University of Kentucky (UK) Human Research Protection Program Emergency Preparedness and Response

Purpose

This document establishes guidance for initiating a response to an emergency/disaster situation impacting the University of Kentucky (UK) Human Research Protection Program (HRPP) including any and all human subject research projects currently underway or to be initiated.

Disasters may come in the form of extreme weather events, other natural disasters such as geophysical or climate-related events, intentional or non-intentional man-made disasters, and/or infectious disease outbreaks.

This guidance is enacted when the Institutional Official (IO), or designee, has indicated an emergency occurred or preparations are needed in response to an event adversely impacting human subject research or HRPP operations. The UK Vice President for Research serves as the IO for the UK HRPP.

Human subject research will return to normal after an assessment to determine that the emergency has ceased.

Policy

The UK HRPP will defer to the VPR, institutional leadership, and emergency response authorities and limit areas of human research studies which may interfere with or negatively impact the participants, research enterprise, or the emergency response.

Responsibilities

The VPR (*Institutional Official*), Office of Research Integrity (ORI) leadership (*Director and Associate Director*), and Institutional Review Board (IRB) leadership (*IRB Chairs*) jointly respond to emergency/disaster situations according to this policy.

The ORI leadership is responsible for periodically evaluating and updating this plan as needed.

Communication and Outreach

The ORI leadership and education team is responsible for creating, disseminating, and maintaining emergency response correspondence in coordination with Research Communications.

The ORI education team maintains email contact listservs for staff, IRB members, and researchers. The team disseminates announcements via Constant Contact and posts announcements and Frequently Asked Questions regarding emergency response on the ORI homepage. ORI maintains an alternate phone list for inter-office communication during emergencies (see Appendix I).

ORI will ensure research teams are notified that a response plan has been activated and what guidance to follow throughout the emergency/disaster.

Procedures

Assess the nature of the event and the appropriate response.

Once the Vice President for Research (VPR), the President of the University, and/or Crisis Management and Preparedness (CMP) have determined the nature and level of the emergency, ORI will consult with the VPR regarding the potential impact on Human Subjects Research. Then, ORI will assist as needed in executing a specific plan to mitigate the effects on current and proposed human research protocols.

If applicable, ORI leadership will contact local authorities, oversight agencies, and/or accreditation organizations to solicit assistance and guidance regarding regulatory flexibility during emergency response.

The ORI may take some or all of the following steps in consultation with VPR and IRB:

- The ORI, IRB, and PIs will utilize remote systems to ensure all appropriate regulations and policies are followed for the protection of human subjects.
- In the event that in-person meetings become impossible due to an emergency and electronic systems have not been compromised, E-IRB and remote electronic meetings conducted by video conference will be utilized to ensure continuity of operations and accommodate time sensitive reviews.
- Should an event result in temporary inability to access E-IRB, ORI, IRB, and researchers will resort to available systems (e.g., voice over internet protocol (VoIP), email, phone, hard-copy documents) to correspond and document status and determinations to permit tier I research to continue to serve and safeguard participants.
- Storage, handling, and control of investigational drugs will be maintained through UK's Investigational Drug Service's Emergency Preparedness Plan (PH08.05.230). Principle Investigators will work with the Investigational Drug Service (IDS) to coordinate alternate means of distribution of investigational products to research participants. If necessary, for treatment purposes, IDS will assist with unblinding investigational products in coordination with the PI and study sponsor.
- Principal Investigators are responsible for maintaining medical device storage, handling, and control with guidance from commercial sponsors. A sample Device Accountability Standard Operating Procedure is available on the ORI website. FDA provides guidance on Hurricane Emergency Preparedness and Medical Devices which is applicable to natural disasters and other situations.
- UK security and police will maintain security of on-site research facilities as well as through normal distribution and surveillance of employee and/or student identification badges.
- The ORI will coordinate with the Center for Clinical and Translational Science (CCTS) to provide accurate outreach information for clinical research participants.

- The ORI will seek agreements with external IRBs if the emergency is local in nature so that new protocols can be approved in the event UK IRBs are unable to remain fully operational.
- The Vice President for Research, in conjunction with the ORI and IRBs, will advise the use of the following criteria to determine which protocols may continue unimpeded, and those that need to be temporarily paused/postponed, or proceed following alternate mechanisms:

Tier I: Continue unimpeded

Research that presents a likelihood of direct benefit to participants including:

Clinical trials with treatment arms (e.g., oncology clinical trials, interventional studies for devices or therapies with significant benefit to subjects). Investigators should weigh the benefits of the treatment arm against the risks of added harm for study staff or research subjects when deciding about continuing these projects.

Non-treatment intervention where stopping intervention would cause harm. For example, studies that include supportive or palliative care, prevention, diagnostic, behavioral or other non-treatment interventions.

Note: Medical protocols may suspend recruitment/enrollment for individuals in the affected area but may continue conducting research activities if the required facilities remain unaffected.

Research that does not involve interaction or intervention that creates increased risks.

Research integral to the effects of or response to the disaster(s) if warranted and appropriate.

Tier II: Modified to continue following alternate mechanisms

Research that involves direct interaction or intervention but can manage risks by conducting study procedures via alternate mechanisms. For example, the use of remote study visits, conference calls, or video conferencing. Or canceling in-person gatherings of people involving research activities and holding meetings such as focus groups and research-related activities, such as community advisory boards and participant and support groups for study participants.

Activities involving data collection that can be conducted remotely (e.g., EMR, previously collected) and studies that do not involve any direct subject contact (e.g., UK Healthcare Zoom, UK Telehealth, REDCap).

Changes to protect the life and well-being of research subjects may be made without IRB approval. Federal regulatory agencies may also authorize global IRB approval of protocol changes without individual modification request. This may include changes such as transitioning to remote contact to permit research to safely continue research.

For FDA-Regulated Research, changes to the protocol or investigational plan to eliminate apparent immediate hazards or to protect the life and well-being of research participants in an emergency may be implemented without IRB approval or before filing an amendment to the investigational new drug

application (IND) or investigational device exemption (IDE) but are required to be reported afterwards. Investigators for FDA-regulated research are advised to collect a list of contingency measures taken; list subjects affected by study number; and indicate the impact on safety or efficacy results, if applicable. For detailed guidance, see Appendix IV: Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies Guidance for Industry, Investigators, and Institutional Review Boards

Check with the study sponsor on reporting requirements. Investigators may submit an aggregate account of changes implemented without prior IRB approval on one protocol violation report.

Include how participants will be informed of changes that may affect their willingness to continue, if applicable.

Submit a Modification Request (MR) for changes to be permanent for any study that continues via alternate mechanisms after the emergency situation has resolved.

Clinical trials that have paused recruitment due to a disaster, should update their study status on ClinicalTrials.gov record accordingly (e.g., active, not recruiting). For questions regarding ClinicalTrials.gov, see Office of Sponsored Projects resource webpage.

Tier III: Paused or Postponed

Studies that involve subject contact in-person or at affected facilities which have no direct benefit to the subject should be paused until further notice.

Examples of paused studies may include:

- Studies collecting human samples or imaging that require study subject contact (e.g., phlebotomy, surveillance biopsy, radiographic imaging, physical examination) without direct diagnostic or therapeutic benefit;
- Community based studies involving group gatherings which increase exposure risk;
- Studies that are not studying the effects of the disaster(s) if the IRB cannot determine the research is integral/warranted/appropriate at that time.
- Any protocol that does not present the likelihood of direct benefit through clinical/therapeutic means to the participant.
- Protocols that require in-person interaction or intervention, especially that which creates increased risk and/or where appropriate alternative facilities cannot be found.
- Protocols that require specific facilities affected by the disaster where no other appropriate alternative facilities can be found.
- Protocols that will have an adverse impact on resources required to address and respond to the disaster/emergency.
- Protocols that require a convened IRB meeting/quorum when one cannot be held remotely.

Resolution and Recovery

The ORI will await a determination from the VPR and CMP regarding when and how research operations can return to normal and notify research teams accordingly.

Plans for resuming human research activities are based on CMP criteria for reopening public activities, available public health guidance, and federal or state government mandates.

Resumption may occur in a phased process.

The phased approach provides a baseline framework from which additional variables may be considered.

Policies and guidance will be dynamic and may accelerate or decelerate based on shifting recovery status and incidence data.

Resuming human research operations must be parallel to and consistent with the institutional and VPR's plan as well as specific facility, college, or unit mandates.

The VPR may require principal investigator/researcher training and submission and review of a formal resumption plan to incorporate safeguards for participants and research staff.

In addition, implementation of precautions, controlled conditions, and safety principles are considered as a prerequisite to resuming activities at all phases.

Investigators may use judgement to continue pauses, modifications, and practices more stringent than allowed, to protect human subjects or research staff.

Preparedness

In order to prevent or minimize the suspension level of Human Subject Research, the following has been/will be implemented as needed:

Education & Training

The ORI will develop and distribute emergency preparedness information and education.

See Appendix II & III

Departmental Network Drive

Departmental data is secured by allowing only certain groups access within the Active Directory. Departmental data is backed up nightly using SpectrumProtect client.

E-IRB

IT support (Research Information Services (RIS)) holds shared responsibility with UK campus IT for the disaster recovery plan for data maintained on E-IRB's UK server:

Backup media is stored in a secure, geographically separate location from the original and isolated from environmental hazards.

UK uses Tivoli Storage Manager (TSM) for its restore and backup needs.

Backup/Restores

Servers (including shared network drives):

Backups will be performed daily via campus.

Restores will be performed within four (4) business hours.

Databases:

Backups of production databases will be made both locally and via campus for 30 days according to the following schedule:

Locally:
4 weeks daily backups;
4 weekly backups;
1 monthly backup;
2 weeks of transaction logs
Campus:
30 days of daily full SQL backups
Restores of a complete database will be performed within four (4) business hours. Partial database restorations are dependent on data consistency issues and may take significantly longer.

Addressing missing functionality (e.g., bugs) and development of new features in E-IRB is ongoing and prioritized by user feedback received either through the EIRBsupport@uky.edu mailbox or by the E-IRB System Administrator. In coordination with the E-IRB Administrator, RIS implements an average of 10 system updates a year. Source: ORI D155 E-IRB Operations

Training Opportunities:

Cybersecurity-

WATCH: Cybersecurity Best Practices - Emails, Messages, & Phishing
WATCH: How to Detect Phishing Emails with Jude Phisherman
WATCH: Cybersecurity Best Practices - Data Security
WATCH: Cybersecurity Best Practices - Personally Identifiable Information
WATCH: Keeping Your Data Safe While Traveling Abroad
WATCH: Restricted Intelligence: Web Series

CERT training-

UK Police Department's Division of Crisis Management & Preparedness now offers Campus Community Emergency Response Team (C-CERT) training for faculty and staff. UK C-CERT members will receive hands-on training in basic disaster response skills, such as fire safety and suppression, light search and rescue, disaster medical operations, team organization, disaster psychology and terrorism.

Contacts:

Crisis Management & Preparedness General Phone: (859)-257-9665
UK Police: (859) 257-8573
UK Public relations: (859) 257-1754
Physical Plant: (859) 257-3844

Resources:

UK Police Crisis Management and Preparedness
UK Cooperative Extension Disaster Preparedness Resources
UK Severe Weather Procedures
U.S. Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response (ASPR)
Kentucky Emergency Management
Crisis Management and Preparedness | University of Kentucky
KY Weather Alerts
KY Health Alerts
Centers for Disease Control and Prevention
National Preparedness Month
Ready.gov

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Appendix I: ORI Alternate Phone List

ORI Contacts webpage

Alternate ORI Phone List distributed via Hard Copy to ORI Staff [contact desiree.penn@uky.edu for edits or additional copies].

Appendix II: UK Crisis Management and Preparedness (CMP) Emergency Preparedness and Response Information

In any emergency, you are responsible for your safety. Think now about what you will do so you can take swift, decisive action when the time comes. The following information is intended to guide you in likely emergencies but cannot take all possibilities into account. If an emergency occurs during class, your instructor will provide further direction based on university and department emergency plans.

Storm Sheltering/Sheltering in Place

During a severe storm, protect yourself from lightning and flying debris. Move to an interior room or hallway on the building's lowest level. Avoid outside doors and windows. Recommended shelter locations are marked on the emergency floor plans posted throughout the building. If a hazardous chemical release occurs outside the building, follow these same procedures. Shut all exterior doors and windows. Isolate yourself from outside air. View UK's severe weather procedures

Building Emergency Action Plan (BEAP) information is housed on the UK Crisis Management and Preparedness site. To access building-specific BEAPs, log in to the BEAP portal with your link blue credentials.

To Report an Emergency or Suspicious Activity

Call the University of Kentucky Police Department at 859-257-8573 (UKPD) from any mobile phone. If the line is unavailable or you are calling from another university location, dial 911.

Evacuation/Fire

We will always evacuate for a fire alarm or when university officials order us to do so. Gather your personal belongings quickly and move to the nearest exit. Evacuation routes are marked on the emergency floor plans posted throughout the building. If a hazardous chemical release occurs inside the building, follow these same procedures.

Active Shooter/Violence

In an active shooter situation or other attack, run – get away from the attacker. If you can't run, hide – barricade yourself in a safe place. If neither of these is possible, fight – do whatever you need to do to stop the attacker.

UK Alert

The university provides emergency notifications through UK Alert, which broadcasts to email, text message, building alarm systems and outdoor sirens. If you receive a UK Alert message during class, notify your instructor and classmates immediately. Visit UK Alert for more information.

