copyというデータの残し方です（Fig. 4）．ダブルチェック体制なので，実施者，確認者という2名のサインが必ず入ります．ダイレクトに測定時間をカルテの中に記入していきます．どこかにメモを取って転記するやり方は転記ミスの原因にもなりますので，すべてのデータが1つしかないという，転記はしないというルールを決め，実施しています．

Fig. 2　Laboratory data

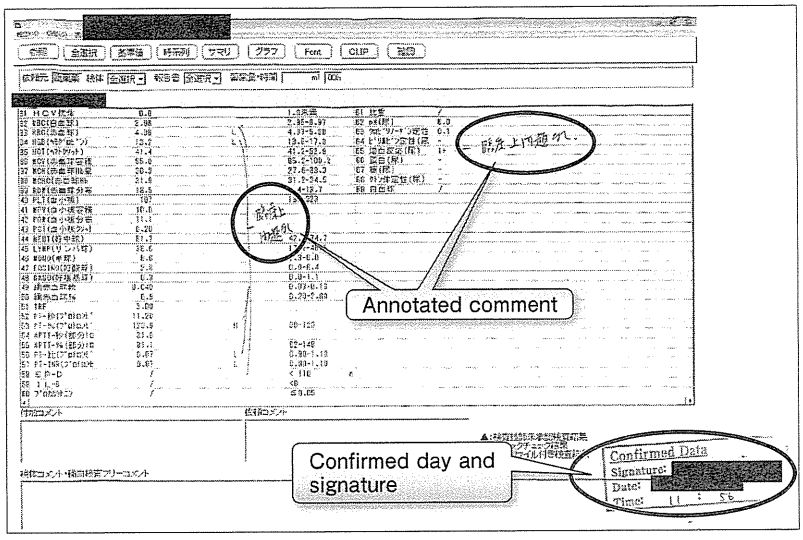


Fig. 3　Electrocardiographic record

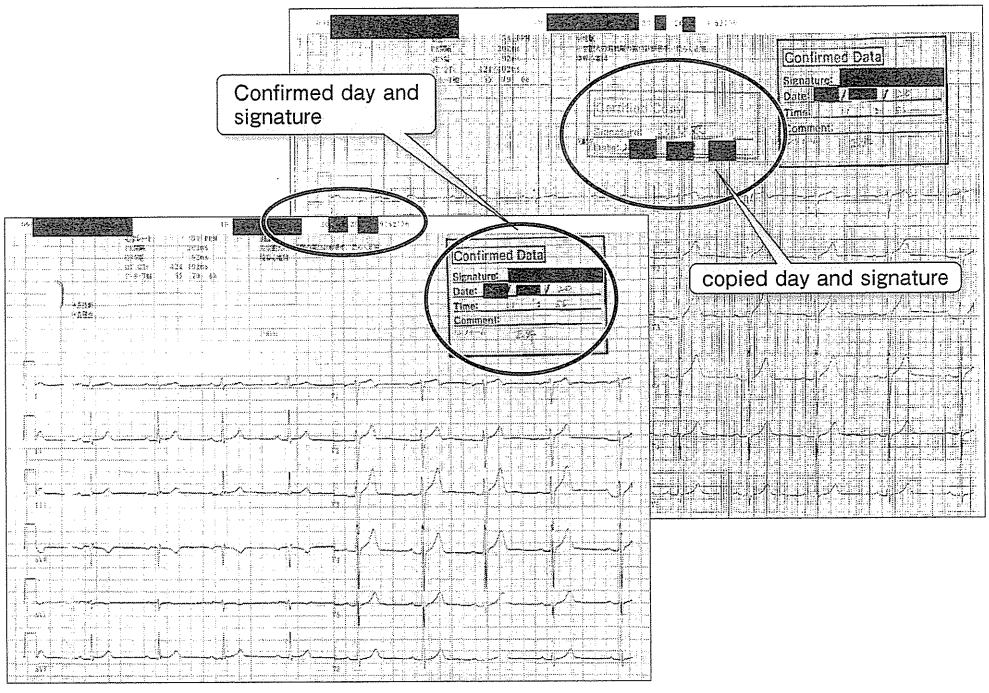
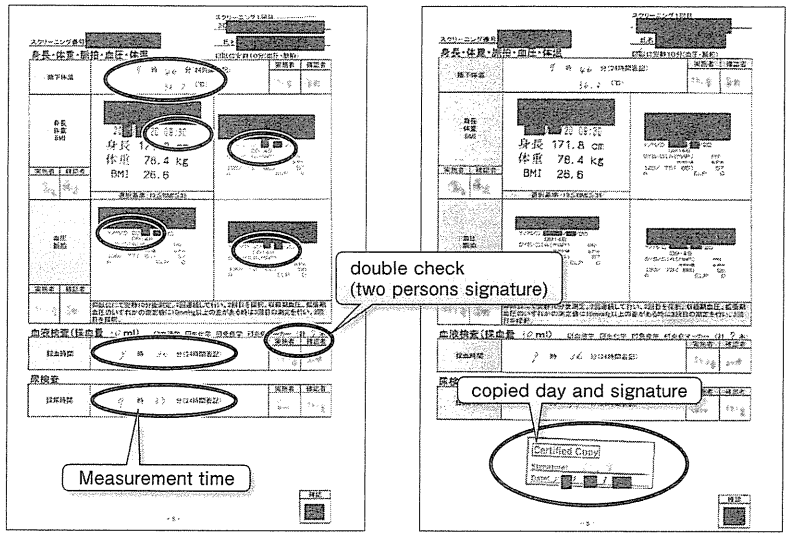


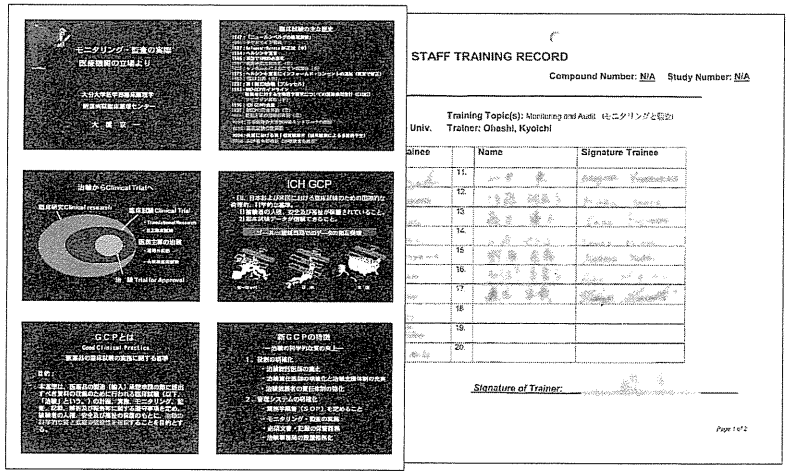
Fig. 4　Medical record



5. さまざまなトレーニング

スタッフのトレーニングは，グローバル試験ではGCPのトレーニング，protocolのトレーニングがよく言われます．他にも試験毎に必要なものがあれば実施します．誰がいつどこで誰に対しトレーニングをしたか，参加者リストを作って保管します．アジェンダや配布資料も保管します．Fig. 5は実際のGCPのトレーニングのデータ，配布資料で，参加者がサインをしていますが，講師のサインもお願いしています．Fig. 6はprotocolのトレーニングです．必ず最初にスクリーニング，入院試験のタイムスケジュール，protocol全体を実施するためのマニュアル，それらをまとめたものを作ります．配布したものをすべて保存

Fig. 5　GCP training



し，参加したスタッフは必ずリストにサインをします．

Emergency careのトレーニング，救急対応は必須のトレーニングの1つです（Fig. 7）．年に一度は必ずトレーニングをするようにしています．救命救急センターのスタッフを講師に呼んで救命のトレーニングをします．人形を使って行っているのですが，患者がベッド上で急変した場合とか，廊下で急に倒れた場合とか，いろいろな状況を想定しトレーニングを行っています．AED（Automated External Defibrillator），救急カートも準備して，さまざまな機器，物品が緊急時にすぐ取り出せる実施体制も確認しています．

まとめますと，早期臨床試験では，多職種で構成するチームが必要です．チームを効果的，効率的に運営するためにプロジェクトマネジメントという手法を導入していますが，チームマネジメントが重要です．スタッフはGCP，protocolのトレーニングはもちろん，救急事態に対応するようなトレーニングも重要です．

