Korean clinical trials: its current status, future prospects, and enabling environment

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History of Korean clinical trials

Clinical trials provide information and important evidence to regulators, physicians, payors, and patients that support decision-making in improving access to better medicines with a meaningful impact on patients.

Over the past two decades, Korean clinical trials have demonstrated unprecedented growth. Regulatory reform, including the adoption of ICH-GCP in 2000 and the introduction of clinical trial authorization in 2002, have led to these changes together with the government's continuous investment in clinical trial capacity building since 2004 such as the “Regional Clinical Trial Center” and “Global Center of Excellence” programs through the Korea National Enterprise for Clinical Trials (KoNECT).

KoNECT has analyzed every year the ClinicalTrials.gov data downloaded from the website, which has the biggest coverage of clinical trials registered by industry sponsors in the world among all primary clinical trial registries for the numbers and shares of the protocols and sites of global industry-sponsored clinical trials in top 30 countries. It also analyzes the Ministry of Food and Drug Safety (MFDS) clinical trial authorization data that are open to public on their website for the trend of clinical trials conducted in Korea. In 2000, the number of clinical trials approved by the MFDS was only 33, including 5 multinational studies. However, this number increased to 679 in 2018, with 289 multinational studies. [1] Seoul became the world’s top city in terms of the number of clinical trials in 2012, and Korea has ranked amongst the top 10 countries that have conducted clinical trials since 2010, according to the analysis of ClinicalTrials.gov by KoNECT.[2]

This has led to the question of what were the drivers of the growth in Korean clinical trials? To answer this question, both domestic and multinational clinical trials have contributed to the growth of Korean clinical trials. Among these, multinational Phase 3 studies and domestic phase 1 studies have largely been increased. Indeed, there was a leap in the number of phase 1 studies by domestic companies in 2011 from 75 to 130, with an increase of 73.3% from the previous year.[3] Among the 130 domestic phase 1 studies, around 40% of the phase 1 studies were for ‘new drugs’ developed by domestic companies, whereas approximately 50% of them were for fixed combination drugs, new formulations of marketed drugs, and others.[4] In 2018, the number of phase 1 trials approved by the MFDS reached 211, which represented an increase of 19.9% from 2017. Among these 211 phase 1 trials, 161 (76.3%) were considered domestic, whereas only 39 were related to new molecular entities, including 37 studies by domestic companies. In the same year, 188 industry-sponsored phase 3 trials were approved by MFDS, and among them, only thirty-one studies were filed by domestic companies.[5] Based on the ClinicalTrials.gov data analysis, the total number of registered industry-sponsored phase 2 and phase 3 studies in 2018 was around 1.4 times and 2.5 times that of phase 1 studies, respectively.[2] However, the ratio of industry-sponsored domestic phase 1 : phase 2 : phase 3 was 6.7 : 1.0 : 1.3 based on the analysis of MFDS data.[5]

A majority of the multinational studies conducted in Korea are funded by foreign sponsors. In 2018,[2] Korea was ranked 11th in its share of global multinational trials, suggesting that Korean companies primarily conduct domestic studies, whereas multinational and multisite studies are conducted in Korea as part of a global development program by global or foreign sponsors.

With reference to therapeutic areas, oncology is the strongest area related to clinical trials in Korea. The number of MFDS-approved oncology studies across domestic and multinational studies was 247 (36.4%) in 2018.[1] Among these, studies in-
volving targeted cancer drugs accounted for 45%, whereas those involving immune-oncology drugs represented 37.2%. According to the MFDS definition of a “new drug,” 60% of the targeted cancer drug trials were for new drugs, whereas only 12% of immune-oncology drug trials were for new drugs.[1]

In 2018, the proportion of clinical trial approval by MFDS was the highest in oncology followed by that in endocrinology (9.8%), gastroenterology (7.9%), and cardiology (7.2%).[1] The distribution of clinical trials in Korea by therapeutic area is somewhat different from the global trend. Korea has a relatively higher proportion of clinical trials related to oncology and endocrinology, with fewer trials involving the central nervous system and a lower proportion of phase 1 and 2 studies across all therapeutic areas.

