REVIEW ARTICLE

New initiatives for transforming clinical research in Korea

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Abstract: Korea has continuously sought to improve its regulatory environment for clinical trials and has invested heavily in clinical trial infrastructure and technology since the early 2000's. A strategic investment through the Korea National Enterprise for Clinical Trials (KoNECT) program began in 2007 and grew to encompass a network of regional clinical trial centers to promote clinical trial capabilities and human resource development. In early 2014, KoNECT became a permanent organization focused on the advancement of the country's clinical trial industry. This was followed by the establishment of the Korea Clinical Trials Global Initiative (KCGI) and the KoNECT Collaboration Center for global clinical trials (KCC). KCGI and KCC are now at the forefront of KoNECT's efforts to promote higher operational efficiency in the country's clinical trials. These new initiatives in clinical research are undertaking multichannel approaches to pursue a cohesive international collaboration model between government, industry and academia for the development of new treatments and improved patient care.

Keywords: Korea clinical trials, new KoNECT, KCGI, KoNECT Collaboration Center, KIIS

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Received: October 26, 2015; **Accepted:** December 22, 2015; **Published Online:** December 31, 2015

Citation: Chee D, Park M S and Sohn J-H, 2015, New initiatives for transforming clinical research in Korea. *Journal of Medicines Development Sciences*, vol.1(2): 27–32. http://dx.doi.org/10.18063/JMDS.2015.02.003.

1. Introduction

In the early 2000's, a standard clinical trial authorization (CTA) process was established in Korea to facilitate the clinical development of new drugs by streamlining the regulatory requirements for clinical trial approval. Together with improvements to Korea's clinical trial approval system and revision of Korean Good Clinical Practice (KGCP) to align with the international ICH GCP guidelines, this enabled the country to participate in larger multinational clinical trials funded by global sponsors. The bridging requirements for registering foreign developed medicinal products were also synchronized by adopting the ICH E5 guidelines.

In addition to extensive regulatory reform, the Korean government accelerated investments in clinical trial infrastructure to strengthen local capabilities for new drug development, attract a greater number of global clinical trials to Korea, and facilitate earlier patient access to new treatments while bolstering the country's economy.

The Regional Clinical Trial Centers (RCTC) program was initiated by the Korean Ministry of Health and Welfare (MOHW) to aid the establishment of clinical trial support systems, including phase 1 units. The RCTC program also sought to improve the professional quality of the clinical trial workforce at major academic medical institutions by awarding USD 5 million for five years to each major center.

In December 2007, the Korea National Enterprise for Clinical Trials (KoNECT) was established by the MOHW as a seven-year program to further develop clinical trial infrastructure to cope with the increasing demand for clinical trials in Korea. The organization continued to stringently select additional centers to bring the total number of RCTCs in the country to fifteen centers and assessed their performance based on predefined qualitative and quantitative goals. KoNECT was also responsible for the launching of a number of clinical trial technology development projects, and operated the 'KoNECT Clinical Trial Training Academy' to provide free training for the clinical trial workforce.

The impetus of regulatory reform combined with the KoNECT program contributed to a dramatic increase in both domestic studies and multinational clinical trials by global sponsors in Korea. The number of Investigational New Drug (IND) approvals for sponsor-initiated multinational clinical trials grew from 5 in 2000 to 291 by the end of 2014, and domestic trials rose to 361 from 28 during the same period (Figure 1).

With the completion of the initial seven-year KoNECT program in early 2014, KoNECT's mission was extended and the organization was established as a legal entity tasked with fostering clinical trial collaboration and improving the country's economy. With continuous investments in infrastructure and human resources, the Korean government has identified new drug development capability as a key driver for Korea's future economic growth. New clinical trial initiatives, namely the Korea Clinical Trials Global Initiative (KCGI) and the KoNECT Collaboration Center for global clinical trials (KCC), were launched in 2014 and 2015, respectively. Since approval of the first new drug developed in Korea in 1999, 24 new drugs have followed the same path.

2. KoNECT

KoNECT was established by the MOHW in 2007 and mandated to lead the RCTC program and two additional projects. The 'KoNECT Clinical Trial Training Academy' is an education and training program for clinical trial personnel while the 'New Clinical Trial Technology Development' program is focused on clinical trial promotion. KoNECT has completed the designation of eight RCTCs in the Seoul metropolitan area, three in Busan and four in other areas of Korea. These 15 RCTCs have served as core sites, responsible for over sixty percent of the total number of clinical trials conducted in the country[1]. In 2010, Seoul was ranked as the most active city in clinical trials in the world in terms of clinical trial sites registered at ClinicalTrials.gov[1] and has maintained the top position in subsequent years till 2014.