The Division of Crisis Management and Preparedness is open every weekday.
Staff members are also on-call after hours, weekends, and holidays.
General Email: CMP@uky.edu
General Phone: 859-257-9665
Fax: 859-257-4143

Appendix III: Hazard Information Sheets

- Active shooter
- Cyberattack
- Earthquake
- Extreme heat
- Flood
- Pandemic
- Power Outage
- Thunderstorm, lightning, hail
- Tornado
- Fire
- Winter storm

BE PREPARED FOR AN ACTIVE SHOOTER

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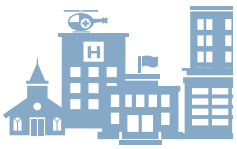
Recent national tragedies remind us that the risk is real. Taking a few steps now can help you react quickly when every second counts.

An active shooter is an individual engaged in attempting to kill people in a confined space or populated area. Active shooters typically use firearms and have no pattern to their selection of victims.



Can happen anywhere

Can happen anytime

IF YOU ARE INVOLVED IN AN ACTIVE SHOOTER INCIDENT

See something, say something.

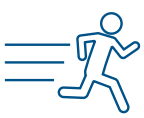
Learn first aid skills so you can help others.

Before you run, know the exits.

Help law enforcement.

Find a place to hide.

Seek help to cope with trauma.



Run

Hide

Fight

HOW TO STAY SAFE

WHEN AN ACTIVE SHOOTER THREATENS

If you see suspicious activity, let an authority know right away.

Many places, such as houses of worship, workplaces, and schools, have plans in place to help you respond safely. Ask about these plans and get familiar with them. If you participate in an active shooter drill, talk with your family about what you learned and how to apply it to other locations.

When you visit a building such as a shopping mall or healthcare facility, take time to identify two nearby exits. Get in the habit of doing this.

Map out places to hide. In rooms without windows, behind solid doors with locks, under desks, or behind heavy furniture such as large filing cabinets can make good hiding places.

Sign up for active shooter, first aid, and tourniquet training. Learn how to help others by taking FEMA's You Are the Help Until Help Arrives course. Learn more at ready.gov/until-help-arrives.

RUN. Getting away from the shooter or shooters is the top priority. Leave your things behind and run away. If safe to do so, warn others nearby. Call 911 when you are safe. Describe each shooter, their locations, and weapons.

HIDE. If you cannot get away safely, find a place to hide. Get out of the shooter's view and stay very quiet. Silence your electronic devices and make sure they won't vibrate. Lock and block doors, close blinds, and turn off the lights. Do not hide in groups—spread out along walls or hide separately to make it more difficult for the shooter. Try to communicate with police silently—such as through text messages or by putting a sign in an exterior window. Stay in place until law enforcement gives you notice that all immediate danger is clear.

FIGHT. Your last resort when you are in immediate danger is to defend yourself. Commit to your actions and act aggressively to stop the shooter. Ambushing the shooter together with makeshift weapons such as chairs, fire extinguishers, scissors, and books can distract and disarm the shooter.

Keep hands visible and empty.

Know that law enforcement's first task is to end the incident. They may have to pass injured persons along the way.

Follow law enforcement's instructions and evacuate in the direction they tell you to.

Consider seeking professional help for you and your family to cope with the long-term effects of trauma.

Take an Active Role in Your Safety

Go to **ready.gov** and search for **active shooter**. Download the **FEMA app** to get more information about preparing for an **active shooter**. Find Emergency Safety Tips

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BE PREPARED FOR A CYBERATTACK

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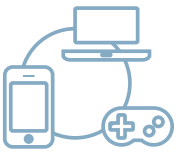
Cyberattacks can lead to loss of money, theft of personal information, and damage to your reputation and safety.

Cyberattacks are malicious attempts to access or damage a computer system.



Can use computers, mobile phones, gaming systems, and other devices

Can include fraud or identity theft

Can block your access or delete your personal documents and pictures

May target children

May cause problems with business services, transportation, and power

PROTECT YOURSELF AGAINST A CYBERATTACK

Keep software and operating systems up-to-date.

Use encrypted (secure) internet communications.

Use strong passwords and two-factor authentication (two methods of verification).

Create backup files.

Watch for suspicious activity. When in doubt, don't click. Do not provide personal information.

Protect your home Wi-Fi network.

HOW TO STAY SAFE
WHEN A CYBERATTACK THREATENS

Keep your anti-virus software updated.

Use strong passwords that are 12 characters or longer. Use upper and lowercase letters, numbers, and special characters. Change passwords monthly. Use a password manager.

Use a stronger authentication such as a PIN or password that only **you would know**. Consider using a separate device that can receive a code or uses a **biometric scan** (e.g., fingerprint scanner).

Watch for suspicious activity that asks you to do something right away, offers something that sounds too good to be true, or needs your personal information. **Think before you click**.

Check your account statements and credit reports regularly.

Use secure internet communications. Use sites that use "HTTPS" if you will access or provide any personal information. Don't use sites with invalid certificates. Use a Virtual Private Network (VPN) that creates a secure connection.

Use antivirus solutions, malware, and firewalls to block threats.

Regularly back up your files in an encrypted file or encrypted file storage device.

Limit the personal information you share online. Change privacy settings and do not use location features.

Protect your home network by changing the administrative and Wi-Fi passwords regularly. When configuring your router, choose the Wi-Fi Protected Access 2 (WPA2) Advanced Encryption Standard (AES) setting, which is the strongest encryption option.

Limit the damage. Look for unexplained charges, strange accounts on your credit report, unexpected denial of your credit card, posts you did not make showing up on your social networks, and people receiving emails you never sent.

Immediately change passwords for all of your online accounts.

Scan and clean your device.

Consider turning off the device. Take it to a professional to scan and fix.

Let work, school, or other system owners know. Information Technology (IT) departments may need to warn others and upgrade systems.

Contact banks, credit card companies, and other financial accounts. You may need to place holds on accounts that have been attacked. Close any unauthorized credit or charge accounts. Report that someone may be using your identity.

File a report with the **Office of the Inspector General (OIG)** if you think someone is illegally using your Social Security number. **OIG reviews cases of waste, fraud, and abuse**. To file a report, visit www.idtheft.gov.

You can also call the Social Security Administration hotline at 1-800-269-0271. For additional resources and more information, visit http://oig.ssa.gov/report.

File a complaint with the FBI Internet Crime Complaint Center (IC3) at www.IC3.gov. They will review the complaint and refer it to the appropriate agency.

Learn tips, tools, and more at www.dhs.gov/stopthinkconnect.

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Take an Active Role in Your Safety

Go to **Ready.gov** and search for **cyberattack**. Download the **FEMA app** to get more information about preparing for a **cyberattack**.

BE PREPARED FOR AN EARTHQUAKE

Earthquakes can collapse buildings and cause heavy items to fall, resulting in injuries and property damage.

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Earthquakes are the sudden, rapid shaking of the earth, caused by the breaking and shifting of underground rock.

Can happen anywhere. Higher risk areas are California, Alaska, and the Mississippi Valley

Give no warning

Cause fires and damage roads

Cause tsunamis, landslides, and avalanches

IF AN EARTHQUAKE HAPPENS, PROTECT YOURSELF RIGHT AWAY

If in a vehicle, pull over and stop.

If in bed, stay there.

If outdoors, stay outdoors.

Do not get in a doorway.

Do not run outside.

HOW TO STAY SAFE
WHEN AN EARTHQUAKE THREATENS

Secure items such as televisions and objects that hang on walls. Store heavy and breakable objects on low shelves.

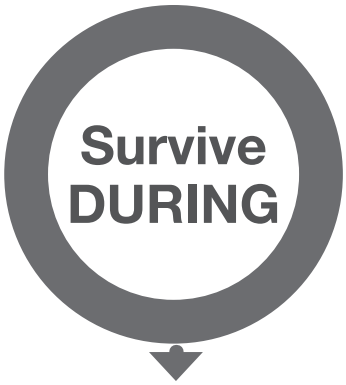
Practice Drop, Cover, and Hold On with family and coworkers. Drop to your hands and knees. Cover your head and neck with your arms. Crawl only as far as needed to reach cover from falling materials. Hold on to any sturdy furniture until the shaking stops.

Create a family emergency communication plan that has an out-of-state contact. Plan where to meet if you get separated.

Make a supply kit that includes enough food and water for at least three days, a flashlight, a fire extinguisher, and a whistle. Consider each person's specific needs, including medication. Do not forget the needs of pets. Have extra batteries and charging devices for phones and other critical equipment.

Consider earthquake insurance policies. Standard homeowner's insurance does not cover earthquake damage.

Consider a retrofit of your building if it has structural issues that make it vulnerable to collapse during an earthquake.



Drop, Cover, and Hold On like you practiced. Drop to your hands and knees. Cover your head and neck with your arms. Hold on to any sturdy furniture until the shaking stops. Crawl only if you can reach better cover without going through an area with more debris.

If in bed, stay there and cover your head and neck with a pillow.

If inside, stay there until the shaking stops. DO NOT run outside.

If in a vehicle, stop in a clear area that is away from buildings, trees, overpasses, underpasses, or utility wires.

If you are in a high-rise building, expect fire alarms and sprinklers to go off. Do not use elevators.

If near slopes, cliffs, or mountains, be alert for falling rocks and landslides.

Expect aftershocks to follow the largest shock of an earthquake sequence.

Check yourself for injury.

If in a damaged building, go outside and quickly move away from the building.

Do not enter damaged buildings.

If you are trapped, send a text or bang on a pipe or wall. Cover your mouth for protection and instead of shouting, use a whistle.

If you are in an area that may experience tsunamis, go inland or to higher ground immediately after the shaking stops.

Save phone calls for emergencies.

Wear sturdy shoes and work gloves.

Take an Active Role in Your Safety

Go to **Ready.gov** and search for **earthquake**. Download the **FEMA app** to get more information about preparing for an **earthquake**.

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BE PREPARED FOR EXTREME HEAT

Extreme heat often results in the highest annual number of deaths among all weather-related disasters.

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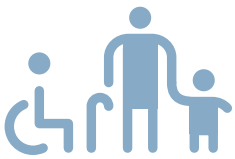
In most of the U.S., extreme heat is a long period (2 to 3 days) of high heat and humidity with temperatures above 90 degrees.



Greater risk

Can happen anywhere

Humidity increases the feeling of heat as measured by a heat index

IF YOU ARE UNDER AN EXTREME HEAT WARNING

- Find air conditioning, if possible.
- Avoid strenuous activities.
- Watch for heat illness.
- Wear light clothing.
- Check on family members and neighbors.
- Drink plenty of fluids.
- Watch for heat cramps, heat exhaustion, and heat stroke.
- Never leave people or pets in a closed car.

HOW TO STAY SAFE

WHEN EXTREME HEAT THREATENS

Find places in your community where you can go to get cool.

Try to keep your home cool:

- Cover windows with drapes or shades.
- Weather-strip doors and windows.
- Use window reflectors such as aluminum foil-covered cardboard to reflect heat back outside.
- Add insulation to keep the heat out.
- Use a powered attic ventilator, or attic fan, to regulate the heat level of a building's attic by clearing hot air.
- Install window air conditioners and insulate around them.

Learn to recognize the signs of heat illness. For more information visit: www.cdc.gov/disasters/extremeheat/warning.html.

Take an Active Role in Your Safety

Go to **Ready.gov** and search for **extreme heat**. Download the **FEMA app** to get more information about preparing for **extreme heat**.

Never leave a child, adult, or animal alone inside a vehicle on a warm day.

Find places with air conditioning. Libraries, shopping malls, and community centers can provide a cool place to take a break from the heat.

If you're outside, find shade. Wear a hat wide enough to protect your face.

Wear loose, lightweight, light-colored clothing.

Drink plenty of fluids to stay hydrated. If you or someone you care for is on a special diet, ask a doctor what would be best.

Do not use electric fans when the temperature outside is more than 95 degrees. You could increase the risk of heat-related illness. Fans create air flow and a false sense of comfort, but do not reduce body temperature.

Avoid high-energy activities.

Check yourself, family members, and neighbors for signs of heat-related illness.

Know the signs and ways to treat heat-related illness.

Heat Cramps

- **Signs:** Muscle pains or spasms in the stomach, arms, or legs.
- **Actions:** Go to a cooler location. Remove excess clothing. Take sips of cool sports drinks with salt and sugar. Get medical help if cramps last more than an hour.

Heat Exhaustion

- **Signs:** Heavy sweating, paleness, muscle cramps, tiredness, weakness, dizziness, headache, nausea or vomiting, and fainting.
- **Actions:** Go to an air-conditioned place and lie down. Loosen or remove clothing. Take a cool bath. Take sips of cool sports drinks with salt and sugar. Get medical help if symptoms get worse or last more than an hour.

Heat Stroke

- **Signs:** Extremely high body temperature (above 103 degrees) indicated by an oral thermometer; red, hot, and dry skin with no sweat; rapid, strong pulse; dizziness; confusion; and unconsciousness.
- **Actions:** Call 9-1-1 or get the person to a hospital immediately. Cool down with whatever methods are available until medical help arrives.

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Catalog No. 17233-5

BE PREPARED FOR A FLOOD

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Failing to evacuate flooded areas, entering flood waters, or remaining after a flood has passed can result in injury or death.

Flooding is a temporary overflow of water onto land that is normally dry. It is the most common natural disaster in the U.S.

Results from rain, snow, coastal storms, storm surge, and overflows of dams and other water systems

Develops slowly or quickly. Flash floods can come with no warning

Causes outages, disrupt transportation, damage buildings, create landslides

IF YOU ARE UNDER A FLOOD WARNING, FIND SAFE SHELTER RIGHT AWAY

Do not walk, swim, or drive through flood waters.

Stay off bridges over fast-moving water.

Determine your best protection based on the type of flooding.

Evacuate if told to do so.

Move to higher ground or a higher floor.

Stay where you are.

