Original article

A study on a strategic model to implement remote auditing*

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Abstract

Background: The concept of a risk-based approach [1~5] has already been introduced in preparation for the audit plan in pharmaceutical companies, and the quality assurance in the workplace and regulatory authorities has been implemented in a well-defined manner [6, 7].

Remote auditing is considered as a new method to optimize the risk-based approach, but its implementation has raised concerns from both the auditors and the auditees, which have become an obstacle to achieving remote auditing.

In this study, we identified concerns about remote auditing by questionnaire surveys and developed a strategic model to implement remote auditing to address such concerns.

Methods: First, we developed a questionnaire to confirm the current status of the GCP audit and to identify concerns regarding remote auditing. Second, feasibility and usefulness of remote auditing were assessed in a series of verification experiments using Information and Communication Technology (ICT) tools. Finally, the expected benefits of remote auditing were also investigated by distributing a questionnaire survey to audit sponsors.

Results: A total of 18 pharmaceutical companies, 47 clinical investigator sites, and 14 contract research organizations (CROs) participated in the survey. All investigator site audits (ISAs) were performed on-site.

An auditing model addressing the pre-identified concerns including data access, data security, and remote auditing methods was subjected to verification experiments. The model was found to provide the same level of audit as a conventional on-site audit in terms of the number of observations. The difficulties and measures to overcome in the implementation of future remote auditing were made clear, as well as the potential benefits.

Conclusions: Based on the results of the survey, a strategic model to implement remote auditing was developed to address existing concerns. The remote auditing model was found as feasible and useful as conventional on-site audits. Significant benefits were expected by introducing this model.

Key words

remote auditing, questionnaire survey, risk-based approach, Information and Communication Technology (ICT), data security, data privacy

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1. Introduction

Remote auditing is a method for efficient use of the resources to achieve reduction in costs and risks associated with travel for continuous quality assurance. In recent years, examples of remote auditing in GCP system audits have been introduced, but full-scale implementation was not reported in the world for investigator site audits (ISAs). The primary reason for this poor implementation could be to avoid uncertainty in data security associated with remote data verification.

However, in 2020 with the COVID-19 outbreak, academic institutions started to report their efforts [8~11] to accept remote monitoring at their clinical investigator sites. Yet systematic remote data verification, document review, facility tours, and interviews have not been performed with remote auditing.

2. Method

In this study, we first conducted a questionnaire survey asking the status of GCP audits in Japan and their concerns about remote auditing. Based on the survey results, we examined the feasibility and usefulness of a new remote auditing method to develop a model applicable to all audit procedures using an effective combination of ICT tools. Elements of data privacy and data security protection were carefully considered in our experiments when comparing remote auditing with conventional on-site audits to organize identified concerns.

2.1 Questionnaire surveys on the status of GCP audits

Questionnaire surveys were conducted in Japan with audit sponsors, clinical investigator sites, and contract research organizations (CROs) to view the current status of audit implementation and to identify concerns about remote auditing. Surveys included questions regarding the background and status of conducted GCP audits, audit implementation system, problems found during the general audit and specific questions about remote auditing. The first online survey was conducted from 30th May to 14th July 2020. The questionnaires were sent to 18 pharmaceutical companies (9 Japanese companies and 9 foreign capital companies) among the top 10 Japanese companies and foreign capital companies in terms of R & D expenditure in 2019 based on market research information, etc., as audit sponsors, 520 clinical investigator sites registered in the Massive Network for Clinical Trials (MNCT) as auditees, and 47 CROs registered in the Japan CRO Association also as auditees. The second online survey was sent to the same 18 companies from 16th October to 21st October 2020, focusing on their expected benefits of remote auditing and implementation status of PMDA inspection during the COVID-19 outbreak.

2.2 Verification experiments of remote auditing

Verification experiments of remote auditing were conducted at two clinical investigator sites with experience in clinical trials and with cooperation in this study as shown with the audit plans (Table 1). Prior to conducting the audit, risk assessments were performed at each of the clinical investigator sites with their clinical trial protocols according to the Clinical Research Audit Procedure Guide [12] and remotely audited if its overall risk was seen as low.

In this study, auditor with nine years of experience in more than 55 ISAs and 8 system audits examined four major operational components of GCP audits, namely document review, data review,

interview, and facility tour referring to the PMDA's remote inspection concept [13].

