Good Clinical Practices Explained

The Office for Human Subject Protection (OHSP) is routinely asked questions like what is ‘Good Clinical Practice’, or GCP, do I have to comply with GCP, and am I required to complete GCP training? Let’s set the record straight...

Good Clinical Practice is defined as a “standard for designing, conducting, recording and reporting trials that involve the participation of human subjects” (ICH, 2016). References to ‘GCP’ can sometimes be confusing because some research professionals use the term generically as a way to define how research is conducted, whereas others are actually referencing a specific guidance document on GCP. The concept of GCP is, however, much broader than a single guidance document. Rather, GCP is “an attitude of excellence in research” (Silver-Kessler, n.d.) that encompasses the principles and obligations set forth in the various documents and regulations that guide the conduct of human subject research. In other words, GCP is a compilation of the underlying principles described in the Nuremberg Code, Declaration of Helsinki, Belmont Report, Code of Federal Regulations (Department of Health & Human Service [HHS] and Food & Drug Administration [FDA]), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice, World Health Organization Guideline for Good Clinical Practice, and International Standards Organization (ISO) 14155. Common among these documents are standards (i.e., GCPs) related to:

- Conducting scientifically sound research that is of benefit to society;
- Ensuring a favorable risk: benefit ratio of the research;
- Ensuring subject safety prevails over societal benefit;
- Selecting subjects equitably;
- Obtaining independent ethics committee (i.e., Institutional Review Board [IRB]) approval;
- Protecting vulnerable populations;
- Conducting research in accordance with the approved study protocol;
- Obtaining voluntary informed consent;
- Limiting involvement in the conduct of research to those with adequate qualifications and experience;
- Appropriately accounting for investigational product;

(continued on next page)

Image adapted from Moran, et al., 2013.
Good Clinical Practices Explained (Continued)

- (continued from page 1) Protecting subject privacy and maintaining the confidentiality of the data;
- Assuring data integrity and quality; and
- Appropriately documenting the research.

**What Regulations Am I Required to Comply With?**

The regulations and policies you’re required to comply with depend on the nature of your research and will vary from study to study based on who initiates the research, the interventions, the procedures and risks involved, and the funding source.

From a regulatory standpoint, per institutional policy, all research conducted at the University of Rochester with human subjects must minimally comply with HHS regulations (45 CFR 46). If the research also involves a test article (drug, biologic, device [including in vitro diagnostic devices] or supplement) or is funded by the FDA, study staff must further comply with applicable FDA regulations (21 CFR 50; 21 CFR 54; 21 CFR 56; 21 CFR 312; 21 CFR 812). Additional regulations that may apply include:

- Regulations set forth by different HHS agencies such as the Department of Defense or Department of Education, when an HHS agency funds the research or when the agency imposes requirements based on the study population (e.g., students);
- Regulations defined by the Health Insurance Portability & Accountability Act, when the research involves the use and/or disclosure of protected health information by a covered entity or when the study team includes members of a covered health entity;
- Tribal law, when the research is conducted in a setting governed by tribal law; and
- Regulations from other countries, when the research is conducted abroad (e.g., European Economic Area regulations).

Beyond regulatory compliance, study staff must also minimally comply with institutional policy, policy set forth by the Reviewing IRB, and the IRB-approved study protocol.

**What about Compliance with GCP Guidelines?**

Guidance documents provide recommendations and best practices for how to comply with regulations; they are not, by definition, regulation. In fact, most guidance documents related to the conduct of human subject research published by HHS or the FDA state that the ‘guidance represents the current thinking’ of the agency and the information provided is not legally binding. So, when asked the question ‘do I have to comply with guidance?’ the answer is technically no. However, given the variation in how regulations can be interpreted, following the advice provided in guidance documentation is strongly encouraged. Study teams should equate guidance documents to a playbook or treasure map; if someone provided you a playbook that enhanced your ability to ‘play the game’ or a map of how to reach your goal, wouldn’t you follow it? Following the recommendations provided in published guidance documents better your chances of protecting subjects, collecting quality data and minimizing non-compliance.