HOW TO STAY SAFE

WHEN A FLOOD THREATENS

Know your area's type of flood risk. Visit FEMA's Flood Map Service Center at https://msc.fema.gov/portal for information.

Sign up for your community's warning system. The Emergency Alert System (EAS) and National Oceanic and Atmospheric Administration (NOAA) Weather Radio also provide emergency alerts.

If flash flooding is a risk in your location, monitor potential signs such as heavy rain.

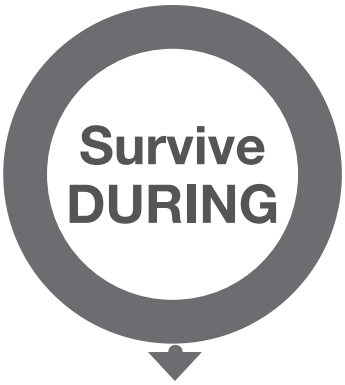
Learn and practice evacuation routes, shelter plans, and flash flood response.

Gather supplies in case you have to leave immediately or if services are cut off. Keep in mind each person's specific needs, including medication. Don't forget the needs of pets. Obtain extra batteries and charging devices for phones and other critical equipment.

Obtain flood insurance. Homeowner's policies do not cover flooding. Get flood coverage under the National Flood Insurance Program (NFIP).

Keep important documents in a waterproof container. Create password-protected digital copies.

Protect your property. Move valued items to higher levels. Declutter drains and gutters. Install check valves. Consider a sump pump with a battery.



Depending on where you are, and the impact and the warning time of flooding, go to the safe location that you have identified.

If told to evacuate, do so immediately. Never drive around barricades. Local responders use them to safely direct traffic out of flooded areas.

Listen to EAS, NOAA Weather Radio, or local alerting systems for current emergency information and instructions.

Do not walk, swim, or drive through flood waters. Turn Around. Don't Drown.® Just six inches of fast-moving water can knock you down, and one foot of moving water can sweep your vehicle away.

Stay off of bridges over fast-moving water. Fast-moving water can wash bridges away without warning.

If your vehicle is trapped in rapidly moving water, stay inside. If water is rising inside the vehicle, seek refuge on the roof.

If trapped in a building, go to its highest level. Do not climb into a closed attic. You may become trapped by rising floodwater. Go on the roof only if necessary. Signal for help.

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Listen to authorities for information and instructions.

Avoid driving, except in emergencies.

Be aware that snakes and other animals may be in your house. Wear heavy gloves and boots during clean up.

Avoid wading in floodwater, which can contain dangerous debris and be contaminated. Underground or downed power lines can also electrically charge the water.

Use a generator or other gasoline-powered machinery ONLY outdoors and away from windows.

Be aware of the risk of electrocution. Do not touch electrical equipment if it is wet or if you are standing in water. If it is safe to do so, turn off the electricity to prevent electric shock.

Take an Active Role in Your Safety

Go to **ready.gov** and search for **flood**. Download the **FEMA app** to get more information about preparing for a **flood**. Find Emergency Safety Tips under Prepare.

BE PREPARED FOR A NOVEL PANDEMIC

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A novel (new) virus, like Coronavirus Disease 2019 (COVID-19), can emerge from anywhere and quickly spread around the world. It is hard to predict when or where the next novel pandemic will emerge.

A pandemic is a disease outbreak that spans several countries and affects a large number of people. Pandemics are most often caused by viruses, like COVID-19, which can easily spread from person to person.

May be spread directly from person to person.

May be spread indirectly. Germs can pass from a non-living object to a person.

May be spread by people who are infected but don't have any symptoms.

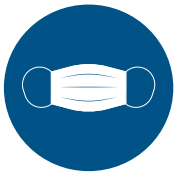
A vaccine, testing, or treatment for the disease may not exist right away. It may take months or years for the majority of the world to become immune to the disease.

IF A NOVEL PANDEMIC IS DECLARED

Wash your hands often with soap and water for at least 20 seconds and try not to touch your eyes, nose, and mouth.

Keep a distance of at least six feet between yourself and people who are not part of your household.

Cover your mouth and nose with a mask when in public.



Clean and disinfect high-touch objects and surfaces.

Stay at home as much as possible to prevent the spread of disease.

Follow the guidance of the Centers for Disease Control and Prevention (CDC) and local authorities.

HOW TO STAY SAFE
WHEN A PANDEMIC THREATENS

Learn how diseases spread to help protect yourself and others.

Take actions to prevent the spread of disease. Cover coughs and sneezes. Stay home when sick (except to get medical care). Wash hands with soap and water for at least 20 seconds.

Plan for schools, workplaces, and community centers to be closed. Investigate and prepare for virtual coordination for school, work (telework), and social activities.

Create an emergency plan so that you and your family know what to do and what you will need in case an outbreak happens. Consider how a pandemic may affect your plans for other emergencies.

Gather supplies in case you need to stay home for several days or weeks. Supplies may include cleaning supplies, non-perishable foods, prescriptions, and bottled water. Buy supplies slowly to ensure that everyone has the opportunity to buy what they need. Remember that not everyone can afford to stock up immediately. Consider avoiding WIC-labeled products so that those who rely on these products can access them.

Review your health insurance policies to understand what they cover, including telemedicine options.

Create password-protected digital copies of important documents and store in a safe place. Watch out for scams and fraud.

Follow the latest guidelines from the CDC and state and local authorities to prevent the spread of disease. Refer to your local and state public health departments for vaccine and testing updates.

Maintain good personal health habits and public health practices. Proper handwashing and disinfecting surfaces help to slow the spread of disease. If soap and water are not available, use a hand sanitizer that contains at least 60 percent alcohol.

Limit close, face-to-face contact with others. Stay at home as much as possible to prevent the spread of disease.

If you believe you've been exposed to the disease, contact your doctor, follow the quarantine instructions from medical providers, and monitor your symptoms. If you're experiencing a medical emergency, call 9-1-1 and shelter in place with a mask, if possible, until help arrives.

Practice social distancing while in public. Keep a distance of at least six feet between yourself and people who are not part of your household. Avoid crowds and large groups of people.

Share accurate information about the disease with friends, family, and people on social media. Sharing bad information about the disease or treatments for the disease may have serious health outcomes. Remember that stigma hurts everyone and can cause discrimination against people, places, or nations.

Know that it's normal to feel anxious or stressed. Engage virtually with your community through video and phone calls. Take care of your body and talk to someone if you are feeling upset.

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Continue taking protective actions, like:

- Staying home when you are sick (except to get medical care).
- Following the guidance of your health care provider.
- Covering coughs and sneezes with a tissue.
- Washing your hands with soap and water for at least 20 seconds.

Follow guidance on the re-opening of businesses, schools, community-based organizations, houses of worship, and workplaces.

Be sure to evaluate your family emergency plan and make timely updates.

Work with your community to talk about the lessons you learned from the pandemic. Decide how you can use these experiences to be more prepared for future pandemics.

Take an Active Role in Your Safety

Go to **Ready.gov** and search for **novel pandemic** and **12 Ways to Prepare** to learn more about how to help you and your family prepare for a disaster. Download the **FEMA app** to get more information about preparing for a novel pandemic. Sign up for the Centers for Disease Control and Prevention subscription services.

BE PREPARED FOR A POWER OUTAGE

Extended power outages may impact the whole community and the economy.

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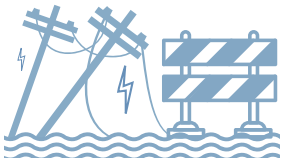
A power outage is when the electrical power goes out unexpectedly.



May disrupt communications, water, transportation

May close retail businesses, grocery stores, gas stations, ATMs, banks, and other services

Can cause food spoilage, water contamination

Can prevent use of medical devices

PROTECT YOURSELF DURING A POWER OUTAGE

Keep freezers and refrigerators closed.

Disconnect appliances and electronics to avoid damage from electrical surges.

Only use generators outdoors and away from windows.

Use alternate plans for refrigerating medicines or power-dependent medical devices.

Do not use a gas stove to heat your home.

If safe, go to an alternate location for heat or cooling.

Check on neighbors.

HOW TO STAY SAFE
WHEN A POWER OUTAGE THREATENS

Take an inventory now of the items you need that rely on electricity.

Talk to your medical provider about a power outage plan for medical devices powered by electricity and refrigerated medicines. Find out how long medication can be stored at higher temperatures and get specific guidance for any medications that are critical for life.

Plan for batteries and other alternatives to meet your needs when the power goes out.

Sign up for local alerts and warning systems. Monitor weather reports.

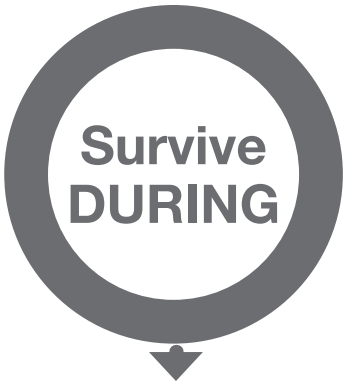
Install carbon monoxide detectors with battery backup in central locations on every level of your home.

Determine whether your home phone will work in a power outage and how long battery backup will last.

Review the supplies that are available in case of no power. Have flashlights with extra batteries for every household member. Have enough nonperishable food and water.

Use a thermometer in the refrigerator and freezer so that you can know the temperature when the power is restored.

Keep mobile phones and other electric equipment charged and gas tanks full.



Keep freezers and refrigerators closed. The refrigerator will keep food cold for **about four hours.** A full freezer will keep the temperature for **about 48 hours.** Use coolers with ice if necessary. Monitor temperatures with a thermometer.

Use food supplies that do not require refrigeration.

Avoid carbon monoxide poisoning. Generators, camp stoves, or charcoal grills should always be used outdoors and at least 20 feet away from windows. Never use a gas stovetop or oven to heat your home.

Check on your neighbors. Older adults and young children are especially vulnerable to extreme temperatures.

Go to a community location with power if heat or cold is extreme.

Turn off or disconnect appliances, equipment, or electronics. Power may return with momentary "surges" or "spikes" that can cause damage.

When in doubt, throw it out! Throw away any food that has been exposed to temperatures 40 degrees or higher for two hours or more, or that has an unusual odor, color, or texture.

If the power is out for more than a day, discard any medication that should be refrigerated, unless the drug's label says otherwise. If a life depends on the refrigerated drugs, consult a doctor or pharmacist and use medicine only until a new supply is available.

Take an Active Role in Your Safety

Go to **Ready.gov** and search for **power outage**. Download the **FEMA app** to get more information about preparing for a **power outage**.

FEMA

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BE PREPARED FOR A THUNDERSTORM, LIGHTNING, OR HAIL

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FEMA P-2143/November 2020

Lightning is a leading cause of injury and death from weather-related hazards.

Thunderstorms are dangerous storms that include lightning.

Include powerful winds

Create lightning and hail

Cause flash flooding and tornadoes

IF YOU ARE UNDER A THUNDERSTORM WARNING, FIND SAFE SHELTER RIGHT AWAY

When thunder roars, go indoors.

Pay attention to alerts and warnings.

Move from outdoors into a building or car.

Unplug appliances.

Do not use landline phones.

HOW TO STAY SAFE

WHEN A THUNDERSTORM THREATENS

Prepare NOW

Know your area's risk of thunderstorms. They can occur year-round and at any hour.

Sign up for your community's warning system. The Emergency Alert System (EAS) and National Oceanic and Atmospheric Administration (NOAA) Weather Radio also provide emergency alerts.

Identify sturdy buildings close to where you live, work, study, and play.

Cut down or trim trees that may be in danger of falling on your home.

Consider buying surge protectors, lightning rods, or a lightning protection system to protect your home, appliances, and electronic devices.

Secure outside furniture.

Survive DURING

When thunder roars, go indoors. A sturdy building is the safest place to be during a thunderstorm.

Pay attention to weather reports and warnings of thunderstorms. Be ready to change plans, if necessary, to be near shelter.

When you receive a thunderstorm warning or hear thunder, go inside immediately.

If indoors, avoid running water or using landline phones. Electricity can travel through plumbing and phone lines.

Protect your property. Unplug appliances and other electric devices.

If boating or swimming, get to land and find a sturdy, grounded shelter or vehicle immediately.

If necessary, take shelter in a car with a metal top and sides. Do not touch anything metal.

Avoid flooded roadways. Turn Around Don't Drown®. Just six inches of fast-moving water can knock you down, and one foot of moving water can sweep your vehicle away.

Be Safe AFTER

Listen to authorities and weather forecasts for information on whether it is safe to go outside and instructions regarding potential flash flooding.

Watch for fallen power lines and trees. Report them immediately.

Take an Active Role in Your Safety

Go to **Ready.gov** and search for **thunderstorm, lightning,** or **hail**. Download the **FEMA app** to get more information about preparing for **thunderstorm, lightning,** or **hail**.

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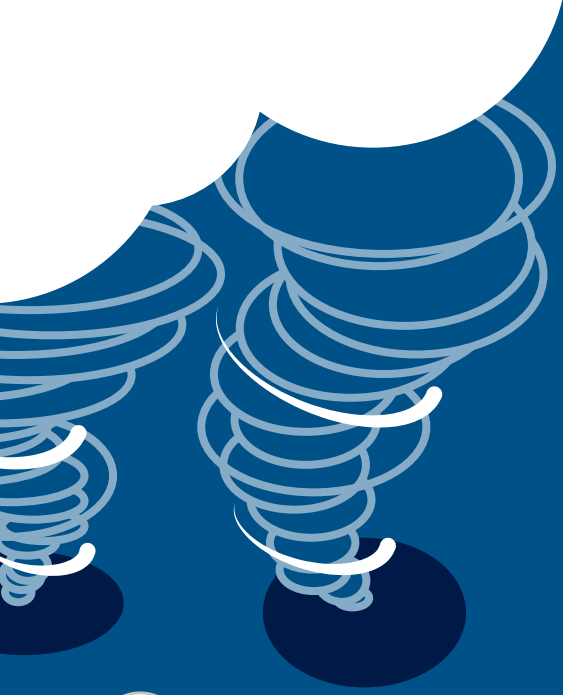

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BE PREPARED FOR A TORNADO

Tornadoes can destroy buildings, flip cars, and create deadly flying debris.

