ABSTRACT

Public disclosure of approved clinical trials in a reliable registry can provide the transparency of the study. Although the registration of clinical trials has increased remarkably, the integrity of the data is not always satisfactory. In this study, we analyzed public clinical trial databases updated by the Ministry of Food and Drug Safety (MFDS) and Clinical Research Information Service (CRIS) registry to provide an overview of the trends of clinical trials approved between 2017 and 2019 in Korea. Information on clinical trials approved between January 1, 2017 and December 31, 2019 was collected from two databases. Trial information was categorized and summarized by study phase, therapeutic area, and location of the participating centers. A total of 655 to 715 clinical trials were newly approved annually by MFDS during the period from 2017 to 2019. Phase 1 clinical trials accounted for the largest proportion (31.0%), followed by phase 3 (29.5%), investigator-initiated trials (24.1%), phase 2 (14.6%), and phase 4 (0.5%). The number of clinical trials classified as an Antineoplastic and immunomodulating agent was the greatest (40.1%) regardless of the study phase. The similar result was obtained from CRIS registry where therapeutic area Neoplasms (15.9%) accounted for the largest number. The number of clinical trials performed in Seoul and Gyeonggi-do was approximately 70% of the total trials. In conclusion, our study provided a comprehensive overview of clinical trials in Korea from 2017 to 2019. The discrepancy between clinical trial registries could be resolved by introducing standardized database and guidelines.

Keywords: Clinical trial; Therapeutics; Registries; Geographic Locations
INTRODUCTION

Prospective registration of clinical trials enables unbiased reporting of the results and ensures transparency [1]. Since 2004, the International Committee of Medical Journal Editors (ICMJE) has required the registration of clinical trials in a public registry as a condition for publication [2]. Since then, prospective registration of clinical trials has increased remarkably [3] and has been accelerated by the legal mandates of registration by regulatory bodies including the United States [4].

Although the number of clinical trials in public registries has increased, the quality of the data in the registries still needs improvement [5]. A worldwide survey of clinical trial registries pointed out that a considerable number of trials missed important information and often was outdated while retrospective registration accounted for a fourth of the total trials [3]. Similar results were reported in a recent study that only 37% of trials were registered in a prospective manner, among which, only 31% of the trials provided study results [6].

In particular, phase 1 clinical trials, which often involve healthy volunteers, have several complicated concerns. Submission of results from phase 1 clinical trials is not mandatory as the trial is not considered as an applicable clinical trial under the Food and Drug Administration Amendments Act [7]. This could make phase 1 clinical trials more vulnerable to biases. Another concern is the overlapping enrollment of healthy volunteers [8] which necessitates sophisticated tracking of phase 1 clinical trials [9].

In Korea, two local databases provide fundamental information on clinical trials. The public database of the Ministry of Food and Drug Safety (MFDS) frequently updates information on the approved clinical trials, and the other is a local clinical trial registry named Clinical Research Information Service (CRIS) [10]. MFDS has provided the approval status of clinical trials, and made registration for the database mandatory since 2019 [11]. CRIS was developed in February 2010 by Korea Centers for Disease Control and Prevention to support registration and report of the study results [10]. Both trial databases are not identical as the former provides all of the information on the clinical trials approved by the regulatory agency whereas the latter is one of the possible public trial registries accepted by ICMJE.

To provide a consistent overview of the approved clinical trials along with its counterpart study for years 2014–2016 [12], we analyzed the characteristics of clinical trials approved in terms of the study phase, therapeutic area, and geographic distribution. The previous study demonstrated an increasing trend of phase 1 clinical trials and a geographic imbalance in Korea. In the current analysis, we set up the study period as 2017–2019, which was prior to the first coronavirus disease 2019 (COVID-19) outbreak in Korea, to avoid the significant impact of COVID-19 on the clinical trial environment [13]. In addition, we newly included CRIS registry into analysis to promote the establishment of a harmonized clinical trial registry in Korea.

METHODS

Data collection

Two local data sources were used for the present analysis. Information on the clinical trials approved between January 1, 2017 and December 31, 2019 was collected from the public database provided by the MFDS (hereafter ‘public database’) [14]. Local registry data
were obtained directly from the CRIS (hereafter ‘local registry’) [15]. The information was analyzed regardless of the current status of the clinical trial.