**Trends of global and Korean clinical trials**

The global clinical trial landscape has shown abrupt changes, particularly with regard to industry-sponsored clinical trials. Indeed, there was a decline of 25% in the number of industry-sponsored clinical trials in 2016 compared with that in 2015 based on ClinicalTrials.gov.[2] The 5-year average growth rate of global clinical trials between 2014 and 2018 showed an actual decrease of 12.2%, despite continuous growth in the number of global drug pipelines in the clinical phase.[2] Clinical trials in Korea are not an exception in terms of the impact of the negative growth in global clinical trials. However, both multinational and domestic studies in Korea were not affected remarkably, and the 5-year average growth rate was −6.4% for the same period. Meanwhile, both global and Korean clinical trials started to increase gradually as of 2018. Indeed, for 2019, an approximate growth rate of 3% is expected in global and Korean clinical trials (Fig. 1).

Based on the analysis by KoNECT of the global industry-sponsored clinical trial share of each country using the ClinicalTrials.gov data, among the top 10 countries, the US showed the highest decrease in the share of clinical trials over the past 5 years (2014–2018).[2] The US has had the largest share of clinical trials in the world. European countries such as Germany and France also showed a big loss in their share of clinical trials in the same period. However, China and Australia demonstrated solid growth in their share of clinical trials. Apart from the top 10 countries, emerging countries such as Russia and Poland showed impressive growth in their respective studies and site shares.[2] As for Korea, it has remained stable in terms of study and site shares (Fig. 2). This trend implies that global clinical trials have become increasingly globalized with more sites in emerging countries and additional countries emerging with better infrastructures and incentive systems for clinical trials. Indeed, Australia has exhibited strong growth since announcing its clinical trial tax incentive scheme, which includes a cash refund for small companies.

**Korean companies and domestic CROs**

A majority of Korean pharmaceutical and biotech companies that have clinical-phase products do not have any teams sufficient enough to manage their clinical trials; thus, outsourcing is reckoned a critical factor for the execution of clinical trials. According to the KoNECT survey of the clinical trial status of Korean companies,[6] the companies spent 56.5% of their R&D expenses on clinical trials, with 46% of the direct costs of the clinical trials paid by CRO services. Based on the survey, 96.4% of companies (out of 56 responders) used CRO services in 2017 for their clinical trials. In addition, 81.1% of the Korean domestic companies hired domestic CROs, with only 18.9% of the
responders reporting that they hired global CROs.[6]
Due to increasing drug development activities and the preference for Korean CROs by Korean companies, the Korean CRO market has demonstrated impressive growth over the past 5 years (2013–2017), with the average annual growth rate of the Korean CRO market (14.0%)[7] surpassing that of the global CRO market (9.9%)[8] for the same period. In addition, the annual revenue and number of domestic CROs are growing, with an average annual growth rate of 27.6%[7] for the same period.

**Discussion**

Korean clinical trials have demonstrated unprecedented growth over the past 2 decades in terms of quality and quantity. The excellence of Korean investigators as well as the regulatory reform and harmonization in early 2000s, coupled with the establishment of the “Clinical Trial Centers (CTCs)” that have world-class facilities including phase 1 units and trained clinical trial personnel, the human research protection program (HRPP) and efficient and experienced IRBs at major university hospitals, have been the key factors in this success, which has attracted global development studies sponsored by not only global companies with their subsidiaries in Korea, but also foreign companies with no presence in Korea.

However, the global trend of clinical studies outside Korea indicates that the growth in clinical trials in established countries including Korea may not be growing as fast, and there seems to be a tendency of a decrease in patients allocated to Korean sites from multi-regional clinical trials including Asia-specific diseases. One reason for this is the rising competition with the emergence of countries such as those in Eastern Europe, Russia, and Latin America along with those improved incentive systems such as Australia. Especially with the extensive regulatory reform of China together with the rapid growth of R&D investment and biotech companies, the number of domestic trials of China has grown dramatically over the past three years, and global sponsors more and more consider China as part of global clinical programs with the shortened clinical trial authorization timeline. Finally, China was ranked as the third clinical trial country in the world as of 2018. Moreover, global pharmaceutical companies have introduced more stringent criteria for making decisions to move forward with their pipeline into late-phase clinical trials to save R&D spending and reinvest it into new early-phase programs. This strategy is termed the “quick-win, fast-fail” strategy.

The Korean government declared that support to the bio-health industry is one of the critical growth engines of the nation. Therefore, the focus of the Korean clinical trial community and the Korean government in clinical trials has been shifting to support drug development by Korean companies. As described earlier, it is encouraging that the number of phase 1 studies by domestic sponsors has been increasing. However, still most of Korean biopharmaceutical companies seem to be remaining at the early clinical development stage with their pipeline and have not formulated near-term plans to move onto late phase clinical trials with their compounds after they have completed phase 1 trials when we see the ratio between early-phase and late-phase clinical trials by domestic companies did not change for the past several years, even though we exclude the phase 1 studies for products that are not regarded as 'new drugs'.