After developing a confidentiality agreement, an audit in four categories (document review, data review, interview, and facility tour) was carried out using the remote auditing method, followed by the conventional on-site auditing method. The number of specified observations and the thoughts of the auditees were compared between these two auditing methods.

The secured, multi-functional hands-free cloud system "T-4PO (e-Sense)" [14, 15], developed by Rozetta and Tobishima Corporation for the construction industry, was adopted for the document review, data review, and facility tour during the remote audit. This system was used with ITC devices, such as smart glasses, smartphones, and tablets. The usefulness of these devices was verified at each audit. In particular, the "VUZIX M400" smart glasses were selected with its excellent Wi-Fi sensitivity, fit, weight, voice recognition, and speaker function [16]. A conceptual diagram of the remote auditing system is as shown in Fig. 1.

In our remote auditing, the clinical investigator

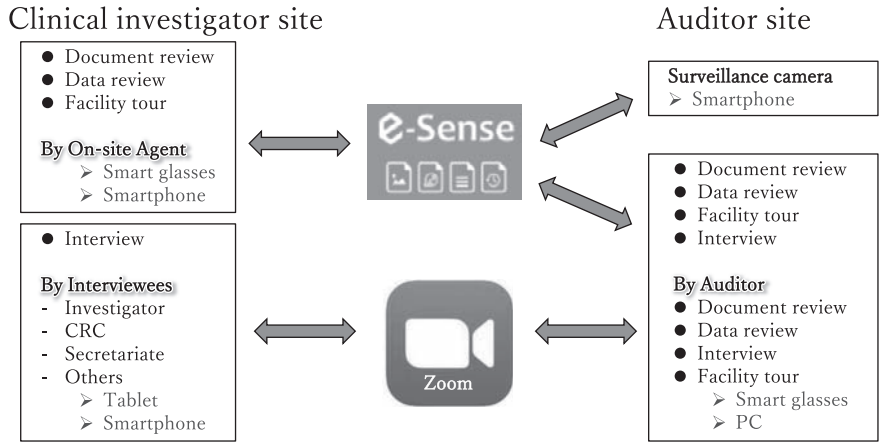
Table 1 Audit plans

Audit No. 01	Date of audit: 08 Sep 2020 and 10 Sep 2020
Title: A randomized controlled trial of best supportive care (BSC) versus photodynamic therapy with ME2906 and PNL6405PLC for patients with peripheral lung cancer	
Principal investigator: Jitsuo Usuda	Location: Nippon Medical School Hospital

Audit No. 02	Date of audit: 17 Sep 2020
Title: Hybrid virtual clinical research in Japanese patients with type 2 diabetes mellitus	
Principal investigator: Hirotaka Nagashima	Location: Tokyo Center Clinic

Scope:
- Principal Investigator oversight
- Informed consent process
- Source data verification
- IRB approvals and communications
- Investigational product handling
- Safety reporting
- Investigator Site File
- Monitoring and Facility

Fig. 1 Conceptual diagram of the remote auditing system



site and the auditor site were connected online, and the audit procedures were examined without visiting the sites. An on-site agent was assigned by the audit sponsor to show trial-related documents and data to the ICT tools to avoid disruption in the daily operations of trial staff at the site. The surveillance camera was used at the auditor site to monitor the auditor from the clinical investigator site and the viewpoint of information security management. For the staff interview during the remote audit, Zoom was used as a familiar web conferencing system at the clinical investigator site. To ensure security during the interviews, necessary measures were taken such as generating a passcode and locking the meeting room during use. The usefulness of three types of ICT devices (smart glasses, smartphone, and tablet) was examined at each audit to see if they met their specific tasks during the remote auditing.

3. Results

3.1 Response to the questionnaire surveys

Eighteen pharmaceutical companies (100%), 47 clinical investigator sites (19%), and 14 CROs (30%) responded to the survey.

3.1.1 Implementation status of GCP audits

All pharmaceutical companies had experience in performing the ISAs as audit sponsors. There was no significant difference in the number of audits between Japanese and foreign capital companies in any of the audit categories.

