National Center for Global Health and Medicine
Center for Clinical Sciences
Department of International Trials

Comprehensive and collaborative training on medical innovations adapted to challenges of clinical trials in Asian and African countries

January 16-25, 2019

A 10 day training on conducting multi-regional clinical research was held in order to provide some guidance to health professionals from five countries, with the ambitious goal of providing new medical treatment to patients with emerging and re-emerging infectious diseases, rare diseases, and intractable diseases around the world.

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序文

この度国立国際医療研究センター臨床研究センターが主催する 2018 年度連携各国を対象にした MRCT 能力開発プログラム「A program focused on comprehensive and collaborative training on medical innovations adapted to challenges of clinical trials in Asian and African countries」実施報告書を発行することになりました。

これは、国立国際医療研究センター臨床研究センターに 2016 年に設立されたインターナショナルトライアル部が実施する国際共同臨床研究ネットワーク拠点形成事業の柱の一つとなる「国際共同臨床研究を実践するための人材育成活動」を報告するものです。

国立国際医療研究センター臨床研究センター・インターナショナルトライアル部は、国際共同臨床研究ネットワークを通じて、新興･再興感染症、難治性疾患、希少疾患、生活習慣病などにおける新たな診断、予防、治療法を開発し、世界の医療向上に貢献することをミッションとしています。新規医薬品や医療機器、および新規医療技術の開発を取り巻く環境は近年大きく変化し、我が国においても医薬品開発における信頼性の確保、効率化や標準化の中で、国際共同臨床研究実施を可能とする体制整備が求められています。これまで国立国際医療研究センターが海外で行ってきた国際医療協力に、国際共同臨床研究を通じた新規医療技術の開発という新たな役割を加えて、世界各国の患者の方々に新たな医療を届ける所存です。そのためには、各国と連携し、連携各国において国際標準の手順に基づいて国際共同臨床研究を実施しうる人材を育成することが極めて重要な活動と位置付けています。

2018 年度は、国立国際医療研究センターの連携国となっているコンゴ民主共和国、インドネシア、フィリピン、タイ、ベトナムそれぞれから 2 名ずつ、合計 10 名を選考し、10 日間に渡る医薬品医療機器総合機構（PMDA）、製薬企業（第一三共株式会社）、学術機関（東京女子医科大学・早稲田大学連携先端生命医科学研究教育施設、聖路加国際大学）、そして臨床現場である国立国際医療研究センター、国立がん研究センターでの講義、ディスカッション、施設見学を織り交ぜた研修プログラムを実施しました。研修後半には成果報告会を実施し、一般の方々を含めアカデミア、製薬会社、CRO などからの多くの方にご参加いただき、各国の現在の臨床試験の状況と課題について共有する良い機会となりました。本活動が今後の連携国との臨床研究実施協力体制の構築の一助になればと願っています。

本活動にご協力いただいた関係各所には謹んで御礼を申し上げたいと存じます。引き続きご指導ご鞭撻のほど何卒よろしくお願い申し上げます。

2019 年 3 月 20 日

国立国際医療研究センター
臨床研究センター長
渡邉　裕司

謝辞

国際共同臨床研究を進める中で国家間の規制の調和や企業との連携、民族差や医療事情の違いなど、越えるべき課題は山積しています。「私たちはパートナー各国からのスタッフと協働することで、これらの課題を解決し、国際共同臨床研究を推進し、グローバルヘルスへ貢献していこうと考えています。」この一文は、国立国際医療研究センター臨床研究センター・インターナショナルトライアル部のパンフレットに記載してあるものです。国際共同臨床研究を推進していくためには情熱を持ち、それを適切に実施しうる人材の育成が欠かせません。私たちは、2016 年に設置したインターナショナルトライアル部に、コンゴ民主共和国、インドネシア、フィリピン、タイ、そしてベトナムの各国からの人材をスタッフとして登用しています。世界中の新興・再興感染症、希少疾患、難治性疾患などで苦しむ患者の方々に新たな医療を提供することを目的に、この度、彼ら海外スタッフが日本人のスタッフとともに国際臨床研究の担い手を育む 10 日間のプログラムを設計、企画、運営実施し、関係各所にその成果を報告する機会を得ることができました。本研修を実施するにあたり、医薬品医療機器総合機構をはじめ多くの機関や職員の皆様からご支援、ご協力を頂きました。こころよく受け入れて下さった機関やご指導下さった皆様に、この場をお借りしまして謹んで御礼を申し上げます。

【ご支援、ご協力いただいた法人様】
独立行政法人 医薬品医療機器総合機構
第一三共株式会社
国立研究開発法人 国立がん研究センター
学校法人 聖路加国際大学 公衆衛生大学院
東京女子医科大学・早稲田大学連携先端生命医科学研究教育施設
国立研究開発法人 国立国際医療研究センター　国際医療協力局、CPC、臨床研究センター治験管理室、薬剤部、国際感染症センター、バイオバンク

【研修生派遣元　※ 50 音順】

コンゴ民主共和国	University of Kinshasa、Institut National de Recherche Biomédicale
インドネシア	University of Indonesia、Sulianti Saroso Infectious Diseases Hospital
フィリピン	University of the Philippines、St. Luke’s Medical Center
タイ	Mahidol University、Prince of Songkla University
ベトナム	Cho Ray Hospital、Bach Mai Hospital

2019 年 3 月 20 日

国立国際医療研究センター
臨床研究センター
インターナショナルトライアル部
エグゼクティブマネジメント室長
飯山　達雄

略語一覧

AMED	Japan Agency for Medical Research and Development
	国立研究開発法人 日本医療研究開発機構
AMR	Antimicrobial resistance
	薬剤耐性
APEC-RHSC	Asia-Pacific Economic Cooperation Regulatory Harmonization Steering Committee
	アジア太平洋経済協力 規制調和運営委員会
ATC	Asia Training Center
	アジア医薬品・医療機器 トレーニングセンター
BIHC	Bureau of International Health Cooperation
	国際医療協力局
CCS	Center for Clinical Sciences
	臨床研究センター
CPC	Cell Processing Center
	細胞調整管理室
CRC	Clinical Research Coordinator
	治験コーディネーター
CRO	Contract Research Organization
	開発業務受託機関
DB	Database
	データベース
DCC	Disease Control and Prevention Center
	国際感染症センター
DIT	Department of International Trials
	インターナショナル トライアル部
FY	Fiscal Year
	会計年度
GCP	Good Clinical Practice
	医薬品の臨床試験の実施の基準
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
	医薬品規制調和国際会議
IEC	Independent Ethics Committee
	独立倫理委員会

INRB	Institut National de Recherche Biomédicale
	コンゴ民主共和国にある 国立生物医学研究所
IRB	Institutional Review Board
	治験審査委員会
MEXT	Ministry of Education, Culture, Sports, Science and Technology
	文部科学省
MHLW	Ministry of Health, Labour and Welfare
	厚生労働省
MRCT	Multi-Regional Clinical Trial
	国際共同治験
MRI	Magnetic Resonance Imaging
	磁気共鳴映像法
NCBN	National Center Biobank Network
	ナショナルセンター・ バイオバンク　ネットワーク
NCC	National Cancer Center Japan
	国立がん研究センター
NCGM	National Center for Global Health and Medicine
	国立研究開発法人 国立国際医療研究センター
PDCA	Plan-Do-Check-Act cycle
	PDCA サイクル
PMDA	Pharmaceuticals and Medical Devices Agency
	独立行政法人 医薬品医療機器総合機構
(R)EID	(Re)-Emerging infectious disease
	（再興）新興感染症
SCOT	Smart Cyber Operating Theater
	スマート治療室
SOP	Standard operating procedure
	標準業務手順書
TWIns	Tokyo Women's Medical University-Waseda University Joint Institution for Advanced Biomedical Sciences
	東京女子医科大学・早稲田大学連携 先端生命医科学研究教育施設
WG	Working Group
	ワーキンググループ
WHO	World Health Organization
	世界保健機関

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1. はじめに

1.1 研修概要

本研修では、アジア・アフリカ各国における治験の実施環境の整備の一環として、5 カ国より 10 名の研修生を迎えました。10 日間の研修プログラムでは、講義やディスカッション、治験実施施設や教育施設、製薬企業等への訪問を通して、日本における治験の実施状況について学びました。

具体的には、アジア医薬品・医療機器トレーニングセンター（PMDA-ATC）主催の MRCT セミナー 2019 の見学を始めとし、臨床試験や医療イノベーションの現況を学ぶ目的で、治験実施施設（NCGM、NCC）や教育施設（TWIns、聖路加国際大学）、製薬企業（第一三共株式会社）を訪問しました。

また、オープンセミナーでのプレゼンテーションを通じて、研修生より各国の治験の状況と課題についてご紹介する機会を設けました。

1.2 研修の目的

本研修の目的は以下の通りです。

- 医療イノベーションや国際共同試験関連の規制・実施体制・課題を学ぶ
- 今後の各国での臨床試験実施体制の整備に寄与する人材を育成する
- 国立国際医療研究センターと各施設とのさらなる協力体制へとつなげる

1.3 研修生の背景

アジア・アフリカの計 5 カ国 10 施設より、少なくとも 1 件以上の臨床研究の経験のある医師を研修生として迎えました。

表 1　研修生出身国・所属先一覧

Country	Institution	Participant Name
The Democratic Republic of the Congo	University of Kinshasa	Yves Lula Ntamba
	Institut National de Recherche Biomédicale	Joelle Lumaya Ambis
Indonesia	University of Indonesia	Anggi Gayatri
	Sulianti Saroso Infectious Diseases Hospital	Nina Mariana
The Philippines	University of the Philippines	Angeline Monica Adalin Arcenas
	St Luke's Medical Center	Mylene Urtula Cornel
Thailand	Mahidol University	Borimas Hanboonkunupakarn
	Prince of Songkla University	Boonjing Siripaitoon
Vietnam	Cho Ray Hospital	Nguyen Chinh Dai
	Bach Mai Hospital	Ngo Thi Phuong Nhung

2.　NCGM 内のプログラム

2.1　臨床研究センター　インターナショナルトライアル部（DIT）

2.1.1　DIT の概要

当部署で実施している、国際共同治験のプラットフォーム構築事業を中心に紹介がありました。国際感染症フォーラムの実施等で産官学の情報交換・連携体制を促進し、国際的な医療課題を解決するような共同開発プロジェクトを生み出す工夫とともに、新興国で国際基準や各国規制を遵守して円滑に国際共同治験を実施するため、DIT が実施している支援等について紹介されました。

各国での適切な治験実施環境を構築すべく、キャパシティビルディングにも取り組んでおり、本研修も単独で終了するものではなく、今後の協業に向けて関係づくりをより一層進めて行きたいというメッセージが送られました。

図 1: DIT プレゼンテーション

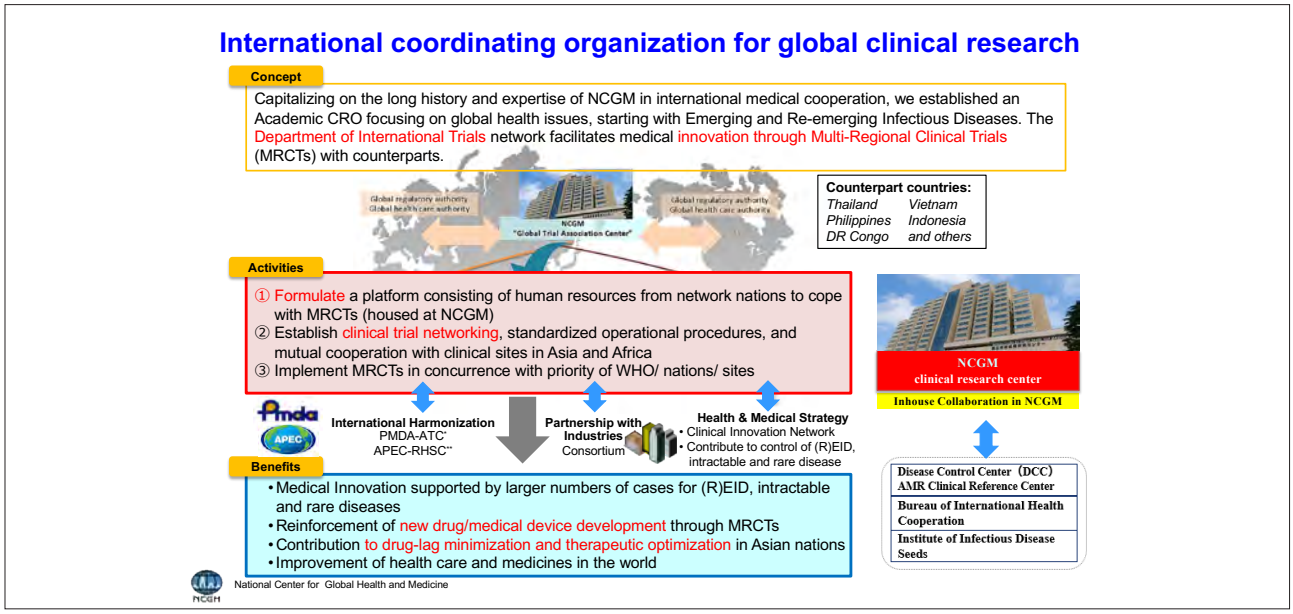

図 2: DIT の役割

2.1.2　MRCT のネットワーク構築に向けて -DIT の研修プラン -

研修の計画・実施に関して中心的な役割を果たしてきた DIT の研修担当者より、臨床研究と治験の違い、治験実施の必要性、特に MRCT において必要となる継続的な知識のアップデート、昨今、全世界的に活発化している規制やデータ収集手法の共通化の動き等について確認しました。

その上で、今後 DIT において計画している国際的な治験専門家の育成プログラムの概要を紹介しました。DIT が目指す、ICH ガイドライン等の国際基準に準じた試験を実施できる人材の育成のため、様々な団体が公表している臨床試験、治験専門家の要件や、トレーニングに必要な要素を参考にしながらプログラムの開発を行っていることを紹介しました。研修生からは

多くの質問が聞かれ、研修生の学ぶ意欲の高さと、治験教育への関心の高さを確認することができました。

さらに、研修生が今後の DIT トレーニングプログラムに期待すること、各研修生が所属する施設における治験の実施状況、今回のプログラムにおける感想や改善点などについて、活発なディスカッションが行われました。

図 3: 各種団体による臨床試験専門家のためのプログラムの紹介

https://mrctcenter.org/clinical-trial-competency/
https://www.diaglobal.org/en
https://acrpnet.org/
https://www.who.int/tdr/publications/year/2016/competency-framework-clinical-res/en/
https://www.transceleratebiopharmainc.com/

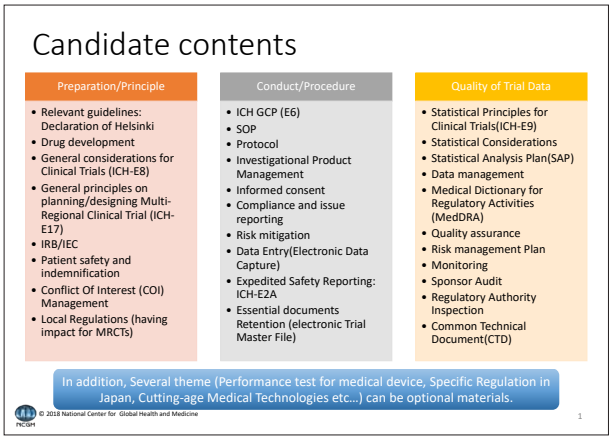

図 4: 研修プログラム内容の例

図 5: プログラムの開始にあたり、DIT スタッフと

2.2 国際医療協力局（BIHC）

組織の概要や NCGM 内での位置づけ、その機能や約 40 年にも及ぶ国際協力の歴史とともに、技術協力事業と政策提言に関する活動について紹介がありました。

技術協力事業には、公衆衛生、母子保健と家族計画、感染症対策、医療施設の整備といった種類があり、例えば医療施設の整備プロジェクトでは、医療技術移転、医療システムや緊急医療システムの整備、経営や医療機器の管理等

を含む病院管理、看護師やその他の医療従事者への教育を含む人的リソースの開発等、医療施設を開設し、維持・管理していくための包括的な支援を提供していることが紹介されました。

こういった技術協力によって得られた課題や知見をもとに、現場の状況を考慮・反映し、政策への提言・助言を行えることも、国際医療協力局の強みであることが紹介されました。

図 6: BIHC 担当者によるプレゼンテーション

2.3 細胞調整管理室（CPC）

細胞治療は多くの変性疾患、非感染性疾患における革新的な医療となっています。細胞治療を実施するためには、特定の要件を満たした施設で処理、培養された良質な細胞が必要となります。実際に、CPC の運営や臨床試験に関わる 2 名の医師より、CPC について紹介がありました。

CPC は、厳格に管理されているクリーンルームであり、微生物の混入を防いで安全に細胞培養を行うためアイソレーターやクリーンベンチを備えています。施設をモニタリング・コントロールする機器類や、病院の建物自体の空調システムや配管設備との兼ね合いも含め、様々な工夫の下に施設が維持されているとの説明を受けました。

図 7: CPC にて、医師、担当者と

1 型糖尿病や慢性膵炎でインスリン治療を行っていても血糖値が不安定な方を対象に、ドナーより提供された膵臓から、膵島細胞のみを分離して移植する膵島移植の臨床試験プロジェクトについても紹介されました。

患者さんの生命維持・生活の質改善に直結する臨床試験プロジェクトの紹介に対し、医師・薬剤師である研修生は大いに興味を持ち、様々な観点から質問が寄せられました。

2.4 臨床研究センター（CCS）

臨床研究センターの組織概要、治験事務局、治験管理室の業務等についての紹介の後、当院で実施している治験のインフォームドコンセントの取得について、プレスクリーニングから患者さんへの治験参加の呼びかけを含む一連のプロセスを追って、治験責任医師、CRC の果たす役割を含む詳しい説明がありました。

外来エリアに位置する治験専用診察室や、中央検査室、治験関連機器を保管する専用の倉庫の様子も、写真で紹介されました。多数の企業治験を同時に実施していく中で、一貫したデータ取得のため企業等から貸与される様々な機器の管理も、治験の適切な実施にあたり重要なポイントとなることが紹介されました。

治験管理室の訪問では治験関連文書が施錠できるロッカーに格納されている様子や、併設されているモニタリング用の個室を見学しました。モニタリング用の個室では、実際に製薬企業のモニターが

図 8: 臨床研究センタープレゼンテーション

作業を実施しており、個室でプライバシーを確保しながらモニタリングを実施する様子が見学できました。膨大な量の治験関連文書を保管するにあたり、過去の文書については一部、外部倉庫と契約して適切に保管できるよう工夫しているといったお話もありました。

薬剤部と治験薬管理庫の訪問では、膨大な量の院内処方の調剤を行う薬剤部の中に、アクセス制限付きで、様々な温度管理に対応できる治験薬管理庫を見学しました。温度逸脱時には担当者のメールアドレスに通知が送信され、担当者はスマートフォン等で常に通知を確認できる体制を整えている旨も説明がありました。

図 9: 治験専用診察室

図 10: モニタリング用個室

図 11: 臨床研究センタープレゼンテーション

2.5 国際感染症センター（DCC）

まず始めに、DCC の活動の紹介がありました。

DCC は、薬剤耐性菌を含む感染症の予防、診断、治療と、それらに携わる専門家や医療従事者の育成を行っています。また、感染症の制御や教育における連携・協力のため、国内外を含む様々な機関とネットワークを形成しています。輸入感染症の早期検出・リスクアセスメントと迅速な対応に向けた研究者の育成を始めとした、感染症の水際対策への活動も実施しています。

DCC の病棟・病室の見学では、第一類感染症、第二類感染症、特定感染症の患者さんを受け入れることのできる病室を訪問しました。感染の拡大を防ぐため、患者さんの移動や物品の受け渡しルートが厳格に管理された隔離室は医療者が必要な治療やケアを提供する妨げとならないよう、様々な工夫がみられました。

図 12: 隔離しながら患者さんを輸送する車いす

図 13: 隔離病室内に設置されている分娩台

図 14: DCC 医師によるプレゼンテーション

2.6　バイオバンク

NCGM 単独の施設としてのみならず、NCBN(National Center Biobank Network) の一施設として、ネットワーク内におけるナショナルセンター間での協力体制の構築や、文書や手続き、手順等の統一化、各センターの役割の明確化など、より広範囲なバイオバンクとしての役割や活動について、紹介がありました。

NCBN は国内 6 ナショナルセンターからなるバイオバンクのネットワークであり、収集される検体の種類は各ナショナルセンターの専門性によって異なります。利用のための問い合わせ窓口は NCBN 事務局で一括して実施されており、ナショナルセンター以外に所属する、国内外の企業を含む研究者も検体の利用申請が可能であることも紹介されました。ネットワークを構成する施設間での情報交換や協議によって、より適切な同意の取得、検体の維持管理、利用提供等への取り組みが進められています。

厳格な温度管理の下、検体を保管している施設を見学し、今後も保管検体が増加することを見越した施設設計であるとの紹介がありました。

提供者からの同意取得プロセスには細心の注意が払われており、また個人情報保護の観点から、提供者の情報を共有する際には匿名化を始めとした非常に厳格な管理が行われているとの説明がありました。

本件の問い合わせ先（NCGM バイオバンク）：ncgmbb@hosp.ncgm.go.jp

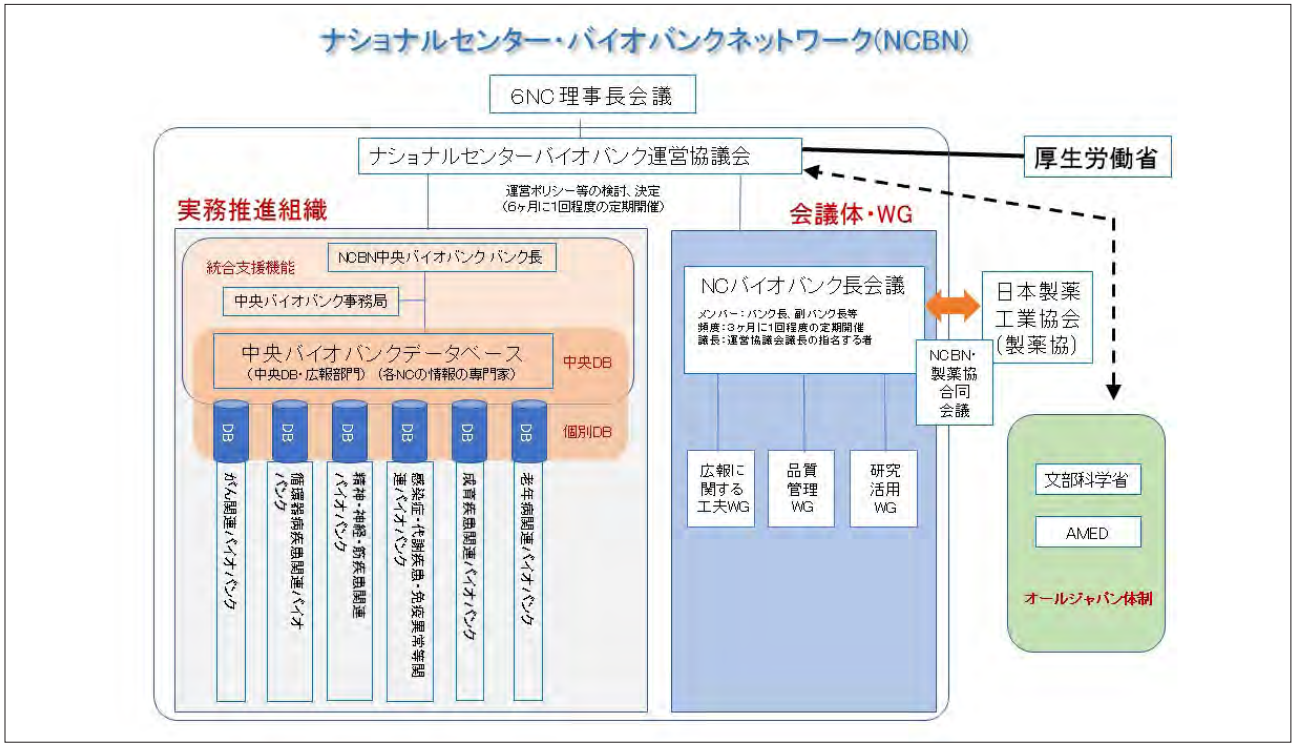

図 15: NCBN の組織体制　https://ncbiobank.org/organization/index.php

図 16: バイオバンクの検体保管庫

図 17: バイオバンク施設にて、担当者と

3.　NCGM 外のプログラム

3.1　医薬品医療機器総合機構（PMDA）

PMDA と NCGM の包括的連携協定に基づき、PMDA アジア医薬品・医療機器トレーニングセンター（PMDA-ATC）主催の国際共同治験セミナー 2019（MRCT Seminar 2019）のオブザーバーとしての見学の機会を得ました。

本セミナーは日本が今まで培ってきた MRCT の計画・デザイン及び実施、臨床データの評価、GCP 調査結果に基づいた承認審査、国際共同治験に基づき承認された医薬品の市販後ベネフィットリスク評価といった知識・経験を活用し、医薬品開発に関する規制の調和を促進することを目的としており、各国規制当局担当者の参加を対象とするものです。

MRCT の計画・デザイン、実施及び結果の評価における留意点、GCP 調査結果を踏まえた承認審査における留意点、MRCT に基づき承認された医薬品の市販後安全性評価に至るまで、包括的かつ各専門家のご経験や事例に基づいた詳細な講義を聴講しました。特に、MRCT の実施や GCP 調査、市販後ベネフィットリスク評価、国際連携と整合性に関して、PMDA のみならず、製薬業界やアカデミアの先生方からのご講義を聴講することで、より実務に即した形で MRCT についての学びを深めることができました。

更に各国規制当局からの参加者より、各国における承認審査の体制や手順の概要、ICH E17 ガイドラインの実装に当たっての課題等が紹介され、DIT 研修生の出身国 5 カ国のみならず、様々な国の医薬品審査・承認制度の概要を知ることできたことは研修生にとって大きな学びとなりました。

PMDA-ATC MRCT Seminar 紹介ページ： https://www.pmda.go.jp/english/symposia/0138.html

図 18: PMDA にて

表 2　PMDA-ATC MRCT Seminar プログラム

（PMDA ホームページより、DIT 研修生が参加したプログラムのみ転載）

PMDA-ATC Multi-Regional Clinical Trials (MRCT) Seminar 2019

Offered by Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs
DATE: January 21-24, 2019 / VENUE: PMDA

DAY 1 (January 21, 2019)
Key note speech Strategies and challenges for drug development - Future movements and backgrounds of development strategies -
History of drug evaluation using overseas data in Japan Q&A
Scientific insights about ethnic factors Q&A
<**Session 1**> Introduction of review systems and regulations by participants
<**Session 2**> International cooperation and alignment • Global platform for medical innovation as an Academic Research Organization (ARO) • Challenge for global cooperation of regulatory agencies Q&A
DAY 2 (January 22, 2019)
<**Session 3**> Points to consider when planning and designing MRCT • Points of attention for consultation about MRCT from PMDA's experience • Case study -Planning and designing MRCT- Q&A
<**Session 4**> Points to consider when evaluating results • Statistical considerations for MRCT based on the ICH E17 guideline • PMDA's experiences to review MRCT results Q&A
DAY 3 (January 23, 2019)
<**Session 5**> Considerations for MRCT operations • Practical issues and solutions on MRCT operations (Investigator's viewpoint) • Practical issues and solutions on MRCT operations (Industry's viewpoint) Q&A
DAY 4 (January 24, 2019)
<**Session 6**> Regulatory review based on results of GCP inspection • How to perform GCP inspection in Japan -Role of GCP inspection in review process- • How to take GCP inspection results into consideration for review from reviewer's perspective • Applicant's experiences to undergo GCP inspection • Trial site's experiences to undergo GCP inspection Q&A
<**Session 7**> Post-market safety evaluation of approved drugs based on MRCT • Global standards for pharmacovigilance • Risk management plan based on the multi-regional clinical development -from perspectives of pharmaceutical companies- • Risk management based on the multi-regional clinical development - from perspectives of regulatory agencies - Q&A

3.2　第一三共株式会社

まず始めに、会社の概要とともに新薬開発のプロセスについて説明がありました。特に、薬剤の候補となる物質が臨床試験でその有効性と安全性を確認される段階になる前の過程で、多くの物質の中からふるいにかけられ、年月をかけてその性質や生体内での働きについて実験を通して確認されるという薬剤開発の基礎の部分について学ぶことができました。

その後は新規医薬品を見出すべく、日々研究が重ねられているラボを見学しました。最新の機器や設備を使用しながら、新薬の開発に向けて研究がおこなわれている現場を見ることができました。

図 19: 第一三共株式会社前にて

研究所には、本製薬会社で開発され、世界中で販売されている医薬品の化学構造体模型と、各薬剤の大まかな歴史に関する展示がありました。研修生が日々の診療で使用している薬剤も含まれていることが印象的でした。

3.3　国立がん研究センター（NCC）

まず、国立がん研究センター中央病院 1 階の玄関から 5 階の先端医療科へ向かいながら、外来診察エリアや外来化学療法エリアを含む各フロアの概要について紹介を受けました。患者さんの動線を考慮した各部門の配置について学ぶことができました。

次に、国立がん研究センター中央病院の概要と国内のがん治療・研究において果たされている役割、先端医療科の役割と組織や設備、実際の試験・それに伴う診療の様子、がんゲノムに関するプロジェクトなどの紹介がありました。

その後、医師主導国際共同治験プロジェクトの具体例について紹介がありました。国際共同治験において、規制要件や言語、文化的背景の異なる国々と協力しながら、また製薬会社より資金や治験薬の提供を受けながら医師主導で治験を実施していく際の課題やその解決方法、過程について紹介されました。

最後に、先端医療科の病棟を見学しました。第 I 相試験を適切に、また患者さんの安全を確保しながら実施するために様々な点を考慮して設計された設備と、物品の配置等を含め、細やかな配慮がされている様子を知ることができました。

図 20: 国立がん研究センター前にて

3.4　聖路加国際大学

本大学では、公衆衛生大学院の先生方に、日本の大学卒後教育システムについて説明を受け、研修生の出身国のシステムと比較しながらディスカッションを実施しました。特に、各国の医療上の課題を解決するにあたり欠かすことのできない公衆衛生学に関する教育体制について情報交換することができました。各国とも、医学部の教育の段階では非常に基本的な部分のみを学習し、公衆衛生学として学ぶには卒後、新たに大学院等に進学する必要があることがわかりました。聖路加国際大学の公衆衛生大学院では、全授業を英語で実施し、世界各国より教

図 21: 聖路加国際病院前にて

授や講師を招聘し、日本に限らず各国から生徒を迎えているとのことでした。e-learning システム等を取り入れることで、働きながら学べる環境も整えられており、研修生にとって、日本での卒後教育について考慮するよい機会となりました。

最後に、聖路加国際病院の外来エリアにて、外国人向けの多言語による相談窓口や、礼拝堂など、歴史ある建物を大切に保存・使用しながら、新しい設備も兼ね備えた施設の様子を見学しました。

図 22: 聖路加国際病院前にて

図 23: 聖路加国際大学公衆衛生大学院の先生方と

3.5 東京女子医科大学・早稲田大学連携先端生命医科学研究教育施設 (TWIns)

2008 年 4 月、東京女子医科大学と早稲田大学は東京女子医科大学・早稲田大学連携先端生命医科学研究教育施設 (TWIns) を立ち上げました。TWIns の T は東京女子医科大学、W は早稲田大学を意味しています。

当施設への訪問で特に研修生の印象に強く残ったのが、細胞シート技術による立体心筋組織の紹介と、スマート治療室 (Smart Cyber Operating Theater; SCOT) への訪問・デモンストレーションの見学でした。

立体心筋組織は細胞シートを重ねて作成された、血管網を有する厚い組織です。この組織が in-vitro と in-vivo での試験を経て、動物モデルへ移植し、心機能の改善が確認されていることが紹介されました。

以下は立体心筋組織に関して発表された論文へのリンクです。

https://www.ncbi.nlm.nih.gov/pubmed/25980939

SCOT の見学においては、手術の安全性と正確性を向上するため、様々な医療機器をネットワーク化し、データを一元的に管理・参照し、直感的に各機器を操作する様子をデモンストレーション・体験しました。外科医の意思決定を支援するための手術部位の 3D 画像の撮影機器や、手術支援ロボットとの連携が可能であることも紹介されました。

図 24: SCOT（Smart Cyber Operating Theater）スマート治療室

図 25: TWIns 前にて

4. 結語

5 カ国より 10 名が参加した本研修は、規制当局による MRCT データの評価の視点、日本における臨床現場や臨床試験の現場、教育研究機関や製薬企業における革新的な研究の事例、また日本の教育システムについて学ぶ機会となりました。

本研修の特徴は日本での MRCT の実際を理解し、各国の状況と比較することができる点です。研修生は各国規制の違いについて理解を深め、協力国間における規制調和の重要性を学ぶことができました。日本において薬剤開発の技術やプロセスの革新がどのように進んでいるかを知ることもできました。加えて、研修生同士、また講師の先生方と自身の経験について共有することができました。

研修生からは、本研修は、臨床試験や技術革新における各国と日本の状況を比較するよい機会となったという意見が聞かれました。終了後のアンケートでは、プログラムの内容と DIT スタッフの対応にについて、全体として満足であったという結果が得られています。

一方で、研修期間が限られていたため、DIT スタッフ等とのより具体的なディスカッションや治験に関するケーススタディの時間が十分に取れなかった点が、改善を希望する点として挙げられており、DIT の研修プログラムにおける今後の課題となりました。

今後に向けて

2019 年 1 月に開催しました「A program focused on comprehensive and collaborative training on medical innovations adapted to challenges of clinical trials in Asian and African countries」は、5 カ国 10 名の研修生を招聘し 10 日間のプログラムにて実施しました。

研修生からは、聴講した PMDA による規制調和の講義、他国の状況を知りえる機会が提供できたことなどに高い評価を得た一方、ケースを用いたディスカッションなど双方でのよりアクティブな研修の要望がありました。

2019 年度以降は、こうした今回の実践からの学びを踏まえて、連携国を活動の中心に置いて 10 年間の予定で国際共同臨床研究のプロフェッショナルを育成するプログラムをあらたに企画開発、実施して参ります。実施の意図は本報告の冒頭でお示しした通り、国際医療協力に加えて国際共同臨床研究を通じた新規医療技術の開発を行い今なお新興・再興感染症、希少疾患、難治性疾患などの疾病に苦しむ患者の方々により良い医療を届けるためでありまして、連携国の状況やニーズに合わせたプログラムの提供を模索してまいりたいと存じます。

企画段階に当たっては、先行研究として米国、欧州、アジアにてすでに展開されているプログラムやカリキュラムをインターネット調査や訪問調査を行い分析し、プログラム設計の基礎材料といたします。調査分析を踏まえてプログラムコンテンツを定義、2020 年以降、新たに研修生を公募しプログラムを実践して参ります。プログラム実施に当たっては、オンサイトのプログラム提供のみならず、e-learning やテレカンファレンスなどの手法も織り交ぜながら、より実践的な国際共同臨床研究をリードするために必要な技術、知識、姿勢を掘り下げるコンテンツを実施していく所存です。企画から実施、評価、改善のいわゆる Plan-Do-Check-Act（PDCA）の 1 サイクルを 5 年としまして、合計 2 サイクル行う計画としています。

引き続き皆様からのご指導ご鞭撻のほど何卒よろしくお願いいたします。

国立国際医療研究センター
臨床研究センター
インターナショナルトライアル部
エグゼクティブマネジメント室長
飯山　達雄

Comprehensive and collaborative training on medical innovations adapted to challenges of clinical trials in Asian and African countries

ENGLISH / 英語

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Preface

The situation surrounding the development of new drugs, medical devices, and medical technologies has significantly changed in recent years. In Japan, there is a need for a system that enables multi-regional clinical research as continuous effort to ensure quality, increase efficiency, and promote harmonization in drug development.

In order to develop a reliable network for multi-regional clinical researches, the Center for Clinical Sciences / Department of International Trials (CCS/DIT) of the National Center for Global Health and Medicine (NCGM) organized a program for capacity building of health professionals intended to implement multi-regional clinical researches in accordance with internationally standardized procedures.

Participants from five countries, from which we currently have representatives in the Department, including the Democratic Republic of the Congo, Indonesia, the Philippines, Thailand, and Vietnam, were invited to join the program. This program focused on a comprehensive and collaborative training on medical innovations adapted to the challenges of clinical trials in Asian and African countries.

Started in 2016, this is the report for FY 2018 of the capacity building division of the CCS-DIT which has a mission to contribute to the improvement of medical care around the world by developing new methods for the prevention, diagnosis, and treatment of emerging and re-emerging infectious diseases, intractable diseases, rare diseases, and non-communicable diseases through multi-regional clinical research.

From lectures to guided visits at the regulatory authority (Pharmaceuticals and Medical Devices Agency (PMDA)), private industry (Daiichi Sankyo Company, Limited), academia (Tokyo Women's Medical University – Waseda University Joint Institution for Advanced Biomedical Sciences (TWIns), and St. Luke's International University), and clinical setting (National Cancer Center Japan (NCC) and NCGM), the 10-day training program for the 10 participants (2 per country) was a great opportunity to exchange views and knowledge between organizers and participants and among the participants themselves.

The open seminar which brought together representatives from academia, clinicians, pharmaceutical companies, and CROs was a good occasion to share about the current clinical trial situation and challenges in each country.

We sincerely thank each one who contributed to the realization of this activity and hope that this program will be a continuous sustainable system for cooperation with counterpart countries.

Hiroshi Watanabe
Director, Center for Clinical Sciences,
National Center for Global Health and Medicine

March 20, 2019

Acknowledgments

There are countless issues to overcome when conducting multi-regional clinical research, including regulatory harmonization among countries, cooperation with the private sector, and differences in culture and medical systems. Founded in 2016, the Center for Clinical Sciences-Department of International Trials of the National Center for Global Health and Medicine aims to promote multi-regional clinical research and contribute to the improvement of global health by collaborating with counterpart countries. The success of a multi-regional clinical research results from the full commitment of skilled professionals. Thus, training researchers is the key to quality clinical research.

A 10-day training was held in order to provide some guidance to health professionals from five countries: the Democratic Republic of the Congo, Indonesia, the Philippines, Thailand, and Vietnam. The guidance is intended to help them conduct multi-regional clinical research, with the ambitious goal of providing new medical treatment to patients with emerging and re-emerging infectious diseases, rare diseases, and intractable diseases around the world.

This training could not be executed without the support and guidance from our collaborators in Japan and in counterpart countries. We gratefully thank the PMDA for the lectures provided to participants. Our gratitude also goes to all the organizations which kindly provided visits and lectures in their facilities, as follows:

- Daiichi Sankyo Company, Limited
- National Cancer Center Japan
- Graduate School of Public Health, St. Luke's International University
- Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University – Waseda University Joint Institution for Advanced Biomedical Sciences (TWIns)

To all National Center for Global Health and Medicine (NCGM) departments whose staff provided visits and lectures to participants, namely: the Bureau of International Health Cooperation, Cell Processing Center, Clinical Trial Management Section, Pharmaceutical Division, Disease Control and Prevention Center, and Biobank, we sincerely acknowledge your cooperation.

We cannot close this chapter without expressing our deep gratitude to all institutions from our counterpart countries who accepted to send their professionals for this program, including:

- The Democratic Republic of the Congo: University of Kinshasa,
  Institut National de Recherche Biomédicale
- Indonesia: University of Indonesia, Sulianti Saroso Infectious Diseases Hospital
- The Philippines: University of the Philippines, St. Luke's Medical Center
- Thailand: Mahidol University, Prince of Songkla University
- Vietnam: Cho Ray Hospital, Bach Mai Hospital

Tatsuo Iiyama

Senior Manager,
Executive Management Office,
Department of International Trials
Center for Clinical Sciences,
National Center for Global Health and Medicine

March 20, 2019

List of Acronyms

AMED	Japan Agency for Medical Research and Development
AMR	Antimicrobial resistance
APEC-RHSC	Asia-Pacific Economic Cooperation Regulatory Harmonization Steering Committee
ATC	Asia Training Center
BIHC	Bureau of International Health Cooperation
CCS	Center for Clinical Sciences
CPC	Cell Processing Center
CRC	Clinical Research Coordinator
CRO	Contract Research Organization
DB	Database
DCC	Disease Control and Prevention Center
DIT	Department of International Trials
FY	Fiscal Year
GCP	Good Clinical Practice
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INRB	Institut National de Recherche Biomédicale
IRB	Institutional Review Board
MEXT	Ministry of Education, Culture, Sports, Science and Technology
MHLW	Ministry of Health, Labour and Welfare
MRCT	Multi-Regional Clinical Trial
MRI	Magnetic Resonance Imaging
NCBN	National Center Biobank Network
NCC	National Cancer Center Japan
NCGM	National Center for Global Health and Medicine
PDCA	Plan-Do-Check-Act cycle
PMDA	Pharmaceuticals and Medical Devices Agency
(R)EID	(Re)-Emerging infectious disease
SCOT	Smart Cyber Operating Theater
SOP	Standard operating procedure
TWIns	Tokyo Women's Medical University-Waseda University Joint Institution for Advanced Biomedical Sciences
WG	Working Group
WHO	World Health Organization

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1. Introduction

1.1 Description of the Training Program

The 2019 NCGM/CCS country-specific MRCT capacity building: "A program focused on comprehensive and collaborative training on medical innovations adapted to challenges of clinical trials in Asian and African countries" was a 10-day training program which aimed to improve capacity of clinical research professionals from five counterpart countries in the conduct of multiregional clinical research.

To build a collaborative standardized network for clinical research implementation between Japan and counterpart countries in Asia and Africa, 10 participants, two per country from the Democratic Republic of the Congo, Indonesia, the Philippines, Thailand, and Vietnam were invited to participate in the program. The program included lectures, discussions, and visits to the PMDA, a pharmaceutical company, clinical research facilities, and educational institutions.

Participants attended the Multi-Regional Clinical Trials (MRCT) Seminar 2019 organized by the PMDA Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) and gained insight into the harmonization of regulatory review of MRCT data.

In order to know the current status of research and medical innovations, lectures and visits were provided from the clinical setting (NCGM, NCC), academia (TWIns and St. Luke's University), and from a private company (Daiichi Sankyo Company, Limited).

In addition, an open seminar during which participants shared presentations on the state of clinical trials in their own countries was held.

1.2 Program Objectives

The program aims:

- To discuss about regulations, implementation mechanisms, and issues concerning multi-regional trials for medical innovations,
- To train professionals who will contribute to the development of clinical trial systems in their countries, and
- To promote cooperation between the National Center for Global Health and Medicine (NCGM) and counterpart institutions.

1.3 Participants

Medical doctors from 10 institutions in four Asian and one African country who had been involved in clinical research participated in the program.

Following in **Table 1** are the participants and their countries.

Table 1. Participants and their country

Country	Institution	Participant Name
The Democratic Republic of the Congo	University of Kinshasa	Yves Lula Ntamba
	Institut National de Recherche Biomédicale	Joelle Lumaya Ambis
Indonesia	University of Indonesia	Anggi Gayatri
	Sulianti Saroso Infectious Diseases Hospital	Nina Mariana
The Philippines	University of the Philippines	Angeline Monica Adalin Arcenas
	St Luke's Medical Center	Mylene Urtula Cornel
Thailand	Mahidol University	Borimas Hanboonkunupakarn
	Prince of Songkla University	Boonjing Siripaitoon
Vietnam	Cho Ray Hospital	Nguyen Chinh Dai
	Bach Mai Hospital	Ngo Thi Phuong Nhung

2. Activities at NCGM

2.1 Center for Clinical Sciences Department of International Trials (DIT)

2.1.1 Overview of the DIT

The DIT's project to build a collaborative platform for multi-regional clinical trials was extensively explained to participants by the DIT representatives. It was explained that DIT promotes information exchange and cooperation among government agencies, companies, and academic institutions by, for example, organizing international forums on infectious diseases, while supporting the seamless execution of multi-regional clinical trials in emerging countries in compliance with international standards and country-specific regulations.

In order to develop a better and solid environment for multi-regional clinical trial programs, DIT is continuously organizing training programs for capacity building of clinical trial professionals in Asian and African countries.

Fig. 1 : DIT presentation

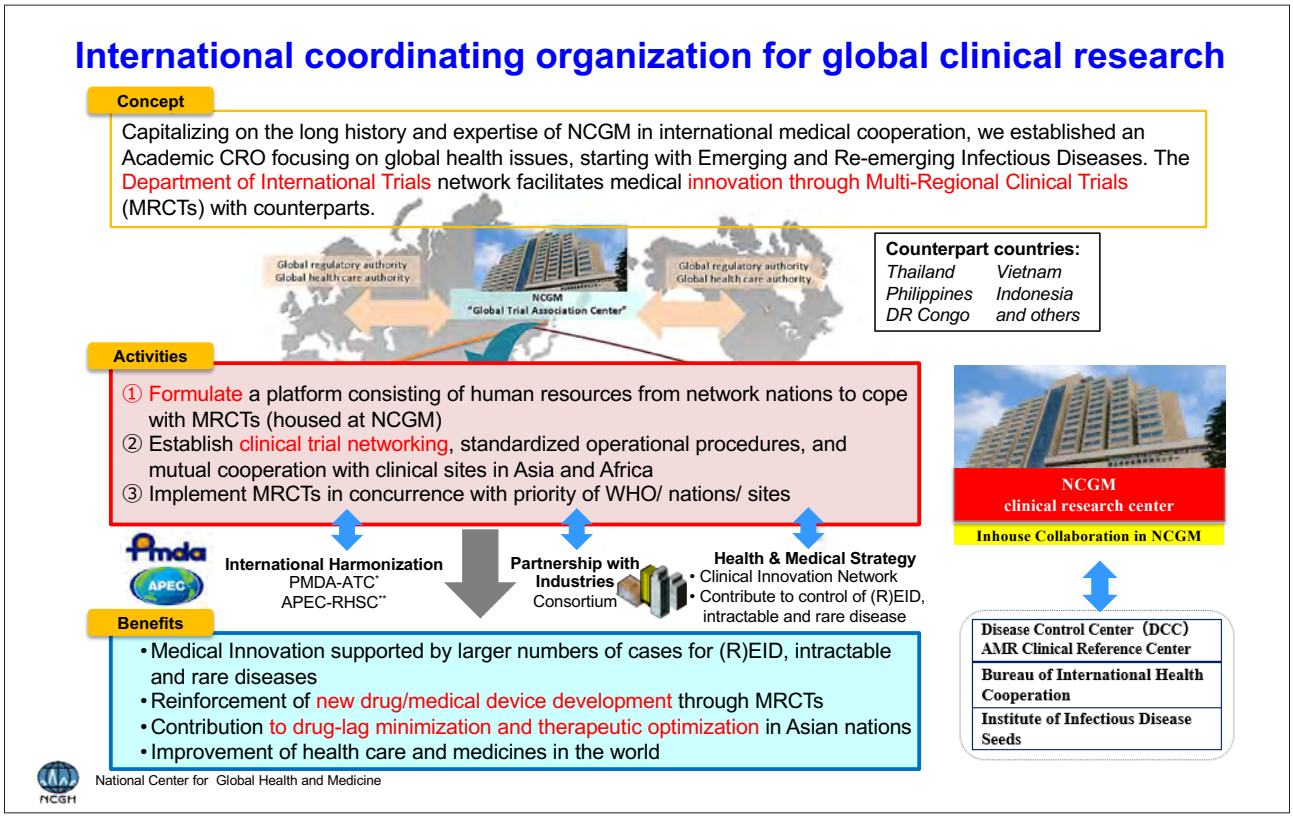


Fig. 2 : Function of DIT

2.1.2 Towards Establishment of an MRCT Network – The DIT Training Plan

DIT's training division provided an overview of types of clinical studies and the necessity of clinical trials. They also insisted on the importance of a continuous updating of knowledge, an increasingly active effort to standardize regulations and data collection methods for MRCTs in recent years. In addition, they presented the outline of a future training program to produce global clinical trial specialists.

To develop the program, the DIT analyzed various programs from other organizations involved in clinical trial training, in order to fulfill the requirements for trained clinical trial professionals.

Trainees will be able to conduct clinical trials in compliance with international standards such as the guidelines issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

After presentations, the interactive discussion focused on the participants' opinions about the current program and suggestions for its improvement, on the state of clinical trials at each home institution, and on their expectations for the future training program.

Fig. 3 : Example of some training program for clinical research professionals

https://mrctcenter.org/clinical-trial-competency/
https://www.diaglobal.org/en
https://acrpnet.org/
https://www.who.int/tdr/publications/year/2016/competency-framework-clinical-res/en/
https://www.transceleratebiopharmainc.com/

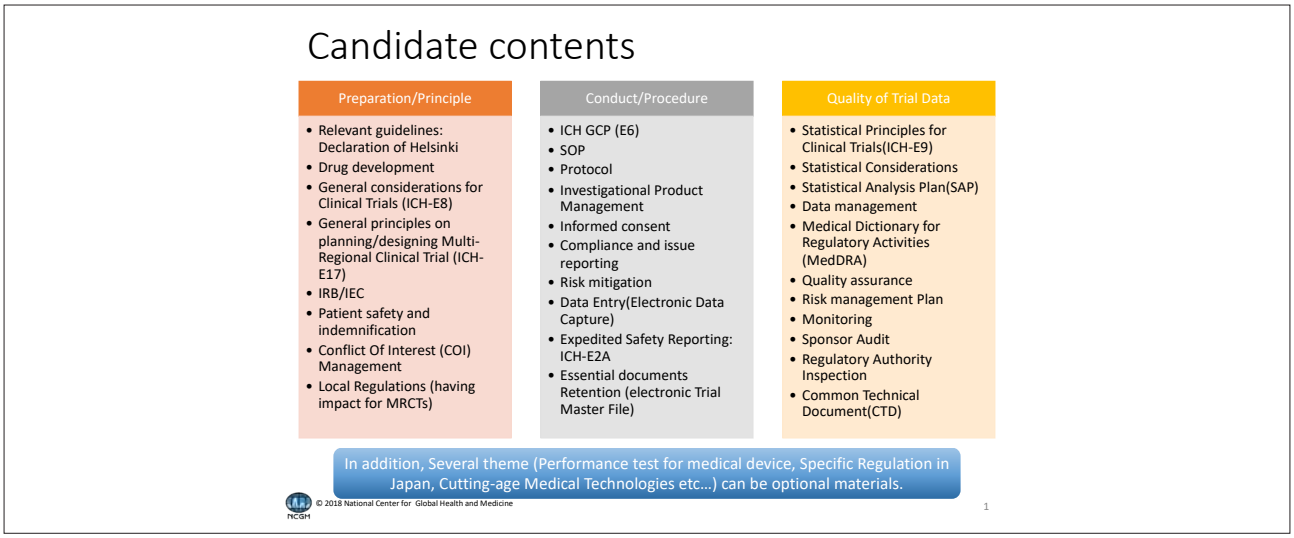


Fig. 4 : Example of candidate program contents

Fig. 5 : With DIT representatives

2.2 Bureau of International Health Cooperation (BIHC)

Fig. 6 : BIHC presentation

As presented by the BIHC representative, the NCGM through the BIHC has a 40-year history of international cooperation, conducting a wide range of technical cooperation projects and policy proposals. The BIHC's technical cooperation projects involve public health, maternal and child health, family planning, infectious diseases control, and the development of medical facilities.

In a project to build a medical facility, for example, the BIHC is providing comprehensive support for opening, managing, and maintaining the facility, which includes support for medical technology transfer, installation of medical systems and emergency care systems, hospital management (e.g., financial management and equipment management), and human resource development (e.g., education of nurses and other medical professionals).

One of the BIHC's strengths is its ability to provide policy-related advice and proposals that reflect local circumstances and based on lessons learned and knowledge acquired through previous technical cooperation projects.

2.3 Cell Processing Center (CPC)

Fig. 7 : In CPC with doctors and other staff

Cell therapy has become an innovative treatment for many degenerative and non-communicable diseases.

To get good quality cells to be used in the therapeutic areas, cells should be treated and cultured under some specific requirements.

The CPC is a series of strictly particle -and microbial-controlled clean rooms equipped with clean benches and isolators to prevent microbial contamination and ensure

cell culture.

The CPC was introduced to participants by two head researchers. One focus is the pancreatic islet transplantation procedure which consists of pancreatic cell culture followed by successful transplantation to Diabetic type 1 patients with uncontrolled glycemia despite insulin therapy and patients with pancreatitis. The presented study provides hope to better improvement of the diabetic's quality of life and in the overall impact to society.

2.4 Center for Clinical Sciences (CCS)

After a brief introduction about the organization of the CCS and its clinical trials-related activities, detailed explanations on the informed consent process were given to participants. Emphasis was on the role taken by the clinician and the Clinical Research Coordinator (CRC) from pre-screening to recruitment of patients.

Participants then visited the Clinical Trial Management Section and the access-restricted temperature-controlled storage room located in the Pharmaceutical Section. During their visit, participants could see the trial-related documents storage and private monitoring rooms.
Discussion focused on how: to protect patient privacy, to keep the trials related document secure, to use smartphones for the remote control of the storage temperature, and to manage equipment in order to ensure consistent data collection.

Fig. 8 : CCS presentation

Fig. 9 : Clinical trial medical examination room

Fig. 10 : Source data verification room

Fig. 11 : CCS presentation

2.5 Disease Control and Prevention Center (DCC)

Activities at the DCC were divided into two parts: the lecture and the facility visit.

During the lecture, DCC's activities were presented. The DCC is engaged in the development of medical experts and infectious disease specialists involved in the prevention, diagnosis, and treatment to fight against antimicrobial resistance

as well as infections.

Aside from clinical care, the DCC has a network with other institutions in and out of Japan for collaboration in infection control, education and training. The DCC is also engaged in risk assessment and actions to protect borders by developing researchers who detect infections early while assessing the need for rapid response.

During the visit, participants could observe some medical wards of the DCC, such as the well-equipped quarantine room with a movement-controlled system to prevent any contamination or spread of emerging and re-emerging infectious diseases while keeping the patient comfortable and the staff free to administer care safely.

Fig. 12 : Quarantine wheel chair for patients with infectious diseases

Fig. 13 : Delivery bed in quarantine room

Fig. 14 : Presentation by DCC

2.6 Biobank

While visiting the Biobank facilities, the staff in charge presented the organization of the National Center Biobank Network (NCBN). The Biobank is part of the NCBN which is a network of six biobanks located at the six national medical centers in Japan. The six national biobanks store samples related to their respective specialties.

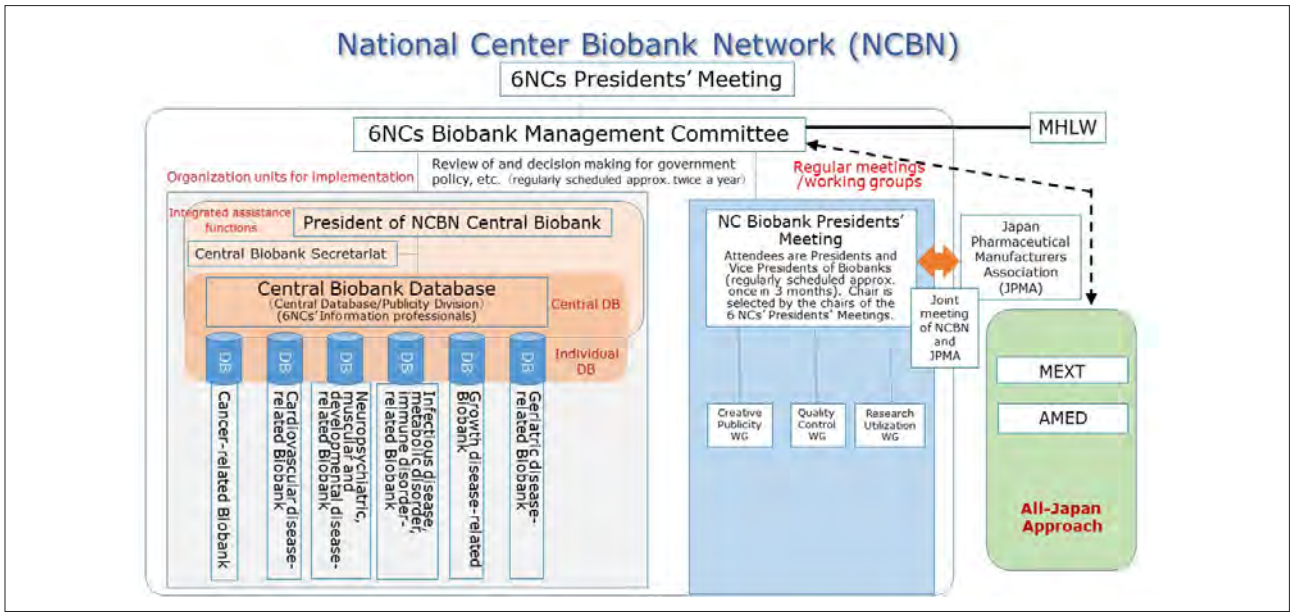


Fig. 15 : NCBN organization structure https://ncbiobank.org/organization/index.php

While each national center biobank collects its related sample, there has been developed a common platform for the management. The application process for getting access to the biodata and the research support services are provided by the central biobank secretariat.
Any researcher who wishes to use biodata can apply to the secretariat and the acquisition of samples is possible for anyone who fulfills the requirements.

The NCGM biobank stores samples (blood, sputum, etc.) obtained from patients with infectious diseases, metabolic disorders, and immune-related disorders. The facility has a remote temperature-controlled room which contains numerous freezers adapted for the storage.

It is worth noting that all sample collection is preceded by a strict informed consent process and data are shared anonymously to protect patient privacy.

NCGM biobank : ncgmbb@hosp.ncgm.go.jp

Fig. 16 : Freezers for sample storage in biobank

Fig. 17 : In the biobank facility with the biobank staff

3. Activities outside of NCGM

3.1 Pharmaceuticals and Medical Devices Agency (PMDA)

There is a strong collaboration between the PMDA and the NCGM in terms of diverse activities.

Participants joined the Multi-Regional Clinical Trials Seminar 2019 organized by the PMDA Asia Training Center (PMDA-ATC) for Pharmaceuticals and Medical Devices Regulatory Affairs .

This seminar is held annually for representatives of relevant regulatory authorities in various countries. Its objective is to promote regulatory harmonization concerning drug development based on the Japanese experience in the reviewing process for drugs and medical devices. This process follows necessary requirements for planning, designing and implementation of clinical trials, clinical data assessment, and post-marketing benefit-risk assessment, all in accordance with the ICH guidelines. Lecturers therefore presented concrete examples of these, with further focus on review toward approval including GCP inspections. Lectures were provided by experts from diverse specialties including PMDA, academia, and industry.

In addition to lectures provided by the organizers, representatives of regulatory authorities from each country presented an outline of the approval review systems and procedures in their countries and discussed issues involving the implementation of the ICH E17 Guideline.

This was a good opportunity for participants to be familiar with the drug review and approval processes of counterpart countries and to get a wide view from different stakeholders, including academia, regulatory authorities, and pharmaceutical companies.

Web page on the PMDA-ATC MRCT Seminar: https://www.pmda.go.jp/english/symposia/0138.html

Fig. 18 : At the PMDA office

Table 2 : PMDA-ATC MRCT Seminar program
(The following information comes from the PMDA web page and lists only the sessions attended by the participants.)

PMDA-ATC Multi-Regional Clinical Trial (MRCT) Seminar 2019

Offered by Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs
DATE: January 21-24, 2019 / VENUE: PMDA

DAY 1 (January 21, 2019)
Key note speech Strategies and challenges for drug development - Future movements and backgrounds of development strategies -
History of drug evaluation using overseas data in Japan Q&A
Scientific insights about ethnic factors Q&A
<**Session 1**> Introduction of review systems and regulations by participants
<**Session 2**> International cooperation and alignment • Global platform for medical innovation as an Academic Research Organization (ARO) • Challenge for global cooperation of regulatory agencies Q&A
DAY 2 (January 22, 2019)
<**Session 3**> Points to consider when planning and designing MRCT • Points of attention for consultation about MRCT from PMDA's experience • Case study -Planning and designing MRCT- Q&A
<**Session 4**> Points to consider when evaluating results • Statistical considerations for MRCT based on the ICH E17 guideline • PMDA's experiences to review MRCT results Q&A
DAY 3 (January 23, 2019)
<**Session 5**> Considerations for MRCT operations • Practical issues and solutions on MRCT operations (Investigator's viewpoint) • Practical issues and solutions on MRCT operations (Industry's viewpoint) Q&A
DAY 4 (January 24, 2019)
<**Session 6**> Regulatory review based on results of GCP inspection • How to perform GCP inspection in Japan -Role of GCP inspection in review process- • How to take GCP inspection results into consideration for review from reviewer's perspective • Applicant's experiences to undergo GCP inspection • Trial site's experiences to undergo GCP inspection Q&A
<**Session 7**> Post-market safety evaluation of approved drugs based on MRCT • Global standards for pharmacovigilance • Risk management plan based on the multi-regional clinical development -from perspectives of pharmaceutical companies- • Risk management based on the multi-regional clinical development - from perspectives of regulatory agencies - Q&A

3.2 Daiichi Sankyo Company, Limited

Research and drug development has been the focus of the Daiichi Sankyo Company, Limited for more than one decade. This global company has successfully launched products that have enhanced many lives around the world.

Activities at the facility were highlighted by a lecture during which the company representative gave a detailed explanation of the drug discovery process, from laboratory to clinical trials including animal studies. Noteworthy is that this process is very long and costly.

Fig. 19 : In front of Daiichi Sankyo Company, Limited

Following the lectures, participants were guided to visit a series of well-equipped laboratories which use cutting-edge technologies for the drug discovery process.
Many of the agents such as antibacterials produced from this company are used by all the participants in their daily practice.

3.3 National Cancer Center Japan (NCC)

After a brief explanation about the hospital structure and services, the researcher from the Department of Experimental Therapeutics presented the current situation of clinical trials in the National Cancer Center Hospital and the achievements which have been made in terms of drug development.

Concerning clinical trial-related activities, the National Cancer Center Hospital has been involved in national trials and now participating in international clinical trials.
In MRCTs, the National Cancer Center Hospital has been facing many challenges such as the cultural and language differences, varying regulatory requirements and management of funds and trial drugs received from pharmaceutical companies.

National Cancer Center Hospital's researchers are also conducting trials for cancer genomics.
Participants much appreciated viewing the well-equipped facilities of the Phase 1 unit for clinical trials.

Fig. 20 : In front of National Cancer Center Japan (NCC)

3.4 St. Luke's International University

To be familiar with the education system in Japan, participants visited St. Luke's International University.
The Dean of the Graduate School of Public Health presented the organization of the program which is mainly designed for current working professionals.

The share time was mainly focused in the comparison between the Japanese education system and that of each participant country.
All courses are provided in English either onsite or using the

Fig. 21 : In front of St. Luke's International Hospital

e-learning system by teachers from multiple borders.

After the exchange, participants were able to visit the multilingual consultation desk, which is a rare service for foreign patients in Japan.

Fig. 22 : In front of St. Luke's International Hospital

Fig. 23 : With St. Luke's International University professors

3.5 Tokyo Women's Medical University – Waseda University Joint Institution for Advanced Biomedical Sciences (TWIns)

In April 2008, under the direction of the Tokyo Women's Medical University and the Waseda University, the Tokyo Women's Medical University - Waseda University Joint Institution for Advanced Biomedical Sciences (TWIns) was created. TWIns is a research and education center for medical engineering. The term "TWIns" stands for the "T" in Tokyo Women's Medical University and the "W" in Waseda University.

Two strong points dominated the visit at the TWIns, first the presentation about the three-dimensional cardiac tissue fabricated using the cell sheet technology and the demonstration of the Smart Cyber Operating Theater (SCOT).

The 3-D cardiac tissue is a thick vascularized tissue created by layering three cell sheets for good vascularization. The tissue has been used successfully both *in vitro* and *in vivo*. In *vivo*, cardiac transplantation in some animal models improved their heart function. This innovation intends to be the future hope for the treatment of heart failure and other cardiopathies.
Following is the link of the published paper related to the 3-D cardiac sheet.
https://www.ncbi.nlm.nih.gov/pubmed/25980939

The SCOT is a cutting-edge operating room that uses computing and networking technologies for the improvement of safety and precision of surgery, in this case especially neurosurgery. This is a decision-making navigation system which helps the surgeon achieve a 3-D image of the lesion during the operation and with the integration of the robotic device; the SCOT helps for the precision guidance.

Fig. 24 : The Smart Cyber Operating Theater (SCOT) room

Fig. 25 : In front of TWIns

4. Conclusion

The 2019 NCGM/CCS country-specific MRCT capacity building: “A program focused on comprehensive and collaborative training on medical innovations adapted to challenges of clinical trials in Asian and African countries", a 10-days training program which brought together 10 participants from 5 countries was an opportunity to learn about the regulatory view for managing MRCT’s data, to familiarize with the Japanese clinical practice and research, to experience the innovative researches from academia as well from industry, and to familiarize with the education system in Japan.

The strength of this program was due to the fact that participants could understand the Japanese side of the MRCT and could compare with their local knowledge. Participants could understand how much regulations are various but there is an important trend of harmonization between collaborative countries. They also could see the advancement of the innovations in the drug development process and engineering. In addition, they could share their own experience with other participants and with lecturers.

In the view point of participants, the program was a good opportunity for them to see a different clinical trial and innovation world from their respective countries.

Globally, they were satisfied with the content of the program and with the support of the DIT staff. Nevertheless, they were concerned about the short timing of the program which didn’t allow them and the DIT staff to have more practical discussion of clinical trial cases.

This aspect is the weakness of the training program.

Future Prospects

Ten researchers from five countries were invited to participate in the 10-day training program held in January 2019, which focused on comprehensive and collaborative training on medical innovations adapted to the challenges of conducting clinical trials in Asian and African countries.

The participants greatly appreciated the lecture on regulatory harmonization given by experts from the PMDA, as well as the opportunity to learn about situations in various countries.
At the same time, however, they suggested that we should include more active training activities such as discussions with experts based on case studies.

Starting in FY 2019, based on the lessons learned from the implementation of the previous programs, we will plan and develop a new training program to produce professionals specializing in multi-regional clinical trials, which will be implemented in counterpart countries over a planned period of 10 years.

As discussed at the beginning of this report, the purpose of the program is to provide international cooperation and develop new medical technologies through multi-regional clinical research and to thereby provide new medical treatment to patients with emerging and re-emerging infectious diseases, rare diseases, intractable diseases, and non-communicable diseases.
We will explore ways to offer a program that will suit the situations and needs of counterpart countries.

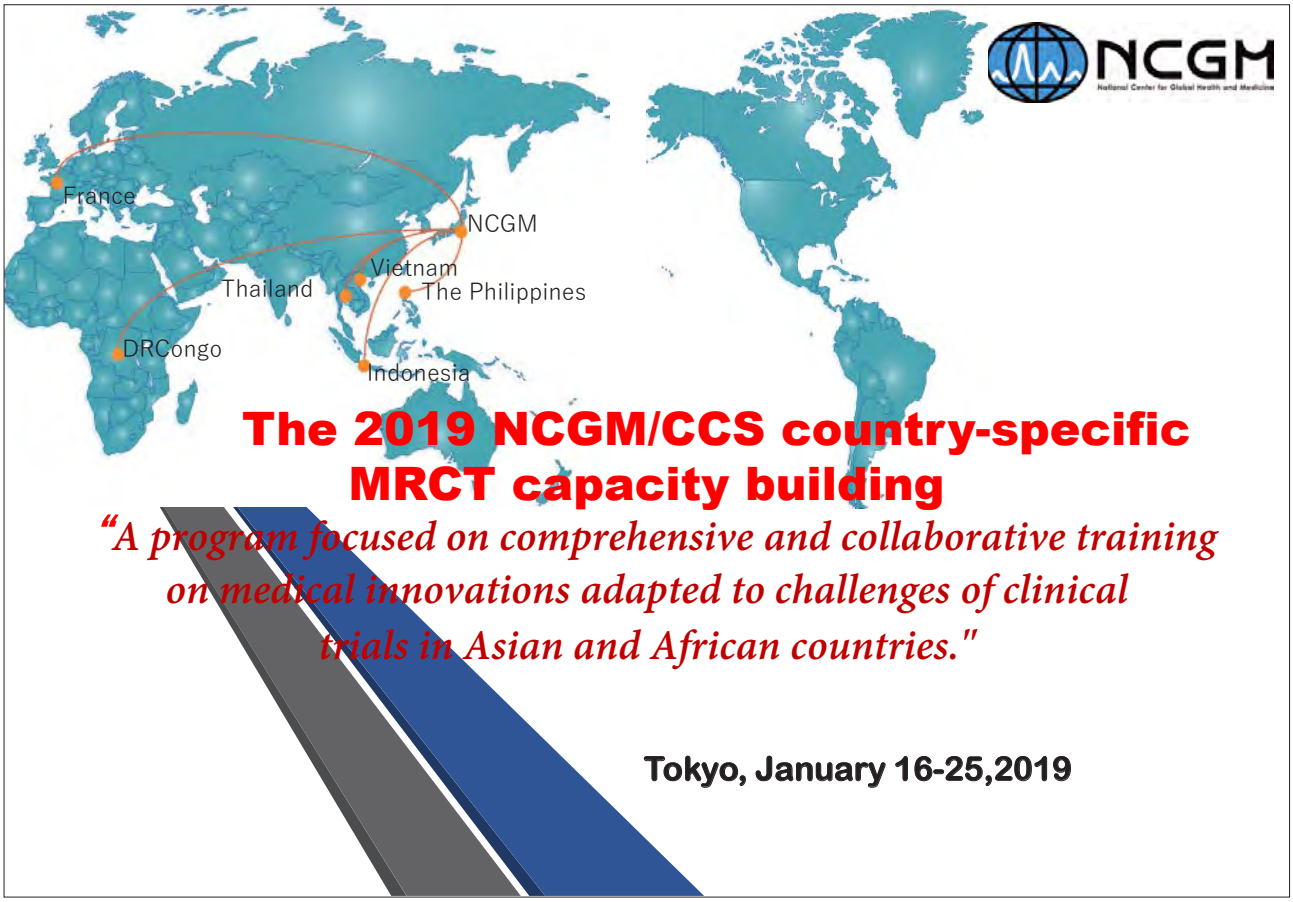
In the planning stage, we will conduct internet-based research and make research visits in order to analyze programs and curricula that have already been implemented in the United States, Europe, and Asia. The analysis will provide basic information needed to design the program.
Based on our research and analysis, we will determine the program content and will publicly solicit applications from prospective participants and begin implementation of the program in 2020. We intend to offer activities that will enable participants to develop skills, knowledge, and attitudes necessary for leading practical multi-regional clinical trials. Such activities will include on-site visits, e-learning, and teleconferences. We plan to apply the so-called, Plan-Do-Check-Act (PDCA) cycle to the program implementation, with two cycles lasting 5 years each.

We appreciate the continued guidance and encouragement provided by the relevant organizations and professionals.

Tatsuo Iiyama

Senior Manager, Executive Management Office,
Department of International Trials
Center for Clinical Sciences,
National Center for Global Health and Medicine

別添 / Appendix


NCGM
France
NCGM
Vietnam
Thailand
The Philippines
DRCongo
Indonesia
The 2019 NCGM/CCS country-specific
MRCT capacity building
"A program focused on comprehensive and collaborative training
on medical innovations adapted to challenges of clinical
trials in Asian and African countries."
Tokyo, January 16-25,2019

別添 2 / Appendix 2　スケジュール / Training Program Schedule

The 2019 NCGM/CCS Counry-Specific MRCT Capacity Building

Duration: Jan. 16- Jan.25, 2019

Date	am/pm	Program	Venue
【Day1】 Jan. 16, 2019	AM		
	PM	Arrival	Airport-> NCGM
【Day 2】 Jan. 17, 2019	AM	Orientation: Life in Japan, Self introduction Introducing NCGM Introducing Department of International Trials (DIT) Introducing Bureau of International Health Cooperation(BIHC) Introducing Cell Processing Center(CPC)	NCGM
	PM	Visit to Daiichi Sankyo Company, Limited	NCGM -> Daiichi Sankyo Company, Limited
【Day 3】 Jan. 18, 2019	AM	Visit to National Cancer Center Japan (NCC)	NCC -> NCGM
	PM	Site tour in NCGM Introducing Center for Clinical Sciences(CCS) Introducing Disease Control and Prevention Center (DCC) Introducing Biobank	NCGM
【Day 4】 Jan. 19, 2019	AM	Visit to National Museum of Emerging Science and Innovation Miraikan	Miraikan
	PM	Discussion on Japan's cutting edge medical technology	
【Day 5】 Jan. 20, 2019	AM	Visit Open Seminar Session venue	NCGM
	PM	Discussion and preparations for the Open Sminar Session	
【Day 6】 Jan. 21, 2019	AM	Participate in PMDA-ATC MRCT seminar 2019	PMDA
	PM	Participate in PMDA-ATC MRCT seminar 2019	
【Day 7】 Jan. 22, 2019	AM	Participate in PMDA-ATC MRCT seminar 2019 Visit to St. Luke's International University Graduate School	PMDA-> St. Luke's International University
	PM	Participate in PMDA-ATC MRCT seminar 2019	St. Luke's International University -> PMDA
【Day 8】 Jan. 23, 2019	AM	Participate in PMDA-ATC MRCT seminar 2019	PMDA -> TWIns
	PM	Visit to Tokyo Women's Medical University-Waseda University Joint Institution for Advanced Biomedical Sciences (TWIns) Open Seminar Session; Clinical Trials-Current Situation and Challenges (Presentation from each country)	TWIns -> NCGM
【Day 9】 Jan. 24, 2019	AM	Participate in PMDA-ATC MRCT seminar 2019 NCGM DIT Lecture/Discussion; Towards a MRCT's Network Establishment -The DIT Training Program-	PMDA -> Meeting Room ->PMDA
	PM	Participate in PMDA-ATC MRCT seminar 2019 Closing Ceremony; Program Completion Certificate Ceremony	PMDA ->NCGM
【Date 10】 Jan. 25, 2019	AM	Fly back Home	NCGM->Airport
	PM		

近年のエボラ出血熱、MERSのアウトブレイク、ジカ熱、インフルエンザ、マラリアなどの新興・再興感染症の流行は公衆衛生にとどまらず、世界的な社会、経済上の話題の一つです。グローバル社会に生きる私たちにとって地域的な感染症の発生は、もはや遠き国のできごとではありません。
国立国際医療研究センター（NCGM）では、起こりうる将来を見据えて、各国が共通の悩みとして持っている新興・再興感染症、希少性疾患、難治性疾患を中心に国際臨床試験を実施しています。
この度、臨床試験を国境を越えてより円滑に実施する体制を構築することを目的に人材育成プログラムを開発し、NCGMが連携している5か国にて候補者の公募、選考を経て、10日間の研修を行います。研修を締めくくるイベントとして、「臨床試験：最新動向と課題」のテーマで成果発表会を企画しました。
皆様のご来場をお待ちしております。

｜プログラム｜

15：30~15：35　開会
15：35~15：55　コンゴ民主共和国からの研修生によるプレゼンテーション
15：55~16：15　フィリピンからの研修生よるプレゼンテーション
16：15~16：35　ベトナムからの研修生よるプレゼンテーション
16：45~17：05　インドネシアからの研修生よるプレゼンテーション
17：05~17：25　タイからの研修生よるプレゼンテーション
17：25~17：30　講評

※プログラムは変更になる場合があります

日時：2019年1月23日（水）15：30-17：30（15：00受付開始）
会場：国立国際医療研究センター研究所AB会議室
参加費：無料（事前登録が必要となります）
登録サイト：お申し込みはコチラ
参加者：60名（定員になり次第締め切ります）
言語：英語
主催：国立国際医療研究センター臨床研究センター
連絡先：03-6228-0445
Email: dit-info@hosp.ncgm.go.jp

NCGM 150TH ANNIVERSARY

別添 4 / Appendix 4　成果報告会案内（英語）/ Open Seminar Flyer (English)

Epidemic of emerging/re-emerging infectious diseases, such as Ebola disease, MERS, Zika, Flu, and Malaria is one of the social and economic topics in global society beyond the public health issue. For us, living in globalization, local infectious disease outbreak is not just the issue in far country anymore. National Center for Global health and Medicine(NCGM) is doing global clinical studies mainly for emerging/re-emerging infectious diseases, rare diseases, and refractory diseases which is the common issue in each country foreseeing possible future situation.
To build a platform for more effective global clinical studies, ten days training program was developed. Trainees were openly recruited from 5 countries which NCGM already have relationship. To present an achievement of trainees, we planned publicly open session with the theme “Clinical trials: current situation and challenges”. We welcome everyone’s participation.

| Program |

15 : 30~15 : 35　Opening
15 : 35~15 : 55 Presentation from DR Cong
15 : 55~16 : 15 Presentation from Philippines
16 : 15~16 : 35 Presentation from Viet Nam
16 : 45~17 : 05 Presentation from Indonesia
17 : 05~17 : 25 Presentation from Thailand
17 : 25~17 : 30　Closing Remarks

※Program may be changed.

Date & Time : January 23, 2019 15 : 30-17 : 30（Doors Open15 : 00）
Venue : National Center for Global Health and Medicine Research Institute Conference AB
Entrée Fee : Free（Prior registration required）
Registration Site : Registration Here
Participants : 60 People（Registration continues until positions are filled）
Language : English
Host :　National Center for Global Health and Medicine
Contact (Tel) : 03-6228-0445
Email: dit-info@hosp.ncgm.go.jp

NCGM 150TH ANNIVERSARY

1. Clinical Trials in DR Congo: Current Situation and Challenges

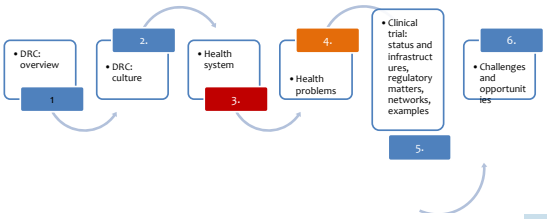
Yves Lula Ntamba / Joelle Lumaya Ambis

Clinical Trials in DR Congo: Current situation and Challenges

Yves Lula, MD
Joelle Lumaya, MD, MSc

1

Outline



2

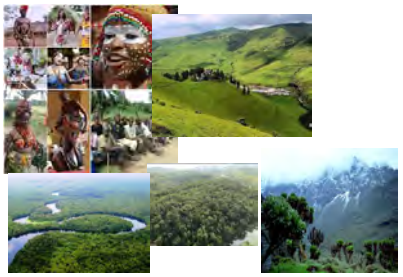
Democratic Republic of Congo (DRC)

- 2nd largest Sub-Saharan Africa country (2,345,409 km²)
- Population: > 70 millions (consumers)
- Borders: 9 countries and Atlantic Ocean
- Human Development Index: 0.457 (176th)
- Poor accessibility within the country (flight needed to reach some places from Kinshasa)
- Urban (30%), rural (70%)
- Climate (tropical wet), 2 seasons (rainy and dry)

By Connormah - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=8986316

3

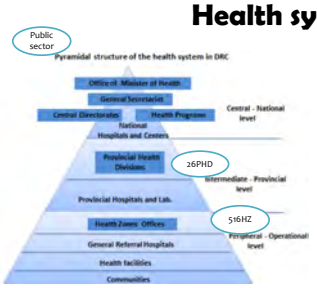
Culture



- More than 400 tribes
- Official language (french)
- 4 national languages (**lingala** most widespread within the country)

4

Health system



- Most healthcare services charge a fee (payment for every single intervention)
- No public insurance
- Assistance provided by NGOs & donors to fight high-burden diseases
- Private sector still growing (in each level), agreements with PHD to be involved in the national policy

5

Health problems

✓ 10 most causes of deaths, all ages

- Malaria
- Lower respiratory infection
- Tuberculosis
- Diarrheal diseases
- Cerebrovascular diseases
- Ischemic heart diseases
- Protein-energy malnutrition
- HIV/AIDS
- Preterm birth complications
- Birth asphyxia and trauma

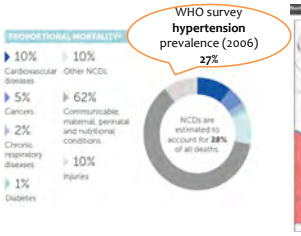
✓ Ten most causes of deaths < 5

- Malaria
- Lower respiratory infection
- Tuberculosis
- Diarrheal diseases
- Protein-energy malnutrition
- Neonatal preterm birth
- Neonatal encephalopathy
- HIV/AIDS
- Neonatal sepsis
- Congenital defects

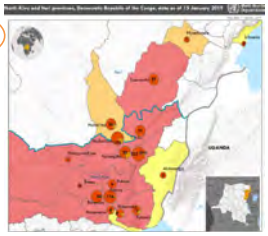
6

Health problems: emerging issues

Non communicable diseases



Ebola outbreak (As of 15 January: 614 confirmed cases, 407 deaths, 237 people discharged from hospitals)



7

Health problems: neglected diseases

Disease	Estimated cases	Rank in Africa
Hookworm infection	31 million	2nd
Schistosomiasis	15 million	3rd
Ascariasis	23 million	3rd
Trichuriasis	26 million	2nd
Lymphatic filariasis	49 million at risk	2nd
HAT	10,269–18,592	1st
Leprosis	3,621	1st

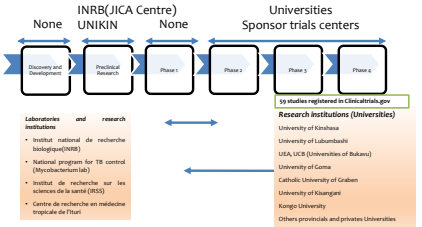
Rimoin AW, Hotez PJ (2015) NTDs in the Heart of Darkness: The Democratic Republic of Congo's Unknown Burden of Neglected Tropical Diseases. PLoS Negl Trop Dis 9(7): e2118.

38.4 million people received treatment in D.R. Congo in 2016

11.5 million people in need did not receive treatment in D.R. Congo in 2016

8

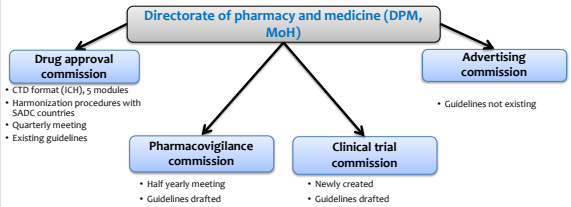
Clinical trials: status and infrastructures



There is a lack of facilities and equipment for drug development and clinical trials

9

Clinical trials: regulatory matters



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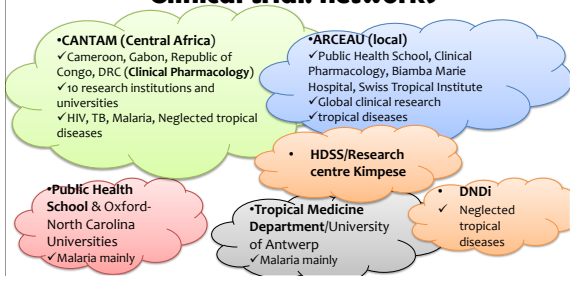
Clinical trial: networks



11

Clinical trial: examples (ongoing)

Study title	Condition	Intervention	Location	Sponsor
Investigational Therapeutics for the Treatment of People With Ebola Virus Disease (multioutbreak, multicentre RCT)	Ebola	Zmapp, mAb114, Remdesevir, REGN-EB3	Beni (Butembo upcoming)	NIH (As of 6 Jan, 44 patients enrolled)
Cohort Event Monitoring Study of Pyramax®	Malaria	Pyramax	DRC (Kinshasa, Kimpese), Congo, Gabon, Cameroon, Ivory Coast, Switzerland	MMV/Shin Poong
Prospective Study on Efficacy and Safety of SCYX-7158 in Patients Infected by Human African Trypanosomiasis Due to T.b. Gambiense	Human African Trypanosomiasis	Acoziborole	Many locations (12) in DR Congo and 1 site in Guinea	DNDi
DIAgnostics for Multidrug Resistant Tuberculosis in Africa	MDR Tuberculosis	Diagnostic Tesst: Deeplex test, InSilixa chip assay, GeneXpert Fluorescein DIAcetate (FDA)	INRB, ITM Antwerp, some countries	Laboratoire de Référence des Mycobactéries

12

Clinical trial: examples (ongoing)

Study title	Condition	Intervention	Location	Sponsor
Diagnostic Tools for Human African Trypanosomiasis Elimination and Clinical Trials: Early Test-of-cure (DITECT-WP4)	African Trypanosomiasis	Diagnostic Test: RNA and neopterin detection	Many sites in the country	Institute of Tropical Medicine (Belgium)
Arresting Vertical Transmission of Hepatitis B Virus (AVERT-HBV)	Hepatitis B	Tenofovir Disoproxil Fumarate, Monovalent HBV vaccine	Kinshasa	University of North Carolina
Community Access to Rectal Artesunate for Malaria (CARAMAL)	Malaria	Rectal artesunate	DR Congo, Nigeria, Uganda	UNITAID, SWISS TPH, CHAI, UNICEF
Fexinidazole in Human African Trypanosomiasis Due to T.b. Gambiense at Any Stage (FEXo09)	Human African Trypanosomiasis	Feninidazole	Many locations in DR Congo	DNDi

13

Clinical trials: challenges

- Poor infrastructures in rural and remote areas (roads, rivers) →logistical challenges
- Security concerns in East part of country
- Language barriers
- Limited number of scientist trained in clinical trial
- Lack of adequate facilities/equipment dedicated to clinical trials

14

Clinical trials: opportunities

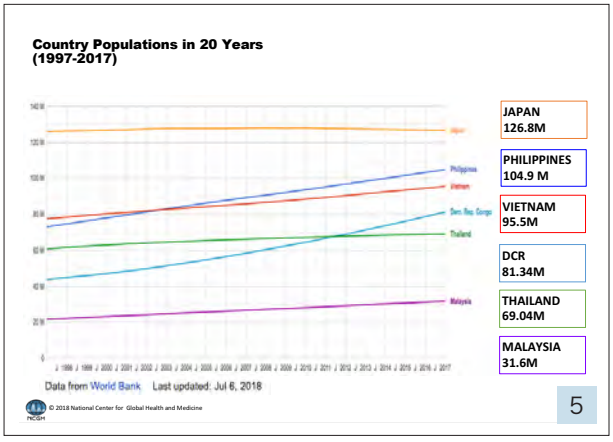
- Variety of diseases (re-emergent, neglected, non-communicable diseases)
- Gene diversity of inhabitants (pharmaco-genetics study)
- Co-existing of various patterns of certain diseases (malaria patterns "tropical-equatorial-mountain")
- Cost-effectiveness (rapid inclusion "less time", reduced cost)
- Existing local CRO (Swiss TPH, DNDi) and ethics committees
- Improvement of regulatory authority over time

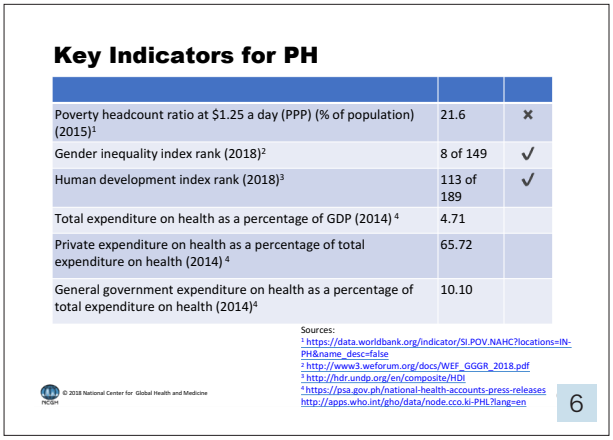
15

16

2. Clinical Trials: Current Situation and Challenges in the Philippines

Angeline Monica Adalin Arcenas / Mylene Urtula Cornel





Q1: What are the potentials for handling clinical trials in the Philippines?

7

Potentials

A. **Research interest is high ; willingness to participate**
B. **Government support : Adequate funds for public and private sectors**
C. **Skilled and experienced human resource/professionals**
D. **Infrastructure and Connectivity**
E. **Regulatory environment**
F. **GCP compliance**

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Research Interest

- High level of interest in research both in private and public hospitals
  - Investigator-initiated trials
  - Sponsor-initiated trials
- Willingness to participate in clinical trials and research
- Encouraged even in postgraduate courses and fellowship programs

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Research Interest

- In clinical trials, Philippines
  - 3rd in SE countries (US NIH)
  - 8th worldwide (European Medicines Agency reports)
- **As of April 2018,**
  - **882** clinical trials
  - **179** ongoing trials in major therapeutic areas
    - Respiratory disease and Lung disease
    - Communicable disease and Infectious disease
    - Diabetic/Metabolic/Endocrine disorders
    - Immune system disorders
    - Vascular disease and
    - Oncology

Source:
https://www.sciencedirect.com/science/article/pii/B9780123815378100111
https://epsi-global.com/locations/philippines/article01.html
http://www.pcrp.org.ph/pdf/GuidelineversionLR.PDF
https://clinicaltrials.gov/ct2/results/browse?cntry=PH&brwse=cond_alpha_all

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Government Support

- **National Unified Health Research Agenda (2017-2022)**
- Guides health research and development efforts in the country
- Envisioned to be inclusive, realistic, and collaborative
- Documents reviewed:
  1. Philippine Health Agenda 2016-2022
  2. DOH Philippine Medium Term Research Agenda
  3. DOST Harmonized Research Agenda
  4. Philippine Development Plan 2017-2022
  5. Sustainable Development Goals

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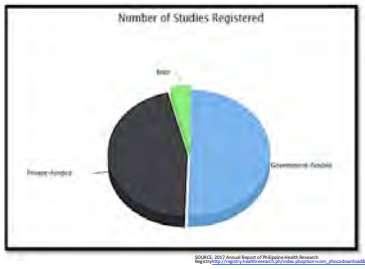
Adequate funds

Clinical Trials in PH (2017)



Funding Agency	Amount
Government (51)	PHP 194M or JPY 405M
Private (44)	PHP 3B or JPY 6B
Private (6)	Undisclosed

SOURCE: 2017 Annual Report of Philippine Health Research Registry

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Human Health Resources

Health Professional	Total	HCW density/ 10000 pop
Nurses	90 308	8.6
Midwives	43 044	4.1
Doctors	40 775	3.9
Medical Technologists	13 413	1.3

Source: Dayrit MM, Lagrada LP, Picazo OF, Pons MC, Villaverde MC. The Philippines Health System Review. Vol. 8 No. 2. New Delhi: World Health Organization, Regional Office for SouthEast Asia; 2018.

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Infrastructure and Connectivity

Group of Islands	Barangay health stations*		Rural health units*		Government hospitals*		Private hospitals*	
NCR	20	0.10%	492	19%	48	11%	115	15%
The rest of Luzon	9 936	49%	1 077	42%	217	50%	410	52%
Visayas	4 815	24%	471	18%	80	18%	87	11%
Mindanao	5 445	27%	547	21%	89	21%	178	23%
Philippines	**20 216**	**100%**	**2 587**	**100%**	**434**	**100%**	**790**	**100%**

Sources: *Department of Health, 2016d; †Department of Health-HFSRB, 2016

- Physical infrastructure of the Philippine health sector
  - 1,224 hospitals
  - 2,587 city/rural health units
  - 20,216 Barangay Health Stations

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Infrastructure and Connectivity

	Hospitals		Beds		Average beds / hospital
	Number	Percentage	Number	Percentage	
Hospital level 1	783	64.0	32 144	31.6	41.1
Hospital level 2	318	26.0	30 781	30.3	96.8
Hospital level 3	122	10.0	38 763	38.1	317.7
Total	**1 223**	**100**	**101 688**	**100%**	**83.1**

Source: Department of Health-HFSRB, 2016

- Physical infrastructure of the Philippine health sector is composed of:
  - 1224 hospitals
  - 2587 city/rural health units
  - 20 216 BHSs

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Infrastructure and Connectivity

- Major private hospitals have world-class facilities
- JCI-accredited
- Major government hospitals have complete diagnostic equipment
- ISO accredited
- Internet connectivity available

Joint Commission International

IMPROVING THE QUALITY AND SAFETY OF HEALTHCARE FOR EVERY PATIENT ACROSS THE GLOBE

International Organization for Standardization ISO 9001:2015

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16

Infrastructure and Connectivity

- Major private hospitals have world-class facilities
- JCI-accredited
- Major government hospitals have complete diagnostic equipment
- ISO accredited
- Internet connectivity available

Table 4.7 Density of diagnostic imaging equipment (per million population), 2012–2016

Group of Islands	Radiography (X-ray)*	Computed tomography (CT)	Mammography*†	Magnetic resonance imaging (MRI)
NCR	112.1	3.4	-	3.3
Luzon	47.6	4.5	-	0.5
Visayas	28.7	2.2	-	0.5
Mindanao	26	3.6	-	0.3
Philippines	44	4.2	22.2	0.8

Notes: *X-ray machines include radiographic (stationary and mobile) and radiographic/fluoroscopic (X-ray machines, but exclude specialized machines such as mobile c-arm, bone densitometer, dental and LINAC machines; **Per million women, age 50–69 years

Source: Calculated by the authors from DOH-Bureau of Health Devices and Technology, 2012–2016

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Clinical Trial Regulatory Process

- Main regulatory institution is the **Philippine Health Research Ethics Boards (PHREB)**
- Level 1 : reviews researches with minimal risk to participants
- Level 2: reviews all types of researches EXCEPT clinical trials required for FDA registration of new drugs. Post marketing studies may also be reviewed.
- Level 3: reviews ALL types of researches including studies required for FDA registration of food, drugs and devices

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Clinical Trial Regulatory Process

- Numerous accredited research ethics committees - (81)
  - **Level 3 – 47**
  - National Capital Region : 28
  - Level 2 – 21
  - Level 1 – 13

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Q2: What are the health challenges in the Philippines?

20

Health Challenges

- Increasing number of diseases
  - Infectious
  - Non-communicable
  - Accidents/ Mental health
- Some laboratories are NOT readily available in the country
- Inaccesibility of the health services to rural areas
- Expensive medications and treatment
- Focused on provision more than research

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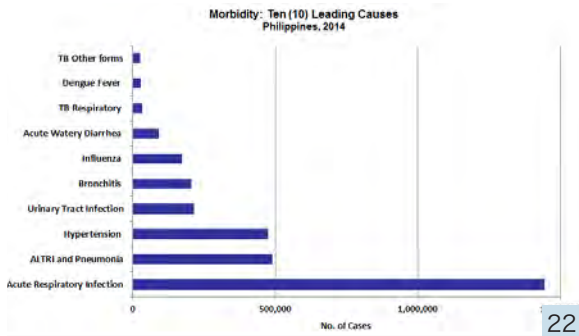
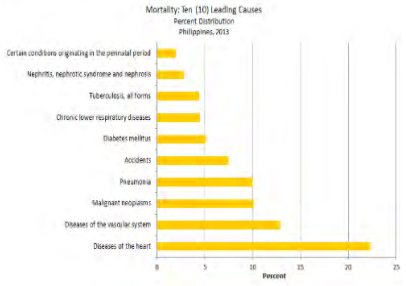
Increasing Number of Diseases



22

Increasing Number of Diseases

Mortality: Ten (10) Leading Causes



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Q3: What can be done to make collaborations more efficient in the future?

24

Collaborations in the future

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- Enhance local and international public-private partn
- Streamline database and registries for public and private research
- Create public awareness regarding research and clinical trials
- Encourage health professionals to attend international conferences
- Increase capacity building
- Focus on translational research
- Participate more in global trials

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Thank you for your kind attention!

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3. Clinical Trials in Viet Nam: Current Situation and Challenges

Nguyen Chinh Dai / Ngo Thi Phuong Nhung

CLINICAL TRIALS IN VIET NAM
Current situation and challenges

Nguyen Chinh Dai, CRH
Ngo Thi Phuong Nhung, BMH

1

Brief introduction about Bach Mai Hospital (BMH), Cho Ray Hospital (CRH)

2

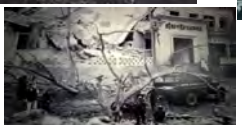
3

BACH MAI HOSPITAL

4

- Founded in 1911, beginning a small contagious hospital as be know with the name is Cong Vong

In 1911



5

Over its 100 years history, Bach Mai has now become a leading comprehensive general hospital with spacious facilities, synchronized modern equipment and qualified staffs.

6

Daily activities
About:
- 200 emergency patients
- *5.400 out-patients*
- *4100 in-patients*

7

Training

10

Nowadays, Bach Mai Hospital has become one of the largest hospital in Viet Nam. It has over 3000 beds with:

3 Institutes

10 Centers

12 Functional Departments

23 clinical Departments

6 Paraclinical Departments

1 Bach Mai Medical College School

8

1. International cooperation
Collaboration (bout training, lecture, research,...) with international organizations in many countries: US (CDC, Washington University, Harvard,..), UK (Oxford,..), Japan (JICA, Nagasaki University, NCGM,..), Sweden (Karolinska Institute, Upsala University,...), Germany, France, Taiwan, ...
2. Science research: all of fields
- In the hospital
- In the country
- International: about drugs, diseases, ...We have been participating in 20 clinical trials, mostly about cancer drugs, hepatitis C drugs, antiviral drug,..

11

Missions:
- Treating patients
- Teaching medical students, post graduates
- Scientific research & International cooperation
- Training & Direction of healthcare

Modern techniques

Robotic surgery

Stem cell transplant

ECMO

Kidney transplant

9

CHO RAY HOSPITAL

The **top referral hospital** of the 37 southern provinces, serves a total population of 40 million.

12

1900

Hôpital Municipal de Cho Lon

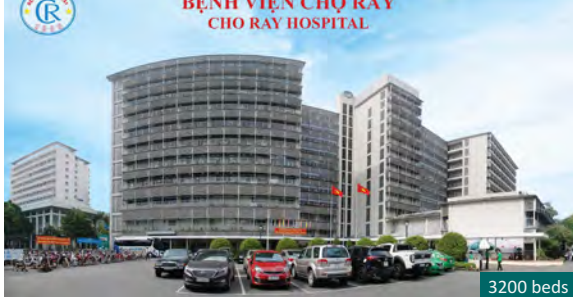
1957

Choray hospital

13

1971 -1974: Constructed new hospital with grant aid from Japan's government

14



15

MISSIONS

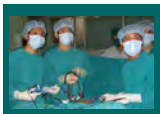
- Treating patients from the southern provinces of Vietnam
- Teaching medical students and post graduates from both local and international institutions
- Undertaking scientific research & directing first line treatment in the region
- International cooperation
- Hospital autonomy in health economics

16

5 Centers

- Training & DOHA
- Blood transfusion
- Oncology
- Cardio-vascular
- DI & ADR

17



36 Clinical Departments

09 Paraclinical Departments

11 Functional Departments

Six Sigma certificate

ISO 15189:2012 Medical Testing Laboratory

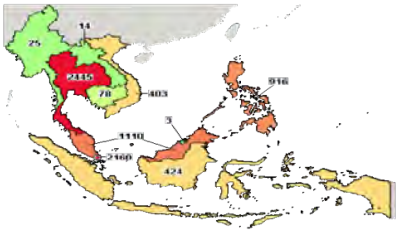
18

STAFF

Doctors	872
Nurses	1668
Technicians	400
Pharmacists	96
Others	904

19

CLINICAL TRIALS IN VIET NAM



https://clinicaltrials.gov/ct2/search/map?map=SE

22

Daily activities

350 emergency patients

1,197,134 1,239,541 1,341,947 1,401,030 1,526,894

5.500 out-patients

123,122 117,803 123,075 125,963 135,195

Length of Hospital stay: 7.1 days

2.700 in-patients

150 surgeries

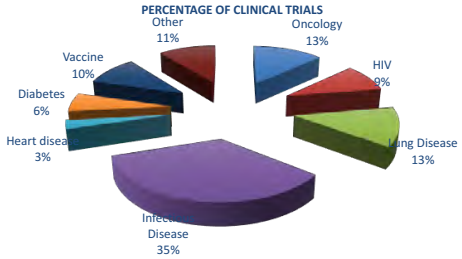
40,544 39,212 38,722 42,890 45,466

120 surgeries/day

2013 2014 2015 2016 2017

20

CLINICAL TRIALS IN VIET NAM



23

Current situation and challenges of clinical trials in Viet Nam

21

List of hospitals able to handle clinical trials in Viet Nam

24

SCIENCE RESEARCH DEPARMENT

- DUTY:
  - Manage: Research, Clinical Trials of International pharmaceutical company, Research of medical students and specialist doctors
  - Establish: Institutional Review Board, Ethics council.

Business Use Only

25

CLINICAL TRIAL IN VIET NAM

- As the importance of biomedical research grows in Vietnam, the government's scientific and ethical standards have become more stringent in an effort to provide a more comprehensive regulatory environment.
- Simultaneously, the Vietnam Ministry of Health is working to expedite the regulatory approval process for clinical trials by providing comprehensive instructions on the requirements for documentation

Business Use Only

26

CLINICAL TRIAL IN VIET NAM

- Submission of application dossier to register a clinical trial
  - Registration of a clinical trial requires the submission of a complete application dossier with the Administration of Science, Technology and Training of the Ministry of Health. The Ministry of Health responds within 15 working days with an approval letter, allowing the investigating organization to take next steps, or rejects the application.

Business Use Only

27

CLINICAL TRIAL IN VIET NAM

- Submission of product dossier
  - Submission of a product dossier and the clinical trial protocol to the Administration of Science, Technology and Training of the Ministry of Health comes after approval of the application dossier.
  - Upon receipt of the product dossier, two examinations are conducted. The first by the Science and Technology Council and the second by the Biomedical Research Ethics Council. Both are within the Ministry of Health

Business Use Only

28

CLINICAL TRIAL IN VIET NAM

- Submission of product dossier(cont)
  - The Science and Technology Council considers the scientific basis of the proposed trial, while the Biomedical Research Ethics Council examines the ethical aspects of the clinical trial.
  - Based on the results of these examinations, the Science and Training Department will request further supplementary documents if it deems the product dossier information to be insubstantial. If results are positive, it will forward the results to the Minister of Health for approval

Business Use Only

29

CLINICAL TRIAL IN VIET NAM

- Requirements and conditions
  - Any investigating organizations seeking the registration of clinical trials must have qualified facilities, equipment and human resources to comply with Good Clinical Practice (GCP).
  - Only central level health institutes the Vietnam Ministry of Health directly manages are eligible to conduct clinical trials. Provincial level health institutes are only allowed to conduct clinical trials in Ho Chi Minh City

Business Use Only

30

CLINICAL TRIAL IN VIET NAM

- Requirements and conditions(cont)
  - All participation in clinical trials must be voluntary. Informed consent must be given by participants. If children, the mentally disabled, people living with HIV/AIDS, pregnant women and others with special conditions wish to volunteer for clinical trials, the Minister of Health must give consent first

Business Use Only

31

CLINICAL TRIAL IN VIET NAM

- The advantages of clinical trials in Vietnam
  - Vietnam's large population is treatment-naïve, providing a vast pool of participants with diseases from both the developed and developing world at a rapid pace for clinical trials. Doctor -patient relationships are strong in Vietnam, and as a result, the retention rate for clinical trials is high.
  - Furthermore, a new law has been implemented by the National Assembly of Vietnam. In previous years, new foreign medicines had to go through clinical trials in their native countries before being circulated in Vietnam for further testing

Business Use Only

32

CLINICAL TRIAL IN VIET NAM

- The advantages of clinical trials in Vietnam
  - Under the new law, effective from January 1, 2017, this time- and resource-consuming requirement has now been waived (if the appropriate clinical data to support a medication's safety and efficacy can be provided).
  - The new law allows Vietnam to focus its time and resources on important clinical trials more efficiently

Business Use Only

33

CLINICAL TRIAL IN VIET NAM

OPPORTUNITIES	CHALLENGERS
• Large amount of patients. • Skilled doctors. • Low cost (patients and investigations). • Well equipped facilities.	• Long time startup. • Public Research Information. • Self report of patients. • Non treatment adherence.

Business Use Only

34

THANK YOU AND HAPPY LUNAR NEW YEAR!!!

35

4. Clinical Trials on Public Institutions in Indonesia

Anggi Gayatri / Nina Mariana

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

Clinical trial on public institutions in Indonesia

Nina Mariana
Anggi Gayatri

1

Indonesia

- Total population → ± 265 millions

2

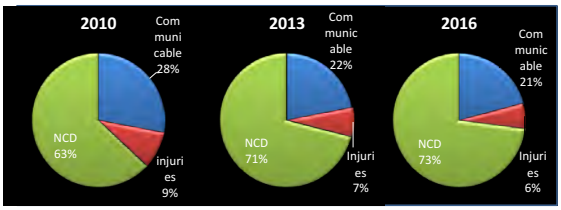
Top 10 causes of disease burden in 2016

1. Ischemic heart disease
2. Stroke
3. Diabetes
4. Tuberculosis
5. Low back and neck pain
6. Neonatal preterm birth complications
7. Sense organ diseases
8. Road injuries
9. Skin diseases
10. Diarrheal diseases

On the road to universal health care in Indonesia, 1990–2016: a systemic analysis for the Global Burden of Disease Study 2016, The Lancet

4

The main causes of burden diseases in Indonesia



Double burden diseases & NCD WHO country profile
MoH of Indonesia

5

SULIANTI SAROSO NATIONAL INFECTIOUS DISEASES HOSPITAL (SS-IDH)

DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS FACULTY OF MEDICINE, UNIVERSITAS INDONESIA

3

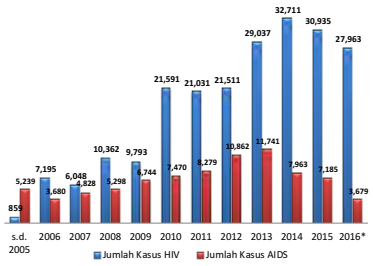
The Challenges

1. Infectious diseases (unfinish)
2. New emerging infectious diseases
3. Evolution from communicable – noncommunicable diseases

→ NCDs are increasingly important while infectious diseases remain a significant part of the diseases burden

6

Number of HIV-AIDS cases in Indonesia



Source: report of counseling service, HIV test and AIDS surveillance

7

TB incidence, Top Ten Countries, 2014

No	TB		MDR TB	
	Absolute incidence rate	% total global	Number of MDR TB case	% total global
1	India	22.7	India	23.7
2	Indonesia	10.3	China	17.3
3	China	9.6	Russian Fed.	13.0
4	Nigeria	5.9	Ukraina	4.3
5	Pakistan	5.2	Pakistan	4.0
6	Afrika selatan	4,8	Philippines	3.7
7	Banglades	3,7	Myanmar	3.0
8	Filipina	3	Uzbekistan	2.3
9	DR Kongo	2,5	Indonesia	2.3
10	Etiopia	2,1	Afrika Selatan	2,1

8

SULIANTI SAROSO
NATIONAL INFECTIOUS DISEASES HOSPITAL
(SS-IDH)

HIV Clinic

9

DOTS TB & MDR TB

10

National referral for ERID;

Variation cases of emerging infectious disease
including
Underinvestigation Mers-CoV,
H5N1, H1N1, H3N1 confirm,
Ebola suspect,
Zika suspect, Diphteri, Rabies,
Meningoxocoma,
MDR TB;

Insulation room for airborne transmission with WHO certified

11

Facilities of Research Services ...

Biological material Storage Facilities

Freezer - 80°C units

Fridge -20°C units

Refrigerator 4°C units

12

Biomolecular Laboratory

13

Monitoring Laboratory for Clinical Research

14

Collaboration

- NCGM
- INA-RESPOND : a multi-centre clinical research network in Indonesia
  - → 7 medical faculties
  - → 9 corresponding hospitals
  - → Eijkman institute

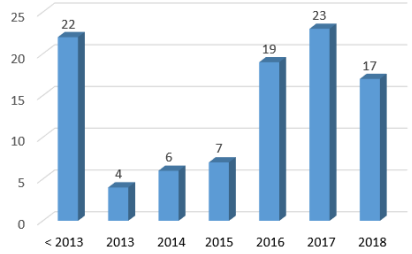
15

Examples of Research Activities

1. A FIRE study : Acute Febrile Illness Study
2. PROACTIVE Study : prospective, observational cohort study of HIV positive antiretroviral-naïve and treatment – experienced individuals
3. AMR study
4. The Study plan: A Randomised Control Trial To Evaluate Efficacy and Safety of Rifampicin 8 mg/kg/day and 12 mg/kg/day For Pulmonary Tuberculosis

16

Clinical trial in Faculty of Medicine, Universitas Indonesia



Source: www.clinicaltrial.gov

17

DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS FACULTY OF MEDICINE, UNIVERSITAS INDONESIA

- Main activities
  - Teaching
  - Research
- Research
  - Operational research → related to teaching hospital (Cipto Mangunkusumo hospital, Persahabatan hospital, etc)
  - Biomedical research → in vitro and in vivo trial
  - Clinical trial

18

Clinical trial

- Chemical medicine
  - Antimalarial for *Plasmodium vivax*
- Herbal medicine
  - Oral VCO (virgin coconut oil) for mild dyslipidemia
  - "Buah Merah" to decrease blood glucose
  - Lumbrokinase (extracted from earthworm) as fibrinolysis agent
- Cosmetics product
  - Sunscreen
  - Topical VCO for anticellulite
  - Topical vitamin C (on going research)

19

Collaboration

- Eijkman institute
- CRSU (Clinical research study unit) at FMUI
- Clinical department at RSCM hospital
- Oxford university

Ethics committee

- Since 1990
- 19 reviewer from variation fields → with GCP certificate
- 4 administration staffs

20

THE IMPACT OF DLBS1033 (LUMBROKINASE) ON FIRBINOLYTIC SYSTEM IN HEALTHY VOLUNTEER

DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS
FACULTY OF MEDICINE, UNIVERSITAS INDONESIA

21

DLBS 1033 (Lumbrokinase)

→bioactive protein fraction, extracted from gastrointestinal system of *Lumbricus rubellus*

- Developed by Dexa Medica company (National pharmaceutical industry in Indonesia)
- Origin of earthworm → Pengalengan, West of Java
- Tablet → 490 mg enteric coated tablet
- In vitro study (by Trisina et al)
  - fibrinogenolytic & fibrinolytic activity
  - Inhibition of platelet aggregation
  - Prolong clotting time

22

Study objectives

- To investigate the impact of DLBS1033
  - on fibrinolytic system → PAP complex, fibrinogen
  - on coagulation system → PT and aPTT
  - antiplatelet effect → platelet aggregation
  - safety profile of DLBS1033 → creatinine, AST and ALT serum

23

Study design

- Sponsored by → Dexa Medica company
- Double blind, randomized, cross-over study (1 week wash out period)
  - Compare to placebo
- Pilot study → 20 healthy subjects
- Drug administration → 3 x 490 mg/day for 1 week

24

PAP *complex*

Parameter	Study drug	Placebo	p	95% CI
	% changes (mean ± SD)	% changes (mean ± SD)		
PAP complex (ng/mL)	**66,7 ± 133,13**	**8,8 ± 108,15**	**0,07 (NS)**	**(-5,34) – 121,09**

Increased of plasminogen activation

Not significant

25

Platelet aggregation

Parameter	Study drug	Placebo	p	95% CI
	% changes (mean ± SD)	% changes (mean ± SD)		
Platelet aggregation (%)	-16,3 ± 26,18	3,9 ± 26,15	**0,032***	(-38,43) – (-1,98)

DLBS1033 could be used as antiplatelet

28

Fibrinogen

Parameter	Study drug	Placebo	p	95% CI
	% changes (mean ± SD)	% changes (mean ± SD)		
Fibrinogen (mg/dL)	0,4 ± 14,91	2,5 ± 18,40	0,729 (NS)	(-15,1) – 10,76

No changed on fibinolysis activity

26

Safety parameter

Parameter	Study drug		Placebo	
	Before	After	before	after
AST	22,5 ± 6,46	21,6 ± 5,97	23,1 ± 5,93	22,7 ± 8,47
ALT	25,4 ± 13,84	24,7 ± 13,98	27,7 ± 16,80	27,8 ± 19,69
Creatinine	0,9 ± 0,11	0,9 ± 0,10	0,9 ± 0,10	0,9 ± 0,12

29

PT & aPTT

Parameter	Study drug	Placebo	p	95% CI
	% changes (mean ± SD)	% changes (mean ± SD)		
PT (seconds)	-0,6 ± 3,53	-0,7 ± 2,43	0,904 (NS)	(-2,03) – 2,28
aPTT (seconds)	0,6 ± 3,97	0,0 ± 3,66	0,691 (NS)	(-2,5)– 3,69

DLBS1033 did not impact on coagulation system

27

Conclusion of lumbrokinase trial

- Effect of DLBS1033 (Lumbrokinase) on healthy subject:
  - No significant impact on increasing fibrinolysis activity
  - No impact on coagulation system
  - Decreased platelet aggregation significantly
  - No impact on liver and renal system function, and no serious adverse event

30

5. Clinical Trials: Current Situation and Challenges in Thailand

Borimas Hanboonkunupakarn / Boonjing Siripaitoon

Mahidol University

Clinical Trials: Current situation and challenges in Thailand

Boonjing Siripaitoon
Division of Allergy & Rheumatology, Prince of Songkla University
Borimas Hanboonkunupakarn
Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University

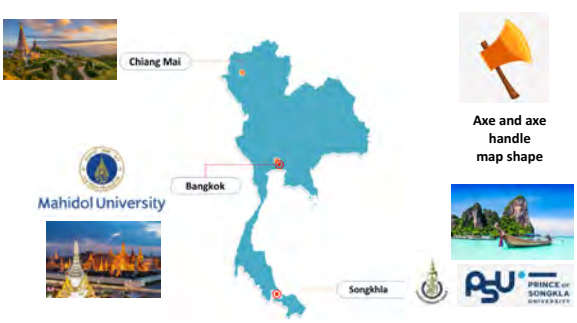
1

Outline

1. Introduction to Thailand
2. Current situation of clinical trials in Thailand
3. The health problems that our country is facing
4. What can be done to make our collaboration more efficient in the future?

2

3



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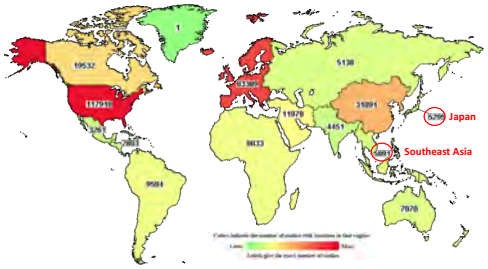
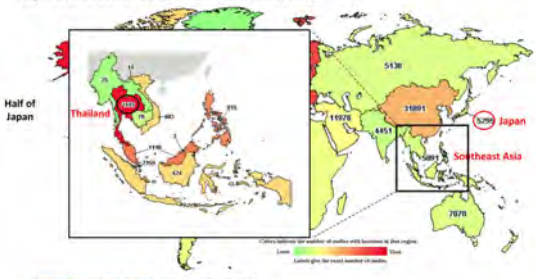
Q1. Current situation of clinical trials



https://clinicaltrials.gov/ access date 18 Jan 2019

5

Q1. Current situation of clinical trials



https://clinicaltrials.gov/ access date 18 Jan 2019

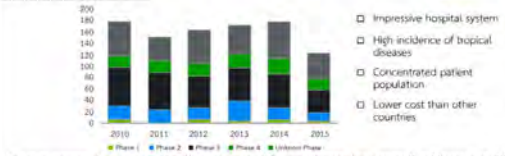
6

Thailand as a clinical trials provider

Thailand is well equipped to be a strong contender in the international clinical research market.

- 111,000 Thai trial participants in **2015**
- 38% of clinical trials had pharmaceutical companies as sponsors.

Number of clinical trials commenced in Thailand, by year and phase



- Impressive hospital system
- High incidence of tropical diseases
- Concentrated patient population
- Lower cost than other countries

Executive summary from prema , http://www.prema.or.th/www/en/images/publications/1.pdf (access date 18 Jan 2019)

7

What is Thailand 4.0 National Plan?

Thailand 4.0 is an economic model that aims to unlock the country from several economic challenges resulting from past economic development models.

Source from https://thaiembdc.org/thailand-4-0-2/

8

Focus on Clinical Research Supporting Five Groups of Technology and Targeted Industries

Source: adopted from Thailand 4.0

	Clinical Research Development and Targeted Industries
Food & Agriculture - Biotech Become the center of premium agricultural products and food, and an exporter of technology in agriculture.	Genomics, Genotype-Phenotype Microclimate Nutrition
Health & Wellness - Biomedical Build medical infrastructure and move Thailand forward to be "Medical Hub" of ASEAN within 2025.	Clinical research management service, Diagnosis and medical devices, well service and treatment innovation, innovative medicine, Thai herb.
Smart Devices & Robotics - Mechatronics Advance as a leader in automatic system, industrial robotics, and service robotics in ASEAN.	Healthcare & medical and service robotics, e.g., robots for elder care.
Digital, IOT and Embedded Technology: Enhance productivity, quality and innovation in various economic activities including agriculture, healthcare, and tourism.	Usage of digital technology to support healthcare industry, e.g., data analytics for research.
Creativity, Culture and High-Value Services Synergize basic cultural assets, innovation and technology to become one of ASEAN's "Creative hubs" within the next ten years.	Clinical research to enhance innovation capability and support innovative ecosystem.

9

Roadmap: Health & Wellness – Biomedical

Ref: http://www.samongthailand.com/thailand4-0/thailandevelopmentstrategy/

1-5 Years	Within 5-10 years	Within 10-15 years
• Generic drug • Biopharmaceutical Products - Biosimilar • Products from probiotics • Herbal Med and Cosmetics • Smart Medical Devices, Robotics for handicapped • Elderly Rehabilitation Centers • Neutraceutical for health and beauty • Medical Tourism	• New Biological Product for Cancer and Allergy • New technology Vaccine • Diagnostic tests with economic potential • Medical Robotics: comply with International Standard • Quality reagents for automated diagnostic services • Smart Village for Aging • Digital Health • Precision Medicine	• Small molecules drug • Drug forTargeted Therapy • New Advanced Vaccine/ new biomaterial product • Medical Robotics and Instruments for surgery • Implanted-devices • Automated diagnostic devices

10

Bio-pharmaceutical value chain supports innovation driven economy in Thailand 4.0 *Source: Deloitte research and analysis*

11

SWOT Analysis for clinical trials in Thailand

STRENGTHS
- Large naive patient population across many disease profiles
- High cost-effectiveness in hosting trials
- High incidence of tropical diseases
- Access to state-of-the-art, readily available medical equipment and facilities
- Significant presence of research based pharmaceutical industry and CROs
- Increasing density of pharmacists

WEAKNESSES
- Lack of government funding to ease the clinical trial approval process
- Limited number of FDA accredited IECs and FDA approvers
- Mandatory approval processes are not sequentially and not in parallel
- Strategy and policies in clinical research areas are short-term focused
- Limited experience in early stage trials

OPPORTUNITIES
- Economic growth potential
- Potential to attract foreign medical specialists as demand increases
- Increased submission / registration fees to address governmental funding gap
- Trend of private hospitals entering into the clinical trial research market

THREATS
- Continued domestic dependency on "value added" rather than "value creation"
- Slow adoption to the trend of collaboration among stakeholders
- Growth potential not scalable with currently available talent
- Increased reliance on effective intellectual property protection

Executive summary from prema , http://www.prema.or.th/www/en/images/publications/1.pdf (access date 18 Jan 2019)

12

- The SWOT analysis found the most important factors for attracting foreign clinical trial investment to Thailand are the large treatment-naïve patient population and the highly skilled workforce.
- The lengthiness of the independent ethical approval process and the import license approval process were considered the biggest impediments to increased foreign investment in clinical research.

13

The procedure of IND review in Thaland

IND submission → IND approval → Conduct clinical trial

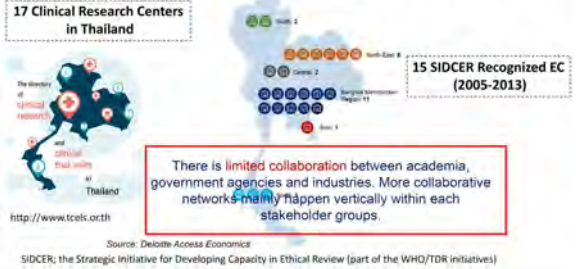
IRB/EC submission → IRB/EC approval → Conduct clinical trial

20 working days for non-phase 1 of chem
60 working days for bio, herbal, vet med, all phase 1

Satita Tonsakulchaisanti, Thai FDA

14

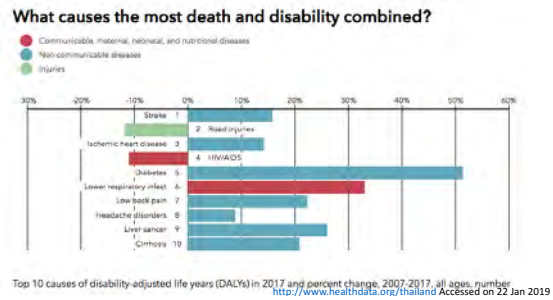
Number and Location of Independent Ethics Reviewers Accredited by TFDA across Thailand, 2016



SIDCER; the Strategic Initiative for Developing Capacity in Ethical Review (part of the WHO/TDR initiatives)

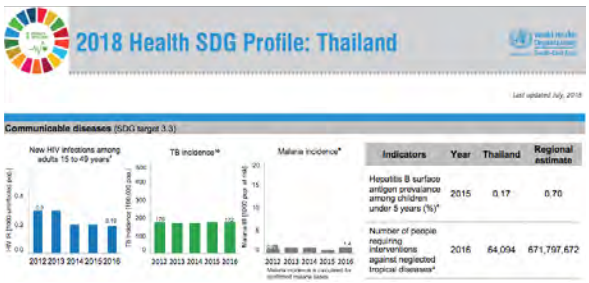
15

Q2. The health problems that our country is facing?



Top 10 causes of disability-adjusted life years (DALYs) in 2017 and percent change, 2007-2017, all ages, number
http://www.healthdata.org/thailand Accessed on 22 Jan 2019

16



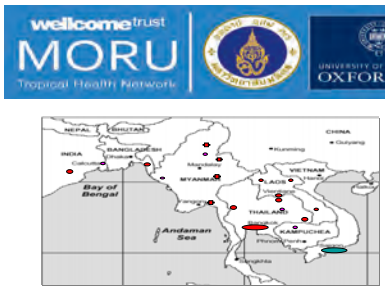
17

Q3. What can be done to make our collaboration more efficient in the future?

1. Trainings and seminars to improve MRCT operation and quality
2. Investigator meeting
3. Country representatives will cooperate/connect to NCGM to conduct MRCT if capable, or to facilitate searching the potential investigators in the special disease areas, and also guide the more efficient clinical trial operation/ trial submission through local regulation
4. Connection between Individual CRC (Clinical Research Center) or MedResNet in Thailand and NCGM would help in searching the potential investigators in special areas and cooperation in conducting MRCT
5. MOU between NCGM with academia or CRC in university hospitals of Thailand for cooperation in conducting MRCT

18

Current projects with international collaboration



19

Tracking Resistance to Artemisinin Collaboration (TRAC study)
TRAC I (2011-2013)

n= 1241, 15 sites in 10 countries

Location of Study Sites and Proportions of Patients with Artemisinin Resistance (red pie).

Artemisinin resistance; PCT1/2 > 5 h, with kelch13 polymorphisms (at or beyond amino acid position 441).

Ashley et al, N Engl J Med 2014;371:411-423.

20

TRACII (2015-2018)

A multi-centre, open-label randomised trial to assess the efficacy, safety and tolerability of Triple Artemisinin-based Combination Therapies (TACTs) compared to Artemisinin-based Combination Therapies (ACTs) in uncomplicated falciparum malaria and to map the geographical spread of artemisinin and partner drug resistance

21

Joint MORU research activities

- Phase I and II trials of antimalarial drugs
  - Pharmacokinetic interactions between primaquine and major blood schizontocides.

22

23

Comprehensive and collaborative training on medical innovations adapted to challenges of clinical trials in Asian and African countries

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Department of International Trials website：
http://ccs.ncgm.go.jp/050/index.html