Fig. 6　Protocol training

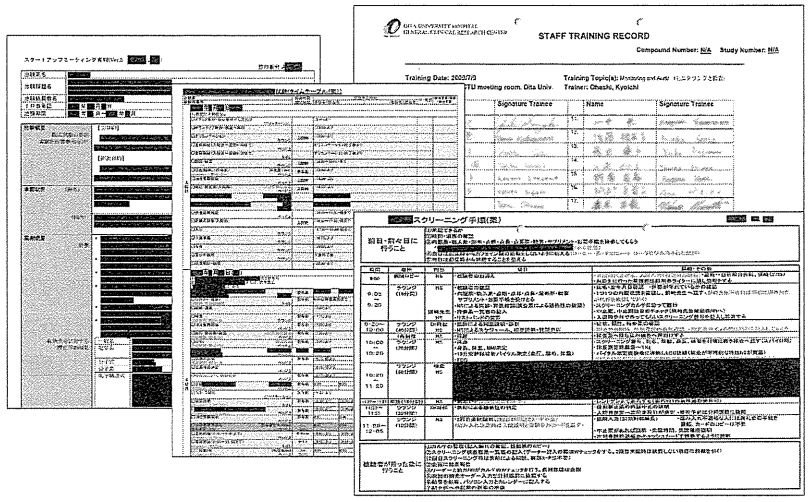
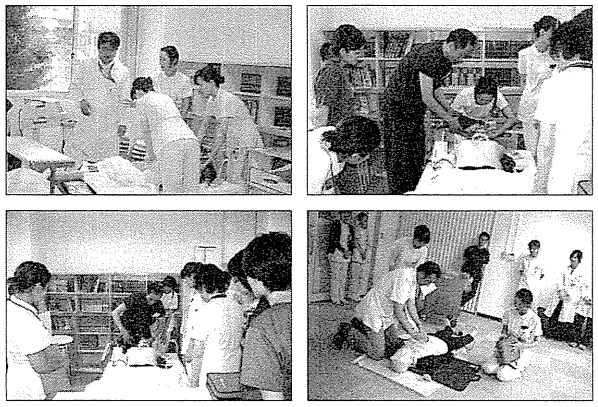


Fig. 7　Emergency care training



臨床評価　39巻2号　2011

患者対象の早期臨床試験をどうしたら効率よく実施できるか

Experience in a multi-center Phase I study in Japanese patients

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1. 背景

日本の題名と英語の題名は少し違いますが，どちらかというと英語の題名のほうが内容を表しています．ある製薬企業がPhase Ⅰを行う施設を探していました．なかなか見つからず，アメリカでも実施できないというところから始まっています．通常Phase Ⅰは健康成人で行うことが多いですし，通常は1つの施設でできます．抗癌剤等で患者さん対象の場合もそれほど施設的には多くありません．その薬は，すぐに想像できることかと思いますが，健康人には投与できない，できないということでもないのですが，生物製剤になります．患者さん対象でPhase Ⅰを行う場合，1つの施設では必要な患者数をリクルートできないという現実に当たったわけです．これはアメリカでも同様です．アメリカと日本でPhase Ⅰを行っています．製薬企業は多施設のPhase Ⅰ studyを行うことに決めまして，6大学のネットワークであるJ-CLIPNET（グローバル早期臨床試験推進のための大学病院ネットワーク）に依頼してきたという話です．

すべての臨床試験に共通しますが，Planning（発案，企画），Execution（遂行，実施），Analysis（解析，分析），Report（報告），とステップを取るわけです．今日の話はPlanning（発案，企画）とExecution（遂行，実施）になります．

2. Phase Ⅰのタイムライン

これ（Fig. 1）は会社が考えてきたタイムラインです．日本では4用量を実施しますが，アメリカは若干早めに計画されています．話が来たのは3月で，日本でまず治験届を9月ぐらいに出せればと考えています．もう少し早くできればそれに越したことはありません．30日間待って，IRBで承認を得てから始めます．これはdose-escalatingのstudyです．次のステップに移るのはここの結果，biomarkerを見てということになりますが，次のステップに移るのに1週間から3週間です．Biomarkerの変化に応じたかたちで，それほど強くない変化なら1週間，中等度の変化なら2週間，かなり抑えることになると3週間の安全性を見たうえで次ステップに移行という計画です．

3月6日に話があり，J-CLIPNETで会議を開き，やるという結論を出しました（Table 1）．厚生労働省の科学研究費で大分大学が中核となり6大学でやっているものです．基盤整備から始まって，実施の話が来たので，6大学でやるという結論を出しました．まずwindow personを決めることになり，私になりました．会社の方と約1か月後に会って，その後9月までいろいろなメールのやりとり等々を行い，9月3日にprotocolが固まりました．そしてprotocolに応じて説明文書を作成しました．9月16日に届出を行いました．初回治験届ですので10月16日まで待つのですが，その間に各施設の責任者を集めPI（principal investiga-

Fig. 1 Time-line for dose-escalating studies enrollment period for each cohort-1

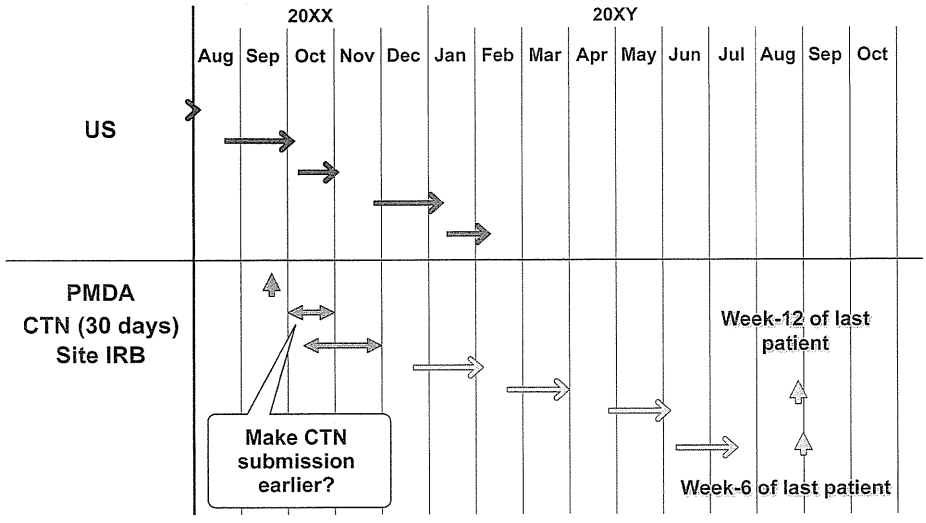


Table 1 Process

20XX	March 06	: The first meeting of J-CLIPNET for Phase I study
		Accept execution, Select a window person (E.U.)
	April 09	: E.U. contact with a responsible person in Pharm Co.
	Sept 03	: Final protocol
	Sept 11	: Final ICF
	Sept 16	: PMDA notification
	Oct 03	: PI meeting
	Oct 08	: Protocol amendment
	Oct-Jan	: IRB in each site
	Dec 06	: FPI

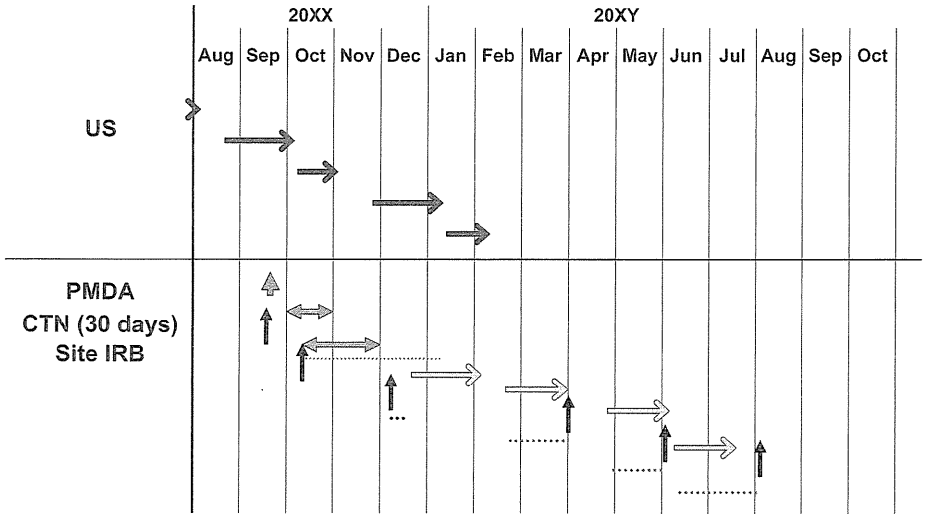
tor) ミーティングを行いました．PMDAからコメントがあり，それに対応してamendmentを作りました．その後にIRBに審査を依頼しました．実際にFPI (first patient in) が最初の施設で12月6日というのがだいたいのタイムラインです．この間のやりとりと，計画と実際について，ご説明します．