Implementation of GCP audits by the sponsors was examined in relation to the average number of annual audits, method of audits, number of auditors per audit, number of days per audit, and actual number of audits. The average number of audits per year is shown in Fig. 2. It ranged from 11 to 30, except for one Japanese company and two foreign capital companies. All ISAs were performed by the on-site audit method. In terms of the number of auditors, all Japanese companies had two to three employees, while four out of nine foreign capital companies (44%) had one employee. The number of days per audit was two to three in all Japanese and foreign capital companies.

3.1.2 Experience of CRO system audits

For CRO system audits by the sponsors, seven out of nine (78%) Japanese companies responded that they conducted an average of one to five audits

Fig. 2　Average number of annual ISAs by sponsor

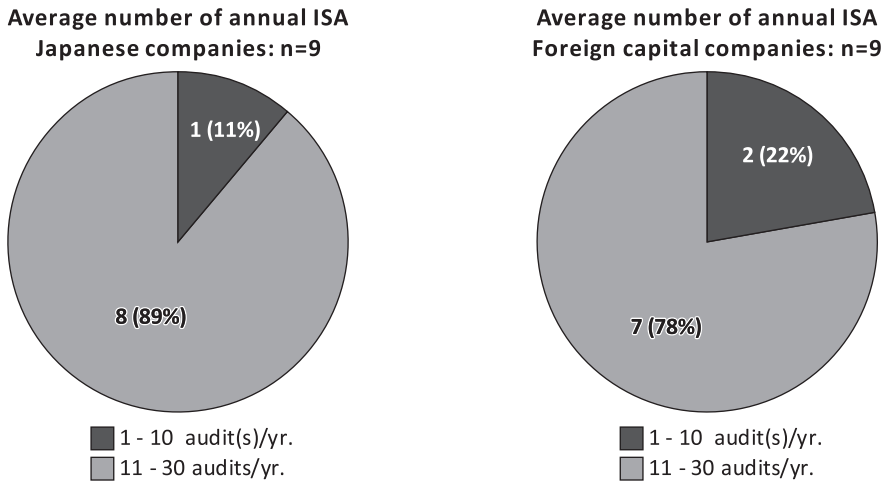
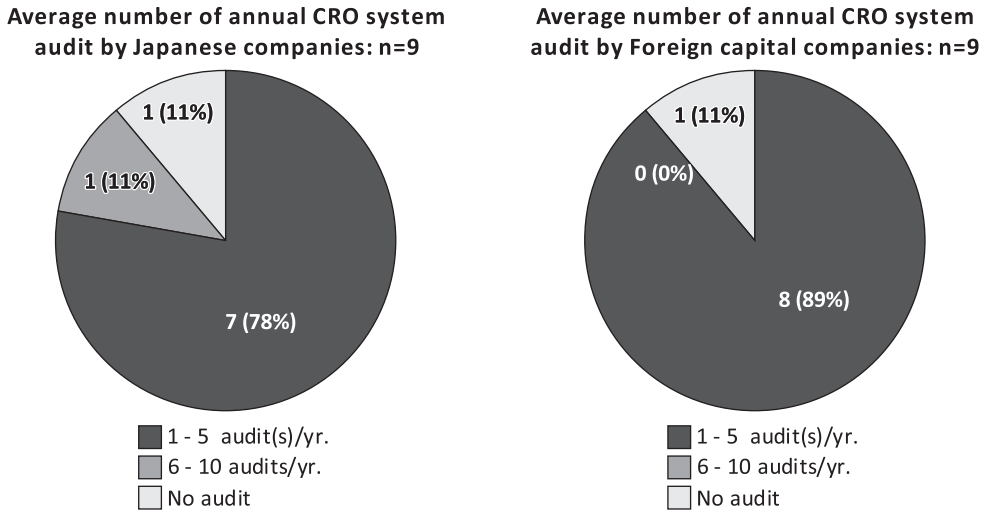


Fig. 3 Implementation status of CRO system audits by sponsors



per year. Eight out of nine (89%) foreign capital companies conducted the same volume of audits (Fig. 3). Regarding the method of auditing, only one Japanese company carried out audits by remote auditing, while the others conducted on-site audits.

Out of 14 CROs, more than half of them responded that their audits were conducted on-site, but 6 companies (43%) experienced a combination of remote and on-site audits.

