Global Health & Medicine. 2025; 7(2):96-105.
POLICY FORUM
DOI: 10.35772/ghm.2024.01082

How to build a better clinical trial ecosystem for future infectious disease emergencies in Japan: Findings from a narrative review and stakeholder meetings

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Abstract: The COVID-19 pandemic posed a serious challenge to national and global pandemic preparedness and response (PPR). Timely identification and development of diagnostics, therapeutics and vaccines through prompt evidence generation from clinical trials was recognized as an important health security agenda. In 2022, under the guidance of Japan Ministry of Health, Labour and Welfare (MHLW), a health policy research team was convened to analyze the COVID-19 related clinical trial ecosystem in the context of PPR in Japan and abroad with a focus on clinical trials for therapeutics. The research mainly composed of the following: a narrative review of relevant peer reviewed journals and grey literature, interview of global experts and stakeholders including those from the United States and the United Kingdom, and a culminating meeting in Japan with various stakeholders. Based on the outcomes of this research, the team makes the following three recommendations: (1) Strengthen the leadership group's role in infectious disease clinical trials, (2) Promote sustained coordination and collaboration among stakeholders, and (3) Apply innovative clinical trial designs and create an enabling research environment. Clinical trials, as a public health good, must be further integrated into healthcare. The team advocates for the implementation of these recommendations at the policy level to help improve the clinical trial ecosystem for future health emergencies in Japan.

***Keywords*:** COVID-19, pandemic preparedness and response, health emergencies, clinical trial ecosystem

Introduction

The COVID-19 pandemic has posed a significant challenge to national and global pandemic preparedness and response (PPR). During the early phase, diagnostics, therapeutics and vaccines were developed rapidly in addition to the various public health measures deployed. Japan also conducted numerous research activities, but it lagged its peer countries in development of essential vaccines and therapeutics.

In 2021, G7 countries set up the 100 Days Mission (100DM), aiming "to develop safe and effective diagnostics, therapeutics and vaccines available within the first 100 days of a future pandemic threat being identified (*1*)". Japan reaffirmed its commitment to PPR and 100DM in 2023 when the G7 summit was held in Japan (*2,3*). World Health Organization (WHO) also emphasizes strengthening of global clinical trial ecosystem as an important global health agenda for PPR (where the clinical trial ecosystem was defined as "the sum of all elements required to fund, prioritize, design, conduct, monitor and report scientifically and ethically appropriate, well-designed, and well-implemented clinical trials as well as features necessary for oversight and coordination") (*4*). Nationally and globally, building of a better clinical trial ecosystem is recognized as of critical importance, which enables rapid development and deployment of medical countermeasures (MCMs) under pandemic conditions.

In 2022, under the guidance of Japan Ministry of Health, Labour and Welfare (MHLW), a health policy research team was convened to investigate the COVID-19 related clinical trial ecosystem in the context of PPR in Japan and abroad. The team was composed of fiver members whose expertise included research and development (R&D) management in multi-country clinical trials, health emergencies, infectious disease epidemiology and biostatistics. The team reviewed the

COVID-19 related R&D activities in various countries, interviewed stakeholders across the globe, and developed policy level recommendations that are supported by various experts. The manuscript summarizes the research findings and sets forth the recommendations as a guide for better PPR through MCMs.

Outline of research project

Narrative review

First, a narrative review was conducted to compare Japan and other countries on clinical trials for therapeutics and vaccines with a focus on the United States (US) and the United Kingdom (UK). The scope included policies relevant to R&D for COVID-19, and supportive infrastructure such as research funding and regulations. The narrative review included articles in peer reviewed journals accessed through PubMed and grey literature such as governmental documents and reports accessed through Google search. Additional relevant literature was identified from key articles and documents. The US and the UK were selected as comparisons to Japan as they were considered to have outperformed Japan in COVID-19 related clinical trials using different approaches (*5-7*). The review also helped to identify potential contacts for the stakeholder/expert interviews.

Interviews of global stakeholders and experts

Second, interviews and focus group discussions with stakeholders were conducted by two research members (HS and KJ). The aim was to further clarify challenges and identify learnings regarding the clinical trial infrastructure through experiences of the COVID-19 pandemic. Potential interview candidates were contacted by email. Additional candidates were contacted as a snowballing sampling where appropriate. The interviews were conducted in person or online with each interview lasting for 30 to 60 minutes. Meeting notes were taken in English or Japanese, and the interviews were recorded when appropriate. After each interview, a summary was created by the interviewers. A total of 27 interviews were conducted (Japan: 16, the US: 7, and the UK: 4).