**Categorization of the clinical trial data**

The study phase information of the clinical trial data from the public database was categorized based on the investigational product (IP) in the clinical trial. Study phase was categorized similarly to the previous literature as follows: phase 1 (study phase noted as ‘0,’ ‘1,’ ‘1/2,’ ‘1/2a’ and ‘1/3’), phase 2 (‘2,’ ‘2a,’ ‘2b’ and ‘2/3’), phase 3 (‘3,’ ‘3a,’ ‘3b’ and ‘3/4’), phase 4, investigator-initiated trials, and ‘Others’ [12]. Information on the study phase from the local registry data was analyzed without any modifications.

Therapeutic area information of the clinical trial data was categorized based on the main IP and study indication in each clinical trial. When the IP code was not specified, other registry data such as ClinicalTrial.gov from the United States National Library of Medicine were consulted [16]. Otherwise, therapeutic area of the trial was coded as ‘Others.’ Each trial was labeled using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) Classification System. Therapeutic area was manually labeled by two investigators in an independent manner. Information on the study phase and therapeutic area from the local registry data was analyzed without any modifications. Therapeutic area in the local registry was coded using the Korean Standard Classification of Diseases (KCD) code [17], which was a local version of the WHO International Classification of Diseases (ICD) code and was analyzed without any modifications.

Study center was grouped by province using clinical trial information from the public database because the local registry did not include all of the participating centers. The study center was counted individually for multicenter trials when counting the total number of clinical trials by province. Otherwise, a multicenter trial was counted as a single trial. Statistical software R version 4.0.3. (R Foundation for Statistical Computing, Vienna, Austria) was used for the analysis.

**RESULTS**

**Summary of clinical trials according to study phase**

As shown in Table 1, a total of 655 to 715 clinical trials were newly approved annually between 2017 and 2019. In detail, phase 1 clinical trials had the largest number, followed by phase 3, IIT, phase 2, and phase 4. The total number of multicenter clinical trials was relatively similar during the study period whereas single center trials increased in 2018 which was maintained in 2019 (Table 1 and Fig. 1).

On the other hand, each phase of the clinical trials showed different trends. 2018 had the highest number of phase 1 clinical trials while phase 3 trials and IIT were the lowest during the same study period. The number of phase 2 clinical trials increased continuously during the period between 2017 and 2019. The number of phase 4 clinical trials was not more than 10 trials per year. Local registry data on study phase was mostly not specified (63.9%), and phase 2 clinical trials accounted for the largest proportion among the labeled data (12.0%) (Table 1).
Summary of clinical trials according to therapeutic area

The greatest number of clinical trials was classified as an Antineoplastic and immunomodulating agent during the 2017–2019 period regardless of the study phase (Table 2 and Supplementary Fig. 1). The second highest number of clinical trials was classified as Alimentary tract and metabolism area during the 2018 to 2019 period while the second highest number of trials classified as Nervous system was in 2017. The number of trials in the Cardiovascular system area was similar during the 2017–2019 period. The number of clinical trials in the Antiinfectives for systemic use area decreased continuously while that of dermatologicals increased continuously from 2017 to 2019 (Fig. 2).

When the therapeutic area was classified as the KCD code, Neoplasms followed by Diseases of the musculoskeletal system and connective tissue and Diseases of the nervous system accounted for the largest number in the specified data (Table 3 and Fig. 3).

Summary of clinical trials according to location

The number of clinical trials performed in Seoul and Gyeonggi-do occupied approximately 70% of the total number of the trials. The number of clinical trials conducted in Seoul...
accounted for more than half (52.6%) and that of Gyeonggi-do accounted for one third of the trials in Seoul (17.1%). The rest of the trials were conducted mostly in metropolitan areas such as Busan, Daegu, Incheon, and Daejeon (Fig. 4 and Table 4).