Despite the observation above and the fact that the majority of biotech companies have a short-term goal of licensing their product at an early stage and that a number of companies plan to conduct late-phase clinical trials in the US, it is still expected to occur that the number of late-phase clinical trials to increase
in coming 3-5 years, particularly the number of phase 2 clinical trials by Korean companies considering that significant number phase 1 trials completed for ‘new drugs’ has been accumulated. With these changes, Korea now requires different strategies and skill sets to keep attracting foreign clinical trials and to support domestic clinical development.

Korea is required to develop a different level of efficiency and quality of clinical trials that can obviously discern Korea from its competitors. With the dramatic improvement of the Chinese regulatory environment and the big market size, China can take the advantage to capitalize on representing the Asia region or Asian population with the broader adoption of ICH E17 guidance on multi-regional clinical trials (MRCT). Korea would be able to be considered as a preferred site for global trials only with outstanding efficiency, speed, and quality of clinical trials in the foreseeable future.

The ongoing ‘Smart Clinical Trial Platform’ program that involves major 7 hospitals is expected to contribute to achieving higher clinical trial efficiency of Korea under the assumption that the platform technologies to be developed through this program are widely adopted by Korean hospitals. Active use of the EMR data in conducting feasibilities and matching patients with the complex inclusion/exclusion criteria would greatly improve efficiency together with a more streamlined and transparent clinical trial authorization process by Korean health authorities.

For domestic companies that develop drugs, they will need to build internal clinical development capacity. They will need to learn how to work with a virtual development team that involves external partners, vendors, and consultants. Capability for well-thought-out clinical development plans including first-in-human study planning, study designs, and protocol concept, choosing right clinical indications for development, selection of right patient populations, recruitment strategies, vendor management, project management, etc. is critical, too.

Both regulators and reviewers should be able to provide more efficient regulatory provisions and review the capacity to guide and expedite successful clinical development in Korea.

Last but not least, Korea will need a new ecosystem that can efficiently support clinical development between companies and patients. Companies need to be able to easily access well-trained and experienced investigators and clinical study groups. Furthermore, they should be able to forge a true partnership with other players in the ecosystem.

To initiate this process, KoNECT has started to work with cooperative study groups such as the Korean Cancer Study Group as well as both global and domestic companies to fulfill the unmet medical needs of patients and to build a new working model between industry and academia. Through these endeavors, KoNECT has witnessed meaningful progress not only in terms of creating new studies for important unmet medical needs but also in new ways of working together through a mutual understanding between industry and physician groups.

Clinical pharmacologist groups also stand at the forefront of the Korean drug development ecosystem, considering that the stage of drug development is at the stage of first-in-human studies for many Korean companies and that the experiences and internal expertise of Korean companies in early-phase clinical development are limited.

**Conclusion**

Since 2007, the Korean clinical trial community across government, academia, and industry has worked together to transform the Korean clinical trial enterprise into a global leader through unprecedented collaborations. Likewise, Korea has become a role model for other countries in how to successfully transform the infrastructure of a country in a relatively short period of time. Further development of the collaborative environment in clinical trials, smart utilization of established clinical research resources including facilities, systems and data, and development of human resources are critical cornerstones for the future growth of the Korean bio-health industry.

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**Conflict of interest**

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**References**

1. https://www.koreaclinicaltrials.org/kr/contents/datainfo_data_01_tab02/view.do Accessed 1 November 2019.
2. KoNECT annual analysis of ClinicalTrials.gov database, Aug. 2019. Internal data
3. http://www.korea.kr/news/pressReleaseView.do?newsId=155943465 Accessed 1 November 2019
4. https://www.mfds.go.kr/brd/m_99/view.do?seq=43284&srchFr=&srchTo=&srchWord=&srchTp=&itm_seq_1=0&itm_seq_2=0&multi_itm_seq=0&company_cd=&company_nm=&page=1 Accessed 1 November 2019
5. KoNECT annual analysis of MFDS clinical trial authorization data, Internal data
6. KoNECT survey on clinical trial activities of companies operating in Korea, 2018. Internal data
7. Clinical Trials Statistics, KoNECT, 2018:22-23.
8. Contract research organizations global market opportunities and strategies to 2021, the business research company. Jul 2018:30-31.