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Original Article



# Establishment of Advanced Regulatory Innovation for Clinical Trials Transformation (ARICTT): a multi-stakeholder public-private partnership-based organization to accelerate the transformation of clinical trials

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## ABSTRACT

Clinical trials have evolved with digital technologies and tend towards patient-centricity. A multi-stakeholder approach is needed to address the emerging complexities in clinical trials. In particular, the introduction of digital technologies and an emphasis on patient-centricity are the major trends in clinical trials. In response, we established a public-private partnership-based organization named Advanced Regulatory Innovation for Clinical Trials Transformation (ARICTT). Eleven organizations in total, from academia, industry, and regulatory agencies, participate in ARICTT. Based on multi-stakeholder collaboration from academia, industry, and government/regulatory bodies, we collected and prioritized current topics in clinical trials based on an internal survey. We established a three-year roadmap with axes that were termed *trend*, *goal*, *structure*, *theme*, *topic*, and *method*. In addition, we planned the development of recommendations based on real-world cases with feasibility studies. We developed appropriate organizational structure to fulfill the roadmap of ARICTT. The selected topics were decentralized clinical trials during the first year, followed by the three topics that were awarded the highest priority according to the internal survey: advances in the informed consent process, supporting sites using digital technology, and an effective recruitment strategy. We developed a case-based recommendation paper presenting an overview of the regulatory landscape and practical considerations with explanatory cases. We also designed and conducted fully decentralized trials to evaluate considerations in real-world settings for the selected topics. Overall engagement and communication were supported by the online platform and annual symposiums. In conclusion, we established a multi-stakeholder, public-private partnership-based organization to accelerate the transformation of clinical trials.

**Keywords:** Clinical Trial; Public Private Partnership; Government Regulation; Guideline

**Reviewer**

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**Author Contributions**

Conceptualization: Chung WK; Data curation: Chung WK; Formal analysis: Chung WK; Funding acquisition: Yu KS; Investigation: Chung WK, Park J; Methodology: Huh KY, Oh J; Project administration: Huh KY, Yu KS; Resources: Yu KS; Software: Chung WK; Supervision: Yu KS, Huh KY, Park J, Oh J; Validation: Yu KS, Huh KY, Park J, Oh J; Visualization: Chung WK; Writing - original draft preparation: Chung WK; Writing - review and editing: Yu KS, Huh KY, Oh J, Park J.

## INTRODUCTION

The clinical trial has been considered to be the gold standard in evaluations of the safety and efficacy of therapeutics [1]. However, with the advent of various novel technologies and given the increasing demand for efficient drug development, more complicated trial methods have been introduced [2]. The concept paper entitled The Renovation of Good Clinical Practice mentioned three new topics in clinical trials: decentralized elements, pragmatic elements, and real-world data (RWD) sources [3].

Newly introduced trial methods are closely associated with the digital transformation in the healthcare system. In recent decades, due to the rapid growth of digital technology and the demand for high-quality medical services, there has been explosive growth in the digital transformation of healthcare systems [4,5]. Clinical trials have also been affected by this digital transformation. The REMOTE trial by Pfizer is a good example of an attempted digital transformation of clinical trials. In this clinical trial, the concepts of web-based recruiting, electronic consent, and a mobile e-diary were successfully applied to demonstrate the feasibility of futurized clinical trials [6]. Furthermore, the recent coronavirus disease 2019 (COVID-19) pandemic makes urgent the acceleration of the digital transformation [7,8].

On the other hand, patient-centricity is emphasized in clinical trials [9-11], defined as "*putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family*" according to AstraZeneca [12]. Patient-centric trials can be an alternative to conventional 'site-centric trials,' which obliges patients to visit the trial sites. The conventional clinical trial model relies greatly on the geographic accessibility of patients as well as continuous evaluations of study endpoints [13]. In contrast, patient-centric trials can remove geographic barriers while providing more real-world evaluations of patients [14].

