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EXPERT OPINION

Best Practices from the American Society of Pain and Neuroscience (ASPN) for Clinical Research During a Pandemic or Emergency

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Abstract: The COVID-19 pandemic caught many areas of medicine in a state of unpreparedness for conducting research and completing ongoing projects during a global crisis, including the field of pain medicine. Waves of infection led to a disjointed ability to provide care and conduct clinical research. The American Society of Pain and Neuroscience (ASPN) Research Group has created guidance for pragmatic and ethical considerations for research during future emergency or disaster situations. This analysis uses governmental guidance, scientific best practices, and expert opinion to address procedure-based or device-based clinical trials during such times. Current literature offers limited recommendations on this important issue, and the findings of this group fill a void for protocols to improve patient safety and efficacy, especially as we anticipate the impact of future disasters and spreading global infectious diseases. We recommend local adaptations to best practices and innovations to enable continued research while respecting the stressors to the research subjects, investigator teams, health-care systems, and to local infrastructure.

Keywords: research, pain, emergency, pandemic, protocols

Introduction

Clinical pain research is fundamental to building mainstream access to innovative treatments and technologies. This work ranges from early first-in-human feasibility investigation to large multi-center prospective randomized trials. In normal times clinical trial participation can be perceived as burdensome, disruptive and inconvenient.[1] Clinical research studies are often an altruistic pursuit, operating in large part due to willing volunteer patient subjects and clinician investigators. A study of civic engagement identified that two-thirds of volunteers decreased or stopped contributing time during the initial phase of the COVID-19 pandemic.[2] Participation in clinical trials, already vulnerable to attrition, witnessed considerable obstacles to subject retention and protocol continuation, and rapid and creative adaptation was necessary to preserve clinical research activities.[3] These adaptations have continued with subsequent surges of COVID strains and can be applied in new health emergencies such as the other viral or bacterial illnesses, natural disasters, war, or economic distress in a community or region.

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Table 1 Recommendations for Clinical Research in a Pandemic or Disaster

Recommendation	Example
Stay consistent with standard research protocols	Maintain IRB and SPIRIT guidelines.
PI and team should assess impact of disaster situation	Is it feasible to execute the original research protocol? What protocol adjustments need to be made? Example: Virtual follow up visits.
Seek guidance from regulatory and political bodies	Acceptability of telemedicine during the COVID19 pandemic.
Crisis protocols should be developed and enacted when needed	Projects may need to be suspended or eliminated via a prioritization system. Determine how to best restart the protocol and if the study can continue despite the interruption.
Ethical principles should be reviewed during extenuating events	Are patients still able to give consent without undue influence due to the disaster?
Creative adaptation of operations	Virtual clinics vs In Person
Critical evaluation of potential bias	Could changes introduced in the recruitment process lead to bias? Virtual or telemedicine options may introduce bias into the recruitment process as it limits to those with internet access.
Review any ethical influences	Consider changes to patient autonomy and ability to provide informed consent.
Assess ability to complete the research	Does the trial need to be halted, or can it be continued with adaptations to the disaster circumstances?

Research regulations, the code of operating trials and ethical principles that govern how research should be conducted, have developed into a standardized international guidance for developing and conducting research ethically and effectively. Strategies for executing research while adhering to recognized regulations during extreme circumstances—for example, in the aftermath of a natural disaster or during a health emergency—are not well defined. The arrival in 2020 of a pandemic of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2; COVID-19) provided an opportunity to take stock of the challenges brought to clinical research in pain medicine and to develop further principles to apply when circumstances such as natural disasters, disease, or other local, regional, or even global disruptions may impact research (Table 1).