IRB審査は施設ごとに行いました (Table 2)．共同IRBにできればそれに越したことはないのですが，まだそこまで至っていなかった状況だとご理解ください．各施設の状況もあり承認日には若干幅があります．申請から承認まではどの施設も2週間でした．最初のプランではPMDAへの届出は下旬を考えたのですが，16日と，若干早めにできました．6施設のIRBすべての承認を得るのにこの期間をみていたわけですが，これだけかかったことになります．第1段階のFPIは予定よりも早く入れました (Fig. 2)．第2段階の最初の

Table 2 Site IRBs

Study Site	Submission document for IRB	IRB
Hamamatsu University School of Medicine, University Hospital	October 23	November 6
Kitasato University East Hospital	October 8	October 22
St. Marianna University School of Medicine Hospital	November 27	December 11
Showa University Hospital	October 27	November 10
Oita University Hospital	December 22	January 13
Ehime University Hospital	December 8	December 22

Fig. 2 Time-line for dose-escalating studies enrollment period for each cohort-2



patientはこれだけタイムラグが出ました．第3段階，第4段階とほぼ尾を引いています．この長さは全施設のIRBの承認が得られた余分のところにマッチしているようなかたちです．

3. 日本とアメリカの違い

当然ながら会社は，日本の試験はアメリカのmirror studyであると考えています．比較するので当然なのですが，protocolも同一です．Protocolの概要から，私から施設に回しコメントをもらいました．するとコメントがかなり出てきました．例えばexclusion criteriaにはHIV (human immunodeficiency virus) antibody positiveがあります．でもprotocolにはHIVをスクリーニングの段階で検査するという記載がないのです．どうしてアメ

リカのprotocolに入れていないのか理由を聞くと，アメリカのドクターたちはHIVテストをスクリーニングに入れると同意を取りづらいということです．HIVの患者さんたちは主治医の治療を長い間受けているので検査をしなくてもすぐにわかるためprotocolに入っていないということです．これは日本では無理な話です．Phase Ⅰで健康人を対象にした場合や，病院で侵襲的な検査をやる場合には必ずHIVの同意書を取りますので，そういうことを説明して入れてもらいました．

PMDAからの指摘でamendmentをした理由です．アメリカのprotocolではWOCBP（women of childbearing potential），妊娠可能女性を入れています．いろいろな避妊法がありますが，日本ではreproduction toxicity studyの結果が出ていなかったので，妊娠可能女性は除いてくださいというPMDAからの指摘がありました．我々もそのとおりだと思います．

前処置をするときにsteroid，acetaminophen，抗ヒ剤を最初に使うのですが，通常使っているacetaminophenの量がアメリカは1,000mg，日本は500mgです．J-CLIPNETの6大学の中でも用量が病院によって違います．Steroidの量も違います．そのへんのところを一緒にできるかという話も出てきました．

特定生物製剤の記録保管の問題です．会社と医療機関の間で違います．生物製剤は会社が10年で，医療機関が30年とprotocolに書いてあるので，日本の基準に合わせてこちらは20年というかたちで修正し，いろいろ細かいことは出てきましたが最終的にはすべてクリアになりました．感心したのはこちらからコメントを出すと3日，4日の間には必ず結論が帰って来ることです．これはもちろん本社とやりとりをし，本社がOKを出してから結論として来るのです．これがとても速く，メール自体は200件ぐらいでしたがスムーズな展開でした．

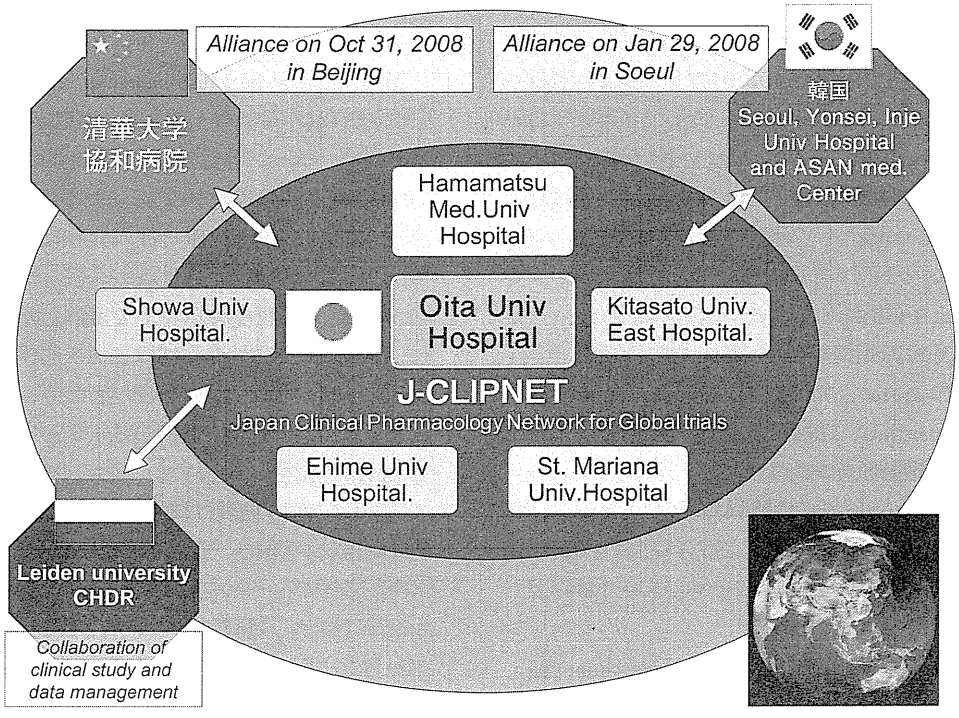
4. 苦労した入院調整

Good pharm-institution communicationということですが我々6大学の各施設に窓口があって，コミュニケーションを進めていきます．私のほうで決められることは決めて流します．Protocolが確定し，実施に至っての一番の問題は患者さんに説明し，同意を取って，投与も入院しなくてはいけないので，入院の調整がとても難しかったことです．特に最後のグループは1グループが何名と決められていますから，最後の患者さんが登録されてからスクリーニング検査をやって，exclusion criteriaを全部チェックし，投与できるかというところまで他の施設は待たなくてはいけません．登録事務局を作り，どこの施設に最後が入ったとなるのですが，その前に患者さんには説明をしているわけです．病院に来る患者さんはほとんどが1か月に1回ですから，1か月前に説明をし，同意をいただいたにも関わらず，他が入ったとなると患者さんに説明して入院日を調整してもらわなくてはいけません．こういうことが何回か起こりました．

当然ながら患者さんはいつでも入院できるものではありません．3回ほど会って駄目という話も出てきました．Phase Ⅰで健康人だったら何名と決めてもよいのですが，患者さんだったら幅をもたせてほしいと感じました．そうしませんと患者さん自身は治療をしにきているのに，急にPhase Ⅰというほとんど治療目的ではない，研究目的なものに参加してくれるという気持ちがあるわけなので，それを無駄にしないようなものを作れたらよかったと思います．

重要なことは正確な情報に基づいて，情報共有と相互理解が必要です．もう1つは正確で速い決断です．それがこのようなネットワークで試験をするうえでは重要です．J-CLIPNETは韓国，中国，オランダとネットワークを組んでいます（Fig. 3）．今回のようなかたちを，今後も発展させていけたらと思っています．

Fig. 3　Alliance of J-CLIPNET



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The current status and policy of early stage clinical trials in Korea

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1. Introduction

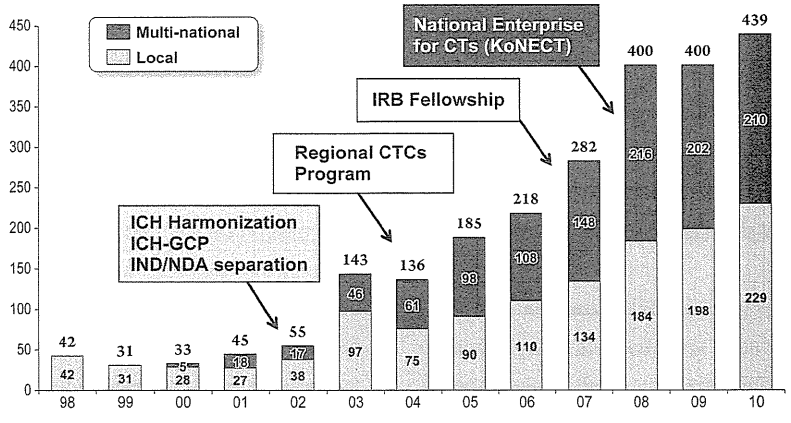
Because many participants are already familiar with the status of clinical trial activity in Korea, as the first part of my talk, I will present a brief update of recent activity and the current global position of Korean clinical trial, especially focusing on early stage clinical trial activity. As a second part, I will talk about our recent policy for improving global competency for clinical trials.

