The past 10 months have been anything but uneventful. On March 13, 2020, the University of Rochester began to issue guidance on the conduct of human subject research in light of the COVID-19 pandemic.

A research ‘pause’ for all research involving direct contact with subjects with no prospect of direct benefit began on March 16, 2020. The ‘pause’ continued through mid-May, when a gradual research reboot was initiated, which also happened to coincide with a period of widespread staff furloughs. Needless to say, the research conducted at the start of the year, may look very different now.

As a result of the ongoing COVID-19 pandemic, study teams have had to:

- Temporarily suspend some (if not all) study activities, including recruitment, enrollment and study visits/procedures;
- Implement alternate methods for conducting select study activities (e.g., utilizing electronic methods to carry out consent discussions and documentation, conducting phone or virtual study visits, decreasing the number of in-person study visits, shipping investigational products directly to subjects);
- Adapt data management and statistical analysis plans; and
- Alter monitoring plans to increase the utilization of remote monitoring.

Federal regulations (45 CFR 46.108; 21 CFR 56.108) and Office for Human Subject Protection (OHSP) policy, require Institutional Review Board (IRB) approval of all research modifications prior to implementation, except where necessary to eliminate apparent immediate hazards to subjects. At the onset of the pandemic, the Research Subjects Review Board (RSRB) anticipated that immediate alterations to some types of research would need to be implemented prior approval, in order to protect the safety and welfare of all involved parties (including the subject and the study team). Anytime an alteration to, or deviation from, the approved research is made prior to IRB approval, study teams are faced with critical, yet often overlooked, ramifications. Study teams must:

a) Ensure the alteration/deviation is adequately documented in the study records;
b) Report the incident per Reviewing IRB policy; and
c) Determine whether modification to the research is required to accommodate future research conduct (i.e., consider whether the incident was an isolated event or if the research requires revision in order to prevent future non-compliance).

Many local study teams have already submitted and received approval for revisions to their research in order to continue research conduct in a manner that is safe for subjects, as well as study team members, and that aligns with institutional guidelines concerning COVID-19. As study teams begin to return to their ‘new normal’ of research conduct, they are reminded to review their study documentation to ensure that any deviations that occurred as a result of COVID-19 are appropriately documented and reported. (continued on next page)
Documenting and Reporting COVID-Related Protocol Deviations (continued)

Documenting Protocol Alterations/Deviations

As a general rule of thumb, study documentation should demonstrate the ‘story’ of the research from start to finish; it should reflect compliance with the IRB approval, study protocol and applicable regulatory requirements. Ideally, an external monitor, inspector or reviewer (or even a new study team member) should be able to review study documentation in retrospect and comprehend what has transpired over the course of the research (from the documentation alone), including any alterations or deviations. Minimally, documentation regarding a protocol alteration/deviation should include:

- Date of the incident;
- Description of the incident, including an explanation for why the incident occurred; and
- Action taken (or outcome) following the event (this may include, as appropriate, documenting who the incident was reported to and when, any tests/treatments/results, date of resolution, sequelae, and corrective and preventative actions).

Based on the nature of the incident, this information is usually documented in either a Note to File, protocol deviation log, or a combination of the two. Templates are available in the OHSP Quality Improvement (QI) Study Documentation Tool Box; alternate options are also readily available through internet searches.

Generally, it is best practice to group as many similar incidents together into one comprehensive piece of study documentation, as appropriate (rather than duplicating documentation efforts multiple times across multiple subjects). For deviations specific to the COVID-19 pandemic, OHSP recommends that study teams create and maintain a ‘global’ COVID-19 Note to File to document and describe the pandemic’s impact on the study overall (see example in Image 1 on the next page) and a separate COVID-19 Protocol Deviation Log to identify subject-specific incidents (see example in Image 2 on the next page). To be clear, this is a recommendation only; alternate documentation methods may be utilized provided the documentation sufficiently describes how COVID-19 impacted the research. For example, if the pandemic had minimal impact on your research or only resulted a few minor deviations, it may be appropriate to document deviations in

Alterations vs. Deviations vs. Violations

As with many things in research, the definition of a specific term depends on who is using the term and in what context. Sponsors, study team members and reviewing IRBs can differ on what constitutes a protocol alteration, deviation, and violation. Some may use these terms, along with protocol variation, exception, non-compliance, and non-adherence, interchangeably. Or, to further complicate matters, they may even be referring to distinct types of events when using each of these terms.