Research Protocols in Times of Non-Emergency

Prior to discussing adaptations, we will review the main structural elements that promote successful and ethical clinical research in pain medicine. Well-designed studies are developed through a systematic approach from questions to outcomes and drive evidence-based medicine.[4] A well-written research protocol can expedite approval times for studies by assisting the investigators in avoiding pitfalls in study design and reducing flaws in data collection and/or analysis. The protocol provides a high-level view of the need for the study, the way the study will be carried out, who will be involved, and the goals of the study. A typical format for a research protocol includes the project summary, rationale, goals and objectives, study design, methodology, safety considerations, statistical analysis, quality assurance, expected outcomes, and ethical considerations (Table 2).[5–8] The 2013 statement from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) group established a 33-item checklist that provides insight for core items that should be included in high-quality research protocols.[7] The full research protocol must be approved by an institutional review board (IRB) and/or research ethics committee (EC).[9] Requirements may vary significantly across institutions and even within the same institution depending on the breadth of the protocol.

Protocol Development, IRBs, Enrollment, Protocols, and Follow-Up Windows

Research protocols are one type of core documents reviewed by the IRB and/or EC prior to initiation of the research study. As mentioned above, a high-quality research protocol is a comprehensive overview of the project design and should contain core elements as outlined in the SPIRIT 2013 checklist.[7]

Table 2 Elements of a Typical Research Protocol

Protocol Element	Description	Vulnerability
Project summary	• Gives a reader a succinct overview of the project and touches upon the core points of the protocol. • The rationale for the project identifies the need for the research and highlights the reason why the information needs to be obtained and the importance it may have for the medical field. • The goals and objectives clearly state the intended endpoints prior to any research being done.	Relevance of the project in the face of pressing matters or safety or hazard
Study rationale	• The design of the study is central to the quality of the data collected. • Should inform the reader as to the study participants, the type of study, criteria for inclusion or exclusion, and the timeline. • The following are examples of types of study design: descriptive research, observational research, intervention studies, and registries. • The study type includes if the study is blinded or not, or if this is an observational study. • The discontinuation criteria are also listed in this portion of the protocol.	The timeline may be prolonged, and this could affect primary endpoints Interventions may be delayed and/or cancelled
Methodology	• Describes the study setting, eligibility criteria, interventions, outcomes, participant timeline, sample size, recruitment (assignment of intervention, allocation sequence generation, allocation concealment mechanism, and implementation), blinding, data collection, and monitoring of harms. • For studies evaluating an intervention, the description of the drug or medical device is provided in this section.	Missing data points may limit the intention to treat feasibility if the study is interrupted
Safety considerations	• Discussion of protecting the safety, rights, and privacy of research. • The investigators must communicate the safety criteria, the planned monitoring of the study, and how any unanticipated outcomes will be managed.	Participant safety compromised by emergency situation Investigator team safety compromised by emergency safety Components of protocol cannot be completed due to emergency conditions
Statistical analysis	• Details the plan for analyzing the data points that are accumulated during the research period. • Examples of details in this section include the total number of participants, the methods of statistical analysis to be utilized, the power of the study, and the selection of study participants.	New statistical analysis and data handling required due to missing data points
Quality assurance	• The plans in place to make sure the protocol is followed as written. • Adverse events need to be monitored by qualified individuals, and a plan must be in place to appropriately respond to such events. • In addition to monitoring adverse events, quality assurance also involves monitoring of any non-adherence to the written protocol.	Increased protocol deviations due to adaptations of the research protocol venues or timing of visits Increased adverse events related to contracting viral pandemic infection or other emergency-related health consequences

(*Continued*)

Table 2 (Continued).

Protocol Element	Description	Vulnerability
Expected outcomes	• How the study will contribute to advancement of knowledge. • How the results will be utilized. • How results might affect health care, health systems, or health policies.	If health systems are overwhelmed, results of the study may not be appreciated or applied If the design is significantly altered, the data collected may not be of high quality and the results could be skewed
Ethical considerations	• Steps involved in maintaining patient confidentiality and safety. • Description of the usefulness of the information collected. • Can also include the process for obtaining informed consent, declaration of any competing interests, and who will have access to the collected data points. • It is also under this section that the importance of addressing gender issues arises.	Ability to provide informed consent may be restricted during an emergency situation Limited patient autonomy during times of stress and need Inequitable access to research based on availability of telemedicine or other resources that are implemented as adaptations to the emergency situation

IRB: The IRB is an FDA-regulated, formal group of individuals assigned to monitor medical research involving human subjects.[10] The IRB must review risks and benefits, choice of subjects, informed consent, safeguards for vulnerable populations, monitoring and observation, and confidentiality.[11] Ultimately, the role of the IRB is to ensure that guidelines are followed for the protection of human participants in clinical trials to include their safety and wellbeing.