There is, of course, a caveat to this, most notably in regards to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (hereinafter ICH GCP) and the International Standards Organization 14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice (continued on next page)
Good Clinical Practices Explained (Continued)

(continued from page 2) (hereinafter ISO 14155). These guidance documents set forth international GCP standards for investigational products; ICH GCP has been adopted as guidance by the FDA and ISO 14155 has been recognized as a consensus standard. These international GCP standards were developed to streamline the drug and device development process and facilitate mutual acceptance of international clinical data by corresponding regulatory authorities (e.g., as support for a marketing application, the US FDA will accept data collected by a trial conducted in Japan, provided the study was conducted in accordance with ICH GCP). As such, study sponsors will often require compliance with ICH GCP and/or ISO 14155 (commonly identified in study protocol, on the protocol signature page or in the investigator agreement). To reiterate, if your study protocol, clinical trial agreement, or any other study-specific documentation indicates that compliance with ICH GCP, ISO 14155 or any other regulation or guideline is required, then the study team is responsible for complying with such requirements (see example in Image 1).

How Does GCP Relate to Social-Behavioral Research?

Despite the word ‘clinical’ in the phrase Good Clinical Practices, the general principles considered to be GCP (bulleted on pages 1-2) still generally apply to social-behavioral research. Remember, as stated previously: GCP encompasses standards across several potential sources of compliance, including ethical principles and federal regulations that apply to social-behavioral research. Moreover, guidelines identified specifically as ‘GCP’ guidance define best practices for reaching your study’s aims and conducting sound research. Those recommendations within the guidance that don’t apply to social-behavioral research (e.g. test article accounta-

14.0 REGULATORY AND ETHICS ISSUES

14.1 COMPLIANCE STATEMENT

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promulgated by the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA), and any applicable national and local regulations including FDA regulations under 21 CFR Parts 11, 50, 56, 312 and 314.

Image 1. Protocol Compliance Statement Example

When is GCP Training Required?

While the University of Rochester has not yet implemented a policy requiring GCP training for study staff (only human subject protection training is required), Sponsors, Department Chairs and Administrators/Supervisors may require GCP training. Routinely, Industry Sponsors conducting research involving investigational products (drugs, devices, and biologies) will require GCP training. Similarly, the National Institutes of Health (NIH) have implemented a policy requiring all “investigators and staff who are involved in the conduct, oversight or management of clinical trials” to complete and maintain GCP training. Of note, NIH’s definition of clinical trials includes trials that are behavioral in nature; the policy defines a clinical trial as “as research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related or behavioral outcomes.” GCP training is available for all University of Rochester faculty, staff and students through the Collaborative Institutional Training Initiative; instructions for accessing the training are available here (Note: Trainees can opt for either an FDA-focused or Social-Behavioral-focused GCP course).

References:

Food & Drug Administration (FDA) Guidance for Industry - E6(R2) Good Clinical Practice: Integrated Addendum (continued on next page)
Good Documentation Practice—
Subject Research Charts

**Good Documentation Practice** (GDP) is a term the pharmaceutical industry often uses to describe best practices surrounding research documentation and its maintenance. Some GDP standards are supported by law or regulation but some are corporate policy or simply current expectation and not supported by regulation.

Below are several ideas for Good Documentation Practice for maintaining subject research charts:

- Signed, original consent forms including all pages of the consent/permission/assent must be maintained for each subject.
- Note the consent discussion in the research chart and/or medical record, as appropriate. A template is available here.
- Conduct a quality check on each obtained consent form, especially at the beginning of a study and when there are consent form version changes. Having a second-set of eyes review an obtained consent form is invaluable; self-audit templates are available here. Identifying any errors in real-time, allows the issue to be fixed, rather than become a systemic issue. Also, it is always better for the study team to identify the issue, rather than an outside auditor.
- Assess inclusion and exclusion criteria with an Investigator confirmation of eligibility with signature and date.
- Assess adverse events at the study visit(s) with a documented review by the Investigator (signature and date). Include an adverse event assessment line to indicate ‘yes/occurred’ or ‘no/none’, which better demonstrates the assessment occurred.
- Study visits are expected to occur as defined in the IRB-approved protocol. If a visit does not occur as expected, a notation explaining the protocol deviation is expected. Consider the use of a deviation log (template found here) and review deviations periodically with the Investigator/designee to assess subject’s participation or the need for protocol modifications.
- Consider creating a Visit Checklist or use a copy of the Schedule (continued on next page)

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Good Clinical Practices Explained (Continued)

(continued from page 3) to ICH E6(R2). (2018, March). Retrieved March 30, 2020 from [https://www.fda.gov/media/93884/download](https://www.fda.gov/media/93884/download)


Good Documentation Practice—Subject Research Charts (Continued)

(continued from page 4) of Events in the protocol to ensure required study procedure(s) are completed at each visit.

- Secure paper documents, like consent forms and data collection forms in a locked area. All electronic data should be stored in a coded manner on a secured, password protected file on computers, with hard-copy source documents secured in a locked area.

