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Trends in Clinical Trial Registration in Dentistry: An Analysis of Registered Clinical Trials in the Clinical Research Information Service from 2013 to 2021 in South Korea

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ABSTRACT

The Clinical Research Information Service (CRIS) in South Korea provides a clinical trial registry platform in which all clinical trials should be mandatorily and prospectively registered. However, to date, the registration status of clinical trials in the field of dentistry has not been investigated. Therefore, this study aimed to provide an overview of the methodological design and trends of the registered clinical trials over a period of nine years. Information about registered clinical trials in the field of dentistry from the CRIS was comprehensively collected from 2013 to 2021. The details assessed from the collected trials include: type of sponsors, recruitment status, study design, randomization, allocation concealment, single or multi-centric, retrospective or prospective registration, and publication status. A total of 65 registered clinical trials were identified. The number of clinical trials in dentistry in South Korea was found to be less; however, an increasing trend was observed in the recent three years. A majority of the trials were interventional (81.5%), single-centered (86.2%), and conducted on patients (81.5%) and in private hospitals (55.4%). A considerable number of trials had an unclear phase, were retrospectively registered, and rarely published. Regarding the quality, most trials have inadequately reported the method of randomization and allocation concealment. The number of clinical trials in dentistry is still low in South Korea, and most of them were registered retrospectively. A poor-quality reporting of methods at several specific areas was observed. It is necessary for dental investigators to raise awareness of the need to register clinical trials.

Introduction

Clinical trials are considered to be the cornerstone of evidence-based practice and have contributed knowledge to the dentistry field, providing high-quality evidence for good practice. Prospective registration of trial details in publicly accessible databases has been suggested as a means of overcoming selective reporting of trials and publication bias by improving transparency and accountability in clinical trials (Dickersin & Min, 1993; Dickersin, Min, & Meinert, 1992; Simes, 1986). Careful assessments of clinical trial registration have clearly proven that the registration process works well as an effective and financially viable methodology that can ensure that the standards for quality reporting of clinical trials are met (McFadden et al., 2015).

In South Korea, the Clinical Research Information Service (CRIS), a non-profit online registration system (https://cris.nih.go.kr), was set up in 2010, wherein all clinical trials or studies conducted in Korea should be mandatorily registered before recruiting their first participant for the trial (Park, 2011). It joined the World Health Organization (WHO) International Clinical Trial Registry Platform as the 11th member of primary registry.

Although clinical trials involving oral health interventions have increased over time, studies have suggested that the reporting of clinical trials is poor in dentistry (Cairo, Sanz, Matesanz, Nieri, & Pagliaro, 2012). Particularly, randomized clinical trials published in various dentistry-related specialties showed that methodological quality is below acceptable levels to adequately lead clinical decision making (Saltaji, Armijo-Olivo, Cummings, Amin, & Flores-Mir, 2017). In fact, few studies have investigated clinical trial registration with a focus on the dental field since the CRIS was set up over 10 years ago.

Therefore, the current study was conducted to collect and analyze information on registered clinical trials in the field of dentistry from the CRIS in order to provide an overview of the methodological design and trends of the registered clinical trials in Korea from 2013 to 2021.