2. Clinical trials in Korea and previous efforts to improve clinical trial infrastructure

Clinical trial activity in Korea has been rapidly grown (Fig. 1) through the government initiative to support regional clinical trial centers started from year 2004. In 2008, the total number of clinical trials approved by KFDA (Korea Food and Drug Administration) in Korea reached over 400. We had more than 200 multinational clinical trials in 2008. However, after the global economic crisis, clinical trial activity in Korea has stagnated. Last year (2010), we had total 439 clinical trials received CTA (clinical trial authorization) from KFDA. Among them, 210 trials were global trials.

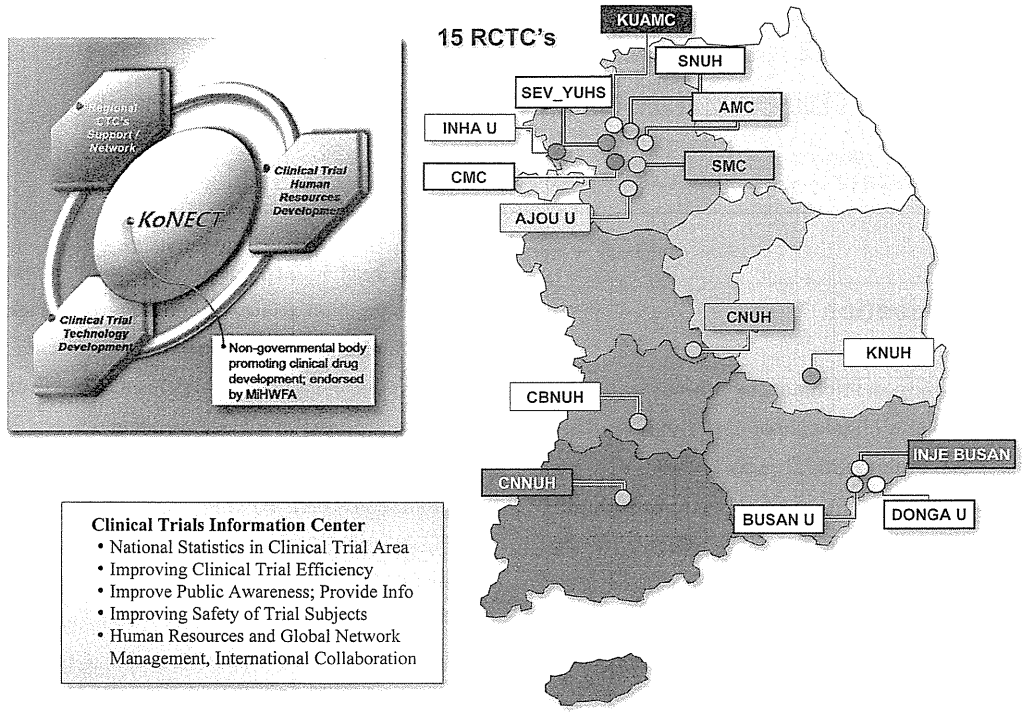
Regional Clinical Trials Centers (RCTCs) program was initiated by the Ministry of Health and Welfare (MOHW) from 2004. In the year of 2007, two more support programs were added to set up educational or training programs for clinical trial related professionals and to support development

Fig. 1　Clinical trials approved by KFDA



* Korea National Enterprise for Clinical Trials (KoNECT), Ministry of Health and Welfare (MOHW)

Fig. 2 Initiatives by MOHW (2004 -): KoNECT (2007 -)



of new technology for clinical trials. These support programs were endorsed to KoNECT (Korea National Enterprise for Clinical Trials), a newly established academic based organization, for more flexible and efficient management. Last year (2010). KoNECT selected the last two Regional Clinical Trial Centers. Currently Korea established 15 regional clinical trial centers nationwide. Eight regional clinical trial centers in Seoul metropolitan area and 3 RCTCs in Busan region (Fig. 2).

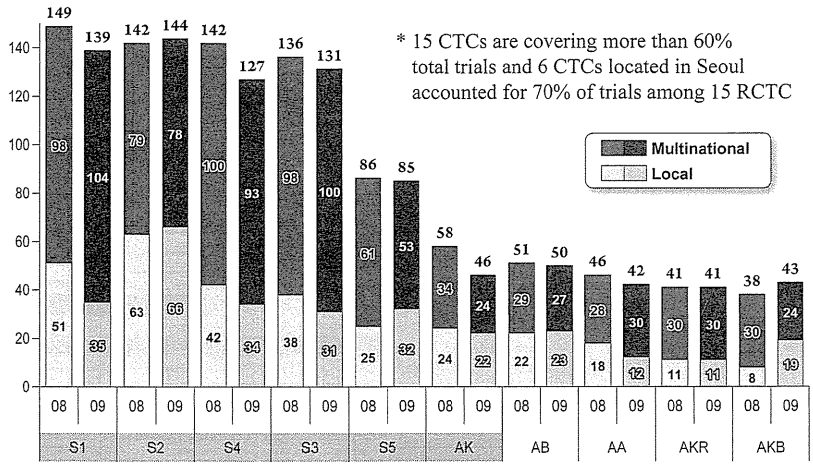
3. Clinical trials in major university hospitals of Korea

Fifteen regional clinical trial centers in Korea are serving as the core sites covering more than 60 percent of total clinical trials conducted in Korea. And especially, 6 major university hospitals located in Seoul are doing major roles (Fig. 3). One problem of clinical trials area in Korea is that industry sponsored trials are too much concentrated in Seoul metropolitan area. It is one of the issues Korea has to solve for future growth.

4. Global position of major Asian countries including Korea in clinical trial sector

Before talking about the current global position of Korea in clinical trial, I would like to briefly show some data on industry-funded trials from clinicaltrials.gov database. Although the database cannot be complete sources, it's very informative to understand the trend of clinical trial activities in the world. The clinical trial activity in the world was continuously growing with about 10 percent per year until 2007. However, owing to global economic crisis, the clinical activity in the world is

Fig. 3 Clinical trials in major hospitals (10) of Korea, 2009



declining from year 2008. The declining rate of protocol number newly registered to the database is about 10 percent per year. The reduction in clinical trial sites is even more dramatic, about 20 percent per year. During last 2 years, the number of trial sites in whole world declined about 40 percent.

Looking over the trend of clinical trial activities in the Asian region (Fig. 4), Korea, China and India are also showing steadily growing activity from the year 2005. The global ranking of clinical trial activity in year of 2010, China, India and Korea shows quite competitive around 13-15th. But if we look at the number of trial sites after 2008, the numbers of sites are stagnated to almost same number in those countries. This means that in the Asian region, these countries are stably conducting clinical trial activity. Relatively, in other countries or other regions, the number of clinical trial sites is getting down. As the results, the rank of Asian countries is going up. How about Japanese situation? If you're looking at the number of Japanese clinical trial sites from year 2008 to year 2010, there's a dramatic increase. This is somewhat good sign of reactivation of clinical trials in Japan.

5. World top 30 cities in clinical trials

Which cities in the world are getting active in clinical trials (Fig. 5)? Here I've listed the top 30 cities in the world. Actually, from 2005 until 2009, almost all of the top 30 cities were from the United States or EU countries. Only Moscow and Seoul were listed in the top 30 cities. Seoul was ranked the 4th city in the world in 2009. However, we can see a very interesting finding in the data in 2010. We can see 4 big cities from Asia in the top 30 cities, Tokyo, Osaka, and Beijing newly listed in the top 30 cities conducting clinical trial activity. Actually last year (2010), Seoul was ranked as second city just behind of Berlin. Tokyo was ranked 6th in the world. Actually, the number of trial sites has been quite increasing in Tokyo area. Osaka was ranked 21st and Beijing in 29th. In early 2000s, there has been a marked decline in activity in Western Europe. It seems like that US clinical trial activity start to be going down. It seems to be very promising sign for the future activation and growing role of East Asian countries in global clinical drug development.