- Data is to be recorded and/or entered and verified in accordance with the approved protocol and any associated manual of procedures.

- Subject research records should be stored as defined in the approved protocol; additional record retention guidance resources can be found here and here.

- Critical or pivotal data points should be considered for an independent check (i.e. second person verification).

- Write dates in day-month-year (i.e. 11APR18) format and time in a 24-hour clock (i.e. 17:00); this decreases doubt surrounding date and time. Use a consistent dating and timing method throughout all documentation to decrease confusion.

- Consider adding an initials line on the data collection forms to indicate who collected the data.

- File documents in chronological order and use divider tabs to easily identify specific content if using a binder.

- Store electronic files on a shared drive, set standard naming and organizational conventions for the folder, add dates to the folder name to know approximately when it was completed, and have the file accessible by the entire study team.

- Consider implementing a quality management plan (QMP) to review study files on a regular basis (e.g. after the tenth enrolled subject). Ensure the results of the QMP are documented and retained.

- Use checklists to aid in protocol documentation and compliance; examples can be found in the QI Study Documentation Tool Box.

Who needs to be listed as a study team member?

The determination of who needs to be listed as a ‘study team member’ on an Institutional Review Board (IRB) submission will depend upon the reviewing IRB’s policies/requirements. Similarly, funding agencies may have differing definitions of who is considered ‘key personnel’. At the University of Rochester, the following individuals must be listed on the Click IRB submission for both studies reviewed by the RSRB and those reviewed by External IRBs, as outlined in the OHSP Guideline for Listing Study Team Members on a Study Application:

- Principal Investigators, Co-Principal Investigators, Sub-Investigators, and Study Coordinators;

- Individuals who interact with human subjects (e.g., conduct the informed consent (continued on next page)
FAQs

Who needs to be listed as a study team member?

(continued from page 5) process, manipulate the subject’s environment for research purposes, conduct research procedures);

- Individuals who have access to identifiable subject data (e.g., for the purposes of study planning, grant/budget oversight, or collecting/reporting/analyzing data); and

- Faculty providing direct oversight of student research.

What about statisticians? Statisticians would only need to be identified as a study team member when/if they have access to identifiable subject data. Bear in mind, this determination may be dependent on the level of access the statistician has to the data. Study data may be coded for the statistician to perform analysis. ‘Coded’ means that the data is still identifiable to the study team because they hold the key linking the identifiable information to the coded information, but if the statistician does not have access to the key, he/she would not be able to identify the data and therefore would not need to be identified as a study team member. For additional information on what ‘coded’ means versus de-identification, see the 2014 Q4 OHSP Newsletter.

What about lab personnel, phlebotomists, and technicians? If an individual is functioning within his or her regular work responsibilities and involvement in the research is limited to those work responsibilities without further contribution to the research, then such individuals do not need to be identified as study team members on the IRB submission. For example, a phlebotomist working at a clinical laboratory who performs a blood draw on a subject via a clinical lab requisition would not be considered a study team member.

What about external study team members? Whether to include individuals or collaborators at sites that are not affiliated with the University, depends on who will serve as the Reviewing IRB for those individual(s). For a full description of these scenarios, see the OHSP Guideline for Listing Study Team Members on a Study Application.

What if I’m using an External IRB? As described in OHSP Policy 504 IRB Reliance and Collaborative Research, all research that will undergo review and approval by an External IRB is required to undergo administrative institutional review via Click IRB, prior to submission to the External IRB. When submitting your Click IRB application for administrative institutional review, study team members should be identified as stated above. For the submission to the External IRB, study teams need to defer to the External IRB’s requirements, which will vary from IRB to IRB.
What is a CV? Do I Need One? How Do I Write a CV?

(continued from page 6) Delegation of Authority Log) need to maintain a CV as part of their regulatory file.

For all other research, maintaining team members CV is good practice. Of note, OHSP Policy 901 Investigator Responsibilities, also requires all Investigators to delegate research activities appropriately as described above; this responsibility is not limited to FDA-regulated research only.

How do I write a CV? Templates and guides for writing a CV are readily available on the internet. Of note, the University of Rochester Medical Center has multiple resources available here, as well as additional templates and examples available here. The National Institutes of Health Office of Intramural Training and Education also has a comprehensive Guide to Resumes & Curriculum Vitae available on the web.

Do I need to sign and date my CV? Neither FDA regulation, nor FDA guidance specify that a CV must be signed and dated. Some Sponsors however, will require that the CV be signed and dated (with a wet signature) to confirm the date and ownership of the document.