Culminating meeting in Japan

Lastly, findings from the literature review and the interviews were summarized for policy implications. The recommendations to the government (MHLW) and the after-mentioned leadership group were drafted by the team thereafter. A group of Japanese experts/stakeholders were invited to a culminating meeting to obtain further input and to reach a consensus on the proposed recommendations as a group. The meeting participants were selected among the interviewees based on their technical expertise and backgrounds, ensuring a diverse set of perspectives. The meeting was held on February 15, 2023, attended by 29 participants (5 from the team; 10 experts/stakeholders including infectious disease specialists, an intensive care unit physician, basic researchers, an expert from an Academic Research Organization (ARO), a representative from a pharmaceutical company and officials from a national funder; 5 from MHLW and 8 observers). A follow-up email was sent and each participant accepted the meeting minutes.

For the purposes of this research, the following findings and recommendations are presented mainly regarding clinical trials on therapeutics, both investigational new drugs and repurposing drugs (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=97*). The recommendations also have some relevancy to the early outbreak observational research for evaluation of epidemiology (*e.g.*, 'first few hundred study') and pathophysiology. The decision to focus mainly on therapeutics in this research was made because the vaccine development had already been addressed separately at the national level such as the foundation of Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response (SCARDA) (*8*).

Findings and recommendations

The team focused on the following three areas from policy implications perspective: (1) Strengthen the leadership group's role in infectious disease clinical trials, (2) Promote sustained coordination and collaboration among stakeholders, and (3) Apply innovative clinical trial designs and create an enabling research environment. Each area was divided into sub-categories, and the recommendations of each sub-category were presented as action items with consideration to the priorities and feasibility at policy level (Table 1).

Strengthen the leadership group's role in infectious disease clinical trials

Reflecting upon the COVID-19 experience, Japanese government has announced establishment of the Department of Infectious Diseases Prevention and Control within MHLW and the creation of Japan Institute for Health Security (JIHS) consolidating the National Institute of Infectious Diseases and National Center for Global Health and Medicine to prepare for pandemics. JIHS and MHLW are expected to lead research pursuits for MCMs. For the purpose of this report, we refer to those groups collectively as the "leadership group". This leadership group will need to take on following roles in a pandemic:

i) Early detection of infectious diseases of a pandemic potential and prioritization of medical countermeasures: Infectious diseases cross borders. Surveillance activities

Table 1. Action items for better clinical trials ecosystem in Japan

Areas / Sub-categories	Action Items
(1) Strengthen the leadership group's role in infectious disease clinical trials	
i) Early detection of infectious diseases of a pandemic potential and prioritization of medical countermeasures	• Establish a process to agree on a prioritization of R&D seeds where the leadership group monitors and analyzes information that comes in from around the globe. • Strengthen trust and collaborative relationships with organizations such as WHO, health agencies in peer countries, local research institutes (ASEAN CDC, Pasteur Institute, Noguchi Memorial Institute for Medical Research, *etc.*) by sending researchers from the leadership group on secondment.
ii) Development of MCMs portfolio	• Researchers from the leadership group participates in considering MCMs portfolio with international stakeholders such as WHO R&D blueprint[1] and share ideas with industry partners and academia.
iii) Funding strategy and its flexibility	• Strengthen funding schemes that can support infectious disease R&D over multiple years. • Establish a body that can provide continuous and flexible funding support for therapeutics and diagnostics development as SCARDA plays a role in vaccine development. This could be achieved by either expanding SCARDA's scope or creating a framework that works closely with SCARDA.
iv) Support and coordination	• Create a function that specializes in research coordination such as CRN in the UK. • Build expertise in clinical trial functions, such as statistical analysis, data management, study management, and ethics review at leadership group. • Engage AMED as a national funding agency and PMDA as a regulatory body to work with the leadership group closely in order to collaborate with academia and industry. • Provide sufficient resources to facilitate and sustain communication with all stakeholders.
(2) Promote sustained coordination and collaboration among stakeholders	
i) Merge academia and industry networks	• Further strengthen a system where AROs can support investigator initiated clinical trials. In addition to setting up appropriate environment, provide sufficient funding and development seeds strategically to academia in order to cultivate talent who can lead clinical trials. • Share available infectious disease seeds between industry and academia to promote collaboration and matching. • Involve the network of local governments and health centers in the clinical trial ecosystem. For example, determine roles of each hospital in a region so eligible patients can be appropriately transferred. Similarly, better understand challenges among various stakeholders, including leadership organization, local governments, and medical institutions in the inter-pandemic period, and take appropriate measures.
ii) Talent exchange and career path design	• Increase opportunities for exchange and improve the flow of talent across public, academia, industry, and clinical sectors. It would be especially beneficial for those from the public sector to gain experience in the private sector. • Design a clear career path for experts in clinical trials and clinical trialists in collaboration with Ministry of Education, Culture, Sports, Science, and Technology. • Ensure benefits, welfare and working environment so that high retention can be achieved for diverse talent within the ecosystem. One idea might be to establish an expert certification system such as CRP in the UK.[2] • Expand programs such as IDES training and FETP to contribute to the clinical trial ecosystem. Design the programs so that their experiences can be effectively utilized in a pandemic. • Send public officials to where clinical trials take place, such as Infectious Disease Designated Hospitals and Clinical Research Core Hospitals, not just during a pandemic but during the inter-pandemic period.
iii) Collective experience and expertise	• Allocate large enough research funds to academia that can be used in the inter-pandemic period. • Review KPIs of Clinical Research Core Hospitals and design incentives such that they conduct large scale clinical trials in a pandemic. • Establish a consortium made up of the stakeholders. (Specific actions described in "(3) Apply innovative clinical trial designs and create enabling research environment"). • Create opportunities to exchange ideas on the clinical trial network from other clinical areas (*e.g.*, cardiovascular, cancer[3], *etc.*).
iv) Seamless data sharing	• Reconstruct how to effectively use data owned by different sectors. Consider establishing a specific team for the data consolidation/sharing.