3.1.3 Experience of ISAs

Out of 97 clinical investigator sites, 75 sites (77%) experienced ISAs, of which 70 received an average of one to five audits a year. All audits were conducted on-site. Out of the 75 clinical investigator sites, 69 (92%) were visited by two to three auditors. Fifty-three sites (71%) responded that each ISA lasted two to three days.

3.1.4 Concerns about remote auditing

All of the audit sponsors (100%), 42 out of 97 (43%) clinical investigator sites and 9 out of 15 (60%) CROs reported some concerns about remote auditing (Table 2). Their primary concerns were data access, data security, audit method, and increase in their workload.

Table 2 Concerns about remote auditing

Concerns	Audit sponsors n=18	Clinical Investigator sites n=97	CROs n=15
Any concerns	18 (100%)	42 (43%)	9 (60%)
Components of concerns （multiple responses permitted）			
Data access	12	11	7
Data security	6	13	1
Audit method	5	10	1
Increase of workload	4	8	-
Limit of remote auditing	-	6	2
General	2	-	-
Lack of industry consensus	-	1	-

3.2　Results of audit experiments

3.2.1　Risk assessment

The risk assessment was made prior to conducting Audit No. 01 and Audit No. 02. As the overall risk was evaluated as low in both audits, the remote audit model was applied to all audit procedures (document review, data review, interview, and facility tour).

3.2.2　Verification experiments in remote auditing

Audit No. 01 and Audit No. 02 were conducted using a complete remote auditing method in comparison with conventional on-site audit procedures (Fig. 4).

Three observations (filing of the essential documents, documentation of staff qualifications, and management of investigational product) were made in Audit No. 01, whereas four observations (version control of the informed consent, agreement with the external laboratory, source documentation, and data reporting in case report form) in Audit No. 02 were identified during the remote auditing. There were no additional observations at the subsequent on-site audit procedures in either Audit No. 01 or No. 02.

Several combinations of ICT tools (smart glasses, smartphone, tablet, PC) were adopted by the auditor, on-site agents, and auditees during the verification experiments. The preferred combination of ICT tools by their users was different depending on the auditing process. In the process of document review, data review, and facility tour, the "smart glasses + smart glasses" combination received the highest evaluation at both sites (Table 3).

The effectiveness of the measures in this remote auditing was evaluated at the clinical investigator sites. As a result, all concerns existing prior to the verification experiments were resolved after using the remote auditing.

3.3　Benefits of remote auditing

We mainly evaluated our remote auditing model in terms of its feasibility and quality in the verification experiments. The benefits expected upon the introduction of remote auditing were examined in cost, delivery (time), travel-related risk, and flexibility by additional questionnaire surveys with 13 audit sponsors. Expectation of cost saving by changing from conventional on-site auditing to remote auditing is shown in Fig. 5. In ISAs in Japan, all audit sponsors except for one (8%)

Fig. 4　Use of ICTs for data review

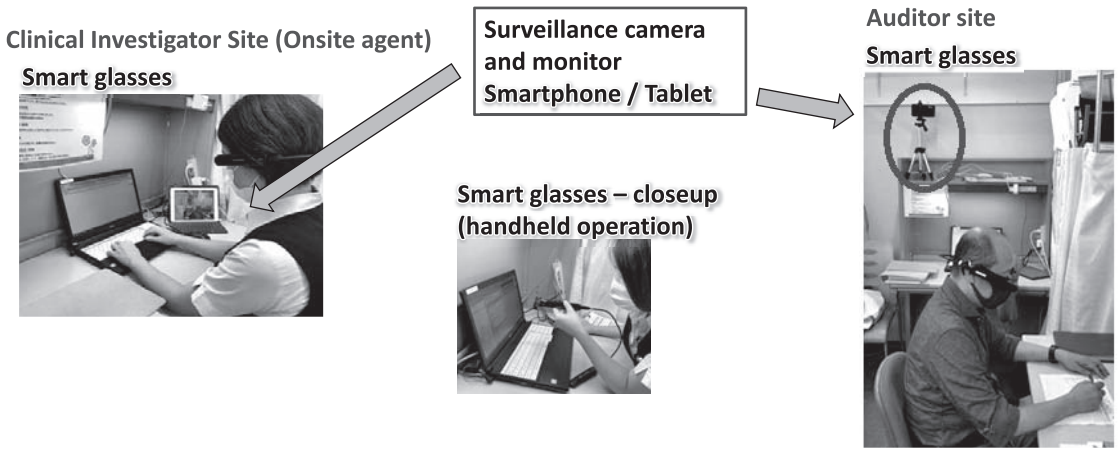


Table 3 Combination of devices for remote auditing

Conbination of devices for remote auditing (◎:Recommended, ○:Acceptable, △:Conditionally, ×:Not acceptable)

