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Review Article

Conducting a three-country clinical trial during the COVID-19 pandemic: experience and future considerations

Sylvia Baedorf Kassis[1,2]*, Weidong Lu[3], Sarah A. White[1,2], Anita Giobbie-Hurder[4], Anna Tanasijevic[3], Hyun-Jung Jung[5], Xiping Zhang[6], Im Hee Shin[7], Sung Hwan Park[8], Young Ju Jeong[8], Chang Yao[6], Jennifer Ligibel[3], Barbara E. Bierer[1,2,9]

[1]Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard, Cambridge, MA, USA
[2]Division of Global Health Equity, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
[3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
[4]Division of Biostatistics, Department of Data Science, Dana-Farber Cancer Institute, Boston, MA, USA
[5]Department of Diagnostics, College of Korean Medicine, Daegu Haany University, Daegu, Republic of Korea
[6]Department of Oncology, Jiangsu Provincial Hospital of Traditional Chinese Medicine, Jiangsu Province, China
[7]Department of Medical Statistics & Informatics, [8]Department of Surgery, Daegu Catholic University, School of Medicine, Gyeongbuk, Republic of Korea
[9]Department of Medicine, Harvard Medical School, Boston, MA, USA

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***Correspondence:**
Sylvia Baedorf Kassis,
E-mail: sbaedorfkassis@bwh.harvard.edu

ABSTRACT

The global SARS-COV-2 pandemic has significantly impacted the delivery of clinical care as well as the conduct of international clinical trials. A coordinated, multinational acupuncture study, consisting of three parallel randomized studies with a planned pooled analysis of individual patient data, was initiated in 2019 with the goal of assessing whether acupuncture relieved hot flash symptoms in hormone receptor-positive breast cancer patients prescribed adjuvant endocrine therapy. Eligibility included persistent hot flashes on endocrine therapy. Participants were randomly assigned to receive either immediate or delayed acupuncture in equal proportions; the primary endpoint was assessed at week 10, after completion of the immediate acupuncture treatments and before the delayed treatment sessions began. The trial was conducted in China, South Korea and United States of America (USA) and was in the midst of enrollment and study procedures when the COVID-19 pandemic began. Despite numerous challenges, the study was nonetheless completed successfully. We deployed a process evaluation method to describe each site's experiences in conducting this multinational study during the pandemic. Using these observations, we offer measures for the planning and conduct of future studies, taking into account preparedness considerations in the event of exigent and demanding global circumstances.

Keywords: Clinical trial, COVID-19 pandemic, Acupuncture, Multinational study, Preparedness, Study completion

INTRODUCTION

Since the beginning of 2020, the COVID-19 pandemic has had a significant effect not only on the delivery of medical care but also on the conduct of clinical trials. Multinational, multi-site clinical research studies—often challenged by alignment and timely completion across countries—experienced further complexities due to COVID-19.[1] Regional differences in severity of illness, social distancing practices, and concerns about infectivity and transmission led to different responses and actions around the world. Nevertheless, many investigators and sponsors were able to adapt their planned clinical research activities to accommodate these differences across the globe, but not without some impact on the research itself.

In this paper, we describe a process evaluation that was carried out to capture the adaptations necessitated by the unanticipated exigent circumstance of the COVID-19 pandemic in the activities of a coordinated multinational trial conducted in China, South Korea, and the United States of America (USA). We discuss the learnings from this process evaluation and use the experience to provide considerations for the conduct of future studies.

BACKGROUND

The acupuncture hot flash study is a supportive care study that was planned in 2017-2018 and initiated in 2019.[2] The study consisted of three separate parallel randomized trials with a planned pooled analysis of individual patient data to assess the impact of acupuncture on hot flash-related symptoms in hormone receptor-positive breast cancer patients undergoing adjuvant endocrine therapy. Eligibility included diagnosis of stage 0-III breast cancer, treatment with adjuvant endocrine therapy for at least 4 weeks, and persistent experience of at least 2 hot flashes/day. Participants were randomized to receive a standardized acupuncture protocol immediately upon randomization (10 weeks of acupuncture twice per week; "immediate acupuncture") or after 10 weeks of a waitlist-control (10 weeks of acupuncture once per week; "delayed acupuncture"). Each site (China, n=40; South Korea, n=40; USA, n=80) independently randomized participants based on the number of hot flashes per day at the time of enrollment (2-6 or ≥7/day). Members of the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) were involved as remote, external advisors to the study teams.