[1]*https://www.who.int/teams/blueprint/* [2]*https://www.ahcs.ac.uk/registration/psa-accredited-register/clinical-research-practitioners/* [3]*https://jcog.jp/en/* AMED: Agency for Medical Research and Development; AROs: Academic Research Organizations; ASEAN CDC: Association of Southeast Asian Nations Centers for Disease Control and Prevention; CRN: Clinical Research Network; CRP: Clinical Research Practitioner; FETP: Field Epidemiology Training Program; ICH-GCP: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice; ICMRA: International Coalition of Medicines Regulatory Authorities; IDES: Infectious Disease Emergency Specialist; KPIs: key performance indicators; MCMs: medical countermeasures. PMDA: Pharmaceuticals and Medical Devices Agency; PPIE: Patient and Public Involvement and Engagement; R&D: Research and Development; UK: United Kingdom; SCARDA: Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response; WHO: World Health Organization.

Table 1. Action items for better clinical trials ecosystem in Japan (continued)

Areas / Sub-categories	Action Items
v) Communication with patients and the public	• Develop guidelines for promotional activities related to clinical trials and PPIE, and proactively use mass media especially in a pandemic to gain understanding for clinical trials. • Promote the importance of PPIE by building PPIE programs into medical education and post-graduate medical trainings.
vi) Networks with stakeholders abroad	• Strategically send researchers and public officials overseas to enhance global research networks. • Develop strategies to support more researchers and experts leading and or participating in global research networks (including securing budget and support). It may be worthwhile to designate a few locations as strategic sites. • Encourage and support Japanese researchers to apply not only to domestic grants, such as AMED, but also overseas funding in partnership with overseas partners.
(3) Apply innovative clinical trial designs and create an enabling research environment	
i) Infrastructure of academia and medical institutions	• Identify hospitals and clinics that can participate in clinical trials through pragmatic approach and create a roadmap to build a broad network of clinical trials. • Reassess research function of specified/class 1/class 2 Infectious Disease Designated Hospitals as well as other hospitals.
ii) Data reliability and flexible regulatory affairs	• Make scenarios where data compiled through pragmatic approach is utilized for emergency approval process in a pandemic, and reach a consensus on its feasibility and the strategies for safety data among stakeholders including PMDA, leadership group, academia, and industry in the inter-pandemic period. • Participate in global discussions related to revisions of ICH-GCP and apply the global standards into redesigning clinical trial infrastructure that also enables pragmatic approach. Continue to work on standardization of regulatory and approval processes using the ICMRA framework. • Have PMDA participate in the research group (consortium) made up on stakeholders within the clinical trial ecosystem (as discussed "(2) Promote sustained coordination and collaboration among stakeholders") or have regular exchange opportunities with PMDA.
iii) Preparation of protocols and simulation	• Have research group (consortium) develop various scenarios in terms of location of outbreak, potential pathogens, and prepare protocols. Hold regular meetings and workshops to conduct simulations. • Have research group (consortium) collaborate with the leadership group as well as funders in order to conduct and review clinical trials based on developed protocols like "drills".