The KoNECT Clinical Trial Training Academy was designed to offer courses on clinical trial topics including GCP for clinical investigators, clinical research coordinators (CRCs), clinical trial pharmacists, clinical research associates (CRAs), data managers/ biostatisticians, pharmaceutical medicine specialists and clinical pharmacologists. The cumulative number of trainees entering the programs over the past 6 years has reached 45,000, including the 10,628 trainees

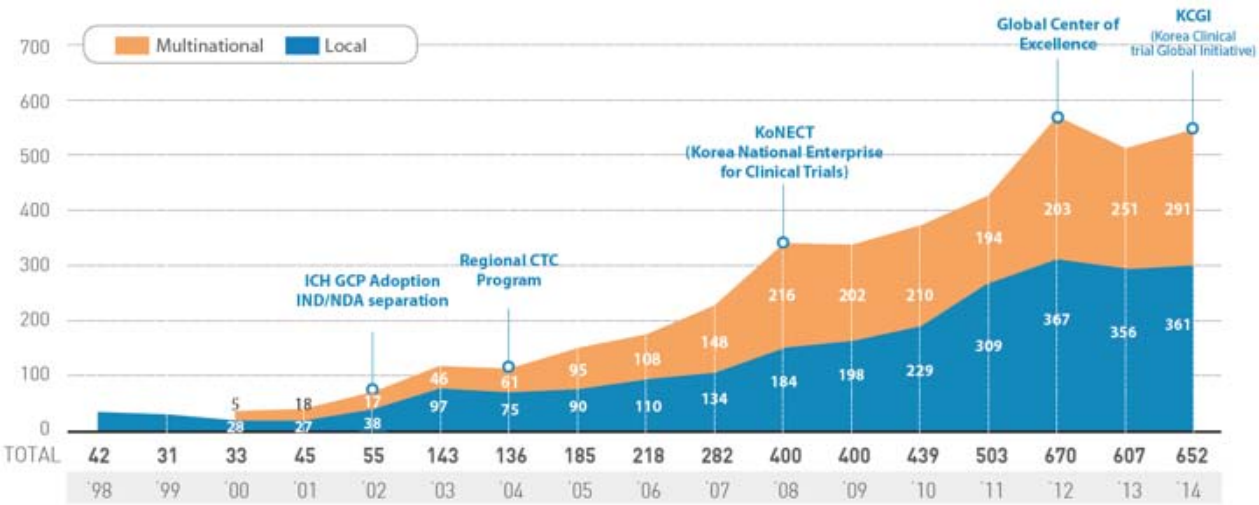

Figure 1. Korean government's initiatives and number of IND approved by Ministry of Food and Drug Safety (MFDS).

who completed the courses. The curriculum consists of lectures and hands-on practice lasting 16 hours or more. Part of the continuing mission of the new KoNECT is to advance the country's capabilities for clinical trials as a solid foundation for clinical development by the Korean pharmaceutical industry.

In addition, there are ongoing efforts to develop a cohesive collaboration model with national and international partners seeking higher operational efficiency and scientific improvements for more effective clinical trials. Building international and regional networks to address the unmet medical needs, especially for regional conditions, is also included in its missions.

Current core activities of the new KoNECT include clinical trial policy development and providing expert recommendations to the government and other stakeholders, the generation and provision of statistics analyzing clinical trials activities and infrastructure, and the strengthening of the industry's overall competitiveness, including local CROs. KoNECT runs an accreditation program for local CROs, auditing selected priority areas of site management, project management, data management and medical writing. The objective of the accreditation program is to help local CROs to continuously improve by providing them with feedback through the evaluation process associated with accreditation.

KoNECT continues to provide year-round training courses for diverse professionals working in the clinical trial industry at different levels such as clinical investigators, clinical trial pharmacists, CRAs, CRCs, and data managers. Training programs are offered at various levels to reflect differences in the experience of the participants[2]. The organization also offers certification programs for CRAs and CRCs, and has developed a Learning Management System (LMS) to efficiently manage all training and certification records.