From a regulatory standpoint, neither the Department of Health and Human Service (HHS) nor the Food & Drug Administration (FDA) regulations define these terms. Rather, with one exception, regulations only refer to ‘changes in research activity’ (investigational device regulations reference, but do not define, ‘deviations from the investigational plan’ [21 CFR 812]). So, by and large (and for the purposes of this article), these terms refer to any instance when the materials the IRB approved, including the protocol and any other submission materials, are not followed (no matter how minor).

For more information on protocol deviations, view the archived 9/12/2019 UR-HRPP Educational Forum titled ‘Protocol Deviations & Violations & Non-Compliance…Oh My!’ in Blackboard.
Documenting and Reporting COVID-Related Protocol Deviations (continued)

(continued from page 2) one COVID-19 Note to File (without requiring an additional deviation log; see example in Image 3 below). Alternately, it may be more appropriate to document deviations in separate COVID-19 Note to Files for each subject. Note: Editable Microsoft Word templates of the documentation demonstrated in Images 1, 2 and 3 below are available in Study Documentation Toolbox provided by the OHSP Division of Quality Improvement.

As a reminder, recall that the use of the words ‘alteration’ and ‘deviation’ here refers to incidents or events that have occurred without IRB approval. As mentioned above, since the pandemic hit, many study teams submitted revisions to their research to accommodate ongoing COVID-related safety guidelines (e.g., conducting virtual study visits via Zoom). Procedures that align with appropriate IRB approvals (continued on next page)
Documenting & Reporting COVID-Related Protocol Deviations (continued)

(continued from page 3) do not require documentation and/or reporting as an alteration/deviation.

**Reporting Protocol Deviations**

Requirements pertaining to reporting research events, including alterations/deviations, will depend on the approved study protocol, nature of the research and corresponding regulations that apply to the research. Minimally, across the board, study teams will need to report deviations per their Reviewing IRB’s policies (the Reviewing IRB is the IRB designated to review and approve the research). Further reporting may also be required as defined by a protocol’s data and safety monitoring plan and/or when the research is conducted under an Investigational New Drug (IND) or Investigational Device Exemption (IDE) through the FDA (based on the nature of an incident, sponsors, including sponsor-investigators, may be required to report incidents to the FDA).

For research reviewed and approved by the Research Subjects Review Board (RSRB), per OHSP Policy 801 and the corresponding Guideline for Reporting Research Events, research events (including alterations/deviations) need to be reported within 10 calendar days if they meet the definition of unanticipated, related, and serious or if they involve increased risk to subjects or other. All other events can be reported in summary at the time of continuing review. As most alterations/deviations that transpired as a result of COVID-19 occurred in order to protect subjects, reporting is required at the time of continuing review.

Report alterations/deviations to the RSRB at the time of continuing review in the Click IRB Continuing Review (CR) submission (see Image 4). If your research is does not require continuing review (i.e., there is no expiration date assigned to the research), this information can be reported to the RSRB in Click IRB via a Report of New Information (RNI), as shown in Image 5. Step-by-step instructions on how to submit CRs and RNIs are available in the Click IRB Study Staff Manual.

For research reviewed and approved by an external IRB, study teams will need to verify reporting requirements with the applicable IRB.

**Questions?** Questions about RSRB reporting requirements can be directed to your IRB Coordinator. Consultation concerning documentation is available through the OHSP-QI team.
The Food and Drug Administration (FDA) Amendments Act of 2007 requires clinical trial registration at the time enrollment begins and for results to be posted at the end of the study for applicable clinical trials on ClinicalTrials.gov (CT.gov). In 2016, the National Institutes of Health and the Department of Health and Human Services (HHS) expanded this requirement for posting information on CT.gov.