[1]*https://www.who.int/teams/blueprint/* [2]*https://www.ahcs.ac.uk/registration/psa-accredited-register/clinical-research-practitioners/* [3]*https://jcog.jp/en/* AMED: Agency for Medical Research and Development; AROs: Academic Research Organizations; ASEAN CDC: Association of Southeast Asian Nations Centers for Disease Control and Prevention; CRN: Clinical Research Network; CRP: Clinical Research Practitioner; FETP: Field Epidemiology Training Program; ICH-GCP: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice; ICMRA: International Coalition of Medicines Regulatory Authorities; IDES: Infectious Disease Emergency Specialist; KPIs: key performance indicators; MCMs: medical countermeasures. PMDA: Pharmaceuticals and Medical Devices Agency; PPIE: Patient and Public Involvement and Engagement; R&D: Research and Development; UK: United Kingdom; SCARDA: Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response; WHO: World Health Organization.

should be strengthened through collaborations with WHO and other countries' surveillance activities led by the leadership group (*9,10*). By using more accurate information obtained in a timely manner, the leadership group will be able to assess the risks of a potential pandemic. This can be shared with stakeholders, such as academia and private industries, to help them determine appropriate R&D priorities.

ii) Development of medical countermeasures portfolio: The leadership group should prepare a therapeutic R&D portfolio based on various pandemic scenarios through clinical trials for promising MCMs. Several stakeholders pointed out that one of the reasons why Japan fell behind in COVID-19 therapeutics and vaccines development was due to the lack of candidate MCMs portfolio at the time when the outbreak was detected (*11*).

iii) Funding strategy and its flexibility: Planning a budget requires a national health security perspective when it comes to R&D activities in infectious diseases. It also requires continued support as R&D activities typically span across multiple years. The our review revealed that more than half of the COVID-19 related grants in Japan did not last for a year, unlike the US and the UK (Figure 1). While such foresight and commitment are necessary to ensure fruitful outcomes from these R&D activities, due to the unpredictable nature of a pandemic, it is often challenging for academia or industry to make such investments proactively. To ensure an effective PPR, aggressive financial support should be made by the government into areas prioritized by the leadership group. Financial support should be both Push (during R&D phase) and Pull (*e.g.*, advanced purchase commitment by the government) to minimize the risks associated with R&D. Keeping the infectious disease R&D infrastructure "warm" even during

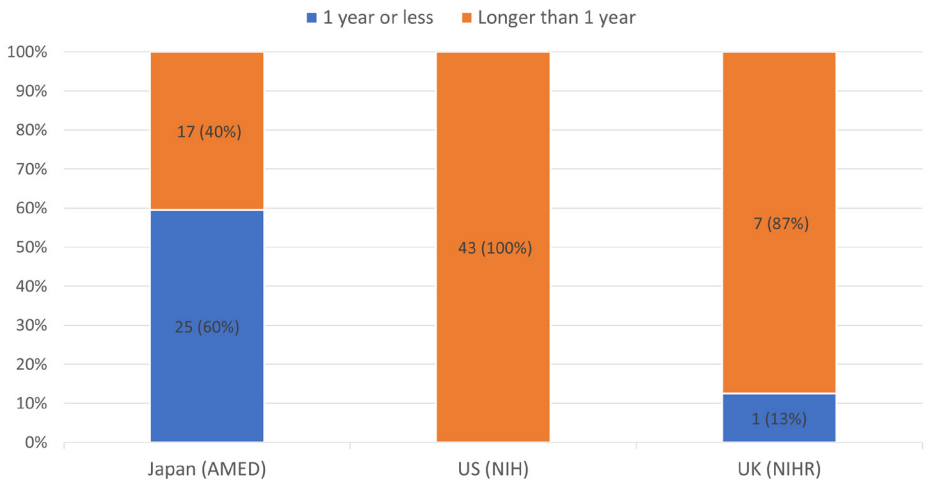

Figure 1. Number and proportion of the funding period of COVID-19 related grants in Japan, the US and the UK. AMED: Agency for Medical Research and Development; NIH: National Institutes of Health; NIHR: National Institute for Health and Care Research.