Enrollment: A comprehensive plan for patient enrollment aims to recruit appropriate patients in sufficient numbers to obtain relevant and conclusive data. If the protocol does not identify patients with appropriate diversity, the generalizability of the results can be compromised.[12] Even outside of a pandemic, barriers reduce or prevent participation in clinical research. These include patient factors, trust issues, scientist barriers, design flaws, and financing barriers.[12] With a multi-site study, a method for providing immediate feedback of trial and enrollment data can be very helpful to monitor the designed enrollment targets.

Protocols: Protocols describe the timeline for the study for each participating subject, beginning with the initial informed consent and enrollment phase, carrying through randomization, interventions, and the follow-up phases. The appropriate spacing of assessment points during the protocol, along with definition of acceptable windows for these events, is also outlined to allow subjects and researchers guidance with some flexibility. The protocol will also delineate expectations for monitoring of compliance and emphasizes patient safety and data integrity through site visits and audits. Furthermore, there should be a provision from the outset as to the primary and secondary endpoints of the research study and potential avenues for dissemination of the study results to the scientific community.

Clinical Research Regulation and Guidance

Research regulations govern how research should be conducted. Regulations governing research aim to minimize safety concerns and protect research participants. Ethical codes provide more in-depth guidance on principles scientists are bound to uphold. These regulations will vary between institutions, nations, and world regions, but some aspects are inclusive of all scientific endeavors.

The Declaration of Helsinki was created by the World Medical Association in 1964 to provide guidance to physicians and other participants in medical research involving human subjects. Good Clinical Practice (GCP) standards throughout the world note openly that they derive largely from this Declaration, which was last revised in 2013.[9] The International Conference on Harmonisation of GCP Guidelines (ICH GCP) is an international ethical and scientific quality standard for trials. The objective of the ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States.[13] The guideline was developed with consideration of the current good clinical practice in these countries, as well as those of Australia, Canada and the Nordic countries.

ICH GCP is part of European guidance, particularly if a study involves investigation of medicinal products. For clinical investigations of medical devices, the standard EN ISO 14155, which outlines good clinical practice, may be followed.[14] With regard to animal studies, experiments on vertebrate animals in the European Union are subject to Directive 2010/63/EU since January 1st, 2013.[15]

The main regulatory body in Europe is the European Medicines Agency (EMA) which promotes and protects human and animal health. The European Clinical Trials Directive harmonizes the rules for the approval of a clinical trial conducted in an EU country. There are numerous national regulatory bodies throughout Europe. For example, the Medicines and Healthcare products Regulatory Agency (MHRA) is the regulatory authority responsible for clinical trial approvals, oversight and inspections in the United Kingdom. In the United States, the Food and Drug Administration (FDA) is responsible for protecting the public health by ensuring the safety, efficacy and security of human and veterinary drugs, biological products, and medical devices.

Recommendation: Wherever possible, standardized research protocols and processes should be applied in order to maintain the consistency of the research outcomes and to uphold the ethical protections for participants. The clinical research team should be aware of and comply with all local regulations and requirements including using IRB review and following SPIRIT guidelines for protocol development.

Challenges to Conducting Clinical Research in Emergent or Distressful Times

The risk of natural disasters and unforeseen circumstances is a constant threat to ongoing clinical research. As the international community is faced with the threat of armed conflict, climate change, authoritarian governmental restrictions, global unrest, or local disruptions, clinical trial sites and personnel may struggle to comply with study protocols during these unforeseen circumstances. Depending on the scope of the disaster, interruption of the research can be a matter of days or years. Large-scale natural disasters such as earthquakes, blizzards, floods, and hurricanes have the potential to compromise infrastructure within hundreds of miles. Other disasters such as tornadoes and fires may have a localized geographical footprint but can completely dismantle operations in the areas they strike. The ability to sustain and adapt clinical research protocols during these times will depend not only on local governmental disaster preparedness and facility planning, but also on the resilience and preparedness of the clinical research team.