CT.gov now assesses civil money penalties against responsible parties and/or submitters who violate this regulation. Violations are identified through evidence collected during FDA Bioresearch Monitoring Program, complaints to the agency, review of public and non-public information available to FDA, and/or information submitted to the CT.gov data bank and the FDA. Violation examples include failing to submit required clinical trial registration and/or results information to the CT.gov data bank, submitting false or misleading information to the CT.gov data bank, or failing to submit or knowingly submitting a false certification to the FDA.

Once a violation has been identified, a Preliminary Notice of Noncompliance letter is sent to the responsible party, which describes the potential violation and requests action to address the potential violation within 30 calendar days of receiving the letter. The FDA will conduct further review and assessment of the CT information submitted and any other relevant information available to FDA.

Failure to comply with requirements may result in further FDA regulatory action including a Notice of Noncompliance, civil penalties, injunction, and/or criminal prosecution. A Notice of Noncompliance gives the recipient an opportunity to remedy the noncompliance no later than 30 calendar days after notification. The notice is posted on the agency’s website and added to the CT.gov data bank.

The FDA does not intend to include potential violations on FDA 483, however information collected regarding potential violations is included in the Establishment Inspection Report and provided to the relevant Center (i.e. Drug Evaluation and Research, Biologics Evaluation and Research, Devices and Radiological Health) for further evaluation.

In determining civil penalties, the FDA considers corrective action taken by the responsible party. If noncompliance is not remedied within 30 calendar days after receiving a Notice of Noncompliance, the Center with jurisdiction generally seeks civil money penalties considering the type of noncompliance and circumstances associated with lack of remediation.

Civil money penalty actions are initiated when the Center with jurisdiction files a complaint with the FDA’s Division of Dockets Management and serves the Complaint to the respondent. Respondents generally pay the penalty or file an answer with the Division of Dockets Management contesting some or all of the allegations. If a respondent chooses to contest the matter, they file a reply within 30 days after the date of the Complaint. The respondent is entitled to a hearing with the Division of Dockets Management (assuming the answer is filed within the time prescribed). Cases not settled will be decided by a presiding officer. After the presiding officer renders an initial decision, either party can appeal to HHS Departmental Appeals Board. The respondent then can appeal the decision to the US Court of Appeals for the District of Columbia or any other circuit in which the respondent resides or transacts business.

Resources:

Support for ClinicalTrials.gov Study Registration

Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank
Use of Care Everywhere & RHIO in Research

Care Everywhere and Rochester Regional Health Information Organization (RHIO) are means of accessing external medical records of URMC patients, and are generally excluded from use in research, except in limited circumstances. Care Everywhere may be used only in the context of patient treatment and only to the extent the records are relevant to the patient’s treatment, this essentially limits the use of Care Everywhere to treatment intervention studies. RHIO requires the researcher to obtain the subject’s authorization on a research-specific RHIO authorization form in order for the RHIO records to be used for research.

**Care Everywhere**

Care Everywhere allows access to progress notes, external lab reports, imaging reports and treatment summaries of providers in healthcare organizations that use the Epic records management system, like URMC. When an Epic user obtains Care Everywhere access, the user must agree to the Rules of the Road which state:

“You warrant and represent … that at the time You are making the request for the patient’s information You are providing treatment to that patient (which may include care coordination for that patient). You understand that You may not request patient information using Care Everywhere for any other purpose, including without limitation healthcare operations, research …”.

A 2018 Epic White Paper on use of Care Everywhere in research underscored that Care Everywhere may not be used for most research, but recognized that hybrid treatment/research studies may be an exception. Based on the White Paper, Care Everywhere may not be used for:

- Cohort identification
- Research study recruitment
- Feasibility analysis
- Retrospective record reviews

This is true regardless of whether the research subject expressly consents to the review of external records during the study, and even if the researcher is a provider with privileges to access external records via Care Everywhere. Researchers who are clinical providers must keep in mind the distinction between those two roles, when deciding whether records can be accessed via Care Everywhere. The URMC Privacy Officer for Research can assist in determining appropriateness of Care Everywhere access.