As for any multinational study, significant effort was devoted to planning and preparing across the three international sites to ensure alignment of procedures, data acquisition, understanding and accommodation of local differences, and a common approach to appropriate regulatory documentation.[3]

However, modifications in study conduct and data collection were required after the emergence of the COVID-19 pandemic. As a result, we sought to understand the impact of the pandemic on clinical trial processes, including necessary local adaptations and modifications, and potential influence on overall data collection and analysis.

PROCESS EVALUATION

After the study was designed, the protocol prepared and approved by each site, and the trial initiated, the study team and members of the MRCT Center maintained regular communication through participation in virtual Investigator's Meetings that were held monthly. Starting in early 2020 the experience of the pandemic was routinely discussed, and its impact and influence on the research were reviewed. At the end of the study, in 2022, each site participated in an in-depth virtual interview about their experience conducting the trial during the COVID-19 pandemic.

Each interview included a site-independent facilitator and at least two site representatives: the senior principal investigator and a staff person who was responsible for the study operations and procedures. Site representatives were sent the following questions in advance: did the pandemic generally affect your clinical work in the hospital? Did you have to make any modifications to the study activities or the timing of the (hot flash) study at your site due to the pandemic? Based on your experience in conducting studies during the pandemic, will you make changes to future study protocols?

During the interview process, the responses to the questions were documented. After the interview, the notes were summarized and returned to the site representatives to review for accuracy. The responses are described below and summarized in Table 1.

Table 1: Site high level responses to process evaluation questions.

Question	Summary of discussion points
Did the pandemic generally affect your clinical work in the hospital?	All three sites described their clinical operations being interrupted for some period of time at the onset of the pandemic. In China and South Korea, medical care includes acupuncture and all clinical activities resumed at the same time. In contrast, the USA noted that clinical acupuncture was resumed later than other clinical care activities.
Did you have to make any modifications to the study activities or the timing of the study at your site due to the pandemic?	All three sites reported having to pause clinical research study activities and participant enrollment for some period of time, although the duration and restrictions varied across sites. The study statistician was consulted to identify an approach to addressing study interruption across the sites.
Based on your experience in conducting studies during the pandemic, will you make changes to future study protocols?	All three sites reported changes and adaptations that will be considered for future study protocols. For example, limiting the number of in person study visits, partnering with community acupuncture clinics, use of electronic consent and data capture, or including mental health measures.

SUMMARY OF EXPERIENCES AND THEMES

Question 1

In response to the first question, regarding the effect of the pandemic on clinical care more generally, all sites reported at least some period of shutdown of acupuncture services and changes in routine follow up visits that impacted their clinical care pathways. The China team reported that the hospital was closed from January to April 2020, but after that four-month hiatus, clinical activities returned to normal, and they were able to continue their clinical and research activities largely without further delay. In South Korea, acupuncture services were suspended between January and March 2020 and unless patients had serious health needs, clinical visits were reduced to minimize contact with others.

In the USA, clinical care of patients, including the delivery of chemotherapy and endocrine therapy continued throughout the pandemic, but acupuncture services were suspended between March and September 2020. Additionally, most routine follow up visits for breast cancer were changed to telemedicine, making it more challenging to recruit additional study participants.

Question 2

The second question asked whether modifications to the study were needed.

All three sites reported having to pause study activities and participant enrollment for some period of time.

In China, the week-10 assessment was delayed for four patients, and the week-20 assessments were performed 10 weeks later in these four. There was one additional patient delayed for the 20-week assessment. There was no attrition from China.

In South Korea, none of the 10-week measurements were delayed, and only one 20-week measurement was delayed. Three patients withdrew during the first 10 weeks and two additional participants withdrew during weeks 10-20.