Recommendation: The principal investigator and research team should assess the geographical extent and infrastructure impact of a disaster situation on the research protocol and feasibility of its execution. This includes appreciating how local needs may be triaged by community leadership.

Evolving Risks to Subjects: The COVID-19 Pandemic and Clinical Research

As the initial cases of COVID-19 were identified in Wuhan, China, in December 2019, the world was largely unprepared for what would follow in the subsequent months. The World Health Organization (WHO) identified the outbreak as "a public health emergency of international concern" in January of 2020 and classified the COVID-19 outbreak as a global pandemic in March 2020.[16] According to the National Institute of Health (NIH), 80% of non-COVID-19 trials were stopped or interrupted early in the pandemic.[17] Many medical professionals involved in clinical research were pulled to work on the front lines during various phases of the pandemic as many communities face critical care shortages. For example, physiatrist pain researchers transitioned from their labs to rehabilitating COVID-19 survivors, and interventional anesthesia pain professionals were recruited from the clinic in order to provide critical care in COVID intensive care units.[18] When care for pain patients was limited to emergent procedures due to limited supplies of personal protective equipment (PPE), the progress of clinical trials slowed. Given the multi-year timelines of many clinical trials, the disruption of the COVID-19 pandemic will likely be felt for many years to come but provides an instructive opportunity for future planning.

Improvement in restrictions led to guidance from the FDA on trial continuation and modifications including use of telemedicine was instrumental in these actions.[19] Additional modifications will need to be built into the system as variation in infection rates and regional variations change with time.

Recommendation: Research teams should evaluate guidance from regulatory and political bodies or seek creation of this guidance.

Challenges of Continuing Clinical Research in an Emergency or Pandemic

Preparedness for future research challenges should be a benefit from the turmoil from infectious disease over the past few years.[20] Infrastructure limitations related to a natural disaster and the challenges during the current pandemic (Box 1) should all be considered when assessing how to proceed with research in times of an emergency situation.

Recommendation: Where possible, crisis protocols should be developed and enacted when needed. Evaluation of the needs of the research study should be performed on a periodic basis as the emergency situation evolves. The frequency of these evaluations will be dictated by the time of situation, and may range from daily, to weekly, monthly or even less often. Ad hoc evaluation as the situation changes should also be performed. When necessary, a project may be eliminated or placed on indefinite hold, thus a prioritization system is needed.

Ethical Considerations for Clinical Research During Pandemics and Natural Disasters

It is important to note that even in the face of natural disasters and pandemics, research needs to be governed by the principles of respect for persons, beneficence, and justice.[21,22] Federal regulations in the US require that any federally funded research undergo IRB review for all but a few carefully described circumstances. None of these exceptions applies to research being performed during a natural disaster according to the principles of US Department of Health and Human Services policy on protections of human subjects.[23] Strategies such as expedited IRB review can be explored in times of natural disaster, if appropriate.

Informed consent is an ethical foundation of human subject protection during clinical research and is the primary mechanism to ensure subjects can exercise the right to refuse experimental interventions. Accordingly, informed consent is consistent with the bioethical principle of respect for patient autonomy.[24] Although informed consent is critical in all clinical research, it has been opined that perhaps consent associated with pain research should be especially robust, requiring particular attention to research design.[25] There are two exceptions to the requirement of informed consent when performing research with human subjects: the "impracticality" exception[21] and the "emergency" exception.[26]

Federal regulations call for protection of vulnerable populations when conducting clinical research.[23] The population of individuals living in times of pandemics and natural disasters can be homeless, impoverished, gravely restricted in activity by governments, without power or clean water, and under extreme financial stress, certainly meeting the definition of vulnerable populations. The clinical research community must adhere to the ethical foundations of human research at all times, and especially during periods of humanitarian disasters. Initiating research studies during a disaster time may require a separate ethical calculus from continuing a study that originated prior to the disaster, and that will require modifications to adapt to a developing situation.