Conversely, in a treatment intervention study, Care Everywhere access is permitted if the external records pertain to the patient’s treatment in the study, e.g. determination of continued eligibility, or an adverse event such as an Emergency Department visit. When researchers apply for Care Everywhere access, the determination of whether access is permitted is fact – dependent, based on each study, with assistance from the Privacy Office.

If the research qualifies for use of Care Everywhere as defined above, the Care Everywhere tool may be used to access the external Epic record, but still, the subject must authorize this via the Informed Consent. The RSRB Biomedical Consent form template includes the necessary disclosure under the “Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes” (It is important to remember when using a sponsor’s template or another Reviewing IRB HIPAA language, this statement should be included in the consent form):

What information may be used and given to others?

Past and present medical records related to the study, including records of external providers that are available via your electronic health record at URMC & Affiliates.

If the research does not qualify for use of Care Everywhere, then the researcher’s only recourse to obtain the external records is (1) get them directly from the external provider based on a Release of Information (ROI) authorization form signed by the subject, if the provider uses the Epic system or (2) get them via RHIO (continued on next page)
Use of Care Everywhere & RHIO in Research

(continued from page 6) (see below) based on a special consent signed by the subject, if the external provider is part of the RHIO system.

Temporary Care Everywhere Exception for COVID Research

Effective September 8, 2020, researchers may use Care Everywhere to access external records that are relevant to an IRB-approved COVID-19 research study, even if they are not treatment intervention studies. This is the result of an amendment to the Care Everywhere Rules of the Road that applies to public health emergencies, and the exception is in effect only through the duration of the public health emergency. (Currently, the COVID emergency extends through January 21, 2021; the end date has been extended several times and may be extended again).

Specifically, the Care Everywhere tool may be used to access external records if:

1. The research is directly related to the treatment, testing or vaccine development of COVID-19
2. The research and access of external records via Care Everywhere is approved by an IRB, and
3. Patient authorization to review external records has been obtained. The current RSRB Biomedical Consent form template includes the necessary language. (It is important to remember when using a sponsor’s template or another Reviewing IRB HIPAA language, this statement should be included in the consent form.)

So, for example, a COVID researcher may access external records via the Care Everywhere tool to identify factors that correlate to a positive COVID test in patients who have left URMC’s medical care and no longer are being treated (e.g. retrospective record review).

Importantly, the external records access via Care Everywhere may not be made by a clinical provider using clinical Care Everywhere privileges. The access must be made by someone with Care Everywhere research privileges. A new research privileges security classification has been developed for this purpose, and will be assigned to qualifying users, with evidence of study approval by an IRB. Epic will automatically turn off the access privilege of researchers across the Epic system when the public health emergency ends. Records previously accessed (under the COVID exception or for clinical purposes) will remain available to URMC users.

RHIO

RHIO is the Rochester Regional Health Information Organization, a secure health information exchange mechanism for 14 counties in upstate New York. Like Care Everywhere, RHIO is intended primarily for providers to access relevant clinical information about patients, but researchers can use RHIO for more research purposes than Care Everywhere, subject to certain conditions.

The primary conditions for direct access to patient records in RHIO for research are:

- The patient has signed an authorization to access records via RHIO, on a form known as a “Level 2” RHIO consent form
- The researcher has applied for and obtained a RHIO Explore + research account that is specific to the study in which RHIO will be used. Researchers who also are clinicians need to remember to access RHIO via their research account when accessing external records for research.
- The researcher must apprise RHIO when the study is over, so that RHIO can terminate the study-specific research account.

Here is an example of a study in which RHIO would be available for external records access, but Care Everywhere is not. Patients in...
Research QI ‘Gold Star’ Award

The QI division is recognizing Principal Investigator Richard Dunne, MD, and the research team within the Department of Medicine, Hematology/Oncology for their quality work on the ‘Induction Chemotherapy for Locally Advanced Esophageal Cancer: A Phase II Study’ study. This engaged study team works in the Wilmot Cancer Institute and includes Austin Glick, Amber Johnson, Christopher LeFeber, Katie Nedrow, and Monica Patel. The study team received the OHSP-QI ‘Gold Star’ award for their demonstrated attention to regulatory compliance/protocol adherence, exceptional subject safety practices, showing great respect for the subjects and their families, and exceptional subject retention practices. Investigator oversight, consenting processes, and inclusion/exclusion criteria documentation were outstanding. Congratulations!