The changing trends in clinical trials demand the rapid advancement of regulations [15]. Decentralized clinical trials (DCTs) represent the very topic where digital technology and patient-centricity combined with regard to the urgent demands induced by the pandemic. The pandemic completely forbade conventional trial-related procedures, whereas the development needs for therapeutics and vaccines were urgent [16]. Accordingly, trial-related procedures outside of trial sites were required, and these are currently being standardized into what are known as DCTs. Regulatory agencies are now confronting the strong demand for the issuance of and guidance on DCTs [17,18].

In response, a sustainable, multi-stakeholder, and public-private partnership-based organization has been suggested [19]. It was evident that the clinical trial transformation would be a continuous trend. Emerging topics are connected to numerous stakeholders in clinical trials, and multi-stakeholder collaboration has become essential. A sustainable multi-stakeholder organization is best realized through a public-private partnership, which is capable of supporting flexible and efficient organizations. There are several pioneering groups in this area, including the Clinical Trials Transformation Initiative (CTTI). CTTI is a public-private partnership-based initiative established through a collaborative effort between Duke University and the US FDA [20]. Currently, there are more than 80 member organizations participating, encompassing government agencies, industry representatives, patient representatives, and investigator groups [20,21]. It has developed various recommendations and resources on emerging issues, including DCTs [22].


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**Figure 1.** Logo of ARICTT.
ARICTT, Advanced Regulatory Innovation for Clinical Trials Transformation.

Korea plays an important role in clinical trials [23,24]. Recent rapid changes in the clinical trial landscape have resulted in many issues related to clinical trials in Korea. Therefore, a systematic response to these changes was required. The clinical policy department of the Ministry of Food and Drug Safety (MFDS) proposed a public-private partnership modeled after CTTI based on the "DCT consultative body" created by the Korea Society of Clinical Development and MFDS. To this end, we aimed to establish a sustainable, multi-stakeholder, public-private partnership-based organization to accelerate the clinical trial transformation, giving it the moniker Advanced Regulatory Innovation for Clinical Trials Transformation (ARICTT) (**Fig. 1**).

## METHODS

### Overall governance: a multi-stakeholder collaboration

We designed a partnership encompassing the stakeholders of clinical trials from the three sectors: academic, industry, and the government/regulatory sector. Academia include trial sites, investigators, and institutional review boards; industry includes sponsors and contract research organizations; government/regulatory includes regulatory agencies and government-supported organizations. Preferred participating parties were a society or association of organizations, rather than a single organization. A roadmap as well as research topics and projects were planned based on multi-stakeholder collaboration.

### Assigning priority to research topic candidates

We gathered and prioritized the emerging topics in clinical trials to set the annual project goals. Topics addressed in other regulatory agencies and in the multi-stakeholder collaboration, including CTTI, were collected. Suggestions from participating parties were also considered. The topics were categorized into themes and adjusted to be in a similar hierarchy.

To set the annual goals and projects, a survey to prioritize the topics was conducted among the ARICTT members. The survey was conducted anonymously. There were three projects annually (except for the first year) based on the initial objectives. Respondents were requested to select five topics in order of priority among the list of collected topics. Then, six candidates (double the number of annual topics) were initially selected based on the sum of the priority scores and the total number of suggestions. Priority was scored on a Likert-type scale ranging from 1 to 5 (1: the lowest priority; 5: the highest priority). The respondents were then requested to score the candidates based on the following three criteria: urgency, impact, and feasibility. The second survey was conducted in real time and respondents were requested to score each criterion on a Likert-type scale ranging from 1 to 5. The scores were summed up


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and the candidates were ranked for each criterion. Furthermore, the scores of all three criteria were summed up without weighting and total ranks of the candidates were determined.