Research QI ‘Gold Star’ Award

The QI division is recognizing Jonathan Huang, DO and the research team within the Digestive and Liver Disease Center for Research for their quality work on the ‘Phase 3, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Selonsertib in Subjects with Nonalcoholic Steatohepatitis (NASH) and Bridging F3 Fibrosis’ study. This engaged study team works in the Medical Center/Ambulatory center in the Department of Gastroenterology, Hepatology, and Endoscopy Center and has a primary aim of upholding the highest of standards and continuing to push the envelope of progression within research.

The study site received the OHSP-QI ‘Gold Star’ award for their commendable attention to regulatory compliance/protocol adherence, exceptional subject recruitment/retention practices, and conduction of excellent research (following the guidelines) supported with high quality, organized study-related documentation. The Investigator oversight, consenting processes, and inclusion/exclusion criteria documentation were also outstanding. Congratulations!

Reminder: Ancillary Committee Process

The University of Rochester’s Human Research Protection Program (UR-HRPP) is comprised of several integrated offices and committees aimed at ensuring individuals involved in conducting human subject research understand and apply their obligations to project the rights, dignity, welfare and privacy of research subjects. An essential component of the UR-HRPP is the collaboration between the Research Subjects Review Board (RSR) and the UR-HRPP Ancillary Committees. The purpose of these ancillary committees is to provide expertise in a given field and ensure (continued on next page)
Reminder: Ancillary Committee Process

(continued from page 7) applicable regulatory requirements are met and adequate resources are available.

A summary of ancillary review requirements is provided in Table 1 below; a full description is provided in Office for Human Subject Protection (OHSP) Policy 503 Ancillary Committee Review.

Critical to this process is planning ahead and ‘doing your homework’ to understand: a) whether ancillary review is required, based on the nature of the research; and b) if ancillary review is required, what the review process is for that committee. Each ancillary committee has their own review process; some committees require a separate application and/or review processes that take place outside of the Click® IRB system. For example, initial review by the Emergency Medicine Research Committee (EMRC) requires the submission of an EMRC cover sheet and study-related documents, as well as the presentation of the research at an EMRC meeting. Some committees further require additional reporting and/or review of modifications and at the time of continuing review. Knowing exactly what each committee’s requirements are, what their review process is, and when their review occurs relative to RSRB review will help study teams plan sufficient time for review and avoid unnecessary frustration.

To reiterate, in regards to ancillary review, it is the Investigator’s responsibility to:

- Ensure all applicable Ancillary Committee approvals are in place prior to enrolling subjects;
- Adhere to applicable Ancillary Committee reporting requirements; and
- Maintain document of all (continued on next page)

Table 1. Summary of Ancillary Committee Review Requirements

<table>
<thead>
<tr>
<th>If the research involves…</th>
<th>Ancillary review is required by…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required for all cancer related research, and includes retrospective, prospective, treatment and non-treatment studies irrespective of the department from which the study originates or where the study will be conducted.</td>
<td>Wilmot Cancer Institute Protocol Review and Monitoring Committee (WCI PRMC) <a href="mailto:WCI_PRMS@urmc.rochester.edu">WCI_PRMS@urmc.rochester.edu</a></td>
</tr>
<tr>
<td>Administration of radiation therapy at URMC &amp; Affiliates</td>
<td>Department of Radiation Oncology Protocol Review Committee <a href="mailto:DROIPR@urmc.rochester.edu">DROIPR@urmc.rochester.edu</a></td>
</tr>
<tr>
<td>Pregnant to post-partum women</td>
<td>Obstetrical Research Committee</td>
</tr>
<tr>
<td>Study procedures on hospitalized newborns</td>
<td>Neonatal Clinical Trials Group 275-1521</td>
</tr>
<tr>
<td>Enrolling patients in the Emergency Department</td>
<td>Emergency Medicine Research Committee 275-1198; <a href="mailto:EMResearch@urmc.rochester.edu">EMResearch@urmc.rochester.edu</a></td>
</tr>
<tr>
<td>• Introduction of recombinant or synthetic nucleic acid molecules (plasmids, gene transfer vectors, viral vectors, etc.) into human subjects; cells that have been treated with recombinant or synthetic nucleic acid molecules into human subjects; introduction of genetically engineered micro-organisms into human subjects; or biohazardous organisms or materials handled at Biosafety Level 2 or higher</td>
<td>Institutional Biosafety Committee 275-2402</td>
</tr>
<tr>
<td>• All research involving procedures that could result in droplet or aerosol COVID-19 exposure (e.g., spirometry and respiratory function testing)</td>
<td></td>
</tr>
<tr>
<td>Obtaining fresh, banked or archived human tissue from Surgical Pathology</td>
<td>Surgical Pathology <a href="mailto:LabSRSS@urmc.rochester.edu">LabSRSS@urmc.rochester.edu</a></td>
</tr>
<tr>
<td>Radioisotopes or radiation-generating devices used for research purposes</td>
<td>Human Use of Radiation Committee 275-3781</td>
</tr>
<tr>
<td>Activities that require access to the UR Center for Advanced Brain Imaging &amp; Neurophysiology (UR CABIN)</td>
<td>UR Center for Advanced Brain Imaging &amp; Neurophysiology 275-4540</td>
</tr>
<tr>
<td>Resources within the Clinical Research Center</td>
<td>Clinical Research Center 275-0653</td>
</tr>
<tr>
<td>Subject recruitment, enrollment or the conduct of study procedures at Highland Hospital</td>
<td>Highland Hospital Administrative Research Review Committee</td>
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</table>
Ancillary Committee Review & COVID-19

