influences on response to medications in movement disorders? Well, there is some data (Table 2). There was a recent Chinese paper by Liu and colleagues that examined the effect of different polymorphisms in the dopamine receptor D3 (DRD3) gene on the motor response to pramipexole in patients with Parkinson's disease. Patients who had the Serine/Serine genotype at the DRD3 gene had a statistically significantly better response to pramipexole (as measured by the UPDRS motor examination score) than patients with other genetic profiles. This provides evidence that different

＊野元正弘. 用量の地域差について. 臨床評価. 2011；38 (4)：690-6.

polymorphisms in a dopamine receptor gene influence the clinical response to a dopamine agonist in Parkinson's disease. In the Greek literature, there is a recent paper demonstrating that different polymorphisms at the DRD3 and serotonin receptor genes influence a patient's susceptibility to tardive dyskinesia in response to neuroleptic medication.

3. Medication regulation in Australia

Turning now to the issue of treatment of Parkinson's disease in Australia, I need to say a few words of introduction to tell you a little bit about the way medications are regulated and funded in Australia. In Australia, most medications are subsidized by the government, that is, the majority of the cost of medication is borne by the government with only a small fraction being passed on to the patient themselves. On average, the monthly cost of any medication that a patient must pay out of their own pocket is about 30 Australian dollars, which is about 2,400 yen. And for pensioners and those on low incomes the cost might only be about 3 or 4 Australian dollars per month. Expensive medications will only be subsidized by the government for special indications or on specialist advice. So general practitioners might not necessarily be allowed to prescribe these more expensive medications and obtain them for a reduced cost for their patient. In Australia, regardless of the fact that we are fortunate to be a wealthy country, patients, regardless of their own financial situation, are generally reluctant to pay extra for unsubsidized medications. There is an expectation in the population that the government will provide most of the costs. To be listed on the Pharmaceutical Benefits Scheme, which subsidizes medications, any new medication in a drug class must demonstrate superiority to an existing drug in that class and/or be offered at or below the price of an existing drug. And this second requirement in particular makes Australia, which has a relatively small population of only 25 million, a relatively unattractive prospect for pharmaceutical companies wanting to launch new and potentially expensive medications into the Australian market, because they will be required to match the price of an already existing product.

Table 2 Pharmacogenetics and movement disorders

- Dopamine receptor D3 (DRD3) gene polymorphisms influence clinical response to pramipexole in PD

Genotype	Response (n = 11)	No response (n = 19)	Total (n = 30)	P
Ser/Ser	9 (81.8%)	6 (31.6%)	15	0.024
Ser/Gly	2 (18.2%)	9 (47.4%)	11	
Gly/Gly	0 (0%)	4 (21%)	4	
Total	11	19	30	

Liu, et al. *Eur J Clin Pharmacol.* 2009 ; 65 : 679-83.

- Polymorphisms in DRD3 and serotonin receptor genes influence susceptibility to tardive dyskinesia in Greek patients

Rizos, et al. *Psychiatr Genet.* 2009 ; 19 : 106-7.

4. Parkinson's disease drugs in Australia

There are a number of subsidized anti-Parkinsonian medications in my country. Levodopa-carbidopa and levodopa-benserazide (both standard and controlled release formulations) are available. Our only catechol-O-methyl transferase inhibitor is entacapone which is available as a stand-alone drug as well as packaged with Levodopa-carbidopa in the form of Stalevo. Of the dopamine agonists, we have several ergot dopamine agonists (bromocriptine, cabergoline, pergolide), but, at the present time, only one non-ergot agent:, pramipexole. We do have access to the parenterally administered dopamine agonist apomorphine. Our only monoamine oxidase B inhibitor is selegiline, and we also have amantadine and anticholinergic medications.

Licensed and available in Australia, but currently not subsidized and, therefore, prohibitively expensive for most patients, are duodopa, the enterically administered levodopa-carbidopa ester, and the transdermal dopamine agonist rotigotine. Unavailable in Australia at this time are rasagiline, tolcapone and ropinirole, although ropinirole is available, but not subsidized by the government, for the treatment of restless legs syndrome.

Table 3 Royal Adelaide Hospital Parkinson's Disease Clinic

- Over 150 PD patients
- Movement disorders neurologists
- PD specialist nurse
- Comprehensive care for early to late disease
- Continuous dopaminergic stimulation (apomorphine, duodopa)
- Deep brain stimulation
- Extensive clinical trials experience including sumanirole, rotigotine, droxidopa, duodopa

5. Royal Adelaide Hospital - Parkinson's Disease Clinic

So with that background, I want to tell you a little bit about the medical management of patients in our Parkinson's disease clinic at the Royal Adelaide Hospital, and I think this would be representative of the situation broadly in Australia (Table 3). In our clinic, we look after over 150 patients with Parkinson's disease. The clinic is staffed by movement disorders neurologists and a Parkinson's disease specialist nurse. We have an interest in providing comprehensive care for patients with early to late disease including the use of continuous dopaminergic stimulation (eg. apomorphine and duodopa). We have strong links with our neurosurgical colleagues for patients having deep brain stimulation, and we look after these patients post-operatively (including programming of stimulators). Our clinic provides a conduit for us to participate quite extensively in clinical trials, and recent trials have included the agents sumanirole, rotigotine, droxidopa and duodopa.

5.1 RAH Parkinson's Clinic: Case note review

For the purposes of this talk, I did a retrospective case note review of 119 patients from our clinic (Table 4). Of these patients, I excluded 28 from the analysis - 18 on the basis that they had Parkinson's disease that had been treated with deep brain stimulation (and, as you know, that fundamentally alters the medication requirement postoperatively) and 10 on the basis that they had a diagnosis other than Parkinson's disease. That left me with 91 patients with medically treated Parkinson's disease. For this analysis I looked at gender, age, disease duration, disease severity according to the Hoehn and Yahr score, and the