### Roadmap

Based on the setting of priority levels, the three-year roadmap of ARICTT was established. The roadmap was constructed based on hierarchical axes given the following titles: *trend*, *goal*, *structure*, *theme*, *topic*, and *method*. The roadmap was set based on the axes for three years. The *trend* axis reflected the overall landscape of the clinical trial environment. The *goal* axis was set to align with the *trend* axis and addressed annual objectives and the directions of ARICTT. The *structure* axis presents the organizational structure of ARICTT to fulfill the goals. The *theme* axis is the upper category of the *topic* axis, which consists of the annual projects to be discussed. The *method* axis describes the detailed methodology to be used to yield the planned project deliverables.

### Development of recommendations based on real-world cases

The direct objective of ARICTT was to develop multi-stakeholder *recommendations* regarding the selected topics. Each *recommendation* was conceptually distinguished from *regulatory guidance*; the former addressed consensus and considerations from the stakeholders of clinical trials while the latter was a formal regulatory or legal document to ensure the quality of clinical trials. We aimed to include practical cases in the recommendations to maximize the implementation in real-world settings.

We created the cases from various research sources. We reviewed clinical trial cases and the literature related to the topics. In addition, to provide a comprehensive and closely related example, we also planned model investigator-initiated trials (IITs) that covered the topics in the recommendations. Expert consultations and questionnaires were also considered.

### Engagement and communication

To promote sustainable engagement, we developed an online platform to plan, communicate, and publicize our actions. The online platform was planned to introduce the roadmap and projects of ARICTT. In addition, the platform was designed to be a communication channel to accommodate opinions or proposals related to the transformation of clinical trials. In addition, we planned an annual symposium to discuss the deliverables from the annual project, encompassing all stakeholders of clinical trials.

## RESULTS

### Overall governance: a multi-stakeholder collaboration

Eleven organizations from academia, industry, and government/regulatory bodies in total participated in ARICTT. Considering the multiple roles of ARICTT, we divided the organizational structure into the following three committees: *a steering committee*, *a specialty committee*, and *an advisory board*. The *steering committee* consisted of representatives of the members, who made decisions about the overall directions and strategies of the projects. *Specialty committees* and *advisory boards* were organized for each project. *Specialty committees* consisted of project members from participating organizations who were recommended or who volunteered. The committee provided input into projects and recommendations. *Advisory boards* consisted of experts from various fields and provided consultations on specific topics, including legal affairs and patient opinions (**Table 1**).


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**Table 1.** Organizational Structure of ARICTT

| Organizational structure | Members of Steering Committee (11 organizations) |
|---|---|
| Steering committee | Academia |
| Make decisions about the overall directions and strategies | Seoul National University, Department of Clinical Pharmacology and Therapeutics |
| Specialty committee | Korean Academy of Medical Science |
| Provide input into projects and recommendations | The Korean Association of Clinical Trials Centers |
| Advisory board | Korean Association of Institutional Review Boards |
| Provide consultations on specific topics (e.g., legal affairs, patient groups) | Industry |
| | Korean Research-based Pharma Industry Association |
| | Korea Society of Clinical Development |
| | Korea Clinical Research Organization Association |
| | Korea Pharmaceutical and Bio-pharma Manufacturers Association |
| | Government/Regulatory |
| | Ministry of Food and Drug Safety |
| | Korea National Enterprise for Clinical Trials |
| | Korea Regulatory Science Center |

ARICTT, Advanced Regulatory Innovation for Clinical Trials Transformation.

## Assigning priority to research topic candidates

A total of 28 topics were gathered and summarized from the sources (**Supplementary Table 1**). The topics were categorized into the following five themes: integrating digital technology, ethical considerations, the design and conduct of clinical trials, novel clinical trial designs, and safety and unmet medical needs. The research topic of the first year was set as 'DCTs' at the planning stage considering the urgent need from the stakeholders.