For international partners seeking collaboration, KoNECT collects, analyzes and provides high-level information on the country's clinical trial infrastructure and capabilities. In September 2015, a new initiative called the KoNECT Collaboration Center for global clinical trials (KCC) was launched to serve as a matrix of collaborative efforts seeking to engage national and international partners in clinical trials.

3. Korea Clinical Trials Global Initiative (KCGI)

Korea has made considerable progress in the field of global clinical development over the past decade through joint efforts by academia, industry and government. However, it is recognized that emerging challenges arising from changes in the global drug development paradigm and the global clinical trial environment must be proactively dealt with. Major issues in new drug development include low productivity, high attrition rates, low efficiency, high costs, and lengthy development timelines. There exists a number of conceptual and operational hurdles that are particularly apparent in the early phase clinical trials such as limited time and resources, difficulties in study design to adequately demonstrate proof of concepts/mechanisms/safety, selection or development of appropriate biomarkers or surrogate endpoints, technical complexities, and scientific rigor.

Korea's success in global clinical development during the past decade has primary centered around late clinical development[3]. In addition to a good track record in late phase trials, unique features of the country's medical environment and healthcare system place it in an advantageous position to conduct early phase trials for global drug development programs. These factors include the quality of medical care and infrastructure such as hospital facilities and equipment. In addition, university hospitals in the country are concentrated in highly populated cities providing large patient pools, and staffed by highly educated and motivated investigators holding university faculty positions. Clinical trial centers in these university hospitals are often located on hospital premises and operated by dedicated hospital personnel.

In order to ensure continued progress in new drug development and to increase the number of high value-added early phase trials, KCGI was launched by the MOHW in 2014. The goals of KCGI include the strengthening of global competitiveness in the clinical trial industry through the development and support of growth engines for the industry, and to promote scientific advancement and operational efficiency in clinical trials through the development of new research methods that incorporate convergence technologies.

KCGI is a government-funded R&D program that supports the setup of research infrastructure and operational systems in CTCs at major leading academic medical institutions. These institutions must each have an established research governance overseeing internationally-accredited human research protection programs and outstanding clinical trial performance. KCGI's Global Centers of Excellence (GCE) program is tasked with supporting investments in research in-

frastructure to focus the efforts of CTCs to become globally competitive in the early phase development in specialized therapeutic areas or areas of unmet medical needs. To date, the GCE program has selected five university hospital CTC consortia, each of which is composed of two to five CTCs located at separate university hospitals (Figure 2). Each consortium receives USD 2 million per year for 5 years. KCGI seeks to promote operational excellence in early phase clinical trials through efficiency, maximization of combined and shared resources, and innovation in trial R&D. Furthermore, KCGI also facilitates relationship building between clinical and nonclinical experts from academia and industry in the earliest possible stages of new drug development in order to minimize future failures and difficulties in clinical development. Five consortia of GCE have their own focal areas of specialization and are making efforts to collaborate on specific aspects of clinical trials. Currently, a number of tools have been developed or are in use, including: mutual recognition systems for IRB review processes, common IRB review application forms, eCRFs which enable auto-migration of Order Communication System (OCS)/Electronic Medical Records (EMR) data, and a clinical data retrieval system for DB (Data Base)-driven feasibility assessment. Pooling of anonymized patient data and the establishment of investigator networks for defined therapeutic areas among institutions within each consortium provide a strong foundation for improving early phase trial productivity.

The Convergence Technologies for Clinical Trials Project provides funding for the development of new clinical trial technologies that improve efficiency and accuracy, or reduce redundancies, errors, time and costs.

To better prepare for the wider changes taking pace in the global clinical environment, KCGI brings GCE personnel together for opportunities to exchange information and share best practices between the consortia. Each unique system of consortia serves as an open platform that can accept the addition of other CTCs. A regular forum is held between institutions that are developing new convergence technologies to share updated information.