Tornadoes are violently rotating columns of air that extend from a thunderstorm to the ground.

- Can happen anytime
- 200+ MPH — Bring intense winds
- Can happen anywhere
- Look like funnels

IF YOU ARE UNDER A TORNADO WARNING, FIND SAFE SHELTER RIGHT AWAY

- Go to a safe room, basement, or storm cellar.
- If you can safely get to a sturdy building, do so immediately.
- If there is no basement, get to a small, interior room on the lowest level.
- Do not get under an overpass or bridge. You're safer in a low, flat location.
- Stay away from windows, doors, and outside walls.
- Watch out for flying debris that can cause injury or death.
- Use your arms to protect your head and neck.

HOW TO STAY SAFE

WHEN A TORNADO THREATENS

Know your area's tornado risk. In the U.S., the Midwest and the Southeast have a greater risk for tornadoes.

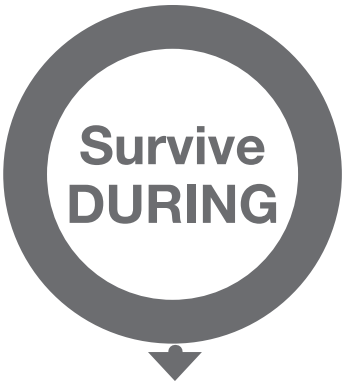
Know the signs of a tornado, including a rotating funnel-shaped cloud, an approaching cloud of debris, or a loud roar—similar to a freight train.

Sign up for your community's warning system. The Emergency Alert System (EAS) and National Oceanic and Atmospheric Administration (NOAA) Weather Radio also provide emergency alerts. If your community has sirens, become familiar with the warning tone.

Pay attention to weather reports. Meteorologists can predict when conditions might be right for a tornado.

Identify and practice going to a safe shelter for high winds, such as a safe room built using FEMA criteria or a storm shelter built to ICC 500 standards. The next best protection is a small, interior, windowless room in a sturdy building on the lowest level.

Consider constructing a safe room that meets FEMA or ICC 500 standards.



Immediately go to a safe location that you identified.

Take additional cover by shielding your head and neck with your arms and putting materials such as furniture and blankets around you.

Listen to EAS, NOAA Weather Radio, or local alerting systems for current emergency information and instructions.

Do not try to outrun a tornado in a vehicle.

If you are in a car or outdoors and cannot get to a building, cover your head and neck with your arms and cover your body with a coat or blanket, if possible.

Keep listening to EAS, NOAA Weather Radio, and local authorities for updated information.

If you are trapped, cover your mouth with a cloth or mask to avoid breathing dust. Try to send a text, bang on a pipe or wall, or use a whistle instead of shouting.

Stay clear of fallen power lines or broken utility lines.

Do not enter damaged buildings until you are told that they are safe.

Save your phone calls for emergencies. Phone systems are often down or busy after a disaster. Use text messaging or social media to communicate with family and friends.

Be careful during clean-up. Wear thick-soled shoes, long pants, and work gloves.

Take an Active Role in Your Safety

Go to **ready.gov** and search for **tornado**. Download the **FEMA app** to get more information about preparing for a **tornado**. Find Emergency Safety Tips under Prepare.

FEMA

FEMA P-2143

BE PREPARED FOR A WINTER STORM

Winter storms create a higher risk of car accidents, hypothermia, frostbite, carbon monoxide poisoning, and heart attacks from overexertion.

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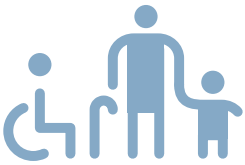
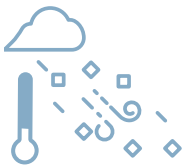
FEMA P-2143/November 2020

Winter storms and blizzards can bring extreme cold, freezing rain, snow, ice, and high winds.



Greater risk



Can last a few hours or several days

Can knock out heat, power, and communication services

IF YOU ARE UNDER A WINTER STORM WARNING, FIND SHELTER RIGHT AWAY

Stay off roads.

Use generators outside only.

Stay indoors and dress warmly.

Listen for emergency information and alerts.

Prepare for power outages.

Look for signs of hypothermia and frostbite.

Check on neighbors.

FEMA

FEMA P-2143/November 2020

BE PREPARED FOR A WILDFIRE

Wildfires can ruin homes and cause injuries or death to people and animals.

A wildfire is an unplanned fire that burns in a natural area such as a forest, grassland, or prairie.

Often caused by humans or lightning.

Can cause flooding or create problems with transportation, gas, power, and communications.

Can damage your property. Set up defense zones to protect your home.

Can happen anywhere, anytime. Risk increases with little rain and high winds.

IF YOU ARE UNDER A WILDFIRE WARNING, GET TO SAFETY RIGHT AWAY

Leave if told to do so.

Listen for emergency information and alerts.

If trapped, call 911.

Use an N95 mask to keep particles out of the air you breathe.

Appendix IV: FDA Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies Guidance for Industry, Investigators, and Institutional Review Boards

Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies

Guidance for Industry, Investigators, and Institutional Review Boards

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. For questions regarding this document, contact (CDER) Office of Medical Policy, CDEROMP@fda.hhs.gov, 301-796-2500.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Clinical Policy (OCLiP)

September 2023
Emergencies

Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies

Guidance for Industry, Investigators, and Institutional Review Boards

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
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Center for Biologics Evaluation and Research
Food and Drug Administration
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Email: ocod@fda.hhs.gov
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Email: CDRH-Guidance@fda.hhs.gov
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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Clinical Policy (OCLiP)

September 2023
Emergencies

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies
Guidance for Industry, Investigators, and Institutional Review Boards[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

Disasters and public health emergencies (PHEs) have the potential to cause major disruptions in the conduct of clinical trials for medical products.[2] Such events can include (but are not limited to) hurricanes, earthquakes, military conflicts, infectious disease outbreaks, or bioterrorist attacks. FDA is issuing this guidance to provide general considerations to assist sponsors, institutional review boards (IRBs), and clinical investigators in assuring the safety of trial participants,[3] maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during disasters and PHEs that may lead to major disruption of clinical trial conduct and operations. The appendix to this guidance further explains these general considerations in a question-and-answer format.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of

[1] This guidance has been prepared by the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Oncology Center of Excellence, and the Office of Clinical Policy at the Food and Drug Administration.

[2] We note that *disasters* and *PHEs*, as those terms are used in this guidance, may include natural catastrophes (e.g., significant earthquakes) and other unanticipated, significant disruptions with the potential to substantially impact the conduct of clinical trials for medical products, including situations where the Secretary of the Department of Health and Human Services has declared a PHE under section 319 of the Public Health Service Act or has declared that circumstances exist justifying the authorization of medical products for emergency use under section 564(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[3] In this guidance, the terms *trial participant*, *participant*, and *subject* are interchangeable.

the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA recognizes that disasters and PHEs can cause major disruptions to the conduct of clinical trials of medical products. For example, disasters or PHEs can lead to population quarantines, trial site closures, travel limitations, interruptions to the supply chain for the investigational product (IP),[4] or other challenges related to the type of disaster or PHE (e.g., site personnel or trial participants infected during an outbreak). These challenges can create difficulties in complying with protocol-specified procedures, including administering or using the IP or adhering to protocol-specified visits and laboratory or diagnostic testing.

FDA is aware that not all trials can be initiated or continued during disasters and PHEs, and for some trials, there may be no alternative to stopping the trial earlier than planned in order to safeguard participants' and trial staff's safety. The determination of whether to continue a trial should be based first and foremost on ensuring that participants will continue to be able to participate safely. The determination should also consider whether the key objectives of the trial can still be met, with appropriate trial modifications implemented. FDA outlines the following general considerations to assist sponsors in ensuring the safety of trial participants, maintaining compliance with GCP, and minimizing risks to trial integrity. The appendix further explains these general considerations by providing answers to questions that the Agency has received about conducting clinical trials during major disruptions.

III. DISCUSSION

A. Considerations for Continuing Trials

- Ensuring the safety of trial participants is paramount. Sponsors should consider above all whether participants can safely continue in the trial, including necessary modifications and risk mitigation steps to ensure safety. Sponsors should also consider whether the trial can continue to meet its key objectives with modifications that adequately address the disaster or PHE circumstances. Study[5] decisions might include those regarding continuing trial recruitment, continuing use of the IP for participants already in the trial, and the need to change participant monitoring during the trial. In all cases, it is critical that trial participants, IRBs/independent ethics committees (IECs), and regulatory agencies are kept informed of changes to the design and conduct of the study as appropriate.

[4] In this guidance, the term *investigational product* refers to investigational human drugs and biological products, as well as investigational medical devices.

[5] In this guidance, the terms *trial* and *study* are interchangeable.

- Sponsors should consider whether the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol, discontinuing the administration or use of the IP, modifying the assessments or assessment schedule, or discontinuing participation in the trial. Such decisions will depend on specific circumstances, including the nature of the IP, the ability to conduct appropriate safety monitoring, the potential impact of the disaster or PHE on the IP supply chain, and the nature of the disease or condition under study in the trial. Sponsors should work with the investigators conducting the trial to assess the individual participant's situation and risk profile when considering their status in the trial.

- Screening procedures (e.g., testing for an infectious disease) that may be mandated by the health care system in which a clinical trial is being conducted may not need to be included as an amendment to the protocol if the sponsor does not plan to incorporate the data collected as part of a new research objective.

- Changes to the protocol or investigational plan to eliminate apparent immediate hazards or to protect the life and well-being of research participants in an emergency may be implemented without IRB approval or before filing an amendment to the investigational new drug application (IND) or investigational device exemption (IDE) but are required to be reported afterwards.[6] FDA encourages sponsors and investigators to work with their IRBs to prospectively define procedures as early as possible in response to major disruptions to ensure participant safety and to prioritize reporting of deviations necessitated by the impact of a disaster or PHE.

- The implementation of alternative processes for the conduct of the study should be consistent with the protocol to the extent possible, and sponsors and clinical investigators should document the reason for any contingency measures implemented. Sponsors and clinical investigators should document how the disaster or PHE led to the changes in study conduct and the duration of those changes, indicate which trial participants were impacted, and document how those trial participants were impacted.

- There may be gaps in data capture, data loss, and difficulties in finalizing and locking datasets because of the disaster or PHE. If changes in the protocol will lead to amending data management, prespecified analyses, and/or statistical analysis plans, the sponsor should consider making such amendments in consultation with the applicable FDA review division. Before locking the database, sponsors should address how protocol deviations related to the disaster or PHE will be handled for the prespecified analyses in the statistical analysis plan.

[6] See 21 CFR 56.108(a)(4), 56.104(c), 312.30(b)(2)(ii), and 812.35(a)(2).

B. Policies and Procedures to Account for Potential Disruptions to Trials

- Sponsors, clinical investigators, and IRBs should consider establishing and implementing policies and procedures, or revising existing policies and procedures, to describe approaches to be used to protect trial participants and manage study conduct during possible disruption of the study. Changes to policies and procedures may address many issues, including the informed consent process; which participants can continue on the IP; study visits and procedures; data collection; study monitoring; adverse event reporting; study oversight; and changes in investigator(s), site staff, and/or monitor(s) due to travel restrictions, quarantine measures, or other safety measures. Policies and procedures should be compliant with applicable (regional or national) laws and regulations for the management and control of the disaster or PHE. Depending on the nature of the changes described above, a protocol amendment or IDE supplement may be required under the applicable regulations.[7]

C. For All Trials That Are Impacted by a Disaster or PHE

Sponsors should provide a description of the impacts on study conduct of the disaster or PHE in a study-specific document with references to appropriate sections of the clinical study report:

1. Contingency measures implemented to manage study conduct during disruption of the study as a result of disaster- or PHE-related control measures

2. Specific challenges faced by the sponsor of the clinical trial as a result of the disaster or PHE

3. A listing of all participants affected by the disaster or PHE-related study disruption by unique trial participant number identifier and by investigational site and a description of how the individual's participation was altered, including missed visits and assessments related to the disaster or PHE

4. Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from IP and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study

Robust efforts by sponsors, investigators, and IRBs or IECs to maintain the safety of trial participants and study data integrity are expected, and such efforts should be documented. FDA recognizes that protocol modifications might occur, including unavoidable protocol deviations

[7] See 21 CFR 312.30(b) and 812.35(a). Under applicable Federal regulations, investigators who are conducting research with Schedule I controlled substances under the Controlled Substances Act must request prior approval from the Drug Enforcement Administration when seeking to conduct research beyond that which is described in the approved protocol (see 21 CFR 1301.18).

due to the disaster or PHE, or control measures implemented in response to the disaster or PHE. Efforts to minimize impacts on trial integrity and to document the reasons for protocol deviations will be important.

APPENDIX: Questions and Answers

Q1. What are some of the key factors that a sponsor should consider when deciding whether to suspend or continue an ongoing study or to initiate a new study during a disaster or public health emergency (PHE)?

Central to any decision should be ensuring that the safety of clinical trial participants can be maintained. Sponsors should assess whether the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing participation in the trial. Such decisions will depend on specific circumstances, including the nature of the investigational product (IP), the ability to conduct appropriate safety monitoring, the potential impact on the IP supply chain, each participant's underlying risk profile and situation during the disaster or PHE, and the nature of the disease or condition under study in the trial. As part of this assessment, sponsors should carefully consider the following aspects of clinical trial conduct when deciding how or whether to proceed with a clinical trial:

- Assessing whether the limitations imposed by the disaster or PHE on protocol implementation pose new safety risks to trial participants, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

- Assessing the availability of technology to communicate effectively and consistently with participants.