the inter-pandemic period will ensure that the R&D portfolio continues to evolve and talent development is uninterrupted.

iv) Support and coordination: The leadership group should coordinate and cultivate relationships with R&D stakeholders. Top-down direction can be effective during a pandemic; however, support for the R&D stakeholders during the inter-pandemic period can help clarify their needs. In the UK, clinical trials were prioritized by Urgent Public Health (UPH) Panel, convened from the members of Department of Health and Social Care (DHSC) and the National Institute for Health and Care Research (NIHR) early in the COVID-19 pandemic (*6*). In emergencies prior to the COVID-19 pandemic, Scientific Advisory Group for Emergencies (SAGE) in the Cabinet Office Briefing Rooms (COBR) was consulted for policy decision making (*12*). In addition, the US and the UK regulatory and funding agencies appeared to have provided more direct, tangible support to academia and industry compared to the Japanese agencies. This likely formed a closer relationship between the equivalent leadership groups and R&D stakeholders in the respective countries. It should also be made easy to provide feedback in both directions to enable continuous communication and collaboration. The leadership group is expected to unite all stakeholders, secure resources, and work with funding and regulatory agencies in order to quickly push promising MCMs to be made available and accessible in a pandemic.

Promote sustained coordination and collaboration among stakeholders

A stakeholder map of infectious diseases clinical trials in Japan was created across 3 topics: R&D, epidemiology/public health, and clinical care (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=97*). To establish a system that enables swift conduct of clinical trials during a pandemic, the stakeholders need regular coordination and collaboration in the inter-pandemic period to establish a working relationship. Below factors are essential to promote stakeholder collaboration:

i) Merge academia and industry networks: Contract Research Organizations (CROs), Site Management Organizations (SMOs), and other medical institutions work together in an industry sponsored clinical trial. Infectious disease R&D activities during a pandemic, however, are not always incentivizing for industries. On the other hand, investigator initiated clinical trials and Specified Clinical Trials (*13,14*) as well as international clinical trials may also be conducted during a pandemic, creating competition for often scarcely available resources. For a pragmatic approach that enables maximum benefit to the citizens, an efficient clinical trial ecosystem needs to be established across all the stakeholders to avoid duplicative work and foster collaborative efforts where appropriate. Academia and medical institutions often lack necessary resources to conduct clinical trials on their own. AROs, in the sense of clinical research support function, are often optimized to conduct industry sponsored clinical trials, leaving them with limited resources left for other clinical research such as investigator initiated clinical trials (*15*). In a pandemic, activities by industry and academia both become vital to the country. These networks should be merged so that roles and responsibilities can be shared and clarified while the leadership group lead these efforts overall (Figure 2).

ii) Talent exchange and career path design: The clinical trial ecosystem is rooted in personal connections. Continuous effort should be made to increase the touchpoints between those who are part of the network. For example, the 100DM provided opportunities for

stakeholders, including policy makers and experts, to meet and discuss the shared goal for Japan. In addition to providing opportunities for people to connect within the network, talent should move from one sector to another to be able to share "lived experiences". This can help activate multi-sectoral collaboration within the ecosystem (*16*). This can help avoid duplicative clinical trials through facilitation of a more collaborative research environment rather than a competitive one.

iii) Collective experience and expertise: While promoting fluid movement of talent, experience and expertise should be systematically accumulated in each organization. While the leadership group should possess the functions and talent in conducting clinical trials, the various stakeholders that are hands-on conducting clinical trials should have the expertise themselves as well. For example, academia should be able to conduct clinical trials on their own and not be dependent on CROs. It is especially important that Clinical Research Core Hospitals, as determined by Medical Care Act, can conduct infectious diseases clinical trials during a pandemic as core of research activities, in collaboration with other community hospitals and clinics (*17*).

iv) Seamless data sharing: Patient data should be more easily sharable among stakeholders for research purposes. This includes data standardization, electronic health records, consent, and ethics review. As an example, in the UK, Health Data Research UK (HDRUK) under Medical Research Council oversees data management. NHS electronic medical records summaries are shared nationally. Clinical trial data is not owned by a specific research organization but is held by NHS. Researchers routinely connect to clinical data collected on the NHS database, which enables analysis of outcome data and helps to avoid additional burden of data collection for research purposes. NHS's digital data is supported by Office for National Statistics (ONS), which is similar to Japan's Statistics Bureau. In Japan during the COVID-19 pandemic, where clinical care was provided (*e.g.*, Designated Medical Institution for Infectious Diseases) (*18*), where patient information was accumulated (*e.g.*, local public health centers), and where clinical trials were conducted (*e.g.*, Clinical Research Core Hospitals) were not functionally well connected, which became a hurdle for conducting clinical trials. There are limitations, such as where Health Center Real-time Information-sharing System on COVID-19 (HER-SYS) and other patient information/management support systems used by local governments cannot be used for research purposes even within the same facility.