KCGI is focused on the improvement of research infrastructure, sharing of knowledge among centers, and the establishment of inter-institutional investigator

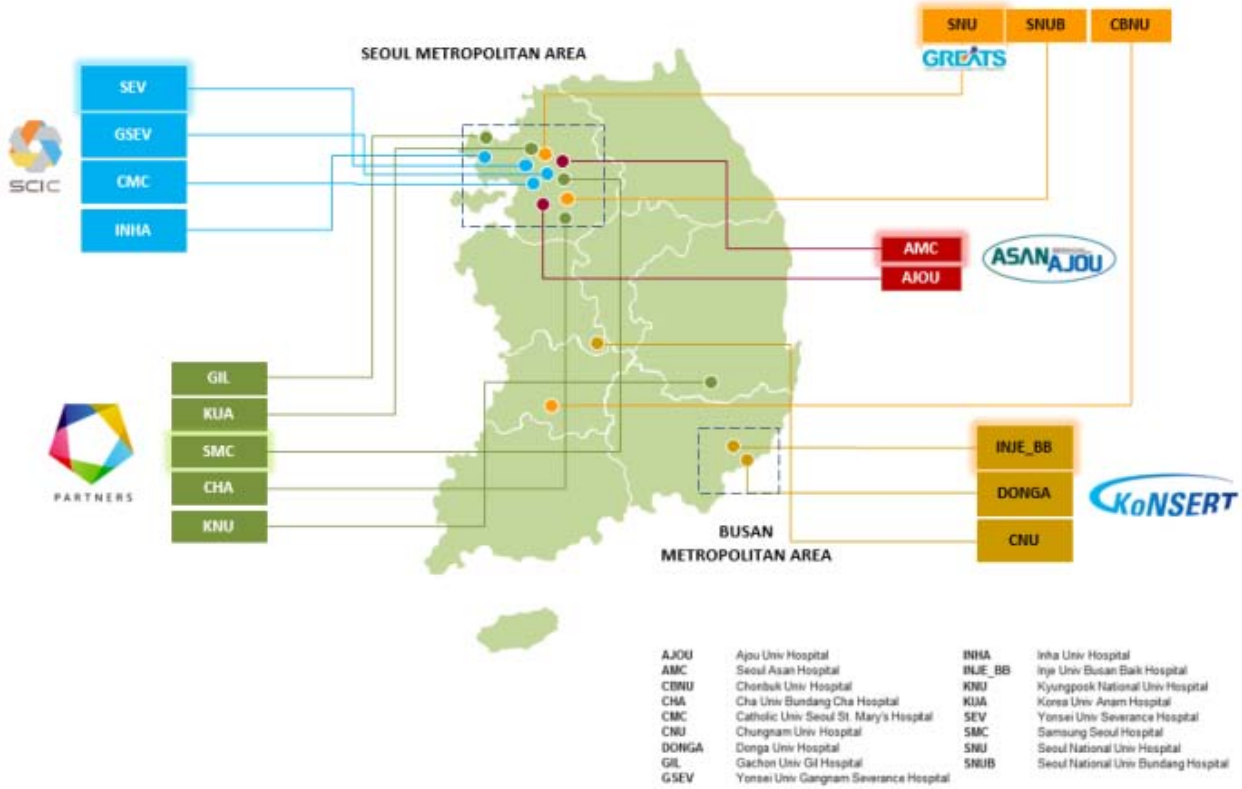

Figure 2. Global Centers of Excellence Project by Korea Clinical Trials Global Initiative (R&D grant of Ministry of Health and Welfare) supports 5 consortia (different colored boxes) located around the nation.

networks, patient databases and registries as a national CTC consortium. The ultimate goal of these efforts is to provide a highly capable clinical trial infrastructure for both global and domestic pharmaceutical companies in their development of new drugs, with a strong focus on early phase development, in addition to the facilitation of academic clinical research to improve healthcare quality.

4. KoNECT Collaboration Center (KCC)

The ineffectiveness and inefficiencies that the clinical trial industry faces remain major challenges worldwide. Recent statistics show that on average, one third of all Phase III studies are terminated due to enrollment difficulties, and nearly 80 percent of clinical trials fail to meet their enrollment timelines[4], indicating that trial planning and management is one of the most critical areas for R&D productivity. Furthermore, difficulty in obtaining reliable information on the regulatory environment and service providers in a new region or country hinders potential sponsors from efficiently assessing new trial sites. KoNECT provides practical services and reliable information to fulfill these needs, and enhance the feasibility of conducting clinical trials in Korea to make significant contribution to the multi-regional clinical trials (MRCT) or global clinical planning by improving the ability of sponsors to engage in informed decision making.

With the support of the Korean government, the KoNECT Collaboration Center for global clinical trials (KCC) was formally opened on September 1, 2015. KCC constitutes an unprecedented systematic clinical trial support system designed to assist sponsors in their MRCT planning by providing helpful services and information.