Procedure	Clinical Investigator site / Auditor site					Comment
	Smart glasses / Smart glasses	Smart glasses / PC	Smartphone / Smart glasses	Smartphone / PC	Tablet / PC	
Document review	◎ (◎/◎)	○ (◎/○)	○ (○/◎)	○ (○/○)	△ (△/○)	Depends
Data review	◎ (◎/◎)	△ (◎/△)	○ (○/◎)	△ (○/△)	△ (△/△)	Security first
Facility tour [1)]	◎ (◎/◎)	○ (◎/○)	△ (△/◎)	△ (△/○)	△ (△/○)	Convenience first
Interview [2)]	× (×/×)	× (×/◎)	× (○/×)	○ (○/◎)	◎ (◎/◎)	Convenience first

1) Pharmacy, laboratory, archiving room etc.

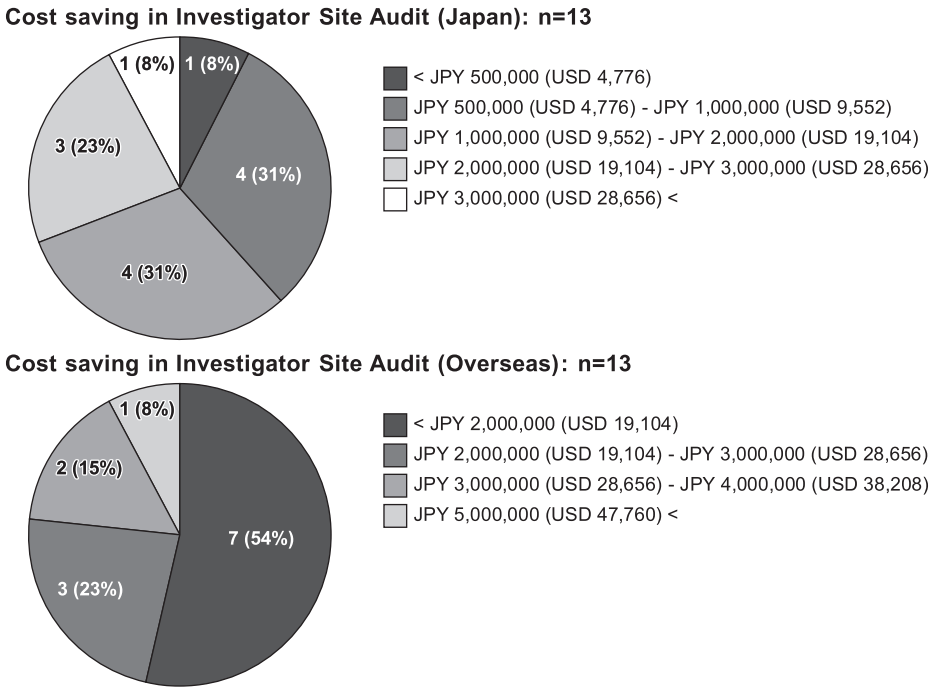
2) Principal investigator, clinical trial office, IRB office, CRC, IT manager etc.

answered that they could save at least 500,000 Japanese yen (USD 4,776) a year and eight of those expected to save more than one million Japanese yen (USD 9,552) a year. In overseas ISAs, 6 out of 13 audit sponsors expected savings of at least two million Japanese yen (USD 19,104) a year.

The expected travel time saved by changing from conventional on-site auditing to remote auditing was more than 15 days/year in five sponsors (38%), 7–15 days/year in four sponsors (31%), and less than 7 days/year in four sponsors (31%) in domestic ISAs. In overseas ISAs, almost 70% of audit sponsors responded that 7–15 days/year could be saved by remote auditing.

