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The Southeast Asian Influenza Clinical Research Network: Development and challenges for a new multilateral research endeavor

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Abstract

The Southeast Asia Influenza Clinical Research Network (SEA ICRN) (www.seaclinicalresearch.org) is a recently developed multilateral, collaborative partnership that aims to advance scientific knowledge and management of human influenza through integrated clinical investigation. The partnership of hospitals and institutions in Indonesia, Thailand, United Kingdom, United States, and Viet Nam was established in late 2005 after agreement on the general principles and mission of the initiative and after securing initial financial support. The establishment of the SEA ICRN was both a response to the re-emergence of the highly pathogenic avian influenza A(H5N1) virus in Southeast Asia in late 2003 and an acknowledgment that clinical trials on emerging infectious diseases require prepared and coordinated research capacity. The objectives of the Network also include building sustainable research capacity in the region, compliance with international standards, and prompt dissemination of information and sharing of samples. The scope of research includes diagnosis, pathogenesis, treatment and prevention of human influenza due to seasonal or novel viruses. The Network has overcome numerous logistical and scientific challenges but has now successfully initiated several clinical trials. The establishment of a clinical research network is a vital part of preparedness and an important element during an initial response phase to a pandemic.

Keywords: Developing networks; Emerging infectious diseases; Clinical research; Pandemic preparedness; Avian influenza; H5N1 influenza; Southeast Asia

1. Introduction

The Southeast Asia Influenza Clinical Research Network (SEA ICRN) is a multilateral, collaborative network based on shared principles of respect and commitment to advance scientific knowledge and management of human influenza through integrated collaborative clinical research (www.seaclinicalresearch.org, Network DSMB Charter: http://www.seaclinicalresearch.org/dsmb.asp). The establishment of the SEA ICRN in 2005 was both a response to the re-emergence of the highly pathogenic avian influenza A(H5N1) virus in Southeast Asia in late 2003 and an acknowledgment that clinical trials on emerging infectious diseases require prepared and coordinated research capacity. The development of the Network took place in several stages, each critical to its short- and long-term success: consensus on key issues among future partners and securing sustained financial support; development of Network research systems and sites able to perform studies to a standard acceptable to regulatory agencies; drafting and implementation of specific research protocols; and development of systems to provide regular, thorough oversight of study activities (Fig. 1).

The Network continues to develop research capacity and evolve increasing efficiency fulfilling the Network's mission. Approximately one year into the development of the Network an internal review aiming to improve our processes identified shortcomings with respect to decision-making and organization at local, regional and international levels. This resulted in restructuring the Network to establish and empower country teams. Future development will continue to require sustained effort and