v) Communication with patients and the public: A clinical trial ecosystem requires cooperation from the patients, the public, and frontline healthcare providers. Understanding of what a clinical trial entails among them becomes even more critical in a pandemic. As such, Patient and Public Involvement and Engagement (PPIE) activities are crucial in order to cultivate a cooperative culture. In the UK where PPIE activities are promoted, clinical trials are perceived as part of health care, and the people understand the importance of participating in clinical trials (*19*).

vi) Networks with stakeholders abroad: The clinical trial ecosystem does not conclude within Japan. In fact, infectious disease R&D should be global. Japanese researchers should actively participate in expert networks, international collaborative frameworks such as GloPID-R, and international platform trials. Increasingly, low and middle income countries in Asia and Africa are also establishing foundations for clinical trials, and many major industries and universities from Western countries are conducting clinical trials across continents.

Apply innovative clinical trial designs and create an

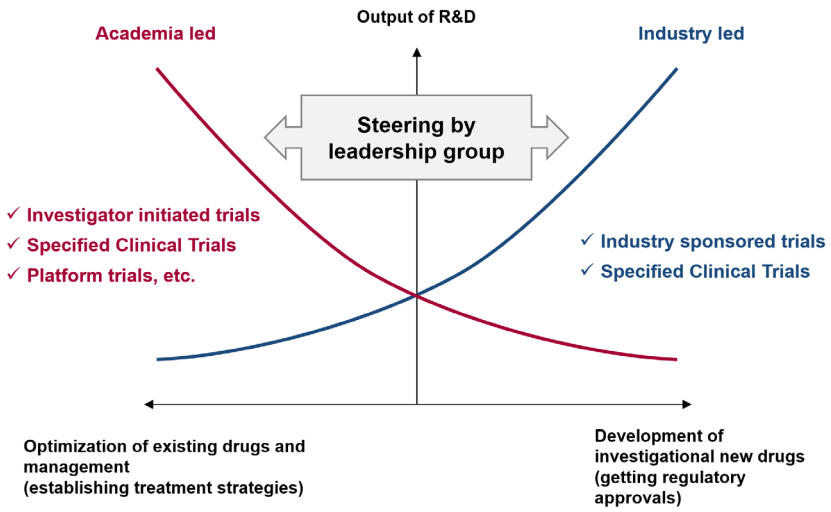

Figure 2. Roles and responsibilities of academia and industries on a clinical trial ecosystem.

enabling research environment

To conduct clinical trials promptly in a pandemic, innovative approaches in trial designs and conducts are essential. In general, evaluation of efficacy of candidate therapeutics is conducted through conventional, strictly managed randomized control trials (RCTs). In the COVID-19 pandemic, however, numerous small non-RCT clinical trials were conducted for the same interventions and was difficult to establish broadly effective evidence (*20*). In a pandemic, efforts need to be made not only to save patients but also to build evidence. Such evidence can be reflected onto the constantly updating therapeutic management strategy to immediately benefit patients (*21*).

One case example that succeeded in doing this was UK's RECOVERY trial (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=97*). RECOVERY trial showed effectiveness of dexamethasone only 3 months into the pandemic, contributing to saving an estimate of over 1 million deaths (*22*). RECOVERY took a pragmatic approach that enabled more subjects to enroll under less strict eligibility criteria compared to a conventional double-blind RCT (rigorous approach).

While the rigorous approach aims mainly to evaluate a specific intervention and obtain regulatory approval, the pragmatic approach aims to find the most beneficial treatment approach for patients (*i.e.* comparative effectiveness research) (Table 2). Investigational new drugs that have been approved through the rigorous approach may go through another clinical trial using the pragmatic approach to optimize its use (*23*). Research based on the pragmatic approach using real world data may also lead to new evidence (*24*).

On the other hand, the US conducted platform trials, such as Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV). This was a public private partnership scheme that kept some elements of the rigorous approach. The two countries had different approaches: the UK promoted public and academia led clinical trials using the pragmatic approach, and the US promoted clinical trials using the rigorous approach supported by public entities such as National Institutes of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA). The difference between the US and the UK in clinical trial design and conduct may be attributed to the differences in healthcare systems and the existing clinical trial infrastructures.