### DISCUSSION

We found that the overall number of clinical trials in Korea from 2017 to 2019 increased by 7.9% compared to previous three-year interval. The increase of phase 1 trials and IIT was another remarkable change, in contrast to the previous predominance of phase 3 trials. In terms of therapeutic area, the number of clinical trials in the Antineoplastic and immunomodulating agent area was still the largest as it was in the previous three years [12]. We also found a relative increase of trials in the Alimentary tract and metabolism area from 157 (8.0%) to 295 (14.2%).
Table 3. Summary of clinical trials according to therapeutic area from local registry from local registry (CRIS)

| Therapeutic area (Classification of Diseases code) | 2017 | 2018 | 2019 | Total |
|-----------------------------------------------------|------|------|------|-------|
| Neoplasms                                           | 27 (6.2) | 132 (16.8) | 224 (19.0) | 383 (15.9) |
| Not specified                                       | 96 (22.1) | 101 (12.8) | 143 (12.2) | 340 (14.1) |
| Diseases of the musculoskeletal system and connective tissue | 76 (17.5) | 116 (14.7) | 144 (12.2) | 336 (14.0) |
| Diseases of the nervous system                      | 38 (8.7) | 71 (9.0) | 111 (9.4) | 220 (9.2) |
| Diseases of the digestive system                    | 39 (9.0) | 77 (9.8) | 97 (8.2) | 213 (8.9) |
| Diseases of the circulatory system                  | 21 (4.8) | 73 (9.3) | 81 (6.9) | 175 (7.3) |
| Endocrine, nutritional and metabolic diseases       | 28 (6.4) | 41 (5.2) | 70 (5.9) | 139 (5.8) |
| Diseases of the genitourinary system                | 14 (3.2) | 37 (4.7) | 68 (5.8) | 119 (5.0) |
| Mental and behavioural disorders                    | 22 (5.1) | 25 (3.2) | 47 (4.0) | 94 (3.9) |
| Diseases of the respiratory system                  | 17 (3.9) | 26 (3.3) | 37 (3.1) | 80 (3.3) |
| Diseases of the eye and adnexa                      | 14 (3.2) | 15 (1.9) | 18 (1.5) | 47 (2.0) |
| Diseases of the skin and subcutaneous tissue        | 7 (1.6) | 12 (1.5) | 30 (2.5) | 49 (2.0) |
| Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 6 (1.4) | 10 (1.3) | 30 (2.5) | 46 (1.9) |
| Symptoms, signs and abnormal clinical and laboratory findings, NEC | 6 (1.4) | 15 (1.9) | 20 (1.7) | 41 (1.7) |
| Factors influencing health status and contact with health services | 6 (1.4) | 9 (1.1) | 15 (1.3) | 30 (1.2) |
| Pregnancy, childbirth and the puerperium            | 7 (1.6) | 6 (0.8) | 10 (0.8) | 23 (1.0) |
| Certain infectious and parasitic diseases           | 6 (1.4) | 3 (0.4) | 10 (0.8) | 19 (0.8) |
| Injury, poisoning and certain other consequences of external causes | 1 (0.2) | 7 (0.9) | 9 (0.8) | 17 (0.7) |
| Codes for special purposes                          | 2 (0.5) | 3 (0.4) | 6 (0.5) | 11 (0.5) |
| Diseases of the ear and mastoid process             | 1 (0.2) | 6 (0.8) | 5 (0.4) | 12 (0.5) |
| Certain conditions originating in the perinatal period | 1 (0.2) | 1 (0.1) | 2 (0.2) | 4 (0.2) |
| Congenital malformations, deformations and chromosomal abnormalities | 0 (0.0) | 1 (0.1) | 2 (0.2) | 3 (0.1) |
| External causes of morbidity and mortality          | 0 (0.0) | 1 (0.1) | 2 (0.2) | 3 (0.1) |
| Total                                               | 435 | 788 | 1,181 | 2,404 |

Results are displayed as the number of clinical trials (percentage).
CRIS, Clinical Research Information Service; NEC, not elsewhere classified.

Figure 3. The number of clinical trials according to therapeutic area (Classification of Diseases code) and approval year (Clinical Research Information Service).
We noted that relative increase in the Alimentary tract and metabolism area was a distinctive trend compared to that in 2014–2016. Despite the increase in phase 1 clinical trials in 2014–2016, the proportion of the Alimentary tract and metabolism was constant. In contrast, the proportion of the area, where most trials were at phase 1 (Supplementary Fig. 1), almost doubled in 2017–2019 compared to that in 2014–2016.