- Assessing the continued availability of the clinical investigator/sub-investigators to provide oversight of the trial and properly assess and manage safety issues that may emerge.

- Assessing whether there will be sufficient clinical trial support staff given the evolving situation and its impact on staff availability. Important questions to be considered include: Are there appropriately trained staff that could be available to handle the expected tasks? Are there adequate equipment and materials for clinical trial support staff?

- Assessing whether clinical investigator sites will remain open to trial participants for required in-person assessments or whether the clinical investigator has the ability to provide required in-person assessments at an acceptable alternate location(s) or whether such protocol-specified, in-person assessments can instead be conducted virtually.

- Assessing the continued availability of clinical trial supplies and continued operations of vendors, especially related to supply of the IP and/or to clinical trial supplies that are essential to maintaining appropriate safety monitoring or other key trial procedures. This should include consideration of product stability (shelf life) if the administration schedule is revised or if the clinical site is unable to properly store the product for the needed duration.

- Assessing the continued availability of and support for information technology systems and any other technological tools that are needed to support the trial.

Important questions to be considered include: Are current contingency plans adequate for the types of disruptions that might be anticipated? What other plans can be put in place to minimize disruptions to trial conduct?

- Assessing whether there will be continued operations of and adequate communications with institutional review board (IRB) or independent ethics committee (IEC) and data monitoring committee (DMC) staff, if applicable, to support trial needs.

- Assessing whether it is feasible to conduct the trial in light of any contingency and/or safety measures implemented by Federal, State, or local authorities.

Involvement of a study's DMC, if one has been established, can provide support for the assessments discussed above. Since a primary responsibility of the DMC is ensuring the safety of trial participants, the DMC's assessment of the impact of modifications of trial conduct during a disaster or PHE is important to consider.

The risks and benefits of continuing a trial are likely different than a decision to initiate a trial. Given an evolving situation, with likely increasing impacts on investigators, staff, and supply chains, sponsors should carefully consider the ability to effectively mitigate risks such that patient safety and trial integrity are assured. In addition, it is important to consider whether initiation of the trial could interfere with public safety measures implemented by Federal, State, or local authorities.

Q2. How should sponsors manage protocol deviations and amendments to ongoing trials during a disaster or PHE?

FDA recognizes that during disasters or PHEs, sponsors of clinical trials may need to modify protocol-specified procedures. As is discussed in the main body of this guidance, for protocol deviations necessitated by the impact of a disaster or PHE, the sponsor should document the specific protocol deviation and the reason for the deviation. The sponsor can document protocol deviations using its standard processes or, given the larger expected number of such deviations in disaster or PHE circumstances, use alternative documentation approaches. For example, if visits are to be conducted by telephone or video contact rather than at the investigational site as specified in the protocol, documentation that provides a listing of all study visits (e.g., listing study reference number, patient ID, date of visit) that are deviations from the protocol because of the disaster or PHE generally would be acceptable. Protocol deviations should be included in final study reports and may also be included in annual reports.

For changes in protocol conduct, under the investigational new drug application (IND) regulations, protocol amendments that are necessary to prevent apparent immediate hazards to trial participants can be immediately implemented with subsequent submission and formal approval by the IRB and notification to FDA through filing a protocol amendment to the IND.[1]

[1] See 21 CFR 56.108(a)(4) and 312.30(b)(2)(ii).

For studies under an IND, 21 CFR 312.30(b) specifies that sponsors must submit a protocol amendment to the IND describing any change in a Phase 1 protocol that significantly affects the safety of trial participants or any change in a Phase 2 or 3 protocol that significantly affects the safety of trial participants, the scope of the investigation, or the scientific quality of the study. Pausing enrollment in a trial to decrease potential exposure to an emerging disease or condition related to the disaster or PHE would not generally be expected to significantly affect trial participant safety, the scope of the investigation, or the scientific quality of the study; therefore, submitting a protocol amendment would not be required under the regulation for such a pause.

Prior to IRB approval of an amendment and submission to the FDA, clinical investigators must document as protocol deviations any modifications to protocol-specified procedures.[2] Consolidating several protocol modifications in a single protocol amendment generally will be considered acceptable but should be submitted expeditiously.

For studies under an investigational device exemption (IDE), 21 CFR 812.35(a) generally requires prior FDA approval before implementing changes to the investigational plan. These requirements do not apply to changes made to protect the life or physical well-being of a trial participant in an emergency, including study-wide changes, but such deviations must be reported to FDA within 5 working days.[3] In addition, under 21 CFR 812.35(a)(3), changes to the protocol that the sponsor determines, based on credible information, do not affect the validity of the results from the study; the likely patient risk-to-benefit relationship; the scientific soundness of the investigational plan; or the rights, safety, or welfare of the trial participants may be made without prior FDA approval if the sponsor reports the modifications to the Agency within 5 days of implementing the changes. Because of the unique and evolving circumstances surrounding the impact of a disaster or PHE, we understand that it may be challenging to submit 5-day reports or notices within the required timeframe. Sponsors may consolidate implemented changes when submitting 5-day reports or notices and should update the IDE as soon as possible.

Q3. With the rapid changes in clinical trial conduct that may occur due to a disaster or PHE, including multiple deviations to address patient safety, what is the recommended way for sponsors and investigators to capture these data?

It is important to capture specific information for individual participants that explains the basis for missing protocol-specified information that includes the relationship to the disaster or PHE (e.g., from missed study visits or study discontinuations due to the event). This information, summarized in the clinical study report, will be helpful to FDA. If it is not possible to immediately capture this information in the case report form(s), sponsors may develop processes that enable systematic capture of these data across the sites in a manner that enables the appropriate analysis when the data are submitted to FDA. Sponsors may also develop processes to capture site-level status, site-level or vendor-level protocol deviations, and process deviations.

[2] See 21 CFR 312.62.

[3] See 21 CFR 812.35(a)(2).

Q4. How should a sponsor submit a change in protocol that results from challenges related to a disaster or PHE?

For **IND studies**, the sponsor should submit a formal amendment to its IND, with the following information added to the cover letter in the subject line:

PROTOCOL AMENDMENT – DISASTER OR PHE TYPE (e.g., HURRICANE, COVID-19)

TITLE OF PROTOCOL

Sponsors should summarize the major changes made to the protocol related to the disaster or PHE in the cover letter and should include a tracked changes version of the protocol to facilitate review. As with other protocol amendments, sponsors may implement protocol amendments due to disasters or PHEs upon submission to FDA if approved by the IRB.[4] Sponsors seeking FDA input prior to implementation should indicate that in the cover letter.

For IDE studies, the sponsor should make a submission to its existing IDE, with the following information added to the cover letter in the subject line, as applicable:

CHANGE IN PROTOCOL SUPPLEMENT – DISASTER OR PHE TYPE (e.g., MILITARY CONFLICT or RADIATION EMERGENCY) or

NOTICE OF IDE CHANGE – DISASTER OR PHE TYPE (e.g., EARTHQUAKE or PANDEMIC), as applicable

TITLE OF PROTOCOL

The submission to the IDE should contain a tracked changes version of the protocol to facilitate review.

Q5. Can a sponsor initiate virtual clinical trial visits for monitoring participants without contacting FDA if there is an assessment by the sponsor and investigator that these visits are necessary for the safety of trial participants, and it will not impact data integrity?

FDA regulations allow for changes to be made to the protocol without prior FDA review or approval if the change is intended to eliminate an apparent immediate hazard or to protect the life and well-being of trial participants in an emergency.[5] Therefore, changes in protocol conduct necessary to immediately assure patient safety, such as conducting telephone or video contact

[4] As noted in the response to Q2 above, changes to a protocol necessary to eliminate an apparent immediate hazard to trial participants may be implemented before FDA and IRB review and approval (see 21 CFR 56.108(a)(4) and 21 CFR 312.30(b)(2)(ii)).

[5] See 21 CFR 56.108(a)(4), 312.30(b)(2)(ii), and 812.35(a)(2).

visits for safety monitoring rather than on-site visits, can be immediately implemented with subsequent review by the IRB and notification to FDA. Since this reflects a protocol deviation (until the amendment is approved), documentation of such deviations, as described above, would generally be acceptable (i.e., a document that lists each deviation, study reference ID, patient ID, and date). For example, this could include documentation that all protocol-specified visits will be done by telephone contact rather than on-site visits and that procedures requiring in-person visits will either not be conducted or will be performed by other means (specified, as appropriate). Since the change to telephone or video contact visits would likely result in some protocol-required procedures not being conducted (e.g., vital signs, blood samples for safety laboratory studies), it is critical that the sponsor evaluate the potential impact of alternative approaches on participant safety and consider how to mitigate risks to participants, including whether to discontinue the IP.[6]

For IDE studies, sponsors are required to report deviations implemented to protect the life or physical well-being of a participant in an emergency to FDA within 5 working days after learning of the deviations.[7] We recognize that challenges related to the disaster or PHE may make it difficult to meet this time frame. Sponsors may consolidate implemented deviations when submitting 5-day reports and should update FDA as soon as possible.

Q6. What factors should sponsors consider when deciding whether to change their clinical trial protocol to include remote clinical outcome assessments during a disaster or PHE?

Some clinical outcome assessments (COAs)[8] can be conducted remotely in clinical trials, including COAs for performance outcome (PerfO), interview-based clinician-reported outcome (ClinRO),[9] patient-reported outcome (PRO), and observer-reported outcome (ObsRO). During a disaster or PHE, investigators might still be conducting in-person assessments on some trial participants, whereas remote assessments may be recommended for others to protect their safety or to respond to measures implemented by Government authorities to protect the public. When

[6] See 21 CFR 312.23(a)(6) and 812.25(c).

[7] 21 CFR 812.35(a)(2).

[8] In this guidance, a *COA* is an assessment of a clinical outcome (i.e., an outcome that describes or reflects how a patient feels, functions, or survives); a *PerfO* is a measurement based on a standardized task performed by a participant that is administered and evaluated by an appropriately trained individual or is individually completed; a *ClinRO* is a measurement by a trained health care professional after observing a trial participant's health condition; a *PRO* is a measurement based on a report that comes directly from the participant about the status of a patient's health condition without amendment or interpretation of the participant's response by a clinician or anyone else; and an *ObsRO* is a measurement based on a report of observable signs, events, or behaviors related to a participant's health condition by someone other than the participant or a health professional (e.g., a parent or caregiver). See FDA-NIH Biomarker Working Group BEST (Biomarkers, Endpoints, and other Tools) Resource, available at https://www.ncbi.nlm.nih.gov/books/NBK326791.

[9] Non-interview-based ClinRO assessments, such as those reliant on diagnostic imaging or physical examination, present a distinct set of challenges and are not addressed in this guidance.

deciding whether to change their clinical trial protocols to include remote COAs, sponsors should evaluate the general and specific considerations outlined below.

General considerations regarding (1) prioritization of trial participant safety and privacy; (2) maintenance of data quality and integrity, including minimizing missing data; and (3) appropriate training for personnel and trial participants, which are discussed elsewhere in this guidance, are also common to all COAs. Other general considerations that are common to all COAs include attention to (1) the potential for increased variability in trial data; (2) the feasibility of conducting a specific type of COA remotely, depending on the context of use; (3) documentation and audit trails; and (4) availability of technology and technical support required for remote assessment. These considerations are explained in more detail below.

Increased Variability in Data: When switching from in-person to remote assessments, sponsors should perform remote assessments in a manner as similar as possible to those done in-person, while protecting trial participant safety and privacy. To the extent feasible, sponsors should ensure that the methods and conduct of remote assessments are consistent across sites, trial participants, and visits to minimize variability in the data. For example, if a sponsor decides that video is their preferred method of remote assessment in a clinical trial, then using different methods to conduct assessments (e.g., both telephone and video in the same trial) may increase variability. Maintaining consistency in assessment methods should be balanced, however, against the need to minimize missing data, and the decision to use different methods should be justified in study documentation.

Feasibility of the Assessment Method Within the Context of Use: Investigators should assess the feasibility of conducting a specific type of COA remotely, which will depend on corresponding trial goals and needs (e.g., ability to conduct the assessment in a way that captures all the data needed to evaluate the endpoint in the trial), given that not all assessments can provide an accurate assessment when done remotely.

Documentation and Audit Trails: Investigators should document and sponsors should include in the clinical trial datasets (1) data on variables related to the trial, (2) whether an assessment was conducted in-person or remotely (including type of technology used), and (3) the date of the assessment and the name of the person who conducted the assessment. Sponsors also should ensure that remote data acquisition, transmission, and storage are secure and that the privacy of trial participants is protected. When sponsors use electronic platforms to perform remote assessments that transmit data directly into trial records, these platforms should use automated audit trails.[10]

Technology and Technological Support: Sponsors planning to use remote electronic assessments as part of a clinical investigation should use appropriate technology and develop procedures for provision of technology and technical support to trial participants, investigators, and/or other trial personnel to facilitate those assessments. For example, sponsors could develop

[10] See the guidance for industry *Computerized Systems Used in Clinical Investigations* (May 2007). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

a plan to accommodate trial participants who are either already enrolled in a trial or may be enrolled in a trial in the future but who do not have access to appropriate communication technology (e.g., cell phones or Internet) by providing trial participants with these technologies.

Specific considerations for certain COA types are explained below.