Fig. 4　Clinical trials activities (ISTs only, rank as no. of sites)

	2005			2006			2007			2008			2009			2010		
1	US	41,030	47.85%	US	37,106	43.54%	US	35,573	40.69%	US	46,649	39.48%	US	34,884	36.91%	US	26,020	33.48%
2	Germany	4,791	5.59%	Germany	5,679	6.66%	Germany	11,841	13.55%	France	13,057	11.05%	Germany	8,107	8.58%	Germany	8,423	10.84%
3	Canada	4,503	5.25%	France	4,434	5.20%	France	3,420	3.91%	Germany	8,477	7.17%	France	7,744	8.19%	France	7,968	10.25%
4	France	3,950	4.61%	Canada	3,942	4.63%	Canada	2,856	3.27%	Japan	4,023	3.40%	Canada	2,894	3.06%	Japan	4,610	5.93%
5	Italy	2,575	3.00%	UK	2,607	3.06%	Spain	2,348	2.69%	Canada	3,862	3.27%	Spain	2,771	2.93%	Canada	2,718	3.50%
6	UK	2,530	2.95%	Spain	2,375	2.79%	Italy	2,154	2.46%	Spain	3,146	2.66%	Belgium	2,676	2.83%	Spain	1,805	2.32%
7	Spain	2,177	2.54%	Italy	2,000	2.35%	UK	2,146	2.45%	Italy	2,774	2.35%	Japan	2,674	2.83%	Italy	1,772	2.28%
8	Netherlands	1,758	2.05%	Japan	1,715	2.01%	Japan	2,022	2.31%	UK	2,709	2.29%	Italy	2,463	2.61%	Czech republic	1,654	2.13%
9	Japan	1,683	1.96%	Poland	1,646	1.93%	Russia	1,793	2.05%	Russia	2,152	1.82%	UK	2,386	2.52%	UK	1,544	1.99%
10	Australia	1,599	1.86%	Russia	1,559	1.83%	Poland	1,741	1.99%	Poland	1,995	1.69%	Poland	2,177	2.30%	Russia	1,534	1.97%
11	Belgium	1,422	1.66%	Netherlands	1,391	1.63%	Belgium	1,670	1.91%	Belgium	1,815	1.54%	Russia	2,138	2.26%	Belgium	1,392	1.79%
12	Poland	1,318	1.54%	Australia	1,360	1.60%	Australia	1,337	1.53%	India	1,560	1.32%	Australia	1,340	1.42%	Poland	1,276	1.64%
13	Sweden	1,227	1.43%	Belgium	1,350	1.58%	Netherlands	1,084	1.24%	Czech republic	1,509	1.28%	India	1,323	1.40%	Korea	1,145	1.47%
14	Denmark	934	1.09%	Brazil	1,071	1.26%	India	1,029	1.18%	Australia	1,483	1.26%	Korea	1,222	1.29%	China	1,076	1.39%
15	Russia	911	1.06%	Argentina	1,036	1.22%	Hungary	983	1.12%	Netherlands	1,419	1.20%	Hungary	1,122	1.19%	India	961	1.24%
16	Czech republic	900	1.05%	Czech republic	1,022	1.20%	Czech republic	947	1.08%	Korea	1,400	1.18%	China	1,091	1.15%	Australia	866	1.11%
17	South africa	804	0.94%	India	996	1.17%	Brazil	849	0.97%	Brazil	1,236	1.05%	Netherlands	1,040	1.10%	Romania	831	1.07%
18	Norway	756	0.88%	Hungary	834	0.98%	Argentina	751	0.86%	Hungary	1,146	0.97%	Romania	983	1.04%	Hungary	819	1.05%
19	Hungary	750	0.87%	Austria	812	0.95%	Korea	748	0.86%	China	1,125	0.95%	Czech republic	971	1.03%	Brazil	678	0.87%
20	Brazil	690	0.80%	Sweden	803	0.94%	Ukraine	748	0.86%	Romania	1,063	0.90%	Brazil	866	0.92%	Ukraine	666	0.86%
21	Finland	649	0.76%	Mexico	790	0.93%	China	745	0.85%	Sweden	1,060	0.90%	Sweden	837	0.89%	Sweden	645	0.83%
22	Mexico	591	0.69%	Korea	753	0.88%	Sweden	729	0.83%	Austria	937	0.79%	Austria	801	0.85%	Slovakia	619	0.80%
23	Argentina	587	0.68%	South africa	744	0.87%	Austria	683	0.78%	Argentina	924	0.78%	Mexico	769	0.81%	Austria	615	0.79%
24	India	550	0.64%	Ukraine	703	0.82%	Mexico	650	0.74%	Mexico	841	0.71%	Slovakia	716	0.76%	Netherlands	601	0.77%
25	Switzerland	481	0.56%	Israel	686	0.80%	Israel	605	0.69%	South africa	799	0.68%	South africa	695	0.74%	Mexico	567	0.73%
26	Austria	478	0.56%	China	666	0.78%	South africa	589	0.67%	Ukraine	783	0.66%	Ukraine	670	0.71%	Greece	539	0.69%
27	Israel	411	0.48%	Denmark	549	0.64%	Romania	536	0.61%	Israel	783	0.66%	Israel	669	0.71%	Israel	482	0.62%
28	Greece	390	0.45%	Romania	467	0.55%	Denmark	506	0.58%	Denmark	744	0.63%	Argentina	625	0.66%	Turkey	438	0.56%
29	China	370	0.43%	Finland	420	0.49%	Taiwan	502	0.57%	Slovakia	674	0.57%	Switzerland	620	0.66%	Argentina	422	0.54%
30	Korea	358	0.42%	Switzerland	410	0.48%	Finland	463	0.53%	Greece	573	0.48%	Taiwan	545	0.58%	Taiwan	392	0.50%

Source: www.clinicaltrials.gov, 2010. 12. 31

Fig. 5　Top 30 cities (ISTs only, rank as no. of sites)

	2005			2006			2007			2008			2009			2010		
1	Houston	674	0.79%	Houston	628	0.74%	Berlin	836	0.96%	Houston	860	0.73%	Houston	710	0.75%	Berlin	764	0.98%
2	New York	673	0.78%	New York	582	0.68%	Houston	776	0.89%	New York	770	0.65%	Berlin	685	0.72%	Seoul	560	0.72%
3	Chicago	580	0.68%	Moscow	517	0.61%	New York	671	0.77%	Berlin	747	0.63%	New York	593	0.63%	Houston	549	0.71%
4	Boston	550	0.64%	Berlin	511	0.60%	Boston	548	0.63%	San Antonio	695	0.59%	Seoul	556	0.59%	New York	441	0.57%
5	Los Angeles	549	0.64%	Chicago	492	0.58%	Chicago	525	0.60%	Philadelphia	638	0.54%	Boston	534	0.57%	Hamburg	415	0.53%
6	Philadelphia	545	0.64%	Philadelphia	484	0.57%	Moscow	523	0.60%	Los Angeles	621	0.53%	Moscow	532	0.56%	Tokyo	372	0.48%
7	Dallas	516	0.60%	Dallas	477	0.56%	San Antonio	506	0.58%	Dallas	619	0.52%	San Antonio	504	0.53%	San Antonio	366	0.47%
8	Atlanta	487	0.57%	Boston	464	0.54%	Dallas	487	0.56%	Boston	591	0.50%	Dallas	473	0.50%	Dallas	360	0.46%
9	San Antonio	463	0.54%	Madrid	442	0.52%	Philadelphia	483	0.55%	Moscow	582	0.49%	Madrid	454	0.48%	Los Angeles	340	0.44%
10	Berlin	448	0.52%	San Antonio	424	0.50%	Los Angeles	472	0.54%	Seoul	573	0.48%	Los Angeles	453	0.48%	Chicago	339	0.44%
11	San Diego	438	0.51%	Los Angeles	420	0.49%	Seoul	423	0.48%	Chicago	567	0.48%	Chicago	422	0.45%	Boston	333	0.43%
12	Toronto	427	0.50%	Barcelona	410	0.48%	Madrid	401	0.46%	San Diego	531	0.45%	Philadelphia	415	0.44%	Moscow	321	0.41%
13	Cincinnati	406	0.47%	Atlanta	391	0.46%	Barcelona	392	0.45%	Atlanta	512	0.43%	San Diego	412	0.44%	Madrid	308	0.40%
14	Montreal	405	0.47%	Baltimore	377	0.44%	Atlanta	384	0.44%	Paris	487	0.41%	Paris	394	0.42%	San Diego	302	0.39%
15	Madrid	400	0.47%	Toronto	374	0.44%	Toronto	363	0.42%	Madrid	484	0.41%	Barcelona	387	0.41%	Miami	287	0.37%
16	Portland	399	0.47%	Miami	358	0.42%	San Diego	347	0.40%	Cincinnati	473	0.40%	Toronto	373	0.39%	Toronto	285	0.37%
17	St. Louis	397	0.46%	San Diego	353	0.41%	Miami	339	0.39%	Miami	471	0.40%	London	365	0.39%	Atlanta	284	0.37%
18	Baltimore	382	0.45%	Montreal	350	0.41%	Cincinnati	335	0.38%	Baltimore	458	0.39%	Baltimore	348	0.37%	Barcelona	282	0.36%
19	Barcelona	379	0.44%	Birmingham	345	0.40%	London	329	0.38%	Barcelona	453	0.38%	Cincinnati	339	0.36%	Philadelphia	280	0.36%
20	Moscow	376	0.44%	Seoul	329	0.39%	Baltimore	326	0.37%	Toronto	432	0.37%	Miami	336	0.36%	London	275	0.35%
21	Birmingham	360	0.42%	Cincinnati	326	0.38%	St. Louis	324	0.37%	Birmingham	431	0.36%	Atlanta	335	0.35%	Osaka	274	0.35%
22	Pittsburgh	359	0.42%	St. Louis	325	0.38%	Paris	314	0.36%	Portland	403	0.34%	Hamburg	317	0.34%	Paris	263	0.34%
23	Indianapolis	351	0.41%	Paris	319	0.37%	Cleveland	308	0.35%	Montreal	386	0.33%	Montreal	314	0.33%	Cincinnati	254	0.33%
24	Rochester	349	0.41%	London	318	0.37%	Rochester	306	0.35%	Phoenix	386	0.33%	Nashville	314	0.33%	Nashville	217	0.28%
25	Paris	349	0.41%	Phoenix	317	0.37%	Hamburg	300	0.34%	Indianapolis	385	0.33%	Phoenix	304	0.32%	Birmingham	212	0.27%
26	Miami	345	0.40%	Cleveland	310	0.36%	Birmingham	298	0.34%	London	380	0.32%	Portland	300	0.32%	Baltimore	208	0.27%
27	Seattle	331	0.39%	Buenos Aires	304	0.36%	Pittsburgh	294	0.34%	Tampa	371	0.31%	Birmingham	282	0.30%	Phoenix	206	0.27%
28	Phoenix	326	0.38%	Portland	302	0.35%	Portland	292	0.33%	St. Louis	363	0.31%	St. Louis	279	0.30%	Montreal	204	0.26%
29	Denver	313	0.37%	Indianapolis	300	0.35%	Nashville	291	0.33%	Rochester	354	0.30%	Rochester	276	0.29%	Beijing	203	0.26%
30	Nashville	311	0.36%	Rochester	295	0.35%	Montreal	286	0.33%	Cleveland	348	0.29%	Budapest	273	0.29%	Rochester	201	0.26%
57	Seoul	205	0.24%															

