Clinical Trials in Singapore

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Introduction

Clinical trials are the gold standard for the evaluation of new treatment strategies. New treatments that have been painstakingly developed in laboratories and shown to be very promising in animal studies will not be adopted in clinical practice, unless they have first been proven effective and safe in clinical trials. Each phase of the clinical trial process crucially affects the eventual conclusions made regarding the usefulness of the treatment. Thus, erroneous methodology at any stage of the clinical trial process can have severe consequences on the final therapies approved for general clinical application.

Singapore is a relatively small country of four million people. As such, it is typically very difficult to conduct large clinical trials within the country alone. However, this does not prevent Singapore from seeking to be the central coordination and data center for such trials. Singaporean investigators could also drive the trial as the main principal investigator (PI), or could function as trial collaborators helping to contribute patients to it. Sufficient patient numbers can be achieved by collaborating with other institutions in the region and beyond by way of multi-center trials.

Singapore is also well placed to conduct smaller (particularly early-phase) clinical trials which, as already indicated, are equally crucial in the clinical trial process. Singapore has developed a strong basic science research program, and early-phase clinical trials provide the bridge in bringing new discoveries “from the bench to the bedside”.

Healthcare Clusters

In Singapore, there is a dual system of healthcare delivery. The public system is managed by the government, while the private system comprises private hospitals and general practitioners. In 1999, the public healthcare system was reorganized into two healthcare clusters: the National Healthcare Group (NHG) and Singapore Health Services
Both clusters provide comprehensive healthcare services ranging from primary health care at outpatient polyclinics to secondary and tertiary specialist care at hospitals and national specialty centers. Patients are free to choose between either healthcare cluster or to utilize private healthcare services.

The National Healthcare Group (NHG) comprises the National University Hospital (NUH), Tan Tock Seng Hospital (TTSH), Alexandra Hospital (AH), the Institute of Mental Health (IMH), the National Skin Center (NSC), and nine primary care polyclinics. Three virtual specialty institutes — The Cancer Institute, The Heart Institute, and The Eye Institute — operate across the cluster.

The Singapore Health Services (SingHealth) cluster comprises five national specialty centers. These are the National Cancer Center (NCC), the National Dental Center (NDC), the National Heart Center (NHC), the National Neuroscience Institute (NNI), and the Singapore National Eye Center (SNEC). The hospitals within SingHealth include Singapore General Hospital (SGH; Singapore's largest acute tertiary hospital), Changi General Hospital (CGH), and Kandang Kerbau Women's and Children's Hospital (KKWCH).

Clinical Trials in the Clusters

National Healthcare Group

Translational research is an essential part of clinical practice in NHG, where the urge to acquire new knowledge complements the desire to deliver quality patient care. A poll in March 2006 revealed that approximately 52% of doctors in NHG conduct some form of clinical research, up from 43% in April 2003. The majority of doctors conduct research in addition to their full-time clinical practice, whereas 5% of doctors allocate at least 1 day a week or more for research.

With more than 800 ongoing research projects, NHG has aligned itself with Singapore's focus on high-growth translational research in the fields of oncology (12%), ophthalmology (9%), cardiology (7%), infectious disease (7%), allied health (7%), psychiatry (7%), and gastroenterology (6%). In 2005, a total of 492 applications for new research projects was received, highlighting an ever-increasing trend. Clinical trials comprise 25% of all NHG research, and include trials on drugs, vaccines, and medical devices. For ongoing drug trials, approximately 14% are phase I studies, 26% phase II studies, 45% phase III studies, and 18% phase IV studies. About 35% of clinical trials in NHG are initiated by investigators (mainly doctors); while the remaining 65% are sponsored by pharmaceutical companies, with NHG principal investigators at the helm.

The growth of clinical trials in NHG is fueled by collaborative research consortia like NUH's Cancer Therapeutics Research Group (CTRG), which was founded in 1997. CTRG addresses the need for high-quality clinical research for antineoplastic drug development in Asia, and has succeeded in forging strong collaborations with prestigious institutions like Sydney Cancer Center and Johns Hopkins Singapore. CTRG has attracted large pharmaceutical corporations to the region by establishing a reputation for early-phase clinical trials in South East Asia and the Asia Pacific. In addition to consortia, there are also established clinical trial units at NUH and the Institute of Mental Health (SingHealth).
Health (IMH), which provide project management expertise and facilities for trial coordination.

In January 2004, the NHG Research & Development Office (RDO) was set up to oversee research governance in the cluster and to provide a one-stop research support service for both investigators and industry partners. NHG hospitals also operate satellite research-coordinating units with a wide range of supporting research laboratories. In April 2004, the ethics committees of the various NHG institutions were centralized into four Domain-Specific Review Boards (DSRB), which is a novel concept of ethics review based on broad but related disease groupings. This has significantly strengthened the NHG Human Subjects Protection Program by ensuring a robust and time-sensitive ethics review with the appropriate scientific expertise and workload. The DSRB framework has facilitated the growth of multi-center trials by reducing trial start-up time through preventing duplicate reviews by each institution. Plans are ongoing for accreditation by the Association for the Accreditation of Human Research Protection Program (AAHRPP) and for an online ethics application and review system.