In the USA, twelve participants experienced interruptions to their acupuncture treatments due to COVID-related shutdowns. Additionally, there were four patients who were lost to follow-up during the early period of COVID shutdown and two who withdrew consent.

Together with the statistician, the study team decided on how best to address interrupted study activities. The following approach was taken to address interrupted participation in the USA; the same was not requested of China or South Korea.

Participants receiving immediate acupuncture who had reached protocol-defined compliant treatment threshold of 75% (15/20 sessions) did not restart acupuncture treatments after the COVID restrictions were lifted; their acupuncture treatments ended in March 2020 and the US study team collected as much data as possible electronically at the subsequent defined timepoints (week 10, week 15, and week 20). Participants receiving immediate acupuncture who did not reach the 75% treatment threshold were paused in their acupuncture sessions; data were collected from the closest upcoming timepoint. The study team had hoped that these patients would resume quickly, but prolongation of the shutdown prompted the decision to restart patients who were interested. Once acupuncture was permitted to resume, available and willing patients in this group (n= 6) were reassessed for eligibility, redid baseline measures, and restarted their treatments from time zero; data captured pre-COVID were excluded from analyses. This approach maintained the time interval between immediate and delayed treatment, permitting the comparison between the two.

Participants receiving delayed acupuncture who had completed 7/10 sessions were considered as protocol-compliant and did not restart their treatments when COVID restrictions were lifted. The study team collected as many week-20 measurements as possible virtually, via email. Participants receiving delayed acupuncture who had started treatments but had not yet reached the treatment threshold of 7/10 were paused and data were collected from the closest upcoming timepoint. Again, this was done because it was unclear when acupuncture could start again. Once acupuncture treatment was allowed to resume, some patients who were interested in restarting (n=6) were reassessed for eligibility, redid their week 10 measures, received acupuncture treatments, and completed the subsequent week 15 and week 20 measures. Since the primary outcome was change in mean weekly hot flash score from baseline to week 10, primary outcomes were evaluated based on pre-COVID baseline-week 10 data, as the delayed group served as a waitlist-control during this period of time. Secondary and tertiary outcomes were assessed using the data collected from week 10 to week 20, when participants were restarted post/during COVID restrictions. Participants receiving delayed acupuncture who were waiting to start acupuncture (e.g., week 1-10) contributed data electronically through week 10 during the shutdown. As noted above, change in hot flash score from baseline to week 10 was the primary outcome, so data from patients who reached week 10 during the shutdown were included in the primary analysis. Once acupuncture treatments could resume, these patients repeated week 10 measures, received acupuncture treatments, and then completed week 20 measures. These post/during COVID data were used for the secondary outcomes of the study.

For all participants, all baseline and week 10 blood draws (USA only) were suspended from March to September

2020 of the COVID-19 pandemic. The blood draws were intended to inform secondary outcomes only. Both the study team and participants being seen in private clinics wanted to minimize unnecessary hospital or clinical visits. The USA team resumed blood draws in September 2020 for participants who were amenable to coming to clinic.

The USA team explained that once recruitment was resumed, study staff commenced reviewing patient visit schedules and using reporting tools in the medical record system to identify potentially eligible patients. This allowed study staff to contact potential participants to discuss the study via telehealth prior to an in-person visit; potential participants were therefore aware of the study and could consider research participation in advance.

One additional reflection of the South Korea team was that once activities resumed, some providers reported feeling uncomfortable with head and face acupoints that required them to be close to the participants' faces, despite study participants and staff wearing masks. However, the investigators and participants executed the protocol as originally proposed and continued the visits as planned.

All three sites reported that research shutdowns were hospital-wide actions based on institutional decision making, not study-specific. As a result, no submission to the research ethics committee was required to notify each institution's ethics board that the study was being put on hold due to the pandemic, nor did the ethics board require notification when study activities resumed. Overall, the pandemic resulted in a delay in enrollment at all sites. Instead of all completing enrollment in 2020, enrollment completed in June 2020, May 2021, and July 2021 for China, South Korea, and USA, respectively.

