South East Asia Infectious Disease Clinical Research Network

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Overview

- Challenges in global health and EID clinical research
- What is the SEA Network?
- What is the Mission? How this is evolving?
- Principles, Structure
- Ongoing and planned research
- Future?

Clinical research to address global health challenges in Emerging Infectious Disease (EID)

- Disproportionally affect populations living in resource poor areas
  - TB (XDR, MDR), malaria
  - Zoonotic diseases: H5N1, Nipah, *S. suis*
- Regulatory level clinical research challenging and novel for many sites in endemic areas
- Recognition and will to address global health issues relatively new
- Career pathways and training programs for clinical research are in developmental stages worldwide

Realities of Clinical Research in Emerging Infectious Diseases

- To advance control, prevention, and treatment requires patient-oriented research
- EIDs are unpredictable in time and location
- Research capacity needs to be co-located with outbreak
- Protocol development and approval process is lengthy and research opportunities lost, e.g. SARS, AI, H1N1
- Fragmented/incomplete clinical data collection e.g. AI
- Lack of evidence-based treatment standards
- Failure to collect or under-utilization of samples
    - Samples are obtained outside research protocols
    - Slow conveyance of data and samples
- Inability to easily integrate epidemiologic, clinical, virologic and research data

New Paradigm for Clinical Research

- Build sustainable clinical research capacity in geographic locations to study endemic diseases of interest and areas where EID are most likely to occur
- Move away from pathogen specific or product specific initiatives
- Work collaboratively across borders and institutions (public and private) sharing data, results and technologies

SEA Network Development

- 2004 - discussions between WHO, NIAID, Wellcome Trust and concurrent discussion among parties in SEA
- 2005 - Wellcome Trust, NIAID, and WHO co-sponsored first WHO consultation on human H5N1 infections and idea of Network was discussed at that meeting
- 2005 - visits to MOH and institutions in affected countries
- 2005 - HCMC - drafting of first treatment protocol
- 2006 - Hanoi - Network kickoff meeting
- 2007 – Initiation of oseltamivir treatment protocol

SEA Infectious Disease Clinical Research Network

- Collaborative partnership of hospitals and institutions in Indonesia, Thailand, Viet Nam, Singapore, UK, and USA
- International partners currently include US NIH's NIAID, Oxford University, Wellcome Trust, and WHO in observer status
- **Mission of the Network is to advance scientific knowledge and management of influenza and other infectious diseases of public health import through integrated clinical research with the aim of improving patient care and human health**