### Table 4. Summary of clinical trials according to province and multicenter status from public database (MFDS)

| Province         | 2017       | 2018       | 2019       | Total       |
|------------------|------------|------------|------------|-------------|
|                  | Multi-center | Single-center | Yearly total | Multi-center | Single-center | Yearly total | Multi-center | Single-center | Yearly total |
| Seoul            | 1,860 (52.5) | 142 (61.7) | 2,002 (63.1) | 1,610 (50.7) | 189 (66.8) | 1,799 (52.0) | 1,730 (52.1) | 162 (57.7) | 1,892 (52.4) | 5,693 (52.6) |
| Gyeonggi-do      | 626 (17.7)  | 18 (7.8)   | 644 (20.3)  | 556 (17.5)  | 35 (12.4)  | 591 (17.1)  | 590 (17.8)  | 31 (11.0)  | 621 (17.3)  | 1,856 (17.1) |
| Busan            | 200 (5.6)   | 22 (9.6)   | 222 (7.0)   | 256 (7.1)   | 5 (1.8)    | 231 (6.7)   | 196 (5.9)   | 3 (1.1)    | 199 (5.5)   | 655 (6.0)    |
| Daegu            | 197 (5.6)   | 3 (1.3)    | 200 (6.3)   | 193 (6.1)   | 6 (2.1)    | 199 (5.4)   | 195 (5.9)   | 12 (4.3)   | 207 (5.7)   | 606 (5.6)    |
| Incheon          | 163 (4.6)   | 12 (5.2)   | 175 (5.5)   | 152 (4.8)   | 6 (2.1)    | 158 (4.6)   | 134 (4.0)   | 15 (5.3)   | 149 (4.1)   | 482 (4.5)    |
| Daejeon          | 105 (3.0)   | 9 (3.9)    | 114 (3.6)   | 65 (2.0)    | 14 (5.0)   | 79 (2.3)    | 75 (2.3)    | 15 (5.3)   | 90 (2.5)    | 283 (2.6)    |
| Gangwon-do       | 96 (2.7)    | 3 (1.3)    | 99 (3.1)    | 68 (2.1)    | 2 (0.7)    | 70 (2.0)    | 69 (2.1)    | 1 (0.4)    | 70 (1.9)    | 239 (2.2)    |
| Jeollabuk-do     | 41 (1.2)    | 13 (5.7)   | 54 (1.7)    | 49 (1.5)    | 17 (6.0)   | 66 (1.9)    | 58 (1.7)    | 13 (4.6)   | 71 (2.0)    | 191 (1.8)    |
| Gwangju          | 59 (1.7)    | 2 (0.9)    | 61 (1.9)    | 47 (1.5)    | 4 (1.4)    | 51 (1.5)    | 63 (1.9)    | 5 (1.8)    | 68 (1.9)    | 180 (1.7)    |
| Gyeongsangnam-do | 49 (1.4)    | 3 (1.3)    | 52 (1.6)    | 46 (1.4)    | 1 (0.4)    | 47 (1.4)    | 60 (1.8)    | 7 (2.5)    | 67 (1.9)    | 166 (1.5)    |
| Jeollanam-do     | 56 (1.6)    | 1 (0.4)    | 57 (1.8)    | 43 (1.4)    | 0 (0.0)    | 43 (1.2)    | 36 (1.1)    | 3 (1.1)    | 39 (1.1)    | 139 (1.3)    |
| Chungcheongbuk-do| 34 (1.0)    | 0 (0.0)    | 34 (1.1)    | 47 (1.5)    | 3 (1.1)    | 50 (1.4)    | 38 (1.1)    | 13 (4.6)   | 51 (1.4)    | 135 (1.2)    |
| Ulsan            | 24 (0.7)    | 0 (0.0)    | 24 (0.8)    | 40 (1.3)    | 1 (0.4)    | 41 (1.2)    | 32 (1.0)    | 0 (0.0)    | 32 (0.9)    | 97 (0.9)     |
| Chungcheongnam-do| 27 (0.8)    | 1 (0.4)    | 28 (0.9)    | 24 (0.8)    | 0 (0.0)    | 24 (0.7)    | 32 (1.0)    | 1 (0.4)    | 33 (0.9)    | 85 (0.8)     |
| Jeju-do          | 6 (0.2)     | 1 (0.4)    | 7 (0.2)     | 7 (0.2)     | 0 (0.0)    | 7 (0.2)     | 8 (0.2)     | 0 (0.0)    | 8 (0.2)     | 22 (0.2)     |
| Gyeongsangbuk-do | 2 (0.06)    | 0 (0.0)    | 2 (0.06)    | 1 (0.03)    | 0 (0.0)    | 1 (0.03)    | 3 (0.1)     | 0 (0.0)    | 3 (0.1)     | 6 (0.06)     |
| Sejong           | 0 (0.0)     | 0 (0.0)    | 0 (0.0)     | 1 (0.03)    | 0 (0.0)    | 1 (0.03)    | 1 (0.03)    | 0 (0.0)    | 1 (0.03)    | 2 (0.02)     |
| Total            | 3,545       | 230        | 3,775       | 3,175       | 283        | 3,458       | 3,320       | 281        | 3,601       | 10,834       |