In the initial priority assessment of the second year's topic, six candidates were initially selected. Three additional topics were finally selected based on the overall rank of the subsequent priority assessment: advances in the informed consent process, supporting sites using digital technology, and effective recruitment strategies. The themes of each topic were 'ethical considerations,' 'integrating digital technologies,' and 'design and conduct of clinical trials,' respectively. Considering the candidates and the balance among the topics, the 'novel clinical trial design' theme was reserved for the third year's projects and would be reassessed considering the ongoing trends in clinical trial environments. The results of the survey are summarized in **Table 2**.

## Roadmap

A three-year roadmap of ARICTT was established. With the discussions of the steering committee, three annual trends were suggested: paradigm shifts after the COVID pandemic (first year), regulatory changes in digital healthcare (second year), sustainable regulatory ecosystems (third year). The *goal*, *structure*, *theme*, and *topic* axes were discussed based on the trends (**Fig. 2**).

**Table 2.** Summary of the priority assessments for the candidates

| Category | Topics | Rank* | | | |
|---|---|---|---|---|---|
| | | Urgency | Impact | Feasibility | Total |
| Ethical considerations | Advances in informed consent process | 1 | 1 | 1 | 1 |
| Integrating digital technology | Supporting sites using digital technology | 1 | 2 | 1 | 2 |
| Designs and conduct of clinical trials | Effective recruitment strategy | 3 | 3 | 4 | 3 |
| Novel clinical trial designs | RWD/RWE in clinical trial | 4 | 3 | 3 | 4 |
| Integrating digital technology | Digital endpoint: development and utilization | 5 | 5 | 5 | 5 |
| Novel clinical trial designs | Registry trials: clinical trials using a patient registry | 6 | 6 | 6 | 6 |

*'1' denotes the highest priority, and '6' denotes the lowest priority.


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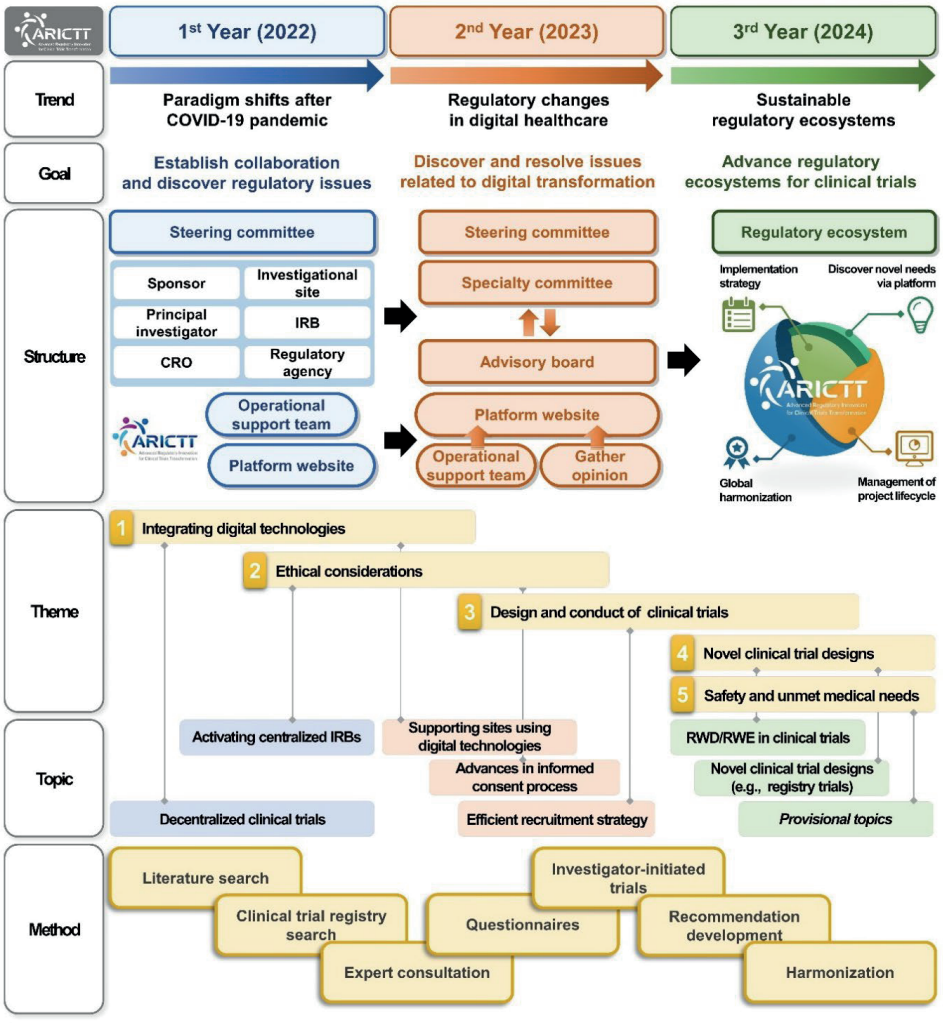