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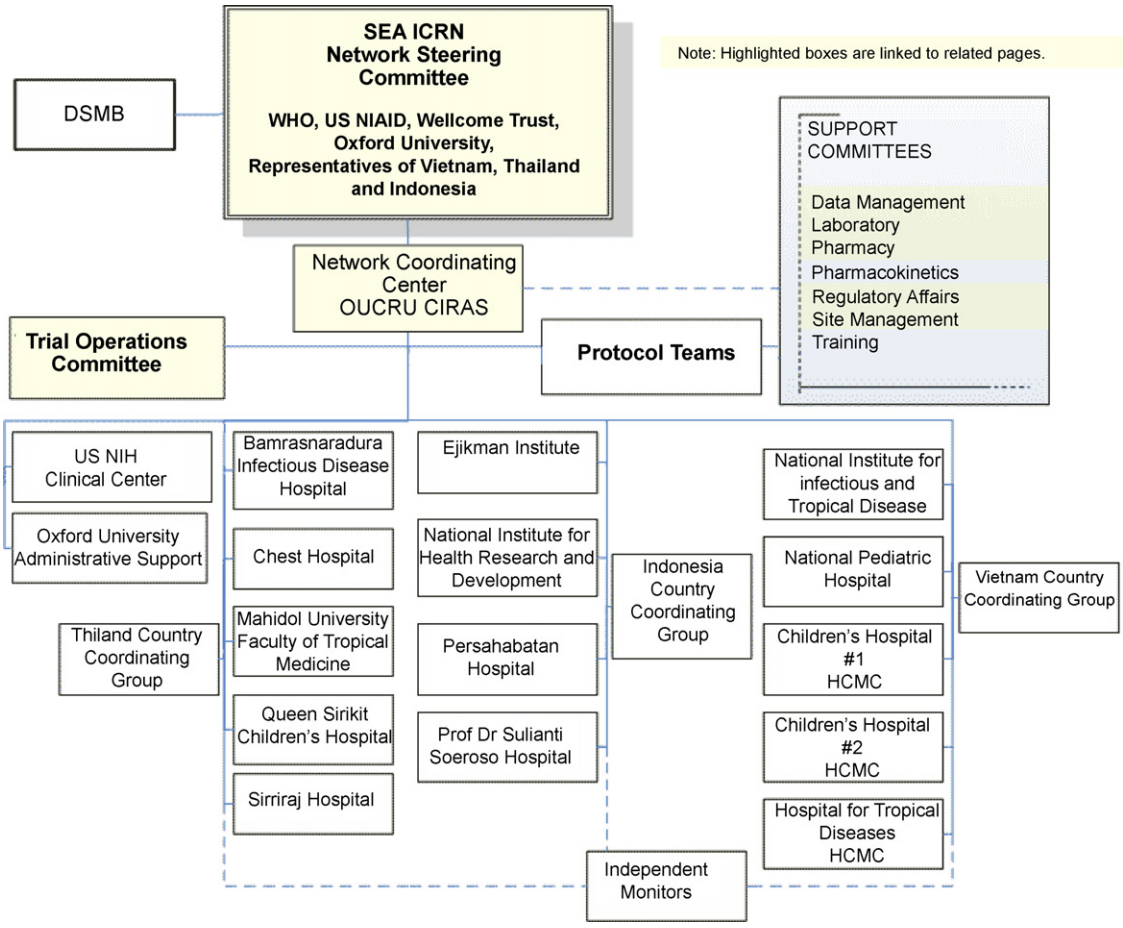

Fig. 1. The SEA ICRN organization chart reflects the need for multilateral consensus and strategic leadership at the Steering Committee level and the importance of empowering sites and individual investigators at the country level through Country Teams. The Network Coordination Center is being strengthened and assists in applying Network systems across the multinational sites. Advisory Committees serve to harmonize disciplines required in integrated clinical research such as research pharmacy, diagnostic laboratories, and regulatory affairs. WHO currently serves as an observer on the NSC whilst providing technical expertise to the Network.

careful thought regarding the training of both senior and junior clinical scientists in writing protocols and grants, implementing educational programs necessary for enhancing regional capacity, adding other partners for future collaborations, and securing long-term financial support.

Mindful of criticisms focusing resources on one disease, a problem referred to as "stovepiping" (Garrett, 2007), the Network will help build the necessary capacity to study other syndromes and consider expansion to other emerging infectious diseases. The development process outlined here likely will be familiar to those who have been involved in starting such clinical research networks in other parts of the world, including but not limited to, those in resource-poor settings, but it may be helpful to others facing similar challenges in clinical research for emerging infectious diseases.

2. The first step: developing consensus

By early 2004 the reemergence of influenza A (H5N1) virus was quickly perceived as a global health threat with pandemic potential (Li et al., 2004). Several researchers and established academic centers in the region responded quickly in developing clinical protocols to gather data that might result in improved clinical management. However, clinical research on human A(H5N1) infections proved difficult because of the relatively small number of affected persons, scattering of cases geographically, political sensitivities, lack of coordinated clinical research capacity across national boundaries and often a global response that focused more on immediate issues and disease control neglected patient-oriented clinical research. Mortality rates for H5NI infections in affected countries were and remain high, ranging from 40–80% (WHO EPR, Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO http://www.who.int/csr/disease/avian_influenza/country/cases_table_2007_08_16/en/index.html). Similar research challenges were experienced during the SARS epidemic (La Montagne et al., 2004). By early 2005, it became clear to those in the SEA region and others globally that a coordinated, multi-country collaboration would be needed for an effective clinical research response to the A(H5N1) virus and pandemic preparedness efforts.