PerfO- and Interview-Based ClinRO-Specific Considerations: For these types of assessments, sponsors should consider (1) appropriateness of remote assessment for the type of clinical data to be collected; (2) special investigator training to administer the PerfO or interview-based ClinRO assessments remotely; and (3) procedures for assessing and confirming the safety of trial participants, their privacy, and appropriate setting and resources to adequately complete the assessment.

Recognizing that components of the PerfO and interview-based ClinRO assessment for some trials may specify visualization or in-person interactions with trial participants that may be difficult to replicate through remote interactions, sponsors should assess whether these components can be evaluated in an alternative way that still permits an accurate clinical assessment. When components of the assessment cannot be accomplished in a remote encounter, investigators should document and sponsors should report in the clinical trial datasets any aspects of the assessment they are unable to accomplish remotely. Sponsors should consider whether the information that can be collected remotely will be sufficient to reliably assess the clinical outcome and support robust conclusions for the study.

PRO- and ObsRO-Specific Considerations: For these types of assessments, sponsors should consider (1) potential for missing data when switching from in-person assessment to remote assessment; (2) whether switching from use of paper- or electronic-based PRO and ObsRO assessments completed independently to assessments administered verbally by another person may lead to bias of scores (e.g., if trial participants try to please the site staff by offering ratings that might not truly reflect their experience); and (3) that data collected with PROs and ObsROs through verbal administration should not be considered a substitute for required safety monitoring throughout the trial.[11]

To minimize potential bias resulting from verbal administration of PRO and ObsRO assessments, sponsors should ensure interviewer training and use of an interview script. Sponsors may also consider using automated virtual interviewers or a trained, neutral third-party interviewer to administer the assessments remotely.

The potential for missing data is also a limitation when switching from in-person to remote assessment using paper-based PRO or ObsRO assessments if the trial participant or observer fails to complete all or part of the questionnaire within a given timeframe. To mitigate potential for missing data, sponsors should consider remote electronic capture of these assessments through technologies that can remind trial participants to complete the questionnaires and/or verbal administration at the time instructed (assuming appropriate steps are taken to minimize

[11] See 21 CFR 312.32(b), 312.56(c), and 812.46.

bias from verbal administration). Investigators should record which assessments were conducted by alternative means on a participant level.

Q7. I am a sponsor and would like to use an alternate laboratory or imaging center[12] for protocol assessments. What should I consider regarding when this approach would be appropriate and how to select alternate laboratories or imaging facilities?

Given that trial participants may not be able to come to the investigational site for protocol-specified visits at which laboratory tests or imaging would be conducted, sponsors should evaluate whether it is feasible to use alternative laboratories or imaging centers. The suitability of such alternative arrangements may vary depending on whether the protocol-specified procedures are related to eligibility criteria, safety evaluations, or endpoint assessments.

In general, if trial participants cannot access a clinical trial site, alternative sites may be used for laboratory tests or imaging assessments that focus on the safety of trial participants when such tests and assessments are routinely performed in those settings (e.g., routine chemistries, blood counts, chest radiographs).[13]

However, if the results of laboratory tests or imaging assessments are the basis for evaluating important (e.g., primary or secondary) efficacy or safety endpoints, sponsors should consult with the relevant FDA review division before considering an alternative site. For example, differences in laboratory measurements or imaging protocols may introduce increased variability in analyses, which should be considered.

When baseline tests are necessary to characterize the eligible study population, potential variation in test performance or precision related to use of an alternative laboratory or imaging center may also warrant discussion with the relevant FDA review division. For example, an inclusion criterion based on a commonly available, routine test performed as a safety screen (e.g., renal function on a metabolic panel) might be amenable to alternative laboratory collection with minimal impact on study results. Using an alternative laboratory for tests related to other eligibility factors could be more likely to affect study integrity (e.g., laboratory tests to identify a tumor biomarker required for inclusion, genetic test to identify a marker that is a critical inclusion criterion). It may be important for such assessments to be standardized at a single site or a few sites. Based on the nature of laboratory tests conducted for the purpose of protocol assessments, the alternative laboratory conducting such tests for investigational purposes will likely be subject to certification and other requirements under the Clinical Laboratory

[12] For IND studies, this would be laboratories and imaging centers not listed on Form FDA 1572.

[13] If a local laboratory or imaging center will be used for certain patients and will not replace the laboratory and imaging center specified in Form FDA 1572 for all patients, these alternative facilities do not need to be listed on Form FDA 1572; it is sufficient to retain documentation of when such facilities were used for protocol specified tests. The sponsor can accumulate these changes and submit this information to the IND, in for example, an information amendment or a protocol amendment.

Improvement Amendments (CLIA).[14] Alternative laboratory and imaging centers may also be subject to additional laws governing their operations. Investigators should record which assessments were conducted by alternative means on a participant level.

Q8. We are instituting trial participant visits remotely through video conferencing. Are there recommendations regarding best practices?

With the increasing use of telemedicine in clinical practice, a number of resources may be available to provide recommendations on best practices. FDA does not endorse any particular telemedicine best practices. However, from an FDA regulatory perspective, important considerations for trial visits through video conferencing include:

- The investigator or study personnel who will conduct remote visits should be trained on how to conduct real-time video conferencing visits (e.g., training on the use of telemedicine for remote clinical trial visits).

- Procedures should be put in place to maintain a trial participant's privacy, as would be done for a clinical visit.

- Both the investigator and the trial participant should confirm their respective identities with one another before engaging in a real-time video conference visit according to an identity verification plan developed by the sponsor.[15]

To provide the same information that would be documented during a face-to-face visit, the date of a real-time video conference visit should be documented in the trial records and, if specified in the protocol, the time of the visit. Investigators should consider asking for the trial participant's location during a video conference visit in case a medical emergency arises during the visit.

FDA considers real-time video interactions, including telemedicine, as a live exchange of information between the trial personnel and trial participants. These interactions are not considered electronic records and therefore are not subject to 21 CFR part 11.[16]

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[14] For more information on the CLIA, see https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/Research-Testing-and-CLIA.pdf.

[15] FDA does not endorse any specific identification method. Sponsors may consider the National Institute of Standards and Technology (NIST) Special Publication 800-63A, Digital Identity Guidelines: Enrollment and Identity Proofing Requirements, available at https://doi.org/10.6028/NIST.SP.800-63a.

[16] See 21 CFR 11.1(b). See also the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003).

Q9. If patients are currently dispensed IP through a pharmacy at the clinical trial site for self-administration at home, can a sponsor switch that to home delivery without amending the protocol?

Home delivery of IP that would not raise any new safety risks may be implemented to protect patients from risks associated with coming to clinical trial sites. In all cases, requirements under FDA regulations for maintaining IP storage conditions in accordance with the investigational plan and for IP accountability remain; these requirements must be addressed and documented.[17] If the protocol indicates pharmacy dispensing for self-administration at home and this is changed to direct-to-patient shipments, then a protocol amendment[18] or change to the investigational plan[19] would be required to permit home delivery of the IP. If the extent of home delivery is limited to certain participants and not the entire population described in the protocol, documenting the change in the mechanisms of distribution of IP administration through protocol deviations may also be acceptable.[20] If the change in the mechanisms of IP distribution is then included in a submission to the existing IND or IDE, such a change may be part of a cumulative submission that includes a number of changes that accrue, rather than an urgent protocol change.[21] Sponsors are also responsible for ensuring that home delivery does not compromise the quality of the product supplied.

Q10. How can the sponsor ensure proper disposal of unused investigational drug product if the participant cannot return to the study site?

FDA regulations outline sponsor and investigator responsibilities for storage conditions and accountability of investigational drug products, including disposition of unused IPs.[22] Under 21 CFR 312.59, the sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator. The regulation further provides that the sponsor may authorize alternative disposition of unused supplies of the investigational drug, provided this alternative does not expose humans to risks from the drug. The procedure for disposition is generally considered part of the investigational plan and is normally described in the study protocol as a study-specific plan for handling the IPs. In most protocols, such plans involve the participant bringing the unused IP to the clinical trial site and then the investigator returning the unused IP to the sponsor or its designee. During a disaster or PHE, if appropriate, a prepaid shipping package can be used by the participant to return IP back to a central location where it

[17] See 21 CFR 312.60, 312.62, 812.100 and 812.140.

[18] See 21 CFR 312.30(b).

[19] See 21 812.35(a).

[20] Investigators must not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects (21 CFR 56.108(a)(4), 312.66, and 812.35(a)). An amendment to the protocol should be considered if a protocol deviation is not isolated or transient. When impacting only a specific region or country, a country-specific amendment may be appropriate.

[21] See 21 CFR 312.30(b), 812.35(a), and 812.150(a)(4).

[22] See 21 CFR 312.57, 312.59, 312.60, and 312.62.

can be accounted for and disposed of per the protocol, but this approach is not the only way to satisfy the regulatory requirements for disposition of unused IP. Regardless of the chosen disposition method, sponsors and investigators must maintain adequate records regarding the disposition of the IP.[23]

Sponsors may consider adopting alternative procedures for disposition of IP that permit sponsors and investigators to fulfill their requirements for maintaining adequate records of IP disposition (including documenting dates, quantity, and use by participants), provided such procedures do not expose humans to risks from the IP.[24] For example, it may be possible to provide the participants with a way to dispose of the IP at their home (such as with a drug disposal pouch) and document such disposal through photo or video that can be transmitted to the investigator or sponsor. FDA does not endorse a particular approach, but relevant considerations (e.g., environmental) associated with specific IPs should be considered when selecting a method for disposal. FDA has provided a consumer update *Where and How to Dispose of Unused Medicines*[25] that provides recommendations to consumers about how to safely dispose of unused FDA-approved medication at home. Sponsors can consider whether any of those recommended methods of disposition are appropriate for approved drugs being studied for a new use in a clinical investigation. As noted in the consumer update, FDA only recommends flushing medications that are on the FDA flush list, which currently does not include unapproved IP.

Investigators proposing alternative disposition methods must obtain authorization of those methods from the sponsor of the trial.[26] Additional restrictions may apply to IPs subject to the Controlled Substances Act.[27]

Q11. If participants are currently receiving an IP at the clinical trial site, can a sponsor switch to use at home?

Sponsors should consider the safety risk to trial participants who would miss receiving an IP because of the inability to come to the clinical trial site during a disaster or PHE. If a sponsor is considering providing alternative arrangements for administration of the IP (e.g., home nursing or alternative sites by trained but non-study personnel), the sponsor is expected to perform a risk assessment that considers the nature of the IP and the potential risks to both the trial participants and the health care providers (HCPs) responsible for administering the product at the alternative site. This risk assessment should include evaluation of risk mitigation steps. Based on this risk assessment, sponsors should consider consulting the appropriate FDA review divisions regarding alternative plans for the administration of IP that is usually administered in a health care setting.

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[23] See 21 CFR 312.57 and 312.62.

[24] Sponsors should consider whether an information amendment should be submitted pursuant to 21 CFR 312.31.

[25] See https://www.fda.gov/consumers/consumer-updates/where-and-how-dispose-unused-medicines.

[26] See 21 CFR 312.59 and 21 CFR 312.62.

[27] See 21 CFR 312.58(b) and 312.69.

Consulting FDA is strongly advised for complex IPs (e.g., cellular therapy and gene therapy products), where potentially altered storage and handling conditions could adversely affect product stability. However, in all cases, applicable requirements for maintaining IP storage conditions in accordance with the investigational plan (before and after reconstitution, if applicable), IP reconstitution specifications per the investigator's brochure, and IP accountability remain and must be addressed and documented.[28] Storage conditions and IP accountability should be considered if the protocol is amended to permit alternative site infusions. Defining circumstances when discontinuing IP administration, while continuing study participation, albeit with potentially delayed assessments, may be an appropriate option when suitable alternative arrangements for administration of the IP cannot be made.

Q12. Considering that there may be delays to on-site monitoring of clinical trials during a disaster or PHE, what are FDA's recommendations, including for remote monitoring, in such circumstances?

FDA recognizes that study monitors may not be able to access the trial sites for on-site visits in a timely manner during a disaster or PHE. Sponsors should work to find alternative approaches to maintain trial participant safety and trial data quality and integrity, such as enhanced central monitoring, telephone contact with the sites to review study procedures, or remotely tracking trial participant status and study progress where appropriate and feasible.

Sponsors should carefully document situations where monitors were unable to access or had to delay monitoring of a clinical site. Sponsors or monitors should also include in their documentation of protocol deviations, or other GCP non-compliance issues identified at clinical sites, whether delayed identification was due to postponed monitoring. FDA recognizes that unique situations at clinical sites may occur due to contingency and safety measures implemented and will consider these circumstances when evaluating inspectional observations.

FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations.[29] The regulations are not specific about how sponsors must conduct such monitoring and are therefore compatible with a range of approaches to monitoring that may vary depending on multiple factors. Therefore, certain aspects of site monitoring visits can be done remotely if technically feasible. FDA understands that during a disaster or PHE, there may be deviations from the timing of on-site monitoring visits set forth in the trial monitoring plan and procedures and that sponsors may consider ways to replace on-site monitoring visits with remote monitoring visits. Further, there may be components of an on-site monitoring visit, as outlined in the trial monitoring plan, that cannot be completed remotely.

During a disaster or PHE, traditional on-site monitoring might be difficult for reasons such as (1) sites may not be able to accommodate monitoring visits (e.g., due to staffing limitations or site closures) or (2) monitors may not be able to travel to trial sites. When planned on-site

[28] See 21 CFR 312.60, 312.62, 812.100 and 812.140.

[29] See 21 CFR 312.50, 312.53(d), 312.56(a), 812.40, 812.43(d), and 812.46.

monitoring visits are not possible, the reason should be documented and available for review by the sponsor and during FDA inspections.