**Figure 2.** Three-year roadmap of ARICTT.
COVID-19, coronavirus disease 2019; ARICTT, Advanced Regulatory Innovation for Clinical Trials Transformation; IRB, institutional review board; RWD, real-world data; RWE, real-world evidence.

The *goal* of the first year was to establish collaborations and to discover regulatory issues. The initial *structure* was a multi-stakeholder committee supported by an operational support team and a platform website. The *theme* and *topic* were integrating digital technologies and DCTs, respectively.

The *goal* of the second year was to discover and resolve issues related to the digital transformation. As three topics should be addressed, the *structure* was functionally differentiated into the *steering committee*, *specialty committee*, and *advisory board* (see *Multi-stakeholder collaboration* in the *Results* section). The themes and topics were selected based on the priority setting (see *Priority setting of the research topics* in the *Results* section).

The *goal* of the third year was to advance regulatory ecosystems for clinical trials. ARICTT would focus on a sustainable *structure* and expand collaborations with global groups. The important *topics* in the novel clinical trial design *theme* would be discussed.


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## Case study of DCTs

IITs on research topics were planned and conducted. The first IIT addressed a fully DCT, with a trial design without visits to the trial sites. The detailed design and the result of the study are described in the literature [25]. The IIT was intended to evaluate the practical feasibility of DCTs within the current regulatory landscape in Korea. We attempted to provide potential considerations when using direct-to-patient delivery and remote informed consent, where only little experience was available currently due to regulatory issues. A subsequent trial was planned and conducted to address more advanced topics related to DCTs while covering the research topics on the roadmap for the second year. The considerations from the studies were provided as a practical example in the ARICTT recommendation on DCTs.

## Development of case-based recommendations

Recommendations for each topic were developed during the regular meetings of the members of ARICTT. During the first year, committee meetings were held monthly, and recommendations with related cases were reviewed and discussed. From the second year, *specialty committee* meetings were held monthly or more frequently to keep track of the development process. An overall review was conducted in the quarterly *steering committee* meeting. The recommendations were discussed with the regulatory agencies in separate meetings.

The recommendations were organized into a general review and element-specific discussions. The general review provided an overview of the background of recommendations and defined the terms related to the topic. In addition, regulatory and legal overviews were included based on expert consultations. We also attempted to set key principles for the recommendations to clarify the main purpose of each recommendation. Element-specific discussions addressed specific considerations for each topic. We sought to facilitate the implementation of the recommendations using practical checklists and informative cases. **Fig. 3** illustrates the structure of the developed recommendations.