At the first World Health Organization (WHO) consultation on human H5N1 infection, jointly sponsored by WHO, National Institute of Allergy and Infectious Diseases (NIAID), and Well-

come Trust in May 2005, there was an extensive discussion on the concept of establishing a regional clinical research network to study influenza and other emerging infectious diseases. Several researchers and institutions from countries across Southeast Asia (SEA) voiced strong support for the research network concept. It was agreed that representatives from various organizations and institutions would discuss the concept with relevant national authorities. Additional discussions were held among potentially interested partners both in Asia and in Europe to assure consensus on key collaboration principles including trust, mutual respect, capacity building, multilateral decision-making and joint leadership.

After this initial step towards consensus, the focus on emerging infectious diseases was narrowed to influenza at the request of one partner with the understanding that the agenda could be broadened in the future as the critical relationships developed and the network matured. It was agreed that by maintaining focus on the scientific mission of the Network, potential differences in priorities and procedures between partners could be overcome. Financial support mechanisms were discussed and arranged through NIAID and Wellcome Trust, establishing both new and leveraging existing financial mechanisms. A Network Steering Committee (NSC) with the responsibility and authority to oversee Network activities and strategic directions was established through nominations by each participating country's ministry of health and representatives from each international institutional partner. The NSC developed a written constitution for the Network that outlined the previously agreed upon principles and fundamental mission parameters. The complete document is available at www.seaclinicalresearch.org but a few key points are worth mentioning. The NSC constitution specified the research focus, compliance with international clinical science and ethics guidelines (Good Clinical Practice, ICH, etc.), principles of trust and collaboration, open data policies, specimen sharing through national authorities and also articulated the role and responsibility of committees and centers in the Network. The NSC also created inclusive publication policies and stressed the importance of developing a training program.

Establishing a common mission, trusting relationships and principles of collaboration was a necessary first step in the development of this Network. During the second half of 2005 discussions with each country's ministry of health were coordinated through the WHO and initial visits to possible clinical study sites undertaken. In October 2005, 6 months after original discussions on the concept of regional clinical research network, representatives from Viet Nam, Indonesia, Thailand, NIH, WHO, Oxford University, and the Wellcome Trust met in Ho Chi Minh City, VN, to discuss design of the first treatment protocol for patients with A(H5N1) or severe human influenza. An official Network kickoff meeting was held in May 2006 in Hanoi, VN, with 122 participants, and enrollment of the first patients in a controlled treatment study began in July 2007.

3. Development of network research systems

It was agreed that no Network-related research would begin without adequate investigator training and site preparation to conduct quality clinical investigation. Developing an integrated research Network from 12 separate sites across 4 countries was challenging. To assist the development of the Network, the Center for International Research Assistance (CIRAS) facilitated the enhancement of local research capacity by assisting and training investigators and their staff, so that they have had the ability to conduct research according to ICH GCP standards. Thus, CIRAS has key training and administrative support functions but was not empowered to conduct research directly.

The initial organization structure was developed around committees focused on key functional areas, such as data management and research pharmacy. Initial committees included pharmacy, data management, clinical, site management, and laboratory, pharmacology all coordinated through the Trial Operations Committee (TOC) and ultimately the NSC. Committees included individuals from across the institutional and country partners. Given that the Network included several countries in SEA it was considered important to create a coordinated federation of sites with dependent key pieces of the Network located within different countries. For example, the reference virology lab was placed in Viet Nam, the research pharmacy training and pharmacology laboratory in Thailand. Each committee developed a specific mission, membership, and work plan to develop the Network's research capacities, e.g. data management system, clinical research sites prepared to conduct trials, pharmacy system, diagnostic country specific laboratory capacity for human and H5N1 influenza which could provide rapid diagnosis in less than 24 h. Each committee focused on developing Network systems and training for their respective areas of responsibility. For example, each research site and laboratory received a comprehensive assessment followed by focused enhancement and training. The Network reference virology laboratory in HCMC hosted colleagues from across the Network for diagnostic training in virology. Each clinical site was assessed and strengthened with identification and training of a Network research team.