Based on these examples, Japan should consider promoting clinical trials with the pragmatic approach in addition to the more commonly practiced rigorous approach. Building evidence effectively in a pandemic by leveraging the advantages of both types of trials

Table 2. Characteristics of rigorous *vs.* pragmatic approach

Characteristics	Rigorous Approach	Pragmatic Approach
Purpose	• Obtain regulatory approval • Mainly approval for investigational new drugs, approval for additional indications	• Identify effective/optimal drugs among already approved drugs (comparative effectiveness) • Mainly drug repurposing
Method, Form of clinical trials*	• RCT (often, one to one comparison)	• Platform Trial, *etc.* (multiple arm comparisons)
Study population, Control group	• Concurrent control • Placebo, Standard of Care	• Concurrent or non-concurrent control • Standard of Care
External validity, Generalizability	• Low (strict eligibility criteria)	• High (simple eligibility criteria)
Obtaining consent	• Compliant with ICH-GCP (In Japan, Ministerial ordinance GCP compliant)	• While ICH-GCP is the standard, operate flexibly based on the circumstances
Trial conductor	• Industry sponsored trials: pharmaceutical companies, CRO • Investigator initiated trials: medical institutions, academia → if clinical trials with similar disease conditions and/or interventions, they can become "competitive"	• Medical institutions, academia → if participating in the same platform trial, becomes "collaborative"
Flexibility in protocol	• In principle, stick with the plan/protocol created prior to the trial initiation	• Can adapt flexibly based on accumulated data
Burden on participating sites	• High (need to secure resources for research conduct)	• Low
Cost per case	• High	• Low

*For the purpose of this table, clinical trials are categorized into two groups; however, not all clinical trials are strictly categorized into one or the other. CRO: Contract Research Organization; GCP: Good Clinical Practice; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; RCT: randomized control trial.

would require solving the following challenges:

i) Infrastructure of academia and medical institutions: As discussed in "*Merge academia and industry networks*", it is difficult to incentivize industries to evaluate the efficacy of existing drugs through pragmatic approach, and thus such clinical trials are often led by academia in other countries. However, in Japan, the academic institutions, such as Clinical Research Core Hospitals, who should be leading such pragmatic approach clinical trials have historically focused on using rigorous approach. Meanwhile, majority of hospitals and clinics that provide clinical care do not necessarily have the resources to conduct clinical trials. The current system is not set up for all stakeholders to be easily engaged in both types of clinical trials. Strengthening of academic institutions that lead clinical trials with rigorous approach and building a broad network of hospitals and clinics that can participate in clinical trials with pragmatic approach will both be important. Particularly, the latter broad research network needs to be promoted in the inter-pandemic period so that participation into clinical trials including platform trials can be possible in an actual pandemic (Figure 3).

ii) Data reliability and flexible regulatory affairs: Pragmatic approach employs a more relaxed eligibility criteria and minimizes additional data collection. This opens a potential risk that it may not have sufficient and accurate safety data. Whether or not evidence collected through pragmatic approach can meet requirements for drug approval process is a topic of debate (*25-27*). On the other hand, just conducting numerous small scale RCTs with rigorous approach may not lead to effective and efficient evidence generation overall. While there are some opposing aspects of the two approaches, how to improve data reliability through pragmatic approach will be a major challenge. This will also require regulatory affairs that can be flexible, reflecting societal needs.

iii) Preparation of protocols and simulation: While the total cost for a platform trial may be lower, the initial cost and time to prepare for a platform trial with pragmatic approach may be greater than multiple conventional RCTs (*28*). In addition, a large-scale trial would require buy-in from medical institutions, patients, and civil society. Time is of essence once a pandemic has begun; protocols should be established prior, and ideally, with ethics review (*29*). Operations and statistical analysis for a platform trial would also be more complex, so additional planning and simulating may be needed.