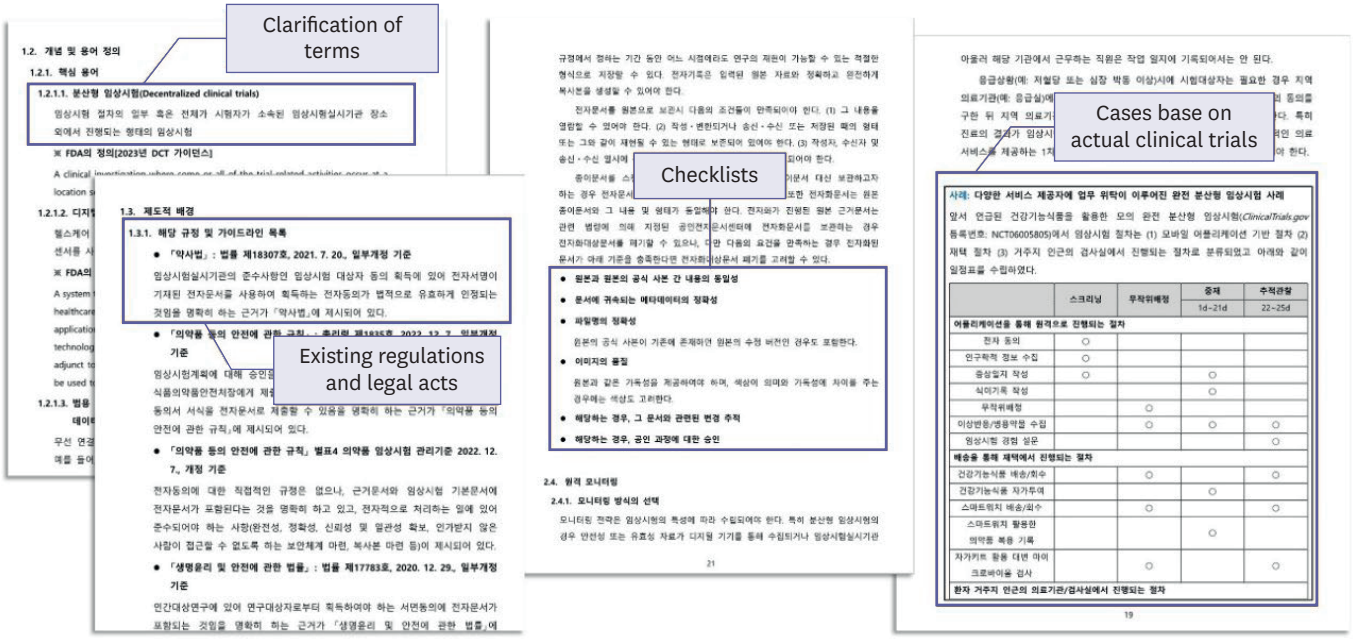


**Figure 3.** Examples of developed recommendations.


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## Engagement and communication

We constructed an online-based platform (arictt.org) to facilitate communication among the members of ARICTT (**Fig. 4**). The platform introduced the background and roadmap of ARICTT. We underscored the engagement of and interactions among the members of ARICTT and the function of the platform; it managed the meeting schedules, meeting minutes, and project output, and advertised our study performance. In addition, we included a communication function based on opinions collected from the board-type replies and questionnaires. The online platform could systematically support the sustainability of ARICTT.

Moreover, the first annual symposium of ARICTT was held in December of 2022. The symposium aimed to gather various stakeholders in clinical trials, including sponsors, investigators, and regulatory agencies. At the symposium, the central IRB project led by the Korean Academy of Medical Sciences was also introduced in collaboration with the DCT recommendation project by ARICTT. In total, seven presentations were prepared by various stakeholders. Detailed contents of the symposium are described in **Table 3**.