The sponsor should consider using a risk-based approach to prioritize sites for remote monitoring, including as many study sites as feasible (and with a frequency as close to that described in the site monitoring plan as feasible).[30,31] The sponsors should also consider additional factors in any risk-based approach (e.g., underlying participant risk profile, type of medical product, ability to obtain the required data remotely). The decision regarding which sites to prioritize for remote monitoring should be guided by centralized monitoring or other information available about site performance (e.g., frequency and severity of protocol deviations previously identified during monitoring visits or currently identified by centralized monitoring, number of randomized active trial participants, experience of site staff, known history of prior major audit or inspection findings).

Remote monitoring should be focused on review of critical study site documentation and source data. If the materials identified for review include participants' medical records that are normally reviewed at the site (and such a review is consistent with the trial participants' informed consent documents), then, to complete source document review, remote review of medical records may be explored. When the study monitor cannot access the site to review critical source documents, requests for review of source documents that may include private health information should be consistent with requirements for source document validation and review as described in the current study monitoring plan or other appropriate study-specific document. When remote monitoring processes and procedures have not previously been described by the sponsor, these processes and procedures should be established (e.g., in a revised study monitoring plan or in updates to existing sponsor policies and procedures).

During remote monitoring, the study monitor should focus on trial activities that are essential to the safety of trial participants and/or data reliability. Sponsors and monitors may wish to consider one or more of the following options to facilitate remote monitoring access to clinical site records:

- If the site can provide appropriate resources and technical capabilities, consider establishing a secure remote viewing portal that would permit site staff to provide access to the site's study documentation and/or trial participants' source documents for the study monitor's review. In addition, the potential for remote access to trial participants' electronic health records can be explored with trial sites.

[30] See the guidance for industry *A Risk-Based Approach to Monitoring of Clinical Investigations: Questions and Answers* (April 2023).

[31] See the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013).

- Sites could upload certified copies[32] of source records to a sponsor-controlled electronic system or other cloud-based repository that contains appropriate security controls. In the setting of a blinded or partially blinded study, if source documents may contain unblinded information, controls to protect the study blind should be in place prior to transfer of source documents (e.g., use of an unmasked study monitor to review source documents, restricted access to folders containing copies of source documents). It is not necessary for the clinical site to have control of certified copies of source documents uploaded to such a repository; however, the clinical investigator should maintain control of the original source records.

Regarding retention of copies of source documents used for remote review, it would not be necessary to retain the certified copies of source documents used for remote review, provided the clinical investigator retains the original source documents according to FDA regulations for the retention of records.[33]

In addition, processes and procedures should be established for the handling of source document copies that were placed in temporary storage locations for remote review and that are no longer needed after the remote monitoring has concluded.

Remote monitoring activities, including remote review of source documents, should be documented in the same level of detail as on-site monitoring activities, and any resulting actions to address issues identified from the remote source document review should be consistent with procedures and processes described in the study monitoring plan.

Q13. During a disaster or PHE, some sponsors have used remote monitoring to oversee study conduct at clinical trial sites, including remote review of source data. Should data that have been remotely monitored be re-monitored during an on-site monitoring visit once the disaster- or PHE-related restrictions that prevented on-site monitoring visits have been lifted?

FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations.[34] These regulations are not specific about how sponsors must conduct such monitoring and are therefore compatible with a range of approaches that may vary depending on multiple factors. The guidances for industry *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring* (August 2013) and *A Risk-Based Approach to Monitoring of Clinical*

[32] FDA guidance on good clinical practice, developed with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), defines a certified copy as "[a] copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original." See the ICH guidance for *industry E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

[33] See 21 CFR 312.62 and 812.140(a).

[34] See 21 CFR 312.50, 312.53(d), 312.56(a), 812.40, 812.43(d), and 812.46.

Investigations: Questions and Answers (April 2023) clarify that sponsors can use a variety of approaches to fulfill their responsibilities for monitoring clinical investigations; these guidance documents also describe monitoring activities that reflect modern, risk-based approaches, including remote monitoring when appropriate.

The decision as to whether remote monitoring conducted for a given site or clinical investigation was adequate or should be followed up with additional on-site monitoring visits should be based on the sponsor's ongoing risk assessment. The sponsor may determine that on-site follow-up of remote monitoring activities is appropriate based on a risk assessment (e.g., sites with certain data anomalies or a higher frequency of errors, important protocol violations, or dropouts relative to other sites). As with on-site monitoring, remote monitoring should be focused on critical data and processes for human subject protection and trial integrity, such as the site's conduct of key study procedures and documentation related to important efficacy endpoints and safety assessments.

Q14. How do I obtain signed informed consent from a hospitalized patient who is in isolation during the disaster or PHE and is physically inaccessible because policies prevent trial staff from entering the patient's room due to a disaster or PHE?

FDA regulations generally require that the informed consent of a trial participant be documented by the use of a written consent document that typically includes the elements of informed consent, as described under 21 CFR 50.25, and that has been approved by the IRB and signed and dated by the trial participant or their legally authorized representative at the time of consent (21 CFR 50.27(a)). When feasible, we recommend a traditional method of obtaining and documenting informed consent using a signed paper copy of the consent form or use of electronic informed consent.[35,36] If neither of these approaches are possible, the following procedures would be considered to satisfy FDA's informed consent documentation requirement.[37]

Method 1: A photograph of the signed informed consent document can be transmitted to the trial staff

1. An unsigned consent form is provided to the patient (e.g., by a health care worker who has entered the room).

2. The investigator or designee arranges a telephone call or video conference call with the patient (and, if desired and feasible, additional individuals requested by the patient (e.g., next of kin)).

[35] See the guidance for institutional review boards, investigators, and sponsors *Use of Electronic Informed Consent: Questions and Answers* (December 2016).

[36] See Q15.

[37] The procedures suggested do not apply to the exception from general informed consent requirements under 21 CFR 50.23 or the exception from informed consent requirements for emergency research under 21 CFR 50.24.

3. To ensure that prospective participants are approached in a consistent fashion, a standard process should be used that will accomplish the following:

    - Identification of who is on the call.

    - Review of the informed consent document with the patient by the investigator or designee and response to any questions the patient may have.

    - Verbal confirmation by the patient that their questions have been answered, that they would like to participate in the trial, and that they have signed and dated the informed consent document that is in their possession.

4. The patient (or an individual in the room) takes a photograph of the signed informed consent document and sends it to the investigator/designee.

5. A trial team member enters the photograph into the trial records along with an attestation that states how that photograph was obtained and that it is a photograph of the informed consent document signed by the patient.

Method 2: A witness can attest to the signature or a recording can be obtained, but a photograph of the signed informed consent document cannot be transmitted

1. An unsigned consent form is provided to the patient (e.g., by a health care worker who has entered the room).

2. The investigator or designee arranges a three-way telephone call or video conference call with the patient, a witness who is not otherwise connected with the clinical investigation, and, if desired and feasible, additional individuals requested by the patient (e.g., next of kin). Alternatively, in lieu of using a witness, a recording of the conversation can be made.[38]

3. To ensure that prospective participants are approached in a consistent fashion, a standard process should be used that will accomplish the following:

    - Identification of who is on the call.

    - Review of the informed consent document with the patient by the investigator or designee and response to any questions the patient may have.

    - Verbal confirmation by the patient that their questions have been answered, that they would like to participate in the trial, and that they have signed and dated the informed consent document that is in their possession.

[38] If an investigator wants to record the telephone or video conference call, the investigator or designee should ensure that the recording is done in a manner consistent with applicable State and local laws and that all parties agree to being recorded.

4. When using a witness, documentation in the trial records includes (1) a signed and dated attestation by the witness who participated on the call that the patient confirmed their agreement to participate in the trial and signed the informed consent document and (2) a signed and dated attestation by the investigator or designee stating why the informed consent document signed by the patient was not retained (e.g., due to potential contamination of the document by infectious material).

   When using a recording in lieu of a witness, documentation in the trial records includes (1) the recording of the conference call and (2) a signed and dated attestation by the investigator or designee who participated on the call stating why the informed consent document signed by the patient was not retained (e.g., due to potential contamination of the document by infectious material).

When either method 1 or 2 is used to document informed consent, the resulting documentation should be (1) collected and archived, as either original paper copies or appropriately certified electronic copies (e.g., using a validated process for scanning paper copies)[39] and (2) retained according to applicable FDA record retention requirements as part of the trial record.[40]

If the patient is unable to provide informed consent and there is a legally authorized representative, investigators must obtain written consent from the patient's legally authorized representative in accordance with 21 CFR 50.27(a).

Q15. What considerations apply to the electronic systems used to generate electronic signatures on electronic clinical trial records, including informed consent documents, during a disaster or PHE?

Electronic systems[41] used to generate electronic signatures[42] on electronic clinical trial records, including informed consent documents, generally must comply with the requirements outlined in

[39] See footnote 32.

[40] See 21 CFR 312.57, 312.62, and 812.140.

[41] For the purposes of this guidance, the term *electronic systems* means systems, including hardware and software, that create, modify, maintain, or transmit electronic records.

[42] For the purposes of this guidance, the term *electronic signature* means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature (21 CFR 11.3(b)(7)).

FDA regulations under 21 CFR part 11 (part 11).[43,44]

FDA is aware that there are multiple commercial off-the-shelf (COTS) software systems providing electronic signature services for electronic clinical trial records. FDA does not certify individual electronic systems or methods to obtain part 11-compliant electronic signatures on electronic records, but COTS vendors may be able to provide sponsors and other regulated entities with information regarding whether their systems are part 11-compliant. Sponsors and other regulated entities should work with COTS vendors to ensure compliance with part 11. For further information regarding part 11 compliance, see the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003) and the additional recommendations proposed in the draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers* (March 2023).[45]

When a part 11-compliant electronic system used to create electronic signatures is not available, regulated entities must have an alternate means of obtaining required signatures[46] (e.g., handwritten[47] wet ink signatures executed on documents, handwritten stylus or finger-drawn signatures executed on electronic documents that are then printed or appropriately witnessed). Alternative methods for obtaining signatures on informed consent documents are described in Q14 of this guidance. When handwritten methods are used, the sponsor and other regulated entities should ensure that all records containing original handwritten signatures are (1) collected and archived, as either original paper copies or appropriately certified electronic copies (e.g., using a validated process for scanning paper copies) and (2) retained according to applicable FDA record retention requirements.[48]

Q16. I am a sponsor of commercial INDs, and electronic common technical document (eCTD) requirements cannot be met due to a disaster or PHE. Whom do I contact for assistance?

Commercial sponsors may qualify for a short-term waiver from the eCTD requirements under section 745A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in unique and rare circumstances and for a limited duration. During a disaster or PHE, rare circumstances may

[43] See 21 CFR 11.1(b), 11.10, and 11.30. See also the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003) and the draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers* (March 2023). When final, this guidance will represent FDA's current thinking on this topic.

[44] For electronic records that are not subject to part 11, sponsors and other regulated entities should rely on their internal business practices to determine acceptable electronic signature methods and controls.

[45] When final, this guidance will represent FDA's current thinking on this topic.

[46] See 21 CFR 50.27(a).

[47] See 21 CFR 11.3(b)(8) for the definition of a *handwritten signature*.

[48] See 21 CFR 312.57, 312.62, and 812.140.

arise in which a sponsor cannot meet eCTD requirements (e.g., if computer operations are impacted). For information on requesting a short-term waiver from eCTD requirements, see section III.E of the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (eCTD guidance) (February 2020).

Companies experiencing technical difficulties with transmission of their electronic submissions to FDA should consult FDA's electronic submission staff for technical assistance, rather than submitting a waiver request, as described in section III.E of the eCTD guidance.

Q17. During a disaster or PHE, participants may no longer be able to travel to a central location for administration of an investigational drug that is scheduled on a recurring basis. Can the IP be shipped to a local HCP who is not a sub-investigator to administer the product to a participant while still maintaining integrity of the trial? If so, what else would be needed regarding trial monitoring and IRB oversight?

Specific circumstances for a given clinical trial would affect the feasibility and appropriateness of shipping IP to locations other than clinical trial sites as specified under an IND, as well as administering the IP. Depending on how the IP(s) being evaluated in the trial are administered, it would be important that any alternative location have appropriately trained personnel and oversight by physicians with sufficient experience regarding the class of products involved to assure trial participant safety comparable to administration at a trial site.

In this guidance, local HCPs who are administering drugs in a manner that does not differ from their normal clinical practices would not be considered sub-investigators and need not be listed on Form FDA 1572.[49] FDA recommends that these HCPs be listed in site records, such as a log of activities delegated by the investigator. Any changes to a trial protocol to permit HCPs to administer the investigational drug generally must be reviewed and approved by an IRB.[50]

The above paragraph describes administration of the IP by local HCPs who are practicing medicine within their scope of practice. In contrast, if a sponsor will be asking local HCPs to perform study-specific research procedures or assessments that represent a direct and significant contribution to the clinical data for the study (e.g., assessing drug response for a patient or performing a procedure unique to the study and not part of routine medical care), these HCPs would be considered sub-investigators that must be listed on Form FDA 1572.[51]

[49] For the definition of a *sub-investigator*, see 21 CFR 312.3(b); for the requirement to list sub-investigators on the FDA Form 1572, see 21 CFR 312.53(c)(1)(viii).

[50] As noted in the response to Q2 above, changes to a protocol necessary to eliminate an apparent immediate hazard to trial participants may be implemented before FDA and IRB review and approval (see 21 CFR 56.108(a)(4) and 21 CFR 312.30(b)(2)(ii)).

[51] 21 CFR 312.53(c)(1)(viii).

IP may be shipped from a central distribution site directly to an HCP, provided that such shipping is done under the supervision of the investigator using procedures that ensure accountability and product quality (i.e., that storage conditions, as defined in the protocol, for the IP were maintained during shipping, and the drug packaging was intact upon receipt).