As a result of the COVID-19 pandemic, the following additional ancillary review requirements have been put into place (as these are expected to be temporary measures, they have not been formally incorporated into OHSP Policy 503):

- All research enrolling individuals with COVID-19 or suspected of having COVID-19 (both interventional and observational) must undergo review by the COVID-19 Ancillary Review Committee. This review occurs prior to Research Subjects Review Board review and can be initiated by completing the Notification of Intent form. A PDF of the completed Notification form should be uploaded into the “Other Attachments” section of the Click IRB application.
- In addition to the review requirements identified in Table 1, the Institutional Biosafety Committee is also reviewing all research involving procedures that could result in droplet or aerosol COVID-19 exposure (e.g., spirometry and respiratory function testing).

Questions concerning ancillary review can be directed to the relevant ancillary committee or your IRB Coordinator.

Reminder: Ancillary Committee Process

(continued from page 8) Ancillary Committee approvals/acknowledgements.

Ancillary Committee Review & COVID-19

Research Clean Out

Is your research continuing to move slowly due to the COVID-19 pandemic? While many study team members find themselves busier than ever, implementing research related to the COVID-19 pandemic or finding creative ways to keep their non-COVID research progressing, others may be finding themselves working remotely and/or with unfamiliar time on their hands. Time is something all study team members cherish and typically never seem to have enough, so use this time wisely – conduct your ‘clean out’, if you will!

If you have extra time to fill, now may be the time to...

- Review your regulatory binders and study documentation to ensure they are current, complete and accurate. Self-audit tools are available through OHSP’s Division of Quality Improvement.
- Request a Study Start-Up Consultation for research that’s been approved by the reviewing Institutional Review Board but has not yet been initiated (Note: These are currently being conducted remotely via Zoom.)
- Conduct short training refreshers with your study team. Need ideas? Pick an old OHSP Newsletter article to review and discuss. Pick a couple topics to review that have previously been a source of non-compliance and assign each topic to a team member for presenting to the group. Have a contest to see who can complete the Quality Improvement Crossword Puzzle in the 2015 Q3 OHSP Newsletter. Check out readily available (free!) recordings/training opportunities available through the Office for Human Research Protections, the Food and Drug Administration, the Office of Research Integrity, Transcelerate BioPharma and the Society for Clinical Research Sites, the Global Health Training Initiative and Forte Research Systems.
- Update your Curriculum Vitae (see FAQ on page 6).
- Conduct appropriately distanced or remote team building activities (google it – there’s a lot of ideas on the web!).
Reminder: New Guidance on eConsent Using REDCap Available

The Office for Human Subject Protection recently posted the University’s new Guideline for Using REDCap for Electronic Informed Consent (eConsent) on their policy & guideline website (under “1200 - Miscellaneous UR Policies/Guidelines”).

If you intend to use eConsent, please ensure this guideline is read in full before moving forward. The timing of this guideline relates to the COVID-19 pandemic and the need for remote consent in these studies due to quarantine and visitor limitations, so priority of review is being given to these studies; please be patient and do not rush to submit a modification unless it is a very pressing matter.

• **For existing, approved research studies**, a modification must be submitted to the IRB and approved to update the consent process to include eConsent with REDCap. The consent process in the protocol should be updated consistent with the information in the guideline, and the modification must be approved before contacting Academic IT.

• **For new research studies**, the consent process in the protocol should include the information in the guideline, and the new study must be approved before contacting Academic IT.

For questions, please e-mail your IRB Coordinator or use the Who is my IRB Coordinator? on the OHSP website, if you do not know who to contact.