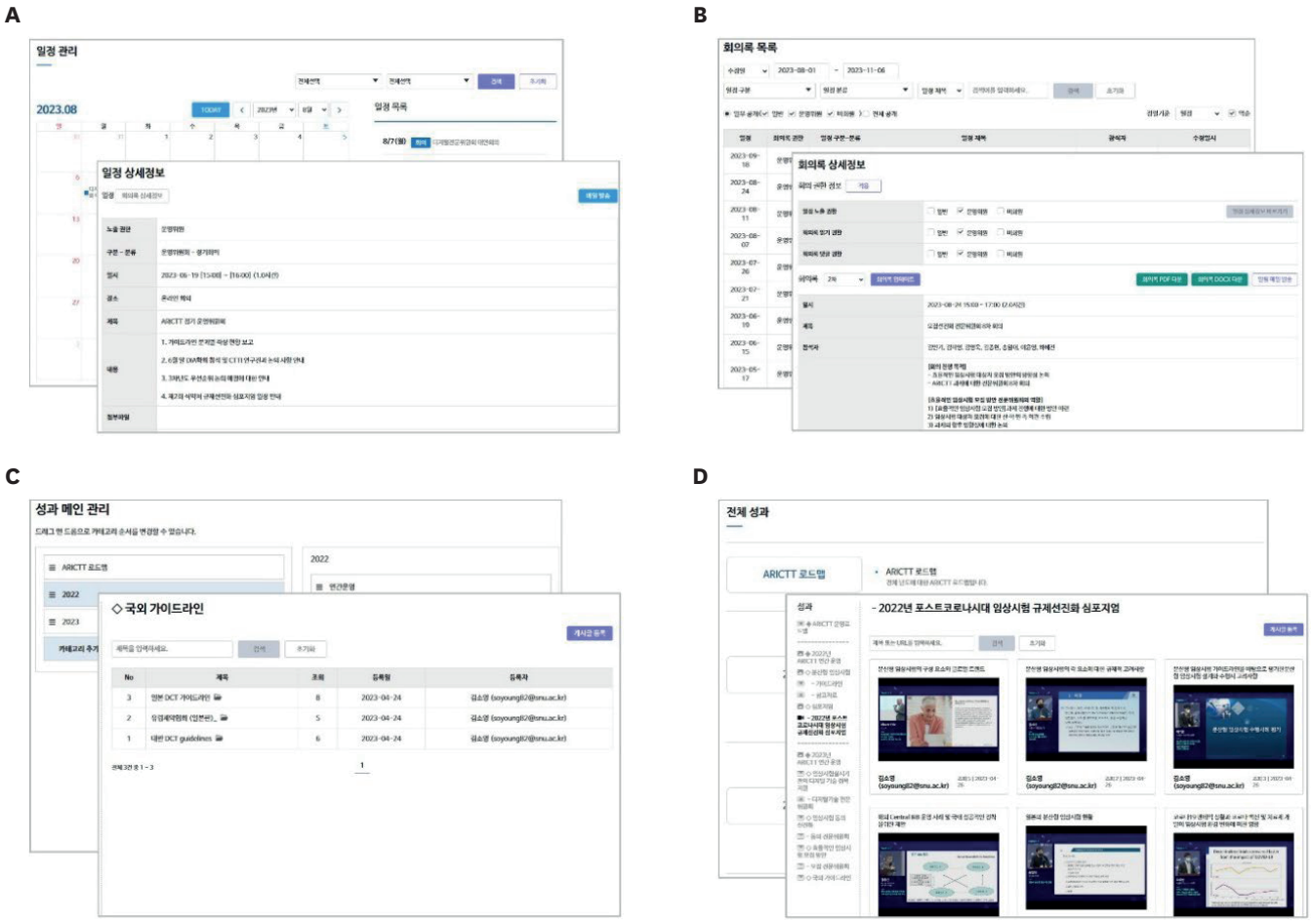


**Figure 4.** ARICTT online platform: schedule management (A), meeting minute management (B), project output management (C), and advertisements (D). ARICTT, Advanced Regulatory Innovation for Clinical Trials Transformation.