All audit sponsors responded that remote audits could also reduce travel-related risks such as infection, natural disasters, and traffic accidents associ-

Fig. 5 Expected cost savings by moving to remote auditing in ISAs



ated with their business trips. The most anticipated improvement in flexibility was “duration of audits” (11) followed by “place of audit” (10), “agenda of audit” (9), and “adjustment in audit schedule” (8).

4. Discussion

4.1 Implementation status of GCP audits

With regards to the audit sponsors, Japanese companies were likely to spend more resources (more auditors per audit) on ISAs than foreign capital companies. Their audit method was limited to on-site by visiting the clinical investigator sites in ISAs. It was also found that complete remote audits were not performed in CRO system audits that did not involve reviewing a subject’s personal data or medical information. If this remote audit model is accepted by audit sponsors and auditees, it will bring a change in quality assurance work. This will also lead to the realization of continuous quality assurance activities in the future.

4.2 Verification experiments of remote auditing

The main features of this remote auditing model are the utilization of the ICT tools and visualization of the security countermeasures. In this system, documents and data are reviewed and facility tours are conducted with direct viewing via ICT tools in cooperation with the on-site agent without intruding into the system of the clinical investigator site, such as viewing electronic medical records from outside. Therefore, neither the sponsor nor the clinical investigator sites need to introduce an expensive system for the purpose of data verification.

The hypothesis of no difference in the number of findings between remote and on-site auditing was proven in our study, and the feasibility and usefulness of our remote auditing model were also confirmed. We believe this success comes from the strategic approach of this model based on the identified concerns about remote audits in our study and appropriate measures were incorporated as a response.

After the completion of a series of experiments, new challenges were observed for the future implementation of this remote auditing model in the real world. The biggest challenge will be to assign appropriate on-site agents. In the case of clinical trials sponsored by a pharmaceutical company, it could be relatively easy to solve the problem by assigning the Clinical Research Associates (CRAs) to deal with that role along with their routine monitoring activity, but in the case of investigator-initiated clinical trials or clinical research, it should be considered individually.

However, the status of digitalizing clinical trial procedures at the clinical investigator sites may affect the feasibility of remote auditing. In recent years, the introduction of electronic document management systems for clinical trials has become popular, but according to our survey conducted in May 2020, only 27% of Institutional Review Boards (IRBs) have applied such a system [17]. As the local IRB is the most common type in Japan, it may suggest a limited level of digitalization and difficulty in applying remote auditing at the clinical investigator sites.

The electronic document management system is expected to reduce the number of documents to be reviewed at the clinical investigator sites, which will lead into more efficient audits regardless of the method of auditing (remote or on-site). We hope that more investigator sites will apply this remote auditing model to perform continuous quality assurance activities and build on best practices.

4.3 Expected benefit of remote auditing

While reducing travel-related risk by introducing a remote audit model was clearly predicted, the expectation of reducing cost and time was also significant. In addition to those benefits, this model can be applied not only to GCP audits but also to any GxP audits, clinical trial monitoring, and regulatory inspections. It is easy to use as this model does not require procurement of an expensive system or external access of the auditee's electronic systems.

4.4 PMDA inspection under the COVID-19 outbreak

In Japan, the inspection of clinical investigator sites has been suspended since March 2020, except for the investigation of sponsors [18~20]. Normally, PMDA inspection at the sponsor's office is conducted in approximately six hours. Due to the COVID-19 outbreak, however, current inspections are conducted remotely by using web conferencing systems, file sharing technology, document viewing using cameras, etc. Our survey confirmed that the total time required for PMDA inspection was significantly shorter than in the past. In our study, eight companies underwent PMDA inspection between April and October 2020, during which the common inspection time was one to three hours. This may be due to the changes in a series of inspection procedures associated with the remote practice, although there is a concern that the quality assurance by PMDA might be affected. Measures should be established to enable immediate resumption of inspections for clinical investigator sites and to ensure that the inspection system is appropriate. We hope our remote audit model can help.

5. Conclusion

A strategic model to implement remote auditing was developed to address the concerns identified in the questionnaire survey. In verification experiments, our remote auditing model was found to provide the same level of audit as a conventional on-site audit in terms of the number of observations. In addition, the security measures taken were reassuring. The difficulties and measures to overcome in the implementation of future remote auditing were made clear, as well as the potential benefits.

Conflict of Interest

The authors have no conflicts of interest directly relevant to the content of this article.

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