**Singapore Health Services**

SingHealth’s quest is to further develop as a renowned organization at the cutting edge of medicine and to continue providing high-quality health care. Being the largest provider of healthcare services to the national population, its research strategy naturally prioritizes translational research and clinical trials as part of its plan to become a regional medical hub. In the financial year 2005, there were 650 ongoing research projects and 304 phase I-IV ongoing clinical trials, with 662 publications. Clusterwide high-growth translational research is active in the fields of oncology (18%), cardiology (20%), gastroenterology (18%), renal medicine (8%), and hematology (6.9%). For ongoing clinical drug trials, 14% are phase I studies, 34% phase II studies, 56% phase III studies, and 9% phase IV studies. In 2005, a total of 105 applications for new clinical trials were received, highlighting an ever-increasing trend. About 22% of clinical trials in SingHealth are investigator-initiated trials, while 78% are sponsored by biopharmaceuticals and medical devices.

With the arrival of the Duke-NUS Graduate Medical School (GMS) on the Outram campus by 2008, there are plans to foster synergistic academic research and clinical trial partnership with Duke University Medical School. All SingHealth medical centers and hospitals will be affiliated with the Duke-NUS GMS.

In order to provide a more seamless integration of bench-to-bedside research within SingHealth, five research focus groups have been established to provide intellectual ferment and cross-talk, shared core facilities, joint research projects, and program development to further encourage innovation and discoveries for downstream clinical benefits. The research focus groups include experimental medicine, prospective medicine, bioimaging, cell therapy, and clinical trials.

In terms of physical infrastructure, the NCC, NDC, NHC, SNEC and part of the NNI (NNI-SGH campus) are colocated with SGH in an area called the Outram campus, which also houses the SingHealth research complexes as well as the Ministry of Health’s Health Promotion Board and Health Sciences Authority. Changi General Hospital has a dedicated phase I clinical trials facility directed by its Clinical Trials & Research Unit, which has been operational since 1998.
All SingHealth institutions have their own Institutional Review Board (IRB) as they are specialized centers, except for CGH, SGH, and KKWCH. All IRBs are aiming for AAHRPP accreditation by 2007.

**Clinical Trials and Epidemiology Research Unit**

The Clinical Trials and Epidemiology Research Unit (CTERU) was established in November 1996 to assist in the conduct of national-level clinical trials and related studies in Singapore. The intention was that clinical trials in Singapore needed to be conducted in line with established international standards. In particular, CTERU seeks to support flagship clinical trials that are of high scientific value and have the potential to influence clinical practice. This is done by providing expertise in areas such as systematic reviews, study design, project management, data management, statistical analysis, and reporting. Relying on funding from the National Medical Research Council of Singapore, these services are provided without charge to Singapore-based investigators for academic research purposes.

CTERU currently supports more than 35 clinical trials, many of which are multi-center randomized trials. In addition, CTERU also actively participates in other scholarly activities like teaching and training, conducting statistical consultation clinics, helping to develop clinical practice guidelines, as well as contributing to various research and professional committees.

The presence of evidence-based medicine specialists, as well as medical statisticians engaged in applied biostatistics research, allows CTERU to provide added value to investigators. Evidence-based medicine specialists are able to conduct meta-analysis and systematic reviews that supplement the findings from clinical trials. Similarly, applied biostatistics research can lead to improvements not only in clinical trial design, but also in the utilization of the data obtained. Thus, CTERU is regarded as a full scientific collaborator in clinical trials rather than just a service provider.

**Future Outlook**

Singapore has identified the biomedical sector as a key area that it hopes to develop. Clinical trials are a vital component of the clinical research process, and their development must be seen as part of the country’s overall effort to position itself as a biomedical hub. However, the conduct of high-quality clinical trials requires proper planning, implementation, analysis, and reporting. Only when this is done can the findings of clinical trials be correctly interpreted and applied into clinical practice.

With the unique combination of support available from the healthcare clusters as well as from organizations like the CTERU, it is hoped that Singaporean investigators will be increasingly well positioned to conduct clinical trials. More than that, Singapore should seek to play a key role in the establishment of regional trial groups spearheaded by Singaporean investigators. Having such trial groups will greatly facilitate the conduct of multi-center trials and also attract interest from pharmaceutical companies keen to conduct clinical trials in the region.
Within the clusters, there is an increased need to focus efforts on translational research that has clinical significance, especially investigator-initiated clinical trials. In addition, there needs to be continued investment in research manpower for both investigators and trial coordinators. This will bolster the support for and management of clinical trials at the site level. Finally, there is also a need to continue to seek improvements in research quality through an educational quality assurance program and a robust human research protection program.

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