Source: www.clinicaltrials.gov, 2010. 12. 31

6. Early phase clinical trial experiences of Korea

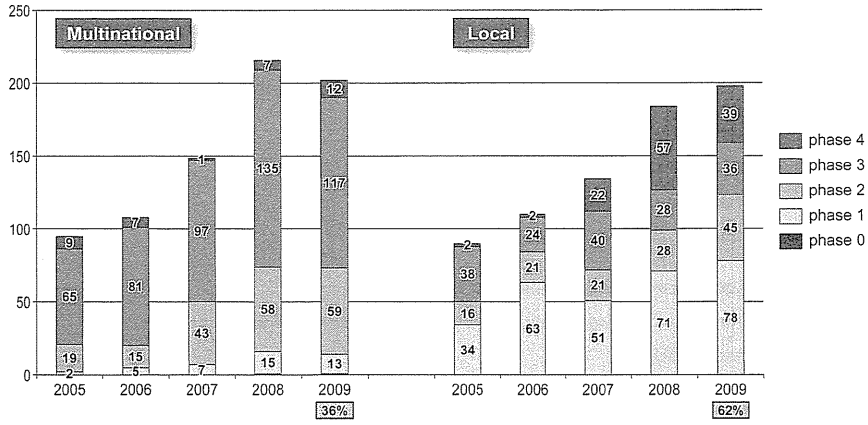
Next, I'd like to briefly talk about early stage clinical trial in Korea (Fig. 6). Actually we have not analyzed last year data yet, so I will just present data until 2009. Before 2007, multinational clinical trials conducted in Korea were almost Phase Ⅲ studies, though there were quite a few Phase Ⅰ, Phase Ⅱa studies. But from year 2008, there was an increasing trend of early phase clinical trials. In the year 2009, the proportion of Phase Ⅰ and Phase Ⅱ trials reached 36 percent.

How about local trials or domestic trials, especially driven by domestic pharmaceutical companies in Korea? A lot of Phase Ⅰ trials has been conducting. But actually these Phase Ⅰ trials are mostly involving new formulations with DDS technology or biosimilar products, requiring some PK, PK-PD or Phase Ⅰc type studies for marketing approval. First-time in man studies from domestic pharmaceutical companies are usually about 5 or 6 per year in Korea.

Looking at the whole picture of total clinical trial activity and comparing the proportion of early phase multinational clinical trials conducted in Korea with western countries. It is still showing emerging country pattern compare to the United States or UK. Recently, many early phase clinical studies for global clinical drug development are off-shoring into Korea, but Phase Ⅰ study still quite limited to oncology area. Phase Ⅱ studies are showing much more diverse pattern in various therapeutic areas, Global Phase Ⅱ studies looks like becoming much more activated in Korea.

How about Phase 0 study experience? Korean FDA doesn't have guidance for exploratory IND study yet. But the KFDA have approved two protocols of Phase 0 study – one in the year 2008, and the other one last year (2010). But the compounds were not agents for therapeutic purpose. Those were the diagnostic agents for PET-imaging category. Until now we do not have any Phase 0 experiences involving therapeutic agents development. Korea shows strong scientific activities in the nuclear medicine field, and we have lot of PET facilities in the country. We have almost 113 PET centers in Korea in fiscal year of 2008, and it's becoming very popular to apply PET/CT in general medical practices. It is the reason why Bayer, a global pharmaceutical company, developed Phase 0 study in Korea.

Fig. 6 Early phase experiences (No. of protocol)



Source: KFDA Data base 2009

7. Policy for improving competency of clinical development, especially focusing early stage

As a second part of my talk, I'd like to briefly mention several policies, and then later, I'll present some movement of Korean government and academia, what we are doing to improve the competency of early stage clinical trial in Korea.

The MOHW and KoNECT are encouraging more close collaboration among academia and drug industries not only for domestic R&D but also for global R&D. Currently, Korean government understands that clinical trial field is one of future knowledge-based technology industry leading bio-and pharmaceutical industries.

8. Global core clinical R&D sites program started to include Asian institutions

Recently, many university hospitals located in Seoul have been establishing close collaborations with some global pharmas and CROs, joining recent strategic initiatives of global pharmas in clinical trials (Fig. 7). GSK (GlaxoSmithKline) actually changed R&D strategy from the centralized to diverse therapeutic area and established a concept of Centers of Excellence in each therapeutic area. Currently, 4 university hospitals located in Seoul are actively collaborating as GSK's Centers of Excellence. In the year 2008, Pfizer started the CORE Research Sites (CRS) program to develop about half of their new pipeline, conducting early phase extrapolating studies through this CRS program. In 2008, 4 big medical university hospitals in Seoul were incorporated as CRS sites of Pfizer, as simultaneously working single consortium. Merck Research Laboratory has recently established a worldwide network especially for developing oncology area. They developed OncoNet program. There are actually 4 university hospitals in Asia working as co-partner in this OncoNet; one in Japan, one in Taiwan and two in Korea. October 2010, Quintiles, leading global CRO, established a strategy similar to the global pharma. They established a new concept called Prime Sites program focusing on early phase trials. Until last year (2010), they selected 8 institutions worldwide, and Seoul National Univer-

Fig. 7 Global core sites program include Asian countries

◈CORE (Center Of Research Excellence) Research Sites, Pfizer, May 2008

- ◆ Pfizer's new Strategy for Phase II projects : 50% of Phase IIs trials will be conducted at CRS sites (9 countries 12 institution as 2010), **India (2009), Hong Kong (2010)**
- ◆ Korea (as Consortium) : Seoul National, Asan Medical Center, Samsung Medical Center, Yonsei Univ. (2008. 5)

◈GSK Centers of Excellence (2007)

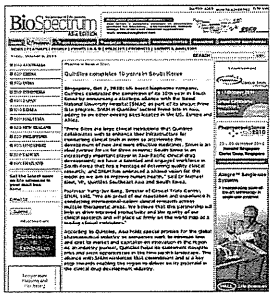
- ◆ 4 Institutions : Seoul National/Asan/Yonsei/Catholic
- ◆ 2008 : 4 Phase I and 8 Phase II trials

◈Merck Research Laboratory : OncoNet (June, 2010)

- ◆ 11 countries, 20 centers : (Korea) Seoul Natl', Yonsei, Japan-1, Taiwan-1
- ◆ 4 OncoNet studies in 2010

◈Quintiles Prime Sites (Oct. 2010)

- ◆ 8th Institutions : **1 in Malaysia, 1 in Korea** ; Seoul Natl' Univ.



sity in Korea and one Malaysian institute were selected as the Prime Sites in Asian region.