Results are displayed as the number of clinical trials (percentage). MFDS, Ministry of Food and Drug Safety.

![Figure 4. The number of clinical trials according to location of the study centers. The number of clinical trials was calculated separately for each center in multicenter trials (Ministry of Food and Drug Safety).](https://tcpharm.org)
2017–2019 (Table 2). We expected that increased development of several popular drug classes in the area (e.g., proton-pump inhibitors [18]) might contribute to the increase.

The predominance of phase 1 clinical trials was aligned with early-stage-focused development led by the domestic biopharmaceutical companies. In a review conducted by Korea National Enterprise for Clinical Trials (KoNECT), industry-sponsored domestic trials were mostly at phase 1; the ratio of phase 1, 2, and 3 trials was 6.7: 1.0: 1.3, respectively [19]. As more than half of the phase 1 trials were associated with fixed combination drugs or new formulations of marketed drugs in Korea [19], the trends of clinical trials could be influenced by several popular drug classes. Similarly, bioequivalence trials highly focused in several therapeutic areas were reported in another study [20].

The concentration of clinical trials in urban areas (e.g., Seoul metropolitan area) was a definite trend in Korea. Seoul occupied more than half of the entire trials (52.6%), similar to 53.5% in the previous report. Another study of oncology clinical trial conducted in Korea between 2007 and 2013 also reported that six large volume hospitals each conducted more than 50 clinical trials while 45% of study centers conducted less than 10 trials [21]. A study on the approved oncology trials in 2019 also revealed that 92% trials were available in Seoul while only 33% in provincial areas [22].

Similar phenomena have been addressed in the United States [23,24]. Volunteers in rural areas tended to participate in clinical trials significantly less than urban counterparts (odds ratio, 0.30–0.46) [24]. Furthermore, proximity to clinical sites were related to patient recruitment and retention. Thus, the geography of clinical trials needs to be taken into account when interpreting and generalizing the results of clinical trials [25].

We also found several discrepancies in the results by the clinical trial registries. For instance, the therapeutic area in Musculo-skeletal system ranked the 6th in the MFDS public database whereas it was 2nd (excluding ‘not specified’) in the CRIS registry. Discrepancies in other therapeutic areas and study phases were also noted, despite the differences in the coding systems (Tables 2 and 3). Especially, as shown in Table 1, most of the study phases (63.9%) were not specified in the CRIS registry.

The discrepancies and errors in the clinical trial registries have been continuously addressed. A cross-sectional study of registered trials in ClinicalTrials.gov and European Union Clinical Trials Register revealed that 16.2% of trials were discrepant on the completion status [26]. Another study regarding pediatric trials in a peer-reviewed journal found that 19 out 20 randomized-controlled trials had medium or high combined discrepancy scores [27]. Similar results were reported in other literature [28,29].

The results of this study indicate that a harmonized clinical trial registry with a regulatory database is necessary for proper evaluation of the clinical trial landscape. Since 2019, all applicants are required to register clinical trial information to the MFDS database [11]. Thus, all clinical trials approved by MFDS could be identifiable. The applicants are recommended to register the information to other public registries including CRIS and ClinicalTrials.gov. However, as there have been no mandates and guidelines for which public registry to choose, each trial could be filed to any registry even in a duplicated manner.
Although the importance of clinical trial registries has been emphasized in a systemic review and meta-analysis [30], registry data have not been properly aligned with publications [31]. Furthermore, data are not often standardized. For example, a bioequivalence trial was previously classified as a separate entity in Korea; however, recently, bioequivalence trials are classified as phase 1 studies since October 2017 [32,33]. Similarly, therapeutic area can be coded with various systems including the WHO-ATC and ICD-11. Duplicate registration of clinical trials (e.g., CRIS and ClinicalTrials.gov) should also be avoided [34]. Without such efforts, an appropriate evaluation for the trends of clinical studies would be seriously hampered.