Recommendation: Ethical principles should be reviewed during extenuating events. The research team should consider the specific influence the disaster may have on autonomy and the ability to provide informed consent without undue influence. Patients with pain disorders may be especially vulnerable and therefore detailed review of each participant's case is encouraged.

Box 1 Critical Challenges Regarding Facility Access

- Limited accessibility of pain clinics mainly for essential or critical visits.
- Difficulty in interacting with homebound patients, or others reluctant to visit clinics.
- Trial operations may expose the staff or patients to the risk of acquiring the infection.
- Continuation of the trial may lead to high participant attrition.
- Inability to meet logistical trial obligations by sponsors as well as contractors (ie, delivery of investigational products, PPE, or site monitoring).
- Deviation from the study timelines may affect data integrity due to delayed assessment and monitoring.

Enrollment and Recruiting

The COVID-19 pandemic substantially reduced recruitment to clinical trials including clinical pain-related research.[20,27] Recruitment impacts came from several sources including local and sponsor-related enrollment pauses and pauses issued by national regulatory bodies, such as the National Institute for Health Research (UK), which announced the pausing of any new or ongoing studies in the National Health Service (NHS) and social care sites unless they were nationally-prioritized COVID-19 studies.[28]

The critical challenges in Box 1 carry significant impact for enrollment and recruiting of patients in pain for research purposes. Although this impact generalizes to all areas of medical investigation, many aspects of pain assessment in particular make overcoming these obstacles through telemedicine and other alternative solutions complex.[29] In addition, virtual or telemedicine options may introduce bias into the recruitment process, due to limits in broadband internet in many areas, including rural areas in developed countries and in developing nations. All communications may be impacted by natural disasters.

Furthermore, research subjects themselves may be reticent to participate in clinical trials during future circumstances of natural disaster or emergency. A study of cancer survivors (907 respondents) asked if the COVID-19 pandemic made them more or less likely to participate in a clinical trial, or if it made no difference. The majority indicated no difference; the remaining respondents were more than seven times more likely to indicate that the pandemic made them less likely to enroll in a clinical trial.[30] An electronic survey of staff at various trial investigator sites (1030 respondents) noted that for the large majority, COVID-19 had affected their ability to conduct ongoing trials, and most believe that COVID-19 had impacted the initiation of new trials. The top four concerns were: ability to enroll patients, ability to recruit patients, financial implications for cancelled studies, and financial implication from delayed milestones.[31] In addition, logistics such as proper PPE and staffing may impact continuation in infectious disease emergencies. Other issues for clinical research during a pandemic or emergency are discussed below, with potential mitigations.

Facility logistics (resources, staff, access): Safe digital working spaces must be created at home for research staff and conversion of physical visits to virtual visits must be supported by information and communications technology (ICT) departments of hospitals. If on-site study activities are unavoidable, it is preferable to transfer participants to the safest possible environments. In conducting pain research, an aspect of trial safety is minimizing all potential discomforts that subjects may experience. For example, in the case of pharmacological research, access to medications and the risks of discontinuation must be addressed as part of the safety of research participants. Where medication supplies may be interrupted, careful management of the absence of medications should be part of the research protocol and participant safety plan.

Research subject availability for in-person assessments: Safety of participants is of primary importance. Risk assessment should be performed, and the feasibility of starting new trials or enrolling new participants should be assessed by researchers and sponsors. In cases in which these two priorities are in conflict, trial participant safety always prevails.

In situations in which follow-up with subjects can continue, care should be taken to ensure that these visits are minimized to collecting essential information only (eg, primary endpoint data and safety reporting) until normal capacity resumes or by the methods of communication noted earlier. Most regulatory bodies have advised that these mitigations will not constitute a substantial amendment for authorization.[32]

Restricted resources (eg, testing or procedures): Prospective protocol abandonments are unacceptable if they can be avoided by any reasonable manner. Thus, modifications can be implemented with advance approval. For example, critical laboratory tests, imaging, or other diagnostic tests may be done at a local laboratory with relevant explanation, or the investigated products may be mailed to the participants' home addresses using dedicated chain of custody couriers.