This is just one example of global pharmaceutical company's early phase R&D in Asia (Table 1). GSK started early phase clinical study in Asia from 2004. The company is expanding early phase clinical studies in Asian region, especially in Korea, Singapore, Hong Kong, Taiwan and recently, early phase studies in India are growing rapidly.

9. Korea is planning to promote global center of excellence as a post-regional trial center supporting program

Recently, clinical trial activity especially those in early stage in Korea look like growing up well. We made a big stride in Korea to promote clinical trials through the regional clinical trial center support program. But in reality, the supports for six university hospitals were already terminated. This year (2011), 3 more university hospital support programs are expected to be finished. So we are worried about how we can continuously keep the trends of improvements in early stage clinical trial competencies. Currently, KoNECT is planning new program especially to promote real global competency of early phase trials area in major university hospitals. It has been planning as the name of Global Center of Excellence support program with competitive and selective basis. We are trying to consolidate the future program with MOHW as early as possible.

10. Strengthening regulatory competitiveness and streamlining for clinical trial approval by KFDA

Next, I will talk about recent movements inside of KFDA. The KFDA has made many revolutions in terms of CTA review systems and clinical trial oversight mechanisms in Korea. From year 2008, after the agency started the APEC harmonization education center program with ICH-GCG (Global Cooperation Group), they're much eager to make new initiatives, to be globalized and to adopt the ICH guidelines more rapidly. They are also doing more effort to reduce CTA review times. In early 2008, the average CTA review time was about 50 days, but recently CTA review time reduced almost around 30 working days. For more global competi-

Table 1 Centrally co-ordinated early phase studies in Asia by GSK from 2004

Country	No. trials*	Type of sites used	
		Academic	Early Phase Unit
Korea	>10	Y	Y
Singapore	>5 <10	Y	Y
Hong-Kong	<5	Y	Y
Taiwan	2	Y	N
Malaysia	2	Y	N
India	2	Y	N**
Thailand	1	Y	N***
China	1	Y	N

* Numbers includes early phase oncology studies
** Sites evaluated and studies planned in 2010 for HVT
*** Site evaluated, plan to use in the future

Presented in DIA 2010

tiveness, KFDA is starting to make more efficient review system especially for Phase I study; especially for normal volunteer study. They've obliged to reduce their review time to 14 working days, comparable with UK and Canada review system.

Last year (2010), the KFDA published the guideline for joint IRB and mutual recognition mechanism for more efficient IRB process especially for multicenter trials. They've also started to allow submission of English version of the protocol for CTA review. However, the drastic changes cannot be achieved at once. Many reviewers have shifted to reviewing the English version, but there are still some, because of some deficiency in understanding the English protocol, are stick to the Korean translation. But I think it will change rapidly. KFDA is trying to activate pre-consultation system before IND and CTA application. They also have a plan to publish exploratory IND guideline this coming June. And this January, KFDA created a Task Force Committee for Master Planning to make long-range road map for improving future competency in clinical trials in Korea.

11. Challenges in clinical trial operations of medical institution and new efforts to overcome

As a last part, I present new movements in academic institutions in Korea. Recently big university hospitals are seriously thinking about global competencies in their clinical research activities. So they are moving to implement GCP concepts in all of clinical researches and to meet the industrial needs for the quality of clinical trial in terms of scientific and ethical aspects. They're looking for institutional oversight system to ensure quality of trials and study subject's right & safety. We have a very tight clinical trial inspection program from KFDA, but there is some lack of quality assurance mechanism inside of medical institutions. Several major university hospitals are setting up institutional clinical research governance system to ensure high quality in clinical trials. In Yonsei University and Seoul National University Hospitals, they've set up a Department of Human Subject Protection, and monitoring mechanism for important clinical trials conducting in their university hospitals. Seoul National University Hospital set up the First Patient Monitoring System for major trials. The first-patient data are comprehensively monitored by the quality assurance people of the clinical trial center. It can detect and correct very early for any missing practice of the clinical investigator team or any faults in following clinical trial process.

Medical Institutions are also looking for streamlining of IRB process and clinical trial supporting process at the institution. Recently, the Korean Association of IRBs collaborated with KFDA developing a joint IRB guideline and mutual recognition guidance. They also developed real working joint-IRB in one city in Daegu, which has 4 medical schools and 1 big general hospital. The 5 hospitals in Daegu city made joint-IRB for multicenter protocol review. As one more important event, 5 major university hospitals IRBs in Seoul have started preliminary mutual recognition system for multicenter trials. So, the principal investigator will just submit the protocol to his institutional review board. If that institution's IRB accepts the protocol, the rest of university hospital IRBs can just review the protocol in expedited review process. For robust IRB operation, many university hospitals in Korea are getting international accreditations to ensure the quality of IRB review system. Until last year (2010), 3 university hospitals got AAHRPP (Association for the Accreditation of Human Research Protection Programs) accreditation, and

21 university hospitals got FERCAP (Forum for Ethical Review Committees in the Asian and Western Pacific Region) accreditation (Fig. 8).

As a governmental activity by the MOHW and KAIRB (Korean Association of IRBs) started a national IRB evaluation program for all registered IRBs in Korea from last year (2010). The final goal of the activity is to establish a national accreditation system for IRBs in the country.

Fig. 8 Korean Association of IRBs (2002-)/MOHW, international accreditation

◈ Initially established as a non-governmental organization

◈ Since 2007, MOHW supports KAIRB activities
- Government grants for IRB fellowship training (2 or 6 mo, 10/yr) at Western IRB
- Developing Joint IRB (in DaeGu) & Mutual recognition (5 major in Seoul)
- National IRBs Evaluation since 2010; currently ongoing

◈ International Accreditation (24 as 2010) & **Institutional Research Governance (Major Univ. Hosp's in Seoul)**

Table 1. Accredited institutions and recognized IRBs in Korea[12, 13]

AAHRPP accredited	FERCAP/SIDCER recognized
Samsung Medical Center [2006]	Seoul National University Hospital (SNUH) Institutional Review Board[2006, 2009]
Severance Hospital, Yonsei University College of Medicine [2010]	Asan Medical Centre Institutional Review Board[2006, 2009]
The Catholic University of Korea Catholic Medical Center [2010]	Kangnam St. Mary's Hospital (KSMH) Institutional Review Board[2007]
	Chonnam National University Hospital Institutional Review Board[2007]
	Inje University Busan Paik Hospital (IJUBPH) Institutional Review Board[2007]
	Hallym University Sacred Heart Hospital Institutional Review Board[2008]
	Daegu Cathulic University Medical Center (DCUMC) Institutional Review Board[2008]
	Kyung Hee University Hospital (KHUH) Institutional Review Board[2008]
	Ajou University Hospital Institutional Review Board[2008]
	Inha University Hospital Institutional Review Board[2009]
	Kangbuk Samsung Hospital Institutional Review Board[2009]
	Chungnam National University Hospital Institutional Review Board (CNUH-IRB)[2009]
	International Vaccine Institute (IVI) Institutional Review Board[2009]

* * *

臨床評価　39巻2号　2011

早期・探索的臨床試験の推進に向けた行政の取組*

Japanese policy for innovative drug development

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1. 日本の現状

今月（2011年1月），内閣官房に医療イノベーション推進室もできまして，医療には厚生労働省だけではなく文部科学省，経済産業省の3省が関わって，横串でやろうということです．その室員も併任しています．本日は早期・探索的臨床試験の取り組みについて重点的にお話をします．

簡単にregulationについて触れます．我が国には薬事法があり，その中で臨床試験は規定されています．50年前から国民皆保険制度を維持しており医療費も高額になっていますので，我が国の冠たる制度を維持していくため健康保険法の中でもevidenceが重視されています．その中で臨床試験をいかに進めていくかを考えなければなりません．薬事申請を目的とする臨床試験はGCP省令が適用され治験が行われます．それ以外の臨床研究ではガイドラインが適用されます．臨床研究は，倫理面ではほぼGCPに準拠した形になりますが，データの管理，試験薬概要書，などは自主管理に任され，治験と臨床研究のダブルトラックであるとの指摘があります．治験データは薬事法の申請データに使えますが，臨床研究の場合は使えません．こうした中，平成20（2008）年から高度医療評価制度もでき，委員の中にはこれを日本版INDに育てていこうという意見もありますが，臨床研究の質の担保についても取り組んできたわけです．