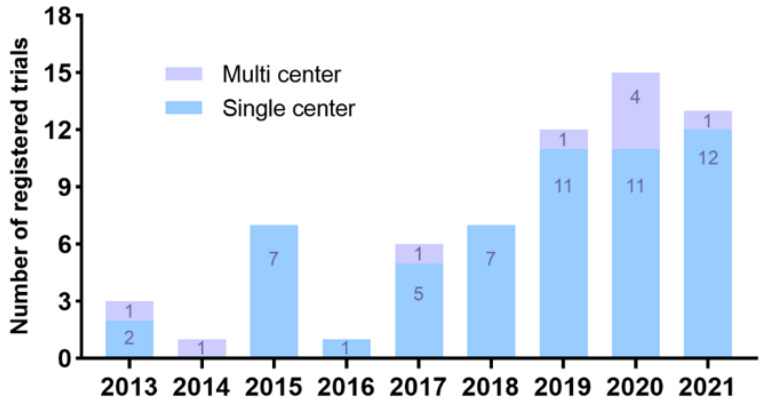
Methods

The study was conducted using data available in the public domain; therefore, the requirement to obtain Institutional Ethics Committee approval was waived. All trials that were registered with the CRIS (https://cris.nih.go.kr) from January 1, 2013 to July 31, 2021 were evaluated. No filters were used with regard to phase, type of trial, recruitment status, and clinical trials in South Korea. The search was conducted using the keyword “dental” and “periodontitis” , also known as gum disease or periodontal disease. The following information was collected for each of the clinical trials obtained from the search: number of centers (single center/multi-center), type of institution undertaking the study (government/private/combined), study design (randomized/single-blinded/double-blinded), type of study (observational/interventional), type of participants (healthy/patients), type of disease condition, phase of clinical trial (Phase 1/2/3/4), publication details (published/not published), nature of sponsors (academic/commercial), prospective or retrospective registration of clinical trials, and methodological quality (details about randomization [method, concealment of allocation]). The general characteristics of clinical trials are presented as descriptive statistics. Categorical data were expressed by calculating the frequency and percentage. All analyses were performed using the IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA).

Results

Number of clinical trials

The search yielded a total of 80 clinical trials, of which 65 trials (3-2013; 1-2014; 7-2015; 1-2016; 6-2017; 7-2018; 12-2019; 15-2020; 13-2021) were found to belong to the field of dentistry over the 9-year period. There seemed to be a growing trend in the number of single-center trial registrations over time. The proportion of dentistry-related trials from every trial registered in the CRSI was only approximately 0.2%. The majority (56/65, 86.2%) of the clinical trials were single-centered; only nine trials were multi-centered. The trend analysis of the total number of registered clinical trials and whether it was a single or multi-center trial is depicted in Figure 1.



Dentistry	3	1	7	1	6	7	12	15	13
All fields	958	1,322	1,731	2,165	2,600	3,388	4,565	5,702	6,429
%	0.31	0.08	0.40	0.05	0.23	0.21	0.26	0.26	0.20

Figure 1. Trends of registered clinical trials in dentistry and overall fields between 2013 and 2021

Settings of the registered clinical trials

Table 1 describes the timing of registration, types of study participants, institutions, and sponsors of the registered clinical trials over the study period. Among the 65 registered trials, 9 (13.8%) were registered prospectively and 56 (86.2%) were registered retrospectively. A majority (53/65, 81.5%) of the registered clinical trials were recruiting patients, whereas the rest were being conducted on healthy participants. With regard to the place of trial, 55.4% (36/65) of the trials were planned to be performed in private institutions/hospitals, whereas 38.5% (25/65) were solely conducted in government organizations, mostly national hospitals. There were also four trials to be combined. With the rise in the number of trials over the years, the rise was mainly in the private sector. Most of the clinical trials were being undertaken as academic studies (57/65, 87.7%). Among them, 31 trials were sponsored by the government while 26 were funded by the private sector.

Table 1. Settings of registered clinical trials in dentistry

	2013(3)	2014(1)	2015(7)	2016(1)	2017(6)	2018(7)	2019(12)	2020(15)	2021(13)	Total(65)
Timing of registration										
Prospective	0	0	1	1	1	0	1	2	3	9
Retrospective	3	1	6	0	5	7	11	13	10	56
Types of participants										
Heathy	0	1	0	0	1	0	3	3	4	12
Patients	3	0	7	1	5	7	9	12	9	53
Types of institution										
Government only	1	0	3	1	2	3	5	5	5	25
Private only	2	0	4	0	3	4	6	9	8	36
Combined	0	1	0	0	1	0	1	1	0	4
Types of sponsors										
Academic, goverment	0	1	3	0	4	2	3	8	10	31
Academic, private	2	0	4	1	2	3	8	5	1	26
Commercial	1	0	0	0	0	2	1	2	2	8

Interventional vs. observational characteristics of the registered clinical trials

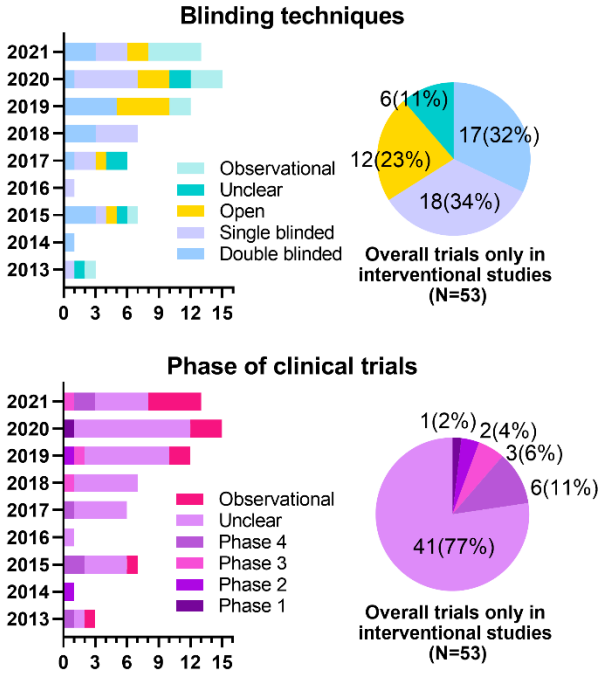


Figure 2. Trends and overall distribution of blinding techniques and phase of clinical trial in the registered clinical trials