Overall, the results of our study could help to facilitate standardization and harmonization of the clinical trial registries. In this study, we revealed that evaluation of multiple registries was necessary due to discrepancies for overview of the clinical trials in Korea. Solutions for the discrepancy would comprise standardized database coupled with streamlined regulations. Technical integration with other global registries (e.g., ClinicalTrials.gov) could also be a possible solution.

Our study has some limitations. As several IPs under the early stage of drug development were yet assigned ATC codes, the therapeutic area should be assigned by subjective judgment of the investigators. The missing information in the registries limited precise analysis of the trends. Further investigations on the study design (e.g., blinding and randomization) need to be performed in future research.

In conclusion, our study provided a comprehensive overview of clinical trials in Korea between 2017 and 2019. The discrepancy between clinical trial registries could be resolved by introducing standardized database and guidelines.

SUPPLEMENTARY MATERIAL

Supplementary Figure 1
The number of clinical trials according to therapeutic area and study phase (Ministry of Food and Drug Safety).

Click here to view

REFERENCES

1. Sim I, Chan AW, G"ulmezoglu AM, Evans T, Pang T. Clinical trial registration: transparency is the watchword. Lancet 2006;367:1631-1633. PUBMED | CROSSREF
2. DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. JAMA 2004;292:1363-1364. PUBMED | CROSSREF
3. Viergever RF, Li K. Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. BMJ Open 2015;5:e008932. PUBMED | CROSSREF
4. Zarin DA, Tse T, Williams RJ, Rajakannan T. Update on trial registration 11 years after the ICMJE policy was established. N Engl J Med 2017;376:383-391. PUBMED | CROSSREF
5. DeVito NJ, Bacon S, Goldacre B. Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study. Lancet 2020;395:361-369.
   [PUBMED] [CROSSREF]

6. Lindsay K, Fusco N, Teeuw H, Mooij E, Scholten R, Voorhees L. Poor compliance of clinical trial registration among trials included in systematic reviews: a cohort study. J Clin Epidemiol 2021;132:79-87.
   [PUBMED] [CROSSREF]

7. Rayi A, Thompson S, Gloss D, Malhotra K. Reporting bias in completed epilepsy intervention trials: a cross-sectional analysis. Epilepsy Res 2018;143:1-6.
   [PUBMED] [CROSSREF]

8. Resnik DB, Kosi G. A national registry for healthy volunteers in phase 1 clinical trials. JAMA 2011;305:1236-1237.
   [PUBMED] [CROSSREF]

9. Allen C, Francis G, Martin J, Boyce M. Regulatory experience of TOPS: an internet-based system to prevent healthy subjects from over-volunteering for UK clinical trials. Eur J Clin Pharmacol 2017;73:1551-1555.
   [PUBMED] [CROSSREF]

10. Huh KY, Hwang JG, Lee S. Trends of clinical trials from 2014 to 2016 in South Korea. Transl Clin Pharmacol 2018;26:172-176.
    [PUBMED] [CROSSREF]

11. Jeon J, Kim H, Yu KS. The impact of COVID-19 on the conduct of clinical trials for medical products in Korea. J Korean Med Sci 2020;35:e329.
    [PUBMED] [CROSSREF]

12. Ministry of Food and Drug Safety. Guidelines on the registration and disclosure of the clinical trial information. Cheongju: Ministry of Food and Drug Safety; 2019.

13. Ministry of Food and Drug Safety. https://nedrug.mfds.go.kr/searchClinic. Accessed July 14, 2021.

14. Clinical Research Information Service [Internet]. https://cris.nih.go.kr. Accessed September 2, 2021.

15. United States National Library of Medicine. ClinicalTrials.gov [Internet]. https://clinicaltrials.gov/. Accessed August 2, 2021.