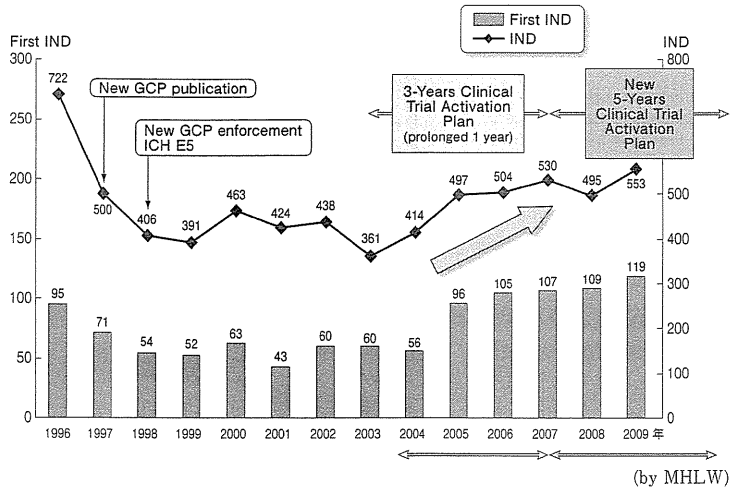
その中で新たな治験活性化5カ年計画を2007年3月より文部科学省と厚生労働省で始めました．治験中核病院10か所と拠点医療機関の30か所を定め，国が支援してきました．ほかにも文部科学省からTR centerの支援がありました．昨年（2010年）事業仕分けがあって30か所の拠点医療機関が20か所に減らされました．プロセスの整備も重要ですが，アウトカムを示していくことが必要で，PDCAサイクル，Plan，Do，Check，Actionというわけで，1年ごとに進捗管理をしていくことが重要になります．

国内のネットワークを推進し，治験の数は増えつつあります（Fig. 1）．さらに国際共同治験も数が増えており2009年度は2割に達しています（Table 1）．さらにグローバル臨床研究拠点も日本で2か所を選定し，日本から企画立案できる体制に支援を開始しています（Fig. 2）．これについては2009年から始めていまして，基本的には1年あたり2億円の支援をしています．

さらに教育にも力を入れています．E-learning，CRC（Clinical Research Coordinator），データマネジャーの研修事業もやっています（Fig. 3）．昨年シンガポールでの国際的なシンポジウムで紹介したところ，アジアの国でもかなり反響がありました．こういうCRCプログラムは日本がリーダーシップを取れるのではないかと思います．

＊ 本講演録の内容は，本誌39巻別冊に掲載した講演録（宮田俊男．臨床評価．2011；39 Suppl XXIX：57-70.）からの進展を反映したものである．

Fig. 1 Number of IND notifications



(by MHLW)

Table 1 Increasing trend toward global MCTs

Trend on IND notifications

	①Total INDs (first time + n times)	②INDs of global MCTs	③Ratio (②/①)
FY 2007	508	38	7.5%
FY 2008	524	82	15.6%
FY 2009	560	113	20.2%

※Tend to be a lot of notifications in oncology

Trend on clinical trial consultations by PMDA

	①Total consultations	②Consultations about global MCTs	③Ratio (②/①)
FY 2007	281	76	27.0%
FY 2008	315	101	32.1%

※Regarding global MCTs, 240 consultations from Apr. 2004 to Apr. 2009

Fig. 2 Global core research center for clinical trial

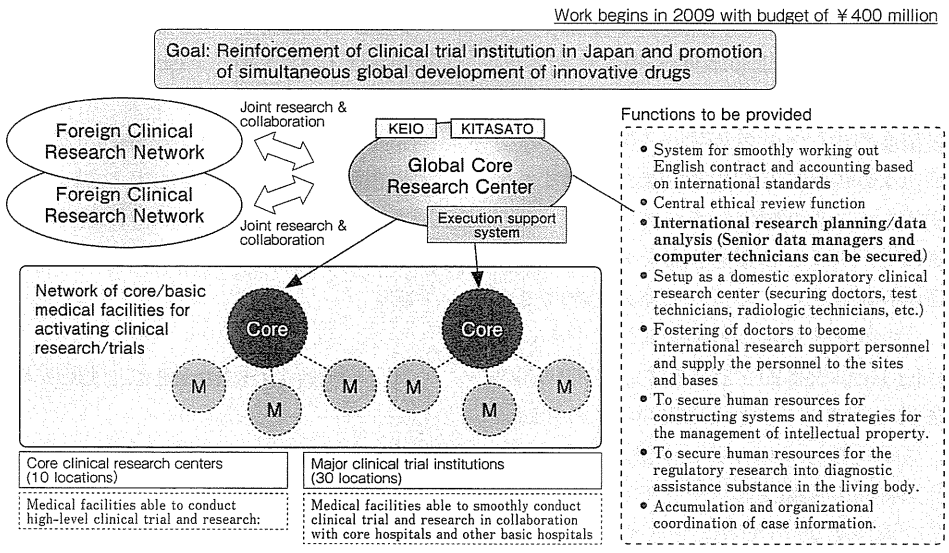
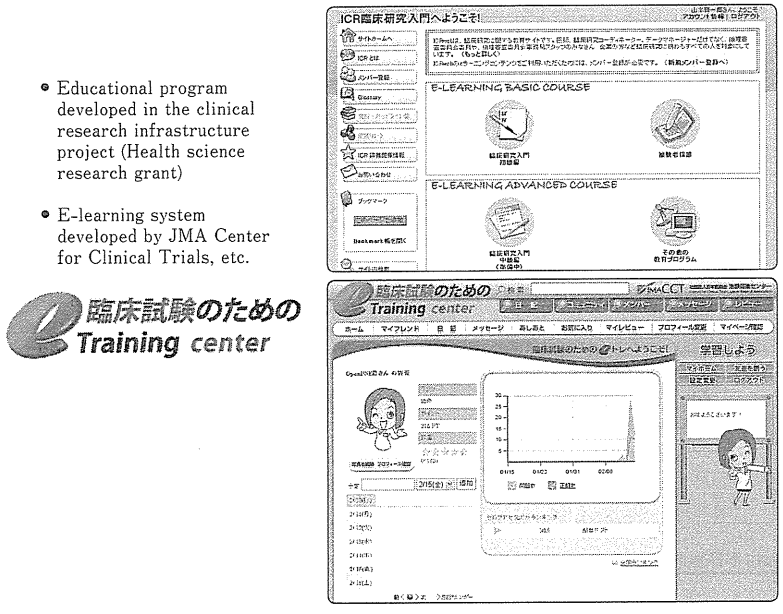


Fig. 3　Tools for self-learning & in-hospital training

- Educational program developed in the clinical research infrastructure project (Health science research grant)
- E-learning system developed by JMA Center for Clinical Trials, etc.



http://www.icrweb.jp/icr/　より

2. ライフ・イノベーションプロジェクト

本日のメインの話は，ライフ・イノベーションプロジェクトです（Fig. 4，5）．我が国で新成長戦略が閣議決定され，本日足立信也前厚生労働大臣政務官もいらっしゃいましたが，政治のリーダーシップの下，我々3省が共同して取り組んできたわけです．重要なことは我が国のインフラ，人材を選択と集中で強化することです．中央社会保険医療協議会の中でも高度医療，先進医療の柔軟化，運用の柔軟の面でも拠点病院の人材のインフラが重要であるとの指摘もあります．

我が国初のシーズであっても欧米でearly stageの臨床試験が実施され，それから日本に遅れてきますので，なかなか1番になれません．こういうところがdrug lagの根本的な問題です．PMDAの審査の速さだけでなく，我が国のシーズをfirst in human，POCに持っていくことが重要です．

中央社会保険医療協議会のデータでも我が国初のシーズでもなかなかPOCがうまくいかず，結局欧米等に承認が先を超され，日本オリジンなのに遅れたケースもありました．我が国初のシーズについては公的なお金もだいぶ入っていますから，血税を無駄にせず，我が国の国民，患者さんにいち早く届けるためにはfirst in human，POC centerをちゃんと整備し，企業に日本でやってもらうことが重要ではないでしょうか．

3省で共同し，厚生労働省からは131億円を予算案としています．国会を通過すれば2011年4月からスタートするでしょう．3番目のところがfirst in humanとPOC centerの事業，さらに薬事戦略相談と申しまして治験の相談よりもその前段階から相談を受けられる，薬事戦略を立てられる，助言を得るような事業を始めようということです．

3. First in humanとPOCの推進

Fig. 6はfirst in humanとPOC centerの構想事業です．整備費として26億円，さらに医師主導治験の研究費として7億円を積んでいて，合計33