In terms of interventional vs. observational study design, 81.5% (53/65) of the registered clinical trials were interventional studies over the 9-year period. Among 53 interventional trials, the number of double-blinded, single-blinded, and open studies was 17 (32.1%), 18 (34.0%), and 12 (22.6%), respectively. However, a clear description regarding the use of blinding techniques is unavailable for six registered clinical trials (Figure 2).
In terms of the phase of clinical trials, 41/53 (77.4%) trials were unclearly reported. Of the remaining 12 clinical trials, six were in Phase 4, three were in Phase 3, two were in Phase 2, and one was in Phase 1of clinical trials (Figure 2).

Dental disease conditions and types of intervention

The distribution of disease conditions in which the clinical trials have been reported to be conducted is presented in Table 2. Periodontitis (23/56, 41.1%) has been the disease condition for which most trials have been frequently and steadily conducted, followed by dental caries (5/56, 8.9%) and edentulous jaw (5/56, 8.9%). For most studies except these three conditions, there was one single study for each condition, with distinct trends of disease conditions studied over time.

Table 2. Dental health conditions mentioned in the registered clinical trials

Disease condition	2013(3)	2014(1)	2015(7)	2016(1)	2017(6)	2018(7)	2019(12)	2020(15)	2021(13)	Total(65)
Tooth extraction	1						1		1	2
Oral lichen planus	1									1
Dental caries	1									1
Periodontitis		1	4		3	3	5	4(2)	3	23(2)
Two jaw surgery			1							1
Dental plaque, scaling			1				1			2
Dental caries			1		1		1(1)	1(1)	1(1)	5(3)
Orthognathic surgery				1						1
Tooth loss					1				1	2
Temporomandibular joint disorder					1				1	2
Dental implant						1		1(1)	(1)	2(2)
Tooth bleaching						1		1		2
Surgical wounf dehicence						1				1
Halitosis						1	1			2
Socket preservation							1			1
Dental surgery							1			1
Periimplantitis							1			1
Basic life support								1		1
Teeth needing extracoronal restoration								1		1
Gingivitis								1		1
Malocclusion, maxillofacial abnormalities								1		1
Missing tooth of maxillary posterior								1		1
Edentulous jaw								3	2	5
Pulpitis								(1)	1	1(1)
Dentition									1	1
Tooth fracture									(1)	(1)
Premolar crown									1	1
Dental noise									1	1

In terms of intervention type, medical device (21/65, 32.3%) and procedure/surgery (13/65, 20.0%) were the two most common types of intervention in the clinical trials in dentistry. Pharmacological intervention was the third (6/65, 9.2%) (Table 3).

Table 3. Types of intervention in the registered clinical trials in dentistry

	2013(3)	2014(1)	2015(7)	2016(1)	2017(6)	2018(7)	2019(12)	2020(15)	2021(13)	Total(65)
Medical device	1		1	1	3	3	1	5	6	21
Procedure/Surgery			1				5	5	2	13
Drug	1	1	1			1	2			6
Behavioral			1		1	1				3
Dietry supplement						1	2	1		4
Others			1			1		1		3
Observational	1		2		2		2	3	5	15

Methodological quality and publication of the registered clinical trials

A total of 47/53 (88.7%) interventional clinical trials were conducted using a randomization technique in their study methodology. Regarding the method of randomization sequence generation, only three trials reported their exact method; two with computer-generated randomization sequence and one with sealed envelope. No trials reported the method of concealing the allocation. Five clinical trials were reported to have been published.

Discussion

This study comprehensively analyzed clinical trials in the field of dentistry registered in the CRIS from 2013 to 2021 in South Korea. During this period, we found that a total of 65 clinical trials had been registered in this field, with an increasing trend in the recent three years. A majority of the trials were interventional, single-centered, used double blinding, and were conducted on patients and in private hospitals. A considerable number of trials had an unclear phase, were retrospectively registered, and rarely published. Regarding the quality, most trials inadequately reported their method of randomization and allocation concealment.