16. Statistics Korea. Korean standard classification of diseases and causes of death [Internet]. https://kssc.kostat.go.kr:8443/ksscNew_web/ekssc/main/main.do#. Accessed November 19, 2021.

17. Oh JA, Lee GM, Chung SY, Cho YS, Lee HJ. Utilization trends of Proton Pump Inhibitors in South Korea: Analysis using 2016-2020 Healthcare Bigdata Hub by Health Insurance Review and Assessment Service. Yakhak Hoeji 2021;65:276-283.
   [CROSSREF]

18. Chee DH. Korean clinical trials: its current status, future prospects, and enabling environment. Transl Clin Pharmacol 2019;27:115-118.
   [PUBMED] [CROSSREF]

19. Huh KY, Kim E, Lee S, Yoo H, Yoon S, Yu KS, et al. Current bioequivalence study designs in South Korea: a comprehensive analysis of bioequivalence study reports between 2013 and 2019. Front Pharmacol 2021;12:651790.
   [PUBMED] [CROSSREF]

20. Shim BY, Park SH, Lee S, Kim JS, Lee KE, Kang YK, et al. Current status and challenges of cancer clinical trials in Korea. Cancer Res Treat 2016;48:20-27.
   [PUBMED] [CROSSREF]

21. Kim W, Jang S, Chang YI. Cardiovascular disease in access to clinical trials for cancer in Korea. Quality Improvement in Health Care 2021;27:20-25.
   [CROSSREF]

22. Friedman DB, Foster C, Bergeron CD, Tanner A, Kim SH. A qualitative study of recruitment barriers, motivators, and community-based strategies for increasing clinical trials participation among rural and urban populations. Am J Health Promot 2015;29:332-338.
   [PUBMED] [CROSSREF]

23. Baquet CR, Commisckey P, Daniel Mullins C, Mishra SL. Recruitment and participation in clinical trials: socio-demographic, rural/urban, and health care access predictors. Cancer Detect Prev 2006;30:24-33.
   [PUBMED] [CROSSREF]
25. Su SC, Kanarek N, Fox MG, Guseynova A, Crow S, Piantadosi S. Spatial analyses identify the geographic
source of patients at a National Cancer Institute Comprehensive Cancer Center. Clin Cancer Res 2010;16:1065-1072.
PUBMED | CROSSREF

26. Fleminger J, Goldacre B. Prevalence of clinical trial status discrepancies: a cross-sectional study of 10,492
trials registered on both ClinicalTrials.gov and the European Union Clinical Trials Register. PLoS One
2018;13:e0193088.
PUBMED | CROSSREF

27. Rosati P, Porzsolt F, Ricciotti G, Testa G, Inglese R, Giustini F, et al. Major discrepancies between what
clinical trial registries record and paediatric randomised controlled trials publish. Trials 2016;17:430.
PUBMED | CROSSREF

28. Walker KF, Stevenson G, Thornton JG. Discrepancies between registration and publication of randomised
controlled trials: an observational study. JRSM Open 2014;5:2042533313517688.
PUBMED | CROSSREF

29. Serpas VJ, Raghav KP, Halperin DM, Yao J, Overman MJ. Discrepancies in endpoints between clinical
trial protocols and clinical trial registration in randomized trials in oncology. BMC Med Res Methodol
2018;18:169.
PUBMED | CROSSREF

30. Baudard M, Yavchitz A, Ravaud P, Perrodeau E, Boutron I. Impact of searching clinical trial registries in
systematic reviews of pharmaceutical treatments: methodological systematic review and reanalysis of
meta-analyses. BMJ 2017;356:j448.
PUBMED | CROSSREF

31. Grey A, Portch R, Gaby A, Grey H, Bolland M. Clinical trial registry documents and publication integrity.
Account Res 2021;28:149-161.
PUBMED | CROSSREF

32. Ministry of Food and Drug Safety. Regulation on approval for investigational new drug application of
drugs, notice No. 2018-77. Cheongju: Ministry of Food and Drug Safety; 2018.

33. Ministry of Health and Welfare. Pharmaceutical Affairs Act, amended by Act No. 14926. Sejong: Ministry
of Health and Welfare; 2017.

34. Viergever RF, Karam G, Reis A, Ghersi D. The quality of registration of clinical trials: still a problem. PLoS
One 2014;9:e84727.
PUBMED | CROSSREF