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PERSPECTIVES

Institutional Change in Clinical Trials through the COVID-19 Pandemic

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To understand the current phenomena of conducting clinical trials in the era of the coronavirus disease (COVID-19) pandemic and adapt to a change in conduct, it might be beneficial to understand the experience of clinical trials from the perspective of "institutional change". This short perspective paper will describe the basic concepts of institutions and institutional change and explore expected or observed institutional changes in clinical trials as a result of the COVID-19 pandemic.

Keywords: Manage Clinical Research Data

Instituitional Theory and Instituitional Change

Although the terms "organization" and "institution" may be used interchangeably in general conversation, their primary purpose should be distinguished in order to discuss them in the social science context. While there are diverse schools and definitions of institutional theories, the term "organization" can be understood as a group of people who have the same objective; for example, family, community, company, and a medical site are forms of "organizations." On the other hand, "institutions" are social constructs composed of cultural-cognitive, normative, and regulative elements that, together with associated activities and resources, provide stability and meaning to social life.[1] Institution in this context does not refer to "site", whereas, it is generally understood to mean formal and informal conventions, norms, and rules that guide action or collective action. Institution can be also described or implied as tangible or intangible forms such as corporate culture, social behavior, attitude, rules, and guidelines. Various levels of institutions exist including global/international level, national level, community level, company level, etc., and some institutions are nested within organizations or institutions. In the context of pharmaceutical development, for example, the ICH guidelines are the major descriptive institutions of the conduct of clinical research on a global level. Furthermore, these guidelines are implemented as regulations in individual countries. The practices of clinical research are also shaped by a variety of regional and national level types of institutions, including those that are informal and tacit, such as regulatory requirements, medial system, company strategy and culture, and so on.

Institutional change is the occurrence of change in an institution that can be explained through several factors[2,3] (**Table 1**). For example, regulatory implementation of new ICH guidelines as step 5, can be understood as "designed", "intentional", "endogenous", "slow", or "top down" institutional change on the national or regional level. As a historical example, the development of institutional practices such as conflict of interest disclosure, clinical trial registry, and data sharing were developed to conduct transparent clinical trials. It was the response to past misconducts, publication bias, and selective reporting that can be identified as "endogenous causes", "top-down", and "slow" institutional changes. One case in Japan, The Clinical Trials Act[4] established in 2017, enforces strict administrative procedures and was developed as a reaction to revelations of misconduct in 2013 relating

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Table 1: Key factors of institutional changes.

Factors	Possible Manifestation
Design	Spontaneous – Designed
Intention	Unintentional – Intentional
Cause	Exogenous – Endogenous
Speed	Rapid – Slow
Direction	Top down – Bottom up

to a cardiovascular drug trial that was pharmaceutically funded and investigator-initiated.[5] The transformation of clinical data collection that occurred during the 2000s from a paper-based case report form (CRF) to an electronic CRF using electronic data capture (EDC) system can be also perceived as institutional change that has characteristics of an "exogenous" with technological progress, "bottom-up", and "slow" dissemination to stakeholders over the years.

Instituitional Changes in Clinical Trials in the Era of COVID-19 Pandemic

Several institutional changes have been observed based on the current impact and potential influence of COVID-19. Holding the IRB in face-to-face meetings, delivery of investigational products (IP), site visits by patients for interventions and assessments, site visits by clinical research associates (CRAs) for source data review, etc. were restricted to prevent the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in most countries of the world, depending on the seriousness of the epidemic in each country.[6] The reaction to these restrictions led or is currently shifting to changes in conducting clinical trials from conventional methods to new methods that incorporate remote operations using recent innovative technologies. Overall, the change could be characterized by rapid institutional change towards remote and decentralized clinical trials. Regulatory authorities, such as founding regulatory members of ICH, rapidly responded by disseminating administrative documents as correspondence relating to the COVID-19 pandemic. Indeed, several regulatory announcements such as those from FDA,[7] EMA,[8] and PMDA[9,10] were spontaneously published that allow alternative methods of conducting the procedures of clinical trials. **Table 2** shows type of regulatory documents and the time from WHO's pandemic declaration. All three regulatory agencies published the documents within the same month of the pandemic declaration.[11] In addition, the COVID-19 taskforce of the Society for Clinical Data Management (SCDM), acting as the international professional organization for clinical data management, rapidly responded by collecting regulatory documents and organized webinars on the overview of changes in regulatory guidelines. The first webinar was held on April 30, 2020.[12]