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**Table 3.** Agenda for the 2022 ARICTT symposium

| Session I. Introduction of Decentralized Clinical Trials and Changes in the Clinical Trial Landscape | Session II. Multiple Site Clinical Trial via Centralized IRB |
|---|---|
| The impact of the COVID-19 pandemic and the development of COVID-19 vaccines and treatments on the changes in the clinical landscape (Academia presenter) | Purpose and current status of operation of centralized IRB (Academia presenter) |
| Elements of the decentralized clinical trial and global trends (Industry presenter) | Institutional establishment of centralized IRB (Academia presenter) |
| The current status of clinical trials in Japan (Academia presenter) | |
| Regulatory considerations related to elements of the decentralized clinical trials (Regulatory presenter) | |
| Assessment of considerations for designing and conducting decentralized clinical trials based on the guidance of the decentralized clinical trial (Academia presenter) | |

ARICTT, Advanced Regulatory Innovation for Clinical Trials Transformation; IRB, institutional review board; COVID-19, coronavirus disease 2019.

## DISCUSSION

A clinical trial represents a type of interplay among multiple stakeholders, including those in academia, industry, and regulatory bodies. The recent outbreak of the COVID-19 pandemic accelerated the adoption of digital technologies in clinical trials while expanding the number and types of stakeholders as well. In response, DCTs, previously referred to as 'virtual trials' or 'mobile trials,' became an important topic in relation to clinical trials.

We realized that emerging issues in clinical trials cannot be addressed without multi-stakeholder collaboration [19]. For example, DCTs involve various stakeholders outside of the trial sites, such as local healthcare personnel, or parties as defined in the traditional Good Clinical Practice publication [9-11]. The newly introduced parties must be covered by the regulatory landscape of clinical trials. The previous top-down approach of the regulatory paradigm could not address emerging topics effectively given that such topics were associated with a myriad of 'invisible' stakeholders. Accordingly, the unexpected 'side effects' from new regulations made it difficult for regulatory bodies to address emerging issues proactively.

CTTI is a remarkable approach to address this problem. Established in 2007, CTTI is based on a private-public partnership between academia and regulatory bodies [20]. The initiative successfully discovered emerging issues in clinical trials (e.g., digital-technology-based clinical trials, novel clinical trial designs) and addressed the issues with various solutions (e.g., recommendations, checklists, templates) [26]. A recent focus is the implementation strategy of the solutions, which ranges from how to measure the implementation status to transforming clinical trial environments over the long term [27].

ARICTT aims to suggest solutions to the emerging topics in a sustainable manner. Trends of clinical trials are incessantly changing. There would be considerable topics still not dealt with in our short but intensive three-year roadmap. For example, the application of artificial intelligence (AI) in clinical trials is one of the important topics. AI could be used in every clinical step, i.e., the pre-clinical study, design, recruitment, conduct, and analysis [28]. As technology is rapidly changing, a long-lasting platform to keep pace with the trends is essential.

Another important topic related to clinical trials is the design of novel clinical trials. In the United States, the 21st Century Cures Act has initiated the proliferation of the use of real-world evidence generated by RWD in drug development [29]. Such data are currently emphasized as an important tool to support randomized controlled trials [30]. One of the major sources of RWD is registries, defined as "organized systems that use observational methods to collect uniform data on a population defined by a particular disease, condition


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or exposure, and that is followed over time" [31]. The source has been integrated in combination with clinical trials, referred to as registry trials. Recently, new registries dedicated to clinical trials have even been attempted [32].

In response to these changes, ARICTT will effectively facilitate collaborations among multiple stakeholders. One of the major efforts ARICTT has made is to bolster the engagement of patients. Considering the feasibility IIT for DCTs, we attempted to evaluate patient experiences in DCTs [25]. In addition, at the second year of ARICTT, we arranged a focus group interview for trial participants in an exploratory effort (*unpublished*). Such patient engagement is a valuable source of recommendation development, and continuous engagement would be of considerable importance. ARICTT thus attempts to provide a sustainable channel for trial participants and patients.

In conclusion, we established a multi-stakeholder, public-private partnership-based organization to accelerate the transformation of clinical trials, and we developed a case-based recommendation system for emerging topics, including DCTs.

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## SUPPLEMENTARY MATERIAL

### Supplementary Table 1

The list of topics proposed

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