Question 3

Finally, in response to the third question, sites reflected on ways future studies might be adapted based on the experience of conducting the hot flash study during a pandemic.

The South Korea team suggested that study visits be reduced whenever possible to limit the frequency of travel to the study site. They noted that they will consider developing a method that allows outcome measurements without a physical visit (e.g., using electronic platforms such as a mobile app). They also suggested measuring changes in psychological symptoms reasoning that external circumstances may affect mental health, which could also impact the study outcomes.

The China team reported their intention to build relationships with smaller acupuncture clinics in geographies closer to participants as a near-future priority. This is a way to make acupuncture more accessible, decreasing the amount of participant travel and ensuring the continuity and integrity of the procedure.

Similarly, the USA team planned to continue their newly adopted practice of utilizing the private acupuncture clinics of study acupuncturists that are in locations that are more convenient for participants. They intend to implement electronic consents more frequently, collect study data electronically via different modalities and data capture tools, and maintain paper data collection only for participants who may not be technologically experienced.

Finally, while not in response to a specific question, it was noted that even though in the USA participants received acupuncture in private rooms, the hospital acupuncture clinic remained closed for an extended period of time due to the pandemic, largely to protect immunocompromised patients coming in for cancer treatments. In contrast, acupuncture resumed earlier in China and South Korea, even though acupuncture is administered in shared rooms with just a curtain as a barrier between patients or communal spaces where there are no curtains between patients, and COVID transmission could theoretically be more of a concern. Possible explanations for this difference could include the fact that the USA site (Boston, Massachusetts) was the epicenter of the USA pandemic at that point in time, the USA site was exclusively an oncology hospital, different prioritization of ancillary services across the sites, or other factors.

DISCUSSION

In the case of this parallel, coordinated multinational clinical trial conducted during a global pandemic, all three country sites successfully completed the study. This was a significant accomplishment given that COVID-19 hampered completion of clinical trials around the world.[4] Based on concurrent observations and later project evaluation methods, here we reflect on factors that may have contributed to this success. We also extrapolate from the interview results to present recommendations for approaches that may support the conduct of multi-national trials more generally.

Maximize collaborative preparation

The study sites attribute some of this study's successful completion to both substantial preparatory work in advance of trial initiation and regular, in-depth communication about emerging issues across the sites once the study was underway. Before the study began, significant effort was devoted to understanding local differences, preparing the sites through organized PI training and site initiation meetings, and harmonizing data collection tools and resources.[4] During the study, there were regular teleconferences to review study progress. As the COVID-19 experience unfolded, with its differences in timing and severity across the three locations, the study teams were already familiar with one

another and their practices. Investigators were comfortable disclosing disruptions and problems and were helpful to one another in addressing challenges as they arose. A strong collaborative foundation can be established early in study planning and execution through regular meetings and consultations.

Consider and plan for potential external issues that may impact the study and its data

The study was designed to test the impact of acupuncture on the frequency and severity of hot flashes in patients with hormone receptor-positive breast cancer undergoing adjuvant hormonal therapy. After being on hormone therapy for at least 4 weeks (and typically much longer), participants were randomly assigned to receive either immediate or delayed acupuncture in equal proportions; the primary endpoint was assessed at week 10, after completion of the immediate acupuncture treatments and before the delayed treatment sessions began. The acupuncture schedule was, therefore, foundational to the study design. The interruptions necessitated by the pandemic prompted the study teams to consider issues of acupuncture delay, interruption, and missingness and whether the impact could be mitigated. As noted above, the study team discussed what they were able to collect during shutdown periods, keeping in mind percent completion of the acupuncture treatment and the study endpoints, and a thoughtful rubric was established. The study question and study design permitted adjustment ("restarting" patients) since the study design was an intervention study for people with hot flashes on persistent hormone therapy and not dependent upon timing of hormone initiation. Future studies can identify important thresholds and processes to address critical interruptions either in advance or in real time should they occur.