Conclusions

In this health policy research, the COVID-19 related R&D activities in various countries were reviewed, multiple interviews with experts and stakeholders were conducted, and the findings were confirmed and summarized at the culminating meeting for future policy implications. As a result, the research team proposed the following recommendations to the government and the leadership group for better PPR through MCMs: (1) Strengthen the leadership group's role in infectious disease clinical trials. The leadership group must take a proactive role in early detection of outbreak, prioritization of MCMs, portfolio development, strategic and flexible funding support, and robust support and coordination for all the stakeholders. (2) Promote sustained coordination and collaboration among stakeholders. Stakeholders in all three areas of R&D, epidemiology/public health, and clinical care should coordinate on a regular basis so that a clinical trial infrastructure can be built that enables rapid launch and conduct of clinical trials in a collaborative manner amid a pandemic. (3) Apply innovative clinical trial designs and create an enabling research environment. The leadership group should employ innovative clinical trial designs and create an enabling research environment (including funding and regulatory support) that helps to generate

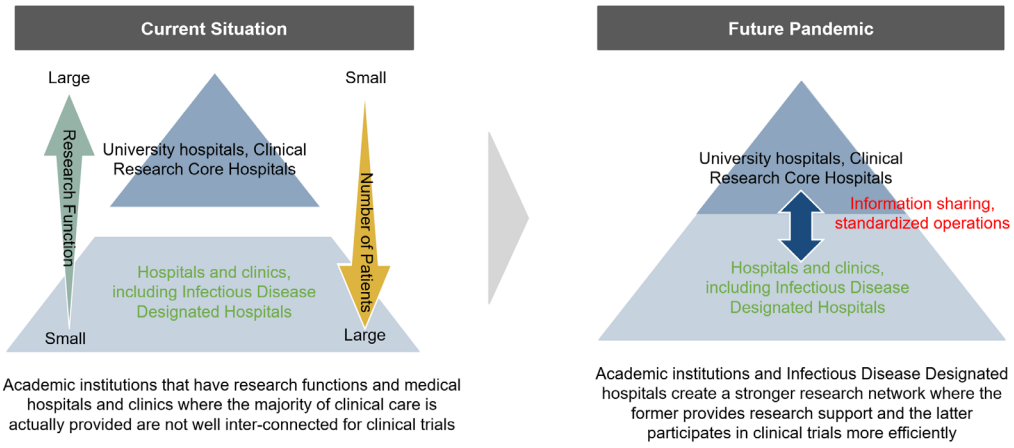

Figure 3. Current situation and future direction of clinical trial infrastructure.

valid evidence promptly, which is then directly reflected onto future clinical practice.

Though available resources are variable between Japan and other countries, the review and stakeholder meetings confirmed that numerous stakeholders in Japan were engaged in the COVID-19 pandemic response. For better future PPR, the discussions converged towards not only the "creation" of a new body or "innovative" solutions but also resource optimization and reallocation where needed. What's critically missing in Japan was the notion that the clinical trials infrastructure should be part of PPR at the policy level, and therefore, the available resources were not designed or well-connected to function efficiently and effectively under the clinical trial ecosystem.

A critical point is that a better clinical trial ecosystem must be promoted even in the inter-pandemic period, actively and constantly conducting clinical trials in infectious disease areas so that MCMs can be tested and brought in as quickly as possible in the event of a pandemic. To do so, in addition to the establishment of the leadership group that is already being discussed, an appropriate enabling environment must be cultivated such that stakeholders involved in infectious disease clinical trials can collaborate flexibly.

Another key point is to foster a "Made WITH Japan" mentality. Monitoring of outbreaks globally and networking with international frameworks as well as international collaborative clinical research groups is crucial. It is not necessary for R&D to be "Made in Japan" or "All Japan".

"Trials save lives (*30*)". Clinical trials as public health good must be further integrated into health care. The research team advocates the recommendations being implemented in a sustained manner in pursuit of a healthier society for Japan.

Acknowledgements

The views represented in this article are those of the authors alone, and they do not necessarily represent the views, decisions, or policies of the MHLW and institutions with which the authors are affiliated. We are grateful to all experts and organizations who participated in the culminating meeting and interview sessions (Appendix, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=97*). We also appreciate Yu Hasegawa and Tomoko Kunimitsu at Mitsubishi UFJ Research and Consulting Co., Ltd. for their assistance in all aspects of this research project. We would like to thank Mieko Kikuchi-Conbere for her valuable feedback and advice on the manuscript.

Funding: The project was funded by Ministry of Health, Labour and Welfare of Japan (21HA2018), and PRESTO, Japan Science and Technology Agency (JPMJPR23R7).

Conflict of Interest: KJ receives consulting fee from Allm Inc. The other authors have no conflicts of interest to disclose.

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Received October 28, 2024; Revised January 21, 2025; Accepted January 31, 2025.

Released online in J-STAGE as advance publication February 6, 2025.

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