Use of Care Everywhere & RHIO in Research

(continued from page 7) the ED who are at risk of cervical cancer will be recruited into a study that provides educational information and reminders to get cervical cancer screening. The researcher wants to access external records to determine compliance 6 and 12 months after the ED visit. Care Everywhere cannot be used, because the treatment relationship ended upon discharge from the ED and the study provides no intervention/treatment to the subject. RHIO can be used, if the patient signs a Level 2 RHIO consent form.

There are research studies in which neither RHIO nor Care Everywhere are available options to directly access external records. A prime example is a retrospective record review. In most cases, these studies are conducted under a waiver of HIPAA Authorization because the volume of records accessed precludes obtaining the subject’s authorization, so there is not opportunity obtain consent via the RHIO Level 2 Consent Form or through the authorization language in the consent form. For this reason, external records cannot be accessed directly. However, RHIO does provide the possibility to request from RHIO’s Secondary Use Committee a data set containing defined patient level data with limited identifiers, for research purposes. Review and approval of submissions can take up to 8 weeks.

Clearly, there are constraints and limitations on use of Care Everywhere and RHIO to obtain external medical records for research purposes. It is wise to consider whether external records will be needed in a research study before enrollment begins, because it can affect the documentation the subject must sign, and how and by whom the records can be accessed. The URMC Privacy Officer for Research can be a useful resource when assessing the available options. Additional information is also available via the recording of the 11/18/2020 Study Coordinators Organization for Research & Education program.

OHSP-QI Consultations: Contact OHSP-QI any time to schedule your team for a study start-up and quality management plan consultation which includes a review of the study’s applicable regulations. All consultations can be conducted via Zoom as a meeting venue.
Subject Educational Materials

Educational materials for subjects are available through the Office for Human Subject Protection’s (OHSP) Participating in Research website. The website includes educational content, printable handouts, and resources for subjects. Printable handouts include:

- **Participating in Research: What You Need to Know**
- **Informed Consent: What You Need to Know**
- **COVID-related handouts: What you can expect during a study visit in the era of COVID-19:** Important Information about COVID-19 and Research Participation; and COVID Research Information Sheets

All handouts are available for study teams to use as they see fit, based on the nature of their research. Approval by the Research Subjects Review Board (RSRB) is not required for use. Study teams utilizing an external Reviewing IRB should verify with their Reviewing IRB whether approval, prior to use, is required.

Additional subject education materials are available through the medical center’s Health Research website, as well as from the Department of Health and Human Service’s Office of Human Research Participation, the Center for Information & Safety on Clinical Research Participation, Children and Clinical Studies, the National Institutes of Health, and Harvard Catalyst.

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**UR-HRPP Educational Materials in Blackboard**

As a reminder, previously conducted Office for Human Subject Protection (OHSP) seminar recordings and slides, as well as Click IRB demonstration videos, are available in the UR-HRPP Educational Materials course in Blackboard (formerly titled OHSP Seminar Materials). The ‘course’ is not a course in the traditional sense, rather it is a repository of training materials that may be used as reference, as well as training, for faculty, staff and students.

A directory of materials, including what resources are available and whether closed-captioning is provided in video content, is available here (use Ctrl+F to search the directory for key words). Content is included on a variety of topics including roles and responsibilities, study team onboarding, departmental/scientific review, IRB review of a protocol, data and safety monitoring plan development, adverse events, and corrective and preventative action plans.

To access the materials, faculty/staff/students must enroll in the course; instructions for doing so are available here.

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Additional subject education materials are available through the medical center’s Health Research website, as well as from the Department of Health and Human Service’s Office of Human Research Participation, the Center for Information & Safety on Clinical Research Participation, Children and Clinical Studies, the National Institutes of Health, and Harvard Catalyst.