Research subject health or safety at elevated risk: In infectious pandemics, pathogen exposure becomes an added risk of participation in some clinical trials. Every attempt should be made to reduce the risk of exposure. Some clinical trials might still be able to enroll new patients during a pandemic without increasing patient exposure if no extra trial visits in hospitals or clinics will be required after discharge, or if the rest of the trial-related data collection can be accomplished remotely. In the instance of natural disasters, enrollment and the informed consent process should be postponed until stable circumstances are reestablished.

Protocol deviations and their impact on quality of clinical trial results: As trial protocol modifications may be required in response to the situation, IRB/EC policies should be adjusted to avoid the need for repeated reporting of protocol deviations. Flexibility may be considered for the timing of scheduled visits, insofar as they do not invalidate results. The IRB/EC may not be able to address deviations in these studies with timeliness if other pandemic or emergency-related studies take priority.

Safety monitoring during the study: At enrollment, patients may be consented for a blanket electronic approval, and this can provide important information to improve future trials.

Adverse events and outcomes that are related to the emergency situation: If emergency situation-related adverse events occur, they can influence the outcome of the study. The consequences to the subject may be far-reaching, such as influencing income level, education, and physical and mental condition. Exacerbations of pain severity in clinical pain research do indeed occur.[33] The adverse events become confounding factors when study results are compiled. Assessment of the expected impact of these confounding factors is necessary and will require careful analysis and statistical assessment to identify any effects. This will complicate data assessment, safety assessment, and adverse event analysis.

Changes in protocol timeline: Modifications to protocol timelines can be made if trials cannot proceed because the enrolled participants cannot safely continue with the trial. Prior to a protocol change, alternatives should be explored. An alternative path is to pause enrollment in ongoing trials, perhaps on a site-specific basis, until the impact of the pandemic or disaster is reduced. Later re-initiation of enrollment to achieve protocol-specified statistical power can begin after the study team and sponsor judge that it can adequately manage risks of the pandemic or disaster. Such an approach is particularly important if concurrent illnesses or ailments, both directly and indirectly related to pandemic, could confound the outcome of study treatment on the main safety and efficacy outcomes.

Opening new protocols or new sites for protocols: The same research challenges affecting open trials will also impact the ability to open new research protocols. The reallocation of staff resources and funding may restrict the ability to afford the research, the resources to open a new protocol, or to expand to a new site. The research team should perform a thoughtful feasibility assessment prior to proceeding with a new protocol.

Losing a site or PI: In extreme cases, the research challenges of the emergency situation or pandemic may interrupt research completely. The facility may become unavailable due to the emergency or disaster situation. Study materials, including the required devices or drugs, may be inaccessible due to disruption of the supply chain. For example, research on parenteral opioids in cancer pain, already presenting a challenge due to reductions in DEA production quotas,[34] may be exacerbated due to pandemic-related supply chain issues. In these instances, the safety and health of the patient participants remains the primary objective. Clear and open communication between the research team and participating subjects is essential as the situation evolves, and suitable alternatives should be developed and offered to subjects. Subjects retain the right to withdraw from participation at any time, and the research team may counsel patients to consider this option for their safety and benefit.

Recommendations:

- *Creative adaptation of operations to include telemedicine and virtual clinics can facilitate continued conduction of clinical research studies including the enrollment of new subjects.*
- *The research team should be vigilant for bias in the recruitment process that might be introduced by these changes.*
- *Further adaptations of operations should be made to preserve the safety of the investigator team and participants.*
- *Risk assessment should be performed, and the feasibility of starting new trials or enrolling new participants should be assessed by researchers and sponsors.*
- *It is expected that the sponsor performs a risk assessment of each individual ongoing trial and the investigator of each individual trial participant and that they implement measures, which prioritize trial participant safety and data validity. In cases in which these two priorities are in conflict, trial participant safety always prevails.*
- *Some clinical trial activities should be postponed until stable and safe circumstances can be reestablished.*
- *IRB and EC should introduce flexibility to allow for expected protocol deviations.*
- *Assessment of the expected impact on outcomes of confounding factors related to the emergency is necessary and will require careful analysis and statistical assessment to identify any effects.*

The Patient/Subject Perspective

Kenneth Kipnis's "bioethical taxonomy of vulnerability in research subjects" describes six domains of vulnerability that research participants may experience at any time.[35] While some domains of vulnerability (such as cognitive and juridic vulnerabilities) may not be directly affected by the emergency's conditions, medical, allocational, and infrastructural vulnerabilities may develop and/or intensify.