Consider flexible adaptations to study procedures

This acupuncture study relied on in-person administration of the study intervention; remote visits via tele- or video conferencing were not possible. Nevertheless, social distancing, required by the pandemic, led investigators to identify local geographic alternatives to the provision of hospital-based acupuncture interventions as a potential adaptation. Local sites, capable of administering the acupuncture, were preferable to requiring participants to travel, often in public transportation, when the equivalent could be delivered more conveniently.

For future studies, flexibility and adaptations in research interventions (e.g., site of performance, timing of administration, remote data collection after the procedures) will be further considered. Study teams should develop proactive plans in the event of study hold, or discontinuation to determine available strategies to minimize study disruption.

The implementation of decentralized clinical trial activities (e.g., electronic consent and study records, telemedicine to replace in-person study visits, local laboratories and imaging facilities, direct shipment of study products to participants' homes, and the use of electronic survey collection tools and remote technologies like mobile trackers) has been one beneficial consequence of the pandemic.[5] Where possible, researchers can also aim to reduce unnecessary travel by participants to the research center, which is associated with time, inconvenience, and costs for clinical trial volunteers.[6] Thoughtful adoption of remote methods of conduct facilitates study participation and supports clinical trial efficiency.

Consider the effect of external circumstances on study participants

The study teams noted the necessity to consider participant psychological stress in response to the pandemic, and appreciated that their ongoing relationship with participants enabled them to intervene.[7] It may be important to gather information on mental health and other factors that could affect the study outcomes, both to determine how to mitigate those factors and to account for them in the analysis of the results. For example, external stressors might impact a study that uses sleep quality as an outcome measure of acupuncture efficacy.

Limitations

This process evaluation was limited by the retrospective and virtual nature of the interviews, mitigated but not eliminated by concurrent notes retained during monthly discussions. Further, these findings and recommendations represent the experience of a single multi-national study, with a finite number of sites, involving acupuncture as the intervention and may not be applicable to other studies.

CONCLUSION

A multinational acupuncture study was completed during the COVID-19 pandemic, illuminating the need to plan for unexpected—although increasingly frequent exigent circumstances. In planning an interventional research study, researchers should consider the impact of external circumstances on their research and plan accordingly. Here, we share perspectives and recommendations to that end. Any adaptation will, however, be highly dependent on the specifics of the study. This study involved administration of acupuncture, an intervention that, by definition, cannot be administered remotely. Other approaches minimized participant and study staff burden and exposure. The established relationships, communication, and commitment to completion helped to minimize disruption. Many of the themes and recommendations elucidated can be applied to other, similarly destabilizing situations.

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REFERENCES

1. AlNaamani K, AlSinani S, Barkun AN. Medical research during the COVID-19 pandemic. World J Clin Cases. 2020;8(15):3156-63.
2. Lu W, Giobbie-Hurder A, Tanasijevic A, Baedorf Kassis S, Park SH, Jeong YJ, et al. Acupuncture for hot flashes in hormone receptor-positive breast cancer, a coordinated multinational study: Rationale and design of the study protocol. Contemp Clin Trials. 2022;121:106885.
3. Baedorf Kassis S, Lu W, White SA, Shin IH, Park SH, Jeong YJ, et al. Developing and implementing a self-monitoring toolkit for a coordinated multinational randomized acupuncture trial. BMC Complement Med Ther. 2022;22(1):161.
4. Hawila N, Berg A. Assessing the impact of COVID-19 on registered interventional clinical trials. Clin Transl Sci. 2021;14(3):1147-54.
5. Leyens L, Simkins T, Horst NK. The COVID-19 pandemic as a catalyst for innovation: a regulatory framework to assess fit-for-purpose innovative approaches in clinical research. Trials. 2022;23(1):833.
6. McDermott MM, Newman AB. Remote Research and Clinical Trial Integrity During and After the Coronavirus Pandemic. JAMA. 2021;325(19):1935-6.
7. Padala PR, Jendro AM, Padala KP. Conducting Clinical Research During the COVID-19 Pandemic: Investigator and Participant Perspectives. JMIR Public Health Surveill 2020;6(2):e18887.

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