In South Korea, the clinical research registry named CRIS, established in 2010, has recommended prospective registry that conforms to the WHO registry criteria. The number of registered clinical trials in all fields has been growing from 68 in 2010 to 6,429 in 2021. As with general increase, we found a recent increase in the number of registered trials in the field of dentistry. However, relative to the growth in general fields, registered clinical trials in dentistry, accounting for approximately 0.2% of all registrations, were still less in Korea. This observation should be considered from various perspectives in this field. First, the field of dentistry occupied 2.5% of annual research development expenditure, funded by government, among all fields of health care in 2018 (Jeon et al., 2020). Second, annual production of dental equipment, including machines, devices, and fillers, also occupied 24.8% of all production of medical equipment in 2018(Jeon et al., 2020). Third, the institute of National Health Insurance Review reported that the dental sector occupies 5.7% of all medical fees with the highest increase rate in 2019 (Kim & Kim, 2020). These facts indicate that the field of dentistry is growing in every direction. We assume that the low registration rate of clinical trials may be not because of less research or the regression of the field of dentistry, but because of investigators' low awareness of the need to register clinical trials.

However, evidence indicates that this phenomenon is not only limited to Korea. A study analyzing registered trials in the Central Trials Registry of India also reported similar results that the number of clinical trials being conducted in this field is relatively less in India. These authors argued that this low rate may be due to the lack of trained researchers in dentistry and sponsors (both private and government) and poor patient awareness about clinical trials. A previous study reported that less than 25% of all randomized controlled trials are registered on an international public access database registry (Smail-Faugeron, Fron-Chabouis, & Durieux, 2015). This situation has also been

shown in the overall low adherence of trial registration and quality reporting in other areas of the oral health sciences (Faggion & Giannakopoulos, 2012).

The timing of registration is another important issue to raise. In this study, 86% of registered trials were registered retrospectively across time in this study. This observation is consistent with an analysis of randomized controlled trials (RCTs) published in the oral health journals, revealing that 91% of RCTs, registered in a trial registry were retrospectively registered (Smail-Faugeron et al., 2015). These findings suggest that retrospective registration may also be a general situation in this field, and previous registrations conducted to date in Korea were unfortunately against the primary aim of the establishment of the CRIS, i.e., prospective registration of trial details in publicly accessible databases. One more point to be noted is that 8 out of 9 trials registered prospectively were sponsored by a government organization. This indicates that investigators may be more alert to the official process of registration when they are sponsored by the government.

The present study found a poor-quality reporting of methods in the dental clinical trials. Detailed information on randomization was significantly lacking in this study. Except a few clinical trials, almost all studies did not provide any information on the method of random allocation, randomization sequence generation, and concealment of allocation. Information on the study phase of trials was also lacking, and 41% of interventional trials provided this unclearly. We assume that other categories need to be added for studies that do not follow the process of drug development because classification of phase applies to drug development. Considering the fact that unclear report about blinding techniques accounted for only 11% of the interventional trials, inadequate reporting of other sections may be improved easily if the system requested the information with clearly defined explanations.

Conclusion

In conclusion, the number of clinical trials in dentistry is increasing but still low in South Korea, and most of them were registered retrospectively. A poor-quality reporting of methods was observed especially regarding the study phase, method of randomization and allocation concealment, and the publication report. It is necessary for dental investigators to raise awareness of the need to register clinical trials.

Implications

Improving the quality of clinical trials is essential to provide high-quality evidence for good practice. Prospective registration of trial details is one of the ways to improve the methodological and reporting quality of clinical trials. This study demonstrated the current status of the quality of clinical trial registration in the field of dentistry and suggests what needs to be improved in the quality of registration in the future.

Limitations

This study has some limitations. First, our search was limited with the keyword “dental” and “periodontitis”; other individual health conditions, such as dental caries and cavity, were not included. This may underestimate the number of clinical trials that are being undertaken in this field. Second, there is a possibility that clinical trials conducted in Korea may be registered in other registration systems e.g., ClincalTrials.gov. However, we conducted a crude search in ClinicalTrials.gov, and Korean clinical trials could hardly be found. Third, with regard to the publication status, we simply looked at the status as mentioned in the trial registry without actually looking into the literature database. There is a possibility that trials may have been published, but the status may not have been updated in the trial registry. Fourth, it should be noted that data on year 2021 only covers first 6 month of the year.

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