Medical vulnerability, or the presence of a health condition for which no satisfactory remedies are currently available, may be particularly heightened in the early stages of a pandemic when risk factors for contracting the novel pathogen are not well-understood and evidence-based therapies have not been established. Social isolation and interruption of access to preventative and follow-up care for chronic health conditions may further impact research participants' medical vulnerability and the safety of undergoing investigational interventions. Shapiro et al noted that such social isolation put many patients suffering from chronic pain at heightened levels of vulnerability, with this phenomenon potentially affecting numerous investigational interventions.[36]

Allocational disadvantage may be heightened by increased strains on socially distributed goods such as money, housing, medical care, employment, insurance, and other employment-related benefits. Financial strain and limited access to basic resources may impact motivation to participate in clinical research, posing new obstacles to recruitment and retention of study participants or increasing the degree to which compensation for research participation constitutes an inducement.

Recommendation: Ethical principles should be reviewed during extenuating events. The research team should consider the specific influence the disaster may have on autonomy and ability to provide informed consent for patients with pain disorders.

Impact of Disasters on Study Conduct and Results

Pauses in activity can lead to protocol deviations, timeline variation, and research subject attrition, all of which detract from the quality of scientific results. Maintaining data integrity during an emergency situation remains critical as missing data is a potential source of bias when analyzing information from clinical trials.[37–40]

Will Continuing the Protocol During Emergency/Pandemic Change Outcomes and the A/E Rate?

In confirmatory trials, the primary analysis is commonly performed on the full analysis set, as this analysis is consistent with the intention to treat (ITT) principle. If data for some subjects are missing for the primary endpoint, it is necessary to specify how all randomized patients can be included in the statistical analysis. Ignoring missing data in the analysis violates the strict ITT principle which requires measurement and analysis of all patient outcomes regardless of protocol adherence. Bias is the most important concern resulting from missing data. The sample size and the variability of the outcomes also affect the power of a clinical trial.[41]

Regarding suspension of studies, a risk/benefit assessment on a trial-by-trial basis should be undertaken. The potential risks should be balanced against the level of risk to which a trial participant would be exposed outside of the trial. Based on the classification put forward by the ADAMON Project, these are categorized as no higher risk than standard medical care (type A), somewhat higher risk than standard medical care (type B), and markedly higher than standard medical care (type C).[42]

Potential options can include withdrawal of participants from the trial or halting it temporarily. In situations in which subjects are approaching completion of their participation in the trial, consideration could be given to ensure that end-of-trial activities are completed to the greatest extent possible so that the participant's data is maximally useful. Physical access requirements for subjects to the site should also be considered.[43]

Partial study results can affect the power of the study and, thus, outcomes. A detailed description of the pre-planned methods used for handling missing data, any amendments of that plan and a justification for those amendments should be included in the clinical study report. One approach would be to omit patients with missing values from the trial analysis.[44] If patients are excluded from the analysis, this may affect the comparability of the treatment groups (for

example, by introducing bias in the estimation of the treatment effect) as well as the representativeness of the study sample in relation to the target population (external validity).

Other approaches include single imputation methods (replacing a missing data point with a single value and analyses are conducted as if all the data were observed), linear mixed models (when a series of outcomes are measured repeatedly over time, mixed-effect models for repeated measures (MMRM)), responder analysis, survival analysis, count data (eg, the number of exacerbations) a weighted approach with time-in-study as an offset variable (eg, Poisson regression), and sensitivity analyses in which the missing data are handled in a different way as compared to the primary analysis.

Merging protocol patients and non-protocol patients to complete a study is a possible approach. This would increase the patient numbers and the power of the study, thereby facilitating completion. However, doing so would represent a trial protocol deviation due to the change in study population. This deviation would need to be discussed/submitted to the sponsor and the local ethics committee/IRB. Consent of the non-protocol patients would need to be undertaken. The merged approach could lead to a result that would be hard to interpret based on the initial study goals.