The remote and decentralized ways of conducting clinical trials such as "virtual trials" or "decentralized trials" are expected to raise the efficiency of the clinical trials, save operational costs, and encourage broader populations in those with geographical restrictions or non-targeted populations in conventional trials. For example, while the safety of trial participants is paramount, remote assessment of patients through the use of phone or video contacts, mobile sensor devices, and electronic patient-reported outcome (ePRO) systems will become more popular.[13] In terms of decentralization, alternative locations of assessments of participants or administration of IP, alternative delivery of IP, and patient home visits by nurses will be conducted instead of visiting trial sites by participants.[14] From the perspective of sponsors, for the oversight of clinical sites, central and remote monitoring by direct capturing of source data, and analyzing EDC data with statistical methods will become the core approach instead of visiting sites by CRA for source data verification.[15]

The implementation of "decentralized clinical trials" accelerated in reaction to these restrictions. Unexpectedly, the coronavirus disease (COVID-19) became the driving force and window of opportunity for these rapid institutional changes (**Table 3**). The institutional changes in conducting clinical trials, new approaches, and alternative measures to conventional methods, can be considered to be "endogenous" as they originated through technological innovation, and "design-based" in terms of existing guidelines and risk-based approaches to monitoring or eSource (such as ICH E6-R2,[16] eSource guidelines from FDA[17] during the 2010s). Since 2020, the coronavirus disease (COVID-19) has been a window of opportunity, allowing institutional change to rapidly accelerate in the implementation and dissemination phase as a reaction to "exogenous causes," specifically, the maintaining of social distance. Once our community experiences the feasibility and efficacy of these alternative measures during the coronavirus disease (COVID-19), certain approaches will remain an affordable option and will gradually become the new standard or, in other words, the "new normal." New institutions will persist in the post-pandemic era if they are nested in CDM community, unless new institutions create new problems or further innovations occur in technologies or methodologies in clinical trial. As observed, institutional changes were rapid and top-down and to adapt these changes, clinical data managers need to gain the knowledge and experience especially in implementing eSource data collection and remote monitoring of these data collection.

Table 2: Reaction to WHO declaration of pandemic from Regulatory Authorities.

Regulatory Authority	Type of documents	Date of publication	Time from WHO pandemic Declaration (2020.3.11)
PMDA	Letter from Chief Executive	31 March 2020	19 days.
FDA	Guidance for Industry, Investigators, and Institutional Review Boards	March 2020	Same month
EMA	Guidance to sponsors	25 March 2020	13 days

PMDA: Pharmaceuticals and Medical Devices Agency, FDA: Food and Drug Administration, EMA: European Medicines Agency.

Table 3: Characteristics of Institutional Changes of Implementation of remote operations by Covid19 Pandemic.

Factors	Direction of Manifestation	Example in Covid19 Pandemic
Design	Designed	Technology and methodology for remote operation (DCT, Telemedicine) was available for implementation
Intention	Unintentional	Triggered by Covid 19 Pandemic as an unexpected event
Cause	Endogenous	Originated through technological and methodological innovation
	Exogenous	Dramatical change in social life style
Speed	Rapid	Rapid implementation since Covid 19 Pandemic
Direction	Top down	Declaration of a state of emergency from the government Rapid Release of Announcements from Regulatory Agency

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Competing Interests

The authors have no competing interests to declare.

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