If the HCP administering the IP is not considered a sub-investigator, the investigator should ensure that they can obtain records regarding administration of the IP by requesting that the trial participants provide consent to allow access to medical records from their local HCPs involving trial-related data, such as measuring vital signs, and results of evaluations of any symptoms or signs occurring with receiving the product. Communicating to the HCP the intent to request such records in advance may facilitate this process.

Consulting the appropriate FDA review division on plans for alternative administration is also recommended as per Q11 above.

Q18. If a trial participant is unable to receive the IP from the trial site but the medical product is legally marketed in the United States for other uses, can the participant or HCP secure the product commercially? Can the sponsor reimburse trial participants for their out-of-pocket expenses in getting the product commercially?

If the product under investigation in a clinical trial is legally marketed and the study does not require blinding, then local sourcing of the product would be acceptable to FDA (e.g., by having the local physician write a prescription for the product instead of shipping the product directly to the participant). Depending on the circumstances for providing the commercially obtained drug to the participant, the sponsor may need to submit a request to charge for the investigational drug under 21 CFR 312.8(a)(3) and satisfy other applicable requirements under 21 CFR 312.8. FDA also would not object if the sponsor reimburses the participant for any costs incurred by commercially purchasing the product or for charges related to the use of the product (e.g., charges related to an infusion).

Per FDA regulations under 21 CFR 312.6, the immediate package of an investigational new drug intended for human use must include a label with the statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use." Per FDA regulations under 21 CFR 812.5, an investigational device or its immediate package for human use must include a label with the statement "CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use." FDA recognizes that a commercially obtained product will not have this statement on its container. In the setting of a disaster or PHE, where alternative arrangements are being made to provide a commercially obtained investigational drug to a participant who is unable to come to the trial site, FDA does not intend to object to the labeling of the investigational drug because it does not include the statement required under 21 CFR 312.6 and the sponsor has not obtained a waiver of that requirement under 21 CFR 312.10. In addition, FDA similarly does not intend to object to the labeling of a commercially obtained investigational device because it does not include the statement required under 21 CFR 812.5 and the sponsor has not obtained a waiver under 21 CFR 812.10.

Q19. Throughout the guidance, FDA recommends that sponsors consult with the review division for certain changes to ongoing clinical trials. For drugs and biological products, is this a reference to scheduling a Type A or Type 1 meeting? How should sponsors contact FDA regarding device clinical trials?

As stated in our guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017), review division regulatory project managers (RPMs) are the primary point of contact for communications between a sponsor and FDA. Both FDA and sponsors use various communication methods to focus discussions to exchange information and resolve issues efficiently. For example, telephone communication between a sponsor and FDA RPM may be more effective for time-sensitive matters. FDA staff try to respond to sponsor questions promptly, while balancing FDA public health priorities and other work obligations. Note that to ensure participant safety, responses to safety-related inquiries will be prioritized over other inquiries. More generally, FDA understands that many questions that arise regarding changes in trial conduct due to a disaster or PHE will need to be addressed expeditiously. RPMs will work with sponsors to determine the best path forward to answer their questions for certain changes in an expedited manner.

To discuss urgent issues related to IDEs managed in CDRH, sponsors should contact the lead reviewer. For IDEs managed in CBER, sponsors should contact the RPM. For FDA feedback on a proposed future IDE study or regarding modifications to ongoing studies that are not urgent (such as a statistical analysis plan to address missing data), a Pre-Submission is recommended. For additional information on Pre-Submissions, please refer to the guidance for industry *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (June 2023).

For general questions regarding FDA policy on clinical trial conduct during a disaster or PHE, sponsors should contact CTconductquestions@fda.hhs.gov.

Q20. How are drug and biological product clinical trials required as postmarketing requirements (PMRs) affected during disasters or PHEs? What about required postmarket device studies?

The information in this guidance applies to all clinical trials, including those postmarketing clinical trials that FDA requires an applicant[52] to conduct[53] for drugs and biological products.

[52] After a company submits a marketing application (e.g., new drug application (NDA), biologics license application (BLA), premarket approval application (PMA), De Novo classification request, or premarket notification (510(k)) for review, the company is referred to as the *applicant*. The person who initiates a clinical investigation is referred to as the *sponsor* (see 21 CFR 312.3 and 812.3(n)).

[53] Specifically, this response is intended to apply to studies or clinical trials required under 505(o)(3) of the FD&C Act (21 U.S.C. 355(o)(3)), confirmatory trials for drugs approved under the accelerated approval pathway (21 U.S.C. 356(c)(2)(A)), deferred pediatric studies (21 U.S.C. 355B), and postmarketing studies required for drugs and biological products developed under the Animal Rule (see 21 CFR 314.610(b)(1) and 610.91(b)(1)); see also the FDA guidance for industry *Product Development Under the Animal Rule* (November 2015).

Many of the considerations outlined in this guidance may also be relevant to postmarket device studies.[54]

Applicants who are required to complete postmarketing clinical trials for drugs or biological products follow a timetable that includes due dates for completing certain milestones in the trial. FDA encourages applicants to inform FDA as soon as possible if they experience delays due to a disaster or PHE that may affect the applicant's ability to meet the applicable interim,[55] trial completion, and/or final report submission milestones. These applicants should propose feasible revised milestones for interim, trial completion, and/or final report submission milestones.[56]

For postmarket device studies, the approved postapproval study protocol or postmarket surveillance plan generally includes due dates for completing certain study milestones. Due dates for certain milestones may also be listed expressly in the order requiring the postmarket study. Applicants required to complete such studies should similarly inform FDA as soon as possible of delays due to a disaster or PHE that may affect the applicant's ability to meet those milestones and propose feasible revised milestones.[57]

Applicants with PMRs or required postmarket device studies should also provide an explanation to FDA of how the disaster or PHE impacts the ability to meet the original milestones. FDA will evaluate the facts and circumstances of the explanation provided, as well as the conduct of the applicant, in determining whether the applicant is in compliance with the applicable authority requiring the postmarketing trial or postmarket device study after an original milestone has been missed.

Additional considerations for drug and biological product PMRs include:

- **PMRs Under Section 505(o)(3) of the FD&C Act**: FDA will continue to make "good cause" determinations on a case-by-case basis for all missed milestones, including those where the applicant asserts that its failure to meet a PMR interim,

[54] For devices subject to premarket approval, FDA may require postapproval studies as a condition of approval (21 CFR 814.82(a)(2)). FDA may also require manufacturers to conduct postmarket surveillance studies of certain Class II and Class III devices under section 522 of the FD&C Act (21 U.S.C. 360l).

[55] *Interim milestones* refer to those due dates scheduled to occur between the final protocol submission and trial completion milestones.

[56] Although a revised trial completion date may be acknowledged by FDA, for drugs and biological product PMRs, the original projected completion date will continue to be displayed on the FDA's Postmarket Requirements and Commitments web page. In the case of Pediatric Research Equity Act postmarketing requirements, if a deferral extension is granted and the final report submission date has been deferred, the new final report submission date will replace the original or previously granted final report submission date.

[57] See the guidance for industry and FDA staff *Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act* (October 2022). See also the guidance for industry and FDA staff *Procedures for Handling Post-Approval Studies Imposed by PMA Order* (October 2022).

trial completion, and/or final report submission milestone is related to the disaster or PHE.[58]

- **Deferred Pediatric Study PMRs Under the Pediatric Research Equity Act (PREA)**:[59] If circumstances involving a disaster or PHE have affected an applicant's ability to complete a PREA PMR, applicants may request a deferral extension of the timeline for a deferral granted by FDA. If an applicant has not obtained a deferral extension and fails to submit required PREA studies by the final report submission date listed in the PREA PMR, FDA is required to issue a noncompliance letter to the applicant.[60]

- **PMRs Under Accelerated Approval**: For confirmatory trials, if an applicant misses an interim, trial completion, and/or final report submission milestone, FDA will review the applicant's explanation for the delay, as well as assess the trial's progress before the disaster or PHE, before determining whether or not the applicant has been compliant with its milestone obligations.

- **Annual Status Reports of PMRs**: Applicants must continue to follow the annual reporting requirements for PMRs[61] and should document in their annual status report the disaster or PHE-related reasons for missing interim, trial completion, and/or final report submission milestones, the reasons for the non-compliance with the milestones, and any steps taken to address factors specific to the disaster or PHE.

Q21. My company is the holder of an approved marketing application for an FDA-approved drug for a specific indication and is also the sponsor of an IND for the same drug being investigated for a new indication to prevent conditions related to a disaster or PHE. If I receive a spontaneous report of a serious adverse event (SAE) that occurred with the approved drug being used in clinical practice for the prevention of the disease or condition related to the disaster/PHE, do I report that event to the IND?

Reports of SAEs that occur in clinical practice with the use of an approved drug or biological product, whether or not the use is included in the approved labeling for that product, must be reported in accordance with the applicable postmarketing reporting requirements under 21 CFR 314.80 and 600.80. Reports of SAEs for approved vaccines are submitted to the Vaccine

[58] See the FDA guidance for industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).

[59] Section 505B(a)(4)(B) of the FD&C Act governs the process and timelines required for requests for a deferral extension for deferred pediatric studies required under section 505B of the FD&C Act (21 U.S.C. 355c) (often referred to as *PREA PMRs*).

[60] See section 505B(d)(1) of the FD&C Act (21 U.S.C. 355c(d)(1)).

[61] See section 506B of the FD&C Act (21 U.S.C. 356b) and 21 CFR 314.81(b)(2)(vii) and 601.70(b).

Adverse Events Reporting System (VAERS), while reports of SAEs for other approved drugs and biological products are submitted to the FDA Adverse Event Reporting System (FAERS).[62]

Serious adverse events that occur during a clinical trial under an IND for an approved drug or biological product being investigated for a new use to treat or prevent a disaster- or PHE-related disease or condition must be reported as an IND safety report per FDA regulations under 21 CFR 312.32 if (1) they are unexpected and (2) the sponsor determines that there is a reasonable possibility that the drug caused the SAE.

Regardless of whether an SAE occurs in the course of clinical practice or during a clinical trial and regardless of where it is first reported, an NDA or BLA holder who is also the sponsor of an IND investigating the same drug for treatment or prevention of a disaster- or PHE-related disease or condition is responsible for monitoring the safety of its drug and evaluating all accumulating safety data.[63] If accumulating safety data, including use in clinical practice, indicates a new potential serious risk associated with the drug, an IND safety report will need to be filed to the IND, and updates will likely need to be made to the investigator brochure and/or the informed consent document.[64] For more information, see the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012).

Q22. If a trial participant experiences an SAE that may be associated with a disease or condition related to the disaster or PHE, should that be reported as an IND safety report? Should these events be reported to the IRB?

Under 21 CFR 312.32, a sponsor must report to FDA any SAE that is both unexpected and for which there is a reasonable possibility that the drug caused the SAE (i.e., there is evidence to suggest a causal relationship between the drug and the adverse event).

Participants in a clinical trial may be diagnosed with a PHE- or disaster-related disease or condition and experience SAEs associated with the disease or condition that are not causally related to the investigational drug. However, it is possible that such SAEs could be causally related to the investigational drug. Establishing a potential causal relationship likely requires more than a single or even a few cases.

FDA had provided additional information about aggregate safety assessment and reporting for INDs in the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012) and has proposed recommendations in the draft guidance for

[62] For more information, see the Vaccine Adverse Event Reporting System, available at https://vaers.hhs.gov/reportevent.html, and the FDA Adverse Event Reporting System (FAERS) Public Dashboard, available at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

[63] See 21 CFR 312.32(b).

[64] See 21 CFR 312.32(c).

industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021).[65]

Where an IND safety report is required to be submitted to FDA under 21 CFR 312.32, the investigator must also send that IND safety report to the IRB.[66] The IRB may have additional reporting requirements regarding the disaster or PHE that apply during the clinical trial.

Q23. Certain clinical trial protocols have an exclusion criterion for receipt of another investigational medical product. If a participant receives a vaccine or other medical product authorized under an emergency use authorization (EUA), would FDA consider this receipt of an investigational medical product?

When a medical product is being used under an EUA, it is an authorized (though not an approved or cleared)[67] medical product for use in clinical care that has met the statutory criteria under section 564 of the FD&C Act.[68] The product is not being studied under an IND or IDE when used pursuant to an EUA, and FDA therefore does not consider an individual's receipt of the product under an EUA as receipt of an IP. In contrast, when the same product is used in a clinical investigation under an IND or IDE, the product's safety and/or effectiveness is being studied for investigational uses, and FDA would consider receipt in this situation to be receipt of an IP.

In the design of a clinical investigation, there may be valid scientific reasons to have an exclusion (and even a discontinuation of study treatment) criterion for receipt of a medical product — a monoclonal antibody or vaccine, for example — whether that product was used under an EUA or not. These scientific reasons may include risks to an individual if they enroll or continue to receive study treatment in a clinical trial after receiving (or having received) the excluded product or the potential impact of the use of the excluded product on trial objectives, such as confounding the determination of effectiveness of the product under investigation.

[65] When final, this guidance will represent FDA's current thinking on this topic.

[66] See 21 CFR 312.53(c)(1)(vii) and 312.66. See also the guidance for clinical investigators, sponsors, and IRBs *Adverse Event Reporting to IRBs — Improving Human Subject Protection* (January 2009).

[67] In this guidance, *approved or cleared*, with respect to devices, refers to FDA permitting the marketing of a device via the premarket approval, premarket notification (510(k)), De Novo classification, or Humanitarian Device Exemption (HDE) pathways.

[68] See section 564(k) of the FD&C Act (21 U.S.C. 360bbb-3(k)); see also guidance for industry *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017).