“Down with GCP? Yeah, you know me!”

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Agenda

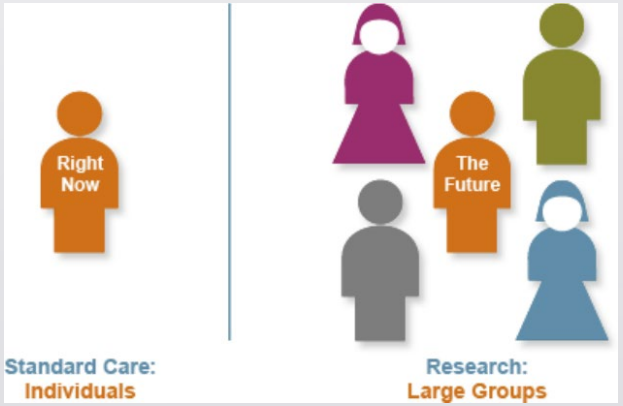
- General Principles, Standards, and Requirements in the Conduct of Clinical Research
- Investigator Responsibilities
- Essential Documents
- Why

Research vs Clinical Care

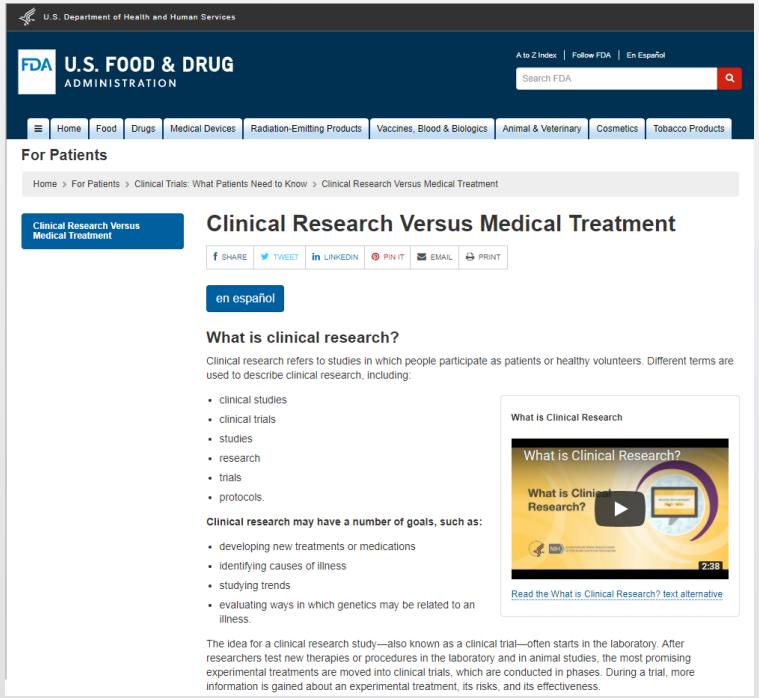
Research is done to help find out if a treatment or procedure is good for a large group of people with a certain disease or condition. Research helps to answer questions for the *future* health of those populations.

Standard medical care,

however, focuses on *individual* needs in the *present*.



Research vs Clinical Care



Clinical Research Versus Medical Treatment		
	Clinical Research	**Medical Treatment**
Intent	Answers specific questions through research involving numerous research volunteers.	Address the needs of individual patients.
Intended Benefit	Generally designed and intended to benefit future patients.	Intended to benefit the individual patient.
Funding	Paid for by drug developers and government agencies.	Funded by individual patients and their health plans.
Timeframe	Depends on the research protocol.	Requires real-time decisions.
Consent	Requires written informed consent.	May or may not require informed consent.
Assessment	Involves periodic and systematic assessment of patient data.	Based on as-needed patient assessment.
Protections	Protected by government agencies, institutional review boards, professional standards, informed consent, and legal standards.	Guided by state boards of medical practice, professional standards, peer review, informed consent, and legal standards.
Certainty	Tests products and procedures of unproven benefit to the patient.	Uses products and procedures accepted by the medical community as safe and effective.
Access to Information	Considered confidential intellectual property.	Available to the general public through product labeling.
Release of Findings	Published in medical journals, after clinical research ends.	Individual medical records are not released to the general public.

https://www.fda.gov/ForPatients/ClinicalTrials/ClinicalvsMedical/default.htm

Laws, Regulations, Policy, Guidance…oh my!

Laws	•A law is developed and passed by a legislative body and signed by an executive authority. Federal laws in the US are passed by Congress, signed by the President, and Published in the US Code
Regulation	•A regulation is a clarification of a law that is developed by the executive branch of the government and is binding. Regulations are considered legally binding by the Courts. Federal Regulations are published in the Code of Federal Regulations (CFR).
Policy	•Policies are developed by individual organizations to interpret laws and regulations and provide additional guidance on compliance. Policies are not binding in the Courts. Policies are subject to audits and inspections.
Guidance	•Guidance documents represent an organization's current thinking on a particular subject. They do not represent or confer any rights for any person and do not operate to bind anyone.

Ethical Principles

Respect for Persons

- Individual autonomy
- Protections for individuals with reduced autonomy

Beneficence

- Maximize benefits, minimize risk
- Favorable risk/benefit ratio

Justice

- Equitable distribution of research costs and benefits

Regulations

- **Department of Health and Human Services (DHHS)**
  - 45 CFR 46 Protection of Human Subjects
- **Food and Drug Administration (FDA)**
  - 21 CFR 50 Protection of Human Subjects
  - 21 CFR 56 IRBs
  - 21 CFR 54 Financial Disclosure
  - 21 CFR 11 Electronic Records and Signatures
  - 21 CFR 312 IND
  - 21 CFR 812 IDE
  - 21 CFR 814 Premarket Approval of Medical Devices

Federal Agencies

Federal agencies have various means to exert their oversight authority, such as through:

- Inspections
- Mandatory reporting letters for IRB findings of:
  - Serious noncompliance
  - Continuing noncompliance
  - Unanticipated problems involving risks to subjects or others
  - Study suspension or termination
- Adverse federal agency findings can result in a range of outcomes, including warnings, implementation of corrective actions, termination of existing studies, and challenges for future funding.

ICH GCP E6 (R2)

- An international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. ICH GCP aims to protect the rights, safety, and welfare of human subjects, improve the quality of data, and facilitate time to market.

Principles of GCP

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)

- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

- The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) | Guidance for Industry (fda.gov)

- The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
- A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.
- The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) | Guidance for Industry (fda.gov)

- Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
- Systems with procedures that assure the quality of every aspect of the trial should be implemented

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) | Guidance for Industry (fda.gov)

ICH GCP E6 (R2): Section 4 - Investigator

4.1	Investigator's Qualifications and Agreements
4.2	Adequate Resources
4.3	Medical Care of Trial Subjects
4.4	Communication with IRB/ IEC
4.5	Compliance with Protocol
4.6	Investigational Product(s)
4.7	Randomization Procedures and Un-blinding
4.8	Informed Consent of Trial Subjects
4.9	Records and Reports
4.10	Progress Reports
4.11	Safety Reporting
4.12	Premature Termination or Suspension of a Trial
4.13	Final Report(s) by Investigator

ICH GCP E6 (R2)

1.34 Investigator

- A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

1.56 Subinvestigator

- Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

ICH GCP E6