Prior to being approved to start clinical research, each site had to comply with the Site Management Committee preparation checklist and pass independent monitoring initiation visits. By imposing this requirement the Trial Operations Committee could be assured that each site had all systems ready to conduct Network research. Due to the focus on influenza therapeutics and the paucity of available drugs the Network wanted to include the development of a Network Pharmacokinetics Lab in the development process. By enhancing an existing laboratory within the Department of Tropical Medicine Mahidol University, Bangkok Thailand, the Network was able to support the enlargement of the facility to enable the conduct of normal volunteer pharmacokinetic studies. Wherever possible, Network partners have built on and enhanced existing capacities and systems to build the appropriate quality and sustainable Network systems.

After development of the research systems and preparing the clinical research sites, it became evident through assessment and reviews that the mission of the Network would be better served by establishing Country Teams to coordinate local research activity, empower local decision making, develop novel research ideas and facilitate relationships and team effective-

ness. The existing Network Committees have been continued in an advisory capacity to protocol teams who are responsible for protocol development and implementation.

4. Oversight systems

Independent oversight of clinical research is critical to quality investigation and protection of human subject rights in compliance with international guidelines. Oversight of Network research includes three necessary components: an independent Data Safety and Monitoring Board, Institutional Review Boards (some identify themselves as Ethics Committees), and independent site monitoring. The process of establishing an independent DSMB included identification of non-conflicted individuals with relevant skills (statistics, ethics, influenza, pediatric clinical trials, international clinical trials, and national representation). Once established the 6-member DSMB members agreed upon a written charter outlining their purpose and operational procedures (DSMB Charter). The new DSMB benefited from experienced support from the Executive Secretary and the CIRAS staff. As for IRB oversight, some countries agreed upon a single consolidated IRB to review and oversee Network research. In Viet Nam, for example, a single country-wide IRB was identified for Network studies involving five VN sites. However, despite best efforts, the first Network protocol wound its way through seven separate IRBs! Independent site monitoring was supported through NIAID to a separate organization not affiliated with the Network. In order to prepare clinical sites many without previous experience, CIRAS conducted mock monitoring visits at every Network site. This training was in addition to the comprehensive ethics, good clinical practices (GCP), pharmacy, data management, and study coordination training that each site received. It is notable, that each of the Network sites passed their initial monitoring visits. This is significant as many of the sites had never previously conducted a regulatory level study.

5. Current development efforts

After initial development of the Network structure and function, it was recognized that there was a need for a stronger Network Coordination Center (NCC) located in the region. Plans are underway which focus on the continued development of independent research capacity such as moving the central data management system, currently located in the United States, to Southeast Asia. The support from CIRAS will gradually decrease as research capacity and experience at Network sites increases. Development of a business plan has also been agreed upon, and the NSC is beginning to discuss future financial support from a broader group of multilateral funders. The NSC is in the process of discussing and reviewing draft documents articulating the process for the inclusion of new partners and countries. Finally the Network training plan is being developed and launched. A scientific English language training program has already been started in Indonesia and Viet Nam. Long and short term training opportunities for doctoral, masters and short term courses for young scientists from Network countries are an integral part of the research capacity building plan. The goal is to empower country teams to identify training needs, individuals for degree training, and specific site needs.

6. Overcoming challenges

The challenges and obstacles facing the development of the SEA ICRN were significant, varied, and probably shared by other investigators seeking to develop large multinational clinical research networks. Efficient, clear communication across four different partner time zones (as much as 12 h apart), many different cultures, and four different languages was a challenge. At the Network's initial kick off meeting in March 2006 simultaneous translation was utilized. CIRAS created a protected share drive where common documents could be reviewed, but information technology security systems developed in recent years in response to terror activity and threats have made semi-secure access impossible and required each individual to have their own password. It was helpful that CIRAS has offices both in the US and in SEA which helped to bridge the time zones. However despite efforts to reduce the need, colleagues on both sides of the globe still spend many late nights or early mornings on teleconferences. Devolving authority and power to the country teams and strengthening the NCC will continue to improve communication.