Extension of a trial or pause of a trial can negatively affect finances and research budgets. These budgets may be stretched due to staff undertaking additional risk assessments, contingency plans, questionnaires, and reports for a variety of stakeholders. In addition, investment in trial-critical electronic systems such as interactive response systems (used for code-breaking and randomization activities or safety reporting systems) may be required.[45]

Recommendation: A trial-by-trial assessment of risks and benefits of each research protocol should be undertaken. Depending on the research protocol and the disaster situation, options include withdrawal of participants from the trial, halting the trial temporarily, or continuing the trial as planned with necessary adaptations to the disaster circumstances. In situations in which subjects are approaching completion of their participation in the trial, consideration could be given to ensure that end-of-trial activities are completed to the greatest extent possible so that the participant's data is maximally useful. Appropriate data handling and statistical analysis techniques should be applied to available results and to address missing data.

Bench and Translational Research

Natural disaster and pandemic situations can challenge bench and translational research. Numerous projects were suspended, and some perhaps even permanently discontinued, when working in wet labs was halted during the COVID-19 pandemic.[46] In this situation, gathering in person in labs is not the only problem to overcome. Lab resources may be diverted to help cope with university, society, and hospital needs. PPE, for example, may be prioritized for front line medical workers. Gloves, sanitizing wipes, and even staff were reallocated to help with the surge of hospitalizations secondary to COVID-19. Lab reagents and culture media might be reallocated to the clinical enterprise. Grant funding awards could be reprioritized.

Recommendation: The same protocol-by-protocol assessment of risks and benefits of bench research projects should be undertaken. Depending on the research protocol and the disaster situation, research may continue or may be suspended or discontinued.

Assessing Feasibility and Suspending Research

A standard approach to emergency or disaster circumstances can guide decisions regarding study suspension or modification (Box 2). As new or existing problems develop, the threshold for conducting research will vary in different parts of the world, but general principles apply in considering this option and reapplying it as needed.

Study viability: Some studies that have been paused or have not yet started may no longer be viable for scientific, clinical, financial, or practical reasons. Assessment of study viability should be undertaken prior to considering restarting a trial. For some studies, viability will depend on study redesign or protocol amendment. For others, funding or changes in resource requirements may be required to re-start and continue to run a trial during the pandemic.[43]

Capacity and site readiness: Delivery of research will be dependent on relevant health and care services being "open for business." This will vary between institutions depending on the type of facility and the type and severity of the disaster or pandemic.

Box 2 Criteria for Study Suspension or Modification Under Emergency or Disaster Circumstances

When should research be suspended or modified?
• Research subject or clinical research team safety is at risk. • Ethical risks of participation (medical vulnerability, allocational disadvantage, infrastructure vulnerability) have changed. • Public health dictates that research resources be used for higher priority (eg, PPE needed, nurses/physicians redeployed, facility availability). • Inability to engage with patient subjects due to infrastructure issues (eg, lack of high-speed internet or audiovisual ability, roads impassable, phones or power out). • Financial crisis of sponsor or site cannot continue due to lack of resources or ability to pay staff.

Recommendation: Evaluation of the needs of the research study should be performed on a periodic basis as the emergency situation evolves. Depending on the research protocol and the disaster situation, research may continue, or may be suspended or discontinued.

Conclusions

Stable times are wonderful for research and advancement of the evidence in any field. Despite the authors of this analysis functioning as pain clinicians and researchers, the guidance that we have offered applies, to a considerable degree, to all clinical research. However, as clinician-researchers who treat and study extremely vulnerable patients, our hope is that publishing this analysis in a pain research journal will guide our pain medicine colleagues in their efforts to be prepared to deal with future pandemics and emergencies when they occur. Unfortunately, difficult situations challenge the ability of the system to produce needed and valuable evidence. The need to develop a roadmap for continuing clinical research in this setting is critical to the creation of sustainable research, safe clinical settings, and reliable data.

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