Major services and features of the KoNECT Collaboration Center include: the KoNECT Integrated clinical trial Information System (KIIS), One-Stop Shop services for clinical trial planning in Korea, a business center with administrative support, a Korean clinical trial interactive gallery and liaison service with clinical trial networks.

4.1 KIIS (KoNECT Integrated clinical trial Information System)

Concerted efforts are being made by the clinical trial industry to tackle inefficiencies in feasibility assessment to achieve more data-driven than opinion-based evaluations[5]. Feasibility refers to the identification and quantification of risks in clinical trial planning, including country and site selection, as well as resourcing partners[4]. According to a recent survey conducted in Europe[6], more than 80% of 253 respondents agreed that they are much more likely to select a trial site if all of the relevant investigator and site specific information is made easily available to them. This indicates that uncertainty and opinion-based practices are still prevalent in feasibility assessment process. The ongoing need for information sufficient to make informed decisions during feasibility evaluations is increasing in emerging economies, as more pharmaceutical companies are moving into these regions[7]. KIIS aims to address these needs by creating an information resource that multiple stakeholders who intend to conduct clinical trials in Korea can use to collaborate with improved efficiency primarily during the feasibility assessment period.

KIIS consists of a web-based information archive established and operated by KoNECT. It provides information on the Korean pharmaceutical market and healthcare system, updated by investigators, clinical trial centers, and clinical trial service providers, including CROs. KIIS currently provides comprehensive information on six major topics including: (i) industry overview, (ii) ongoing and completed clinical trials in Korea, (iii) epidemiology data, as well as patient numbers and distribution data derived from national medical insurance claims in accordance with ICD10 (International Classification of Diseases), (iv) Korean treatment and diagnosis guidelines, (v) site and investigator registry, and (vi) KoNECT partners including service providers (Table 1). KIIS is accessible through the website of the KCC[8] and different levels of authorization are granted to access various levels of information. An online search functionality with multiple predefined conditions and keywords has been implemented to efficiently navigate the data.

4.2 KCC Supports for Clinical Trial Planning in Korea

The KCC supports the planning and conduct of clinical trials in Korea by providing information and other support when requested. The information covers an overview of Korea's healthcare system and industry, the country's clinical trial sites and corresponding experience in clinical trials, IND application and approval processes and requirements, and other relevant regulations. KCC also has the capacity to coordinate

Table 1. Content of KIIS

Category	Content
Industry Overview	Facts and figures on macroeconomic indicators, including datasets for the healthcare system, pharmaceutical and clinical trial industries of Korea.
Epidemiology and Patient Distribution Data	Published Korean epidemiology data relevant to clinical research. Patient numbers and distribution data by ICD10 derived from the HIRA (National Health Insurance Review and Assessment) claims database.
Clinical Trial Experience	Database collating all completed and ongoing clinical trials in Korea listing and comparing trials by site and indication.
Clinical Trial Site Information	Information on clinical trial sites, including facilities, human resources, early phase research capabilities, core research technologies, and clinical trial experience.
Investigator Information	Information on Korean investigators including clinical trial experience, research interests, and training records.
KoNECT Partners	Information on KoNECT partners including clinical trial networks, CROs, local pharmaceutical companies, service providers and consultants.

meetings between sponsors and local service providers in response to specified requests from sponsors.

4.3 Korea Clinical Trial Interactive Gallery

A tour of the Korean Clinical Trial Interactive Gallery at the KCC is available for those seeking to learn more about Korea's clinical trial infrastructure. The exhibition details the development history, capabilities and experience of the Korean clinical trial industry and features major clinical trial centers. This is designed to showcase the country's clinical trial capabilities and environment to international sponsors in an effective way.

5. Conclusion

Over the past few decades, Korea has made concerted effort to establish a favorable and harmonized regulatory environment for global clinical trials, and invested heavily in clinical trial infrastructure. The success of this first phase of transformation has relied upon strong support and financial commitment from the Korean government. The second phase of transformation, which is now being spearheaded by the new KoNECT, is intended to further strengthen the nation's clinical trial capacity and capability for global collaboration with higher efficiency and better science by undertaking multichannel approaches. The purpose is to achieve a cohesive collaboration model between Korean government, industry and academia for improved cooperation with international partners in order to develop new treatments and improve patient care.

Conflict of Interest and Funding

KoNECT is a non-profit organization funded by the Korean Ministry of Health and Welfare (MOHW) with a mission to nurture the country's clinical trial infrastructure and capabilities.

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