There are also differing institutional cultures, competing demands on investigators who mostly continue to undertake their clinical service commitments, and clinical research experience among partners, so that maintaining the Network mission as a priority over the agendas of individual partners will be essential for future success. Protection of an individual investigator's time for research is a novel concept in many countries. Collaboration is preferred over compromise and differences are seen as an opportunity to develop something better or more creative than averaging a middle position.

Trust and relationships with the shared vision of scientific advancement in the management of influenza have been a critical part of the SEA ICRN success in overcoming initial differences. It is notable that while signing MOUs among partner institutions is still in process, there has been little difficulty in drafting and agreeing upon the scientifically focused Network constitution. Finally, the Network is an open organization that hopes additional partners will be interested in joining in the future. At the same time it must balance the addition of new partners and sites with available fiscal and managerial resources. The leadership embodied in the NSC, which possesses years of collective experience working in international research and a history of successful collaboration, enabled the Network to draw from past successes and avoid previous mistakes during the development process.

7. The Network's potential role in an influenza pandemic

Despite our inability to accurately predict the timing or occurrence of a pandemic, global health experts concur that current pandemic preparation is necessary and behind sched-

ule. The establishment of a clinical research network is a vital part of preparedness and an important element during an initial response phase to a pandemic. If sustained transmission of H5N1 virus begins in a Network member country, subjects with pandemic influenza could be enrolled immediately into existing and approved protocols. This would enable vital data pertaining to the management of pandemic illness to be rapidly obtained to inform public health authorities. For example, data on the viral kinetics, clinical course, and impact of antivirals in different patient populations could inform rational use of national antiviral stockpiles. Antiviral susceptibility data and early identification of viral resistance could save lives by guiding appropriate therapeutic interventions.

Further, experienced research teams will be in place along with communication lines to regulatory and oversight authorities allowing acceleration of new protocols should they be needed. If sustained transmission takes place in countries outside the Network, the Network's collective knowledge and experience will be available to those who might need it. The Network is currently leading an effort to develop a collective data base of confirmed H5N1 cases and encouraging cooperation and collaboration from non-member countries. An established, collaborative regional or international research presence for influenza, will enhance collection of critical data for making control and response decisions to sustained person-to-person transmission. This will significantly help clinical and public health decisions and help reduce an epideimc's health impact.

8. Summary

The SEA ICRN was established to face the challenges of gathering essential clinical data to advance understanding of the pathogenesis and management of influenza infections. Successful scientific advancement in emerging infectious diseases research requires preparation and collaboration as infectious pathogens and susceptible populations are not bound by national boundaries. Outbreaks of emerging pathogens may provide little or no warning and arise in sporadic cases across multiple sites and multiple countries. Clinical research in particular requires advanced preparation of sites, protocols, data management systems, pharmacy support, diagnostic laboratories, and oversight groups before the emerging infection is on the horizon.

The challenges of conducting multicenter, international research compound the difficulty of studying an unpredictable disease. Investing in clinical research networks acknowledges these challenges and the importance of being prepared. Over time existing networks will be increasingly efficient in research responses to emerging infectious diseases. However, the global health community must maintain financial commitment to such networks, even when the emerging infectious disease threat is not evident. If the SEA Influenza Clinical Research Network had been in place in 2003, it is probable that our knowledge of the pathogenesis and management of SARS would be further advanced than it is today. The SEA ICRN hopes to continue its mission on influenza and, in the future on other emerging infectious diseases, for years to come. The future success of the Network will rest on the foundation built in these initial years and the ongoing assessment of outcomes and sustainability, but it will ultimately rest on fidelity to advancing science through careful investigation and the Network's founding principles of trust, respect, and collaboration.

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