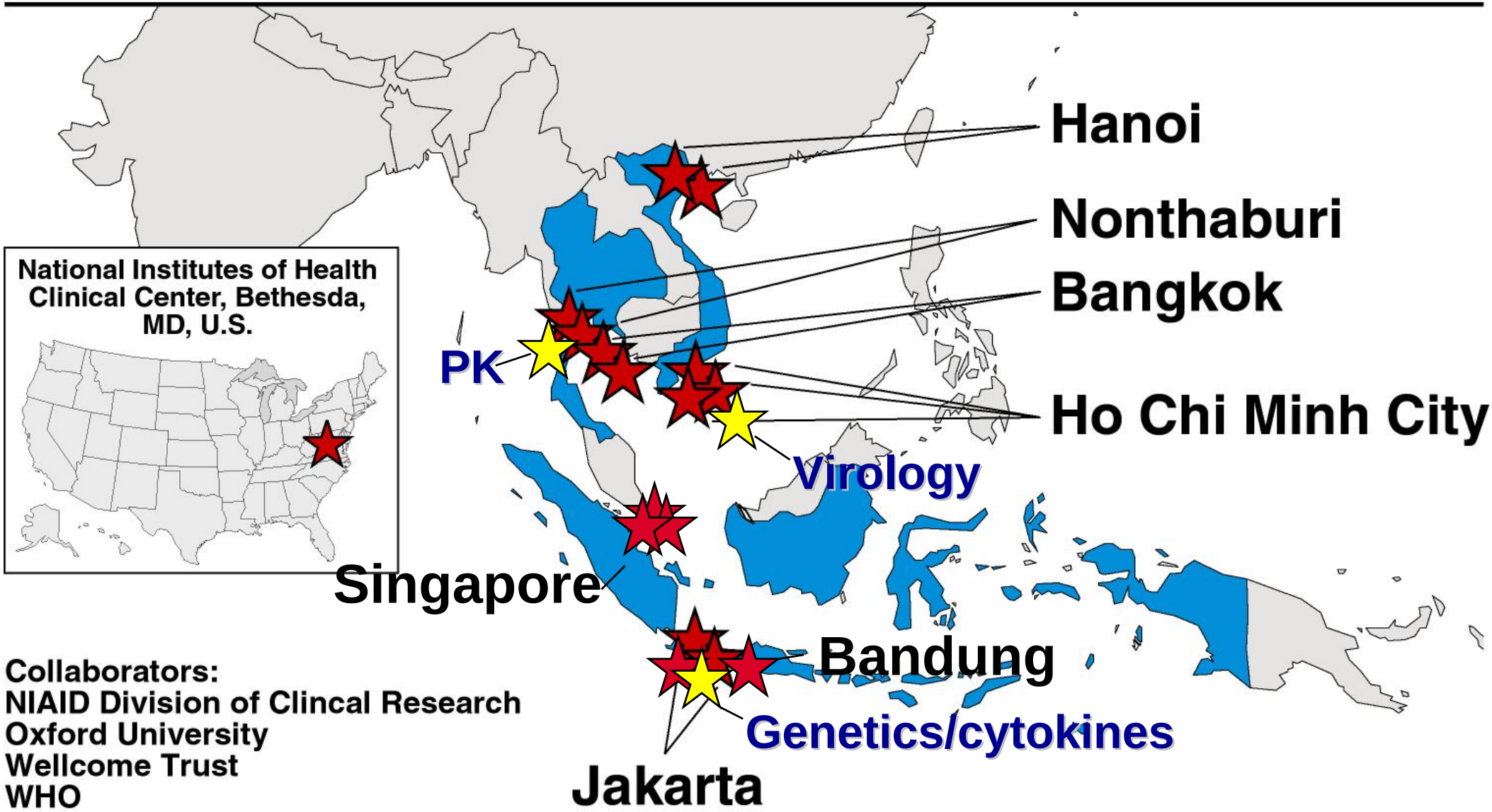
Network Strategies

- Multiple counties, multiple centers
- Regional collaboration in SE Asia
- Clinical management research
  - Initial focus on influenza, expansion to other EID
  - Diagnosis, pathogenesis, treatment, prevention
- Hospital-based, protocol-driven studies
  - Common protocols - comparability of data
  - Agreed data and sample collection methods
  - Shared data to increase power of study

Network Principles

- Develop knowledge on influenza and infectious disease pathogenesis, therapeutics, diagnostics, and prevention through protocol-based studies
- Strong emphasis on building independent research capacity of investigators/institutions
- Compliance with international standards for clinical research
- Prompt sharing of data and isolates with approval of relevant national authorities
- Publication guidelines that are inclusive

SEA Influenza Clinical Research Network



Collaborators:
NIAID Division of Clincal Research
Oxford University
Wellcome Trust
WHO

Participating Sites

4 countries, 17 sites

Thailand 4 sites – supported by **Mahidol Oxford Research Unit**
Siriraj Hospital Mahidol University
Bamrasnaradura Infectious Diseases Institute
Chest Disease Institute
Queen Sirikit National Institute of Child Health

Vietnam 5 sites - supported by **Oxford University Clinical Research Unit**
National Tropical Diseases Hospital, Hanoi
National Pediatric Hospital, Hanoi
Hospital for Tropical Diseases, Ho Chi Minh City
Children Hospital # 1, Ho Chi Minh City
Children Hospital # 2, Ho Chi Minh City

Indonesia 5 sites – supported by the **Eijkman Oxford Clinical Research Unit**
Sulianti Saroso Hospital, Jakarta
Persahabatan Hospital, Jakarta
NIHRD, Jakarta
FKUI RSCM, Jakarta
Hasan Sadikin Hospital, Bandung

New Singapore Sites

Singapore, 4 sites – supported by the NCC Jakarta

Tan Tock Seng Hospital

National University Hospital, National University of Singapore

Changi General Hospital

Reference Laboratories

- Virology Reference Laboratory at the Hospital for Tropical Disease - Oxford University Clinical Research Unit – Ho Chi Minh City, Vietnam
  - Centralized measurement of virology endpoints
  - Qualitative and quantitative RT-PCR
  - Viral culture in state of the art BSL3
  - Antiviral resistance testing: neuraminidase inhibition assay, sequencing
  - Training of other laboratory sites
- Pharmacokinetics Reference Laboratory – Faculty of Tropical Medicine Mahidol University and Mahidol Oxford Research Unit, Bangkok

Diagnostic Laboratories

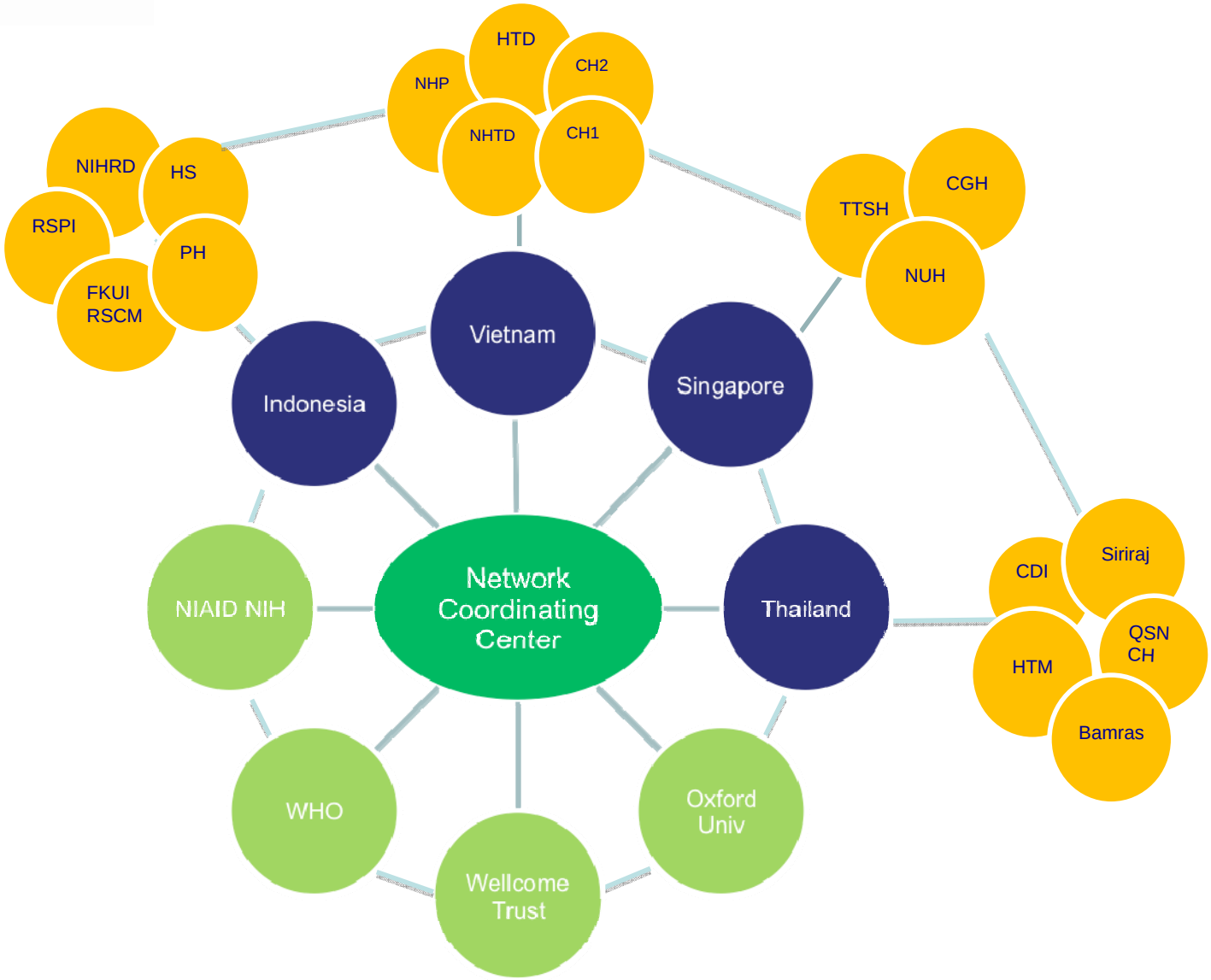
- Hospital sites in Network - ISO certification, EQA, QA/QC
- 10 RT-PCR diagnostic sites
  - Siriraj Virology, Bangkok; NIHRD, Sulianti Soeroso, Persahabatan and Hasan Sadikin Hospitals in Jakarta and Bandung; National Pediatric and National Tropical Disease Hospitals, Hanoi; Hospital for Tropical Diseases and Children's Hospitals #1 and #1 in HCMC, Vietnam
  - Responsible for testing, processing, and storage of specimens
  - Culture capabilities: Future or current 4 BSL-3 laboratories (OUCRU-HTD, HCMC; Siriraj, Thailand; Eijkman Inst and NIHRD, Jakarta)

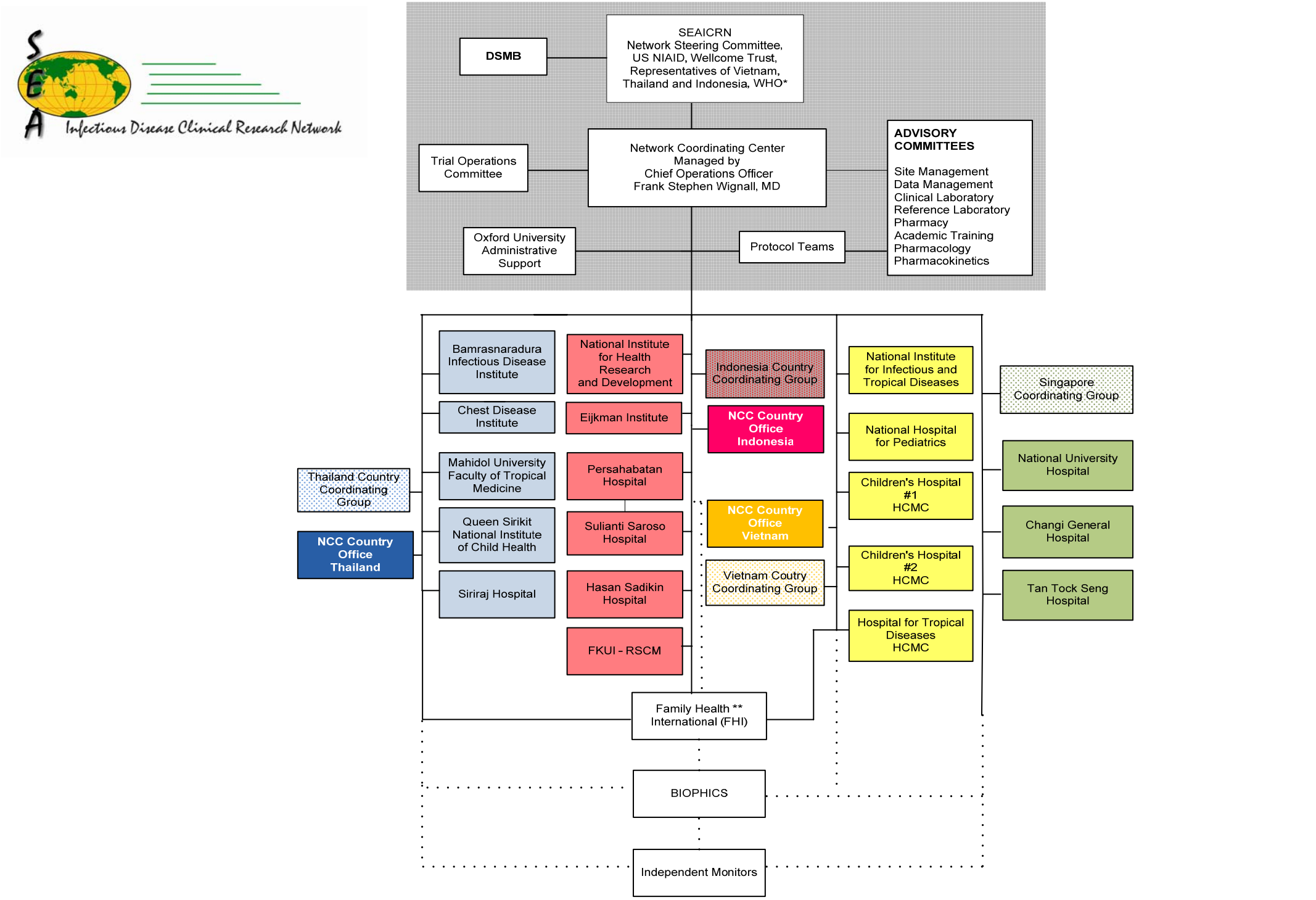
SEA Network Structure

- **Network Steering Committee (NSC)**
  - Composed of one representative from each participating country and international institution
  - Responsible for Network mission, membership, prioritization of clinical trials, oversight of other committees, publication policies, and training
- **Trials Operation Committee (TOC)**
  - Implementation and oversight of specific clinical studies.
  - Oversees subcommittees
- **Network Coordination Center** (NCC)
  - Decentralized with offices in the Eijkman Institute in Jakarta; the Oxford University Clinical Research Unit office, Hospital for Tropical Diseases, HCMC; and in the Mahidol Oxford Research Unit, Bangkok coordination, oversees training activities, communication

Infectious Disease Clinical Research Network

Clinical Sites in SEA Network




SEAICRN
DSMB
Network Steering Committee,
US NIAID, Wellcome Trust,
Representatives of Vietnam,
Thailand and Indonesia, WHO*
Trial Operations Committee
Network Coordinating Center
Managed by
Chief Operations Officer
Frank Stephen Wignall, MD
ADVISORY COMMITTEES
Site Management
Data Management
Clinical Laboratory
Reference Laboratory
Pharmacy
Academic Training
Pharmacology
Pharmacokinetics
Oxford University Administrative Support
Protocol Teams
Bamrasnaradura Infectious Disease Institute
Chest Disease Institute
Mahidol University Faculty of Tropical Medicine
Queen Sirikit National Institute of Child Health
Siriraj Hospital
National Institute for Health Research and Development
Eijkman Institute
Persahabatan Hospital
Sulianti Saroso Hospital
Hasan Sadikin Hospital
FKUI - RSCM
Indonesia Country Coordinating Group
NCC Country Office Indonesia
NCC Country Office Vietnam
Vietnam Coutry Coordinating Group
National Institute for Infectious and Tropical Diseases
National Hospital for Pediatrics
Children's Hospital #1 HCMC
Children's Hospital #2 HCMC
Hospital for Tropical Diseases HCMC
Singapore Coordinating Group
National University Hospital
Changi General Hospital
Tan Tock Seng Hospital
Thailand Country Coordinating Group
NCC Country Office Thailand
Family Health ** International (FHI)
BIOPHICS
Independent Monitors

Clinical Research Capacity Building

- Training of investigators and staff in Good Clinical Practice (635), lab safety (210) and compliance with international standards for clinical research (550)
- Develop Network laboratories for diagnostics, virology, pharmacokinetics, and genetics
- Training program for certificates, MSc (14), and PhD (6) short course in epi, statistics, infection control, clinical trials (79)
- Additional training areas, data management, bioinformatics, pharmacology, ICU management, English language etc (1276)

PROTOCOL DEVELOPMENT PROCESS – SEAICRN

Accum. Duration (days)

CONCEPT DEVELOPMENT

Investigators, NIH & NCC develop Draft Concept

Draft Concept, including budget (local study)

NCC & NSC REVIEW

Country Office Receipt

NCC Office Jakarta Review — NO / YES

NCC Approval — YES / NO

NSC Review and comments

Protocol Administrator Assignment

NSC Approval — NO / YES

WITHIN 40 to 90 DAYS

PROTOCOL DEVELOPMENT

NCC to assign Protocol Development Team, consists of Chairman, Co-Chair, NSC members, Experts, etc

Not done in 40 to 90 days

Draft Protocol (incl. budget & CRF/ PIS / Assent & Monitoring Plan)

FHI Review

- Pharmaco vigilance Plan
- Logistic / Special Equipments
- Data Management Plan
- Drug Manufacturer Review
- DSMB Review
- OXTREC Review & Insurance
- Scientific Review Board Review
- Regulatory Review
- Lab Preparation

NSC Final Approval — NO / YES

CTA Review

- NSC Resubmission
- DSMB Resubmission
- OXTREC Resubmission

NIH

Drug Manufacture

IND

Follow Up Comments

Final Protocol (incl. budget & CRF/ PIS / Assent & Monitoring Plan)

DSMB REVIEW AND EC APPROVAL

Final Protocol Resubmission

Protocol Registration

- DSMB copy
- OXTREC copy
- USFDA – IND copy

Local IRB / Regulatory Review

Local FDA Import License (if needed)

Final Study Approval — NO / YES

Study Drug Shipment

SITE MANAGEMENT

Site Trainings:
- GCP & RE
- Protocol
- Reagent / Lab
- CRF completion
- SOPs

Site Initiation Preparation & Checklist

NCC Approval to screening

Enrollment

CTSS visits

Monitoring

Safety Monitoring

Data Collection

End of Study

Data Analysis

Close Out Study

Final Study Report

Study Publication

SEAICRN Antiviral Studies

- Loading-dose oseltamivir with probenecid (Phase 1)
- Double-blind, randomized, controlled trial to compare standard and higher dose (150 mg bid) oseltamivir therapy in avian influenza or severe human influenza
- PK studies of oseltamivir and IV zanamivir in obese patients
- Oseltamivir for severe influenza in <1 yo
- IV zanamivir in severe influenza
- Long-term neuraminidase inhibitor prophylaxis implemented in Thailand
- Clinical data base for all AI cases: Network and neighbor cooperation.

Immunology Studies

- Standard vs double dose (150 mg bid) oseltamivir therapy
  - Acute measurements of viral loads, cytokines, T and B responses
- Long-term follow-up of H5 survivors*
  - Clinical, PFTs, chest CT; virus-specific antibody, T and memory B cell responses (up to 4 years)#
  - Development of human neutralizing H5 monoclonals#
  - Cross-reactive antibodies and T cells to avian/human viruses
- Community cohort study of pre-season antibody, T and B cell responses in relation to risk of influenza infection/illness#

***Network protocol starting in Indonesia #In progress in Vietnam (NIHE, HTD)**

Trial Oversight Issues

- Independent **Data Safety and Monitoring Board**: multinational composition with experience in tropical research.
- **IRB** oversight
  - IND filed with US Food and Drug Administration, regulatory authorities in participating countries, Oxford University
- **Independent study monitoring** by contract research organization at all sites
- Oversight by **Trial Operations Committee**
  - Protocol team with input from laboratory, clinical, pharmacy, data management, and regulatory groups

Future?

- Advance a paradigm of clinical research preparedness – standard pre-approved protocols, ICF, CRFs and lab standards
- Collaborations with promising later stage products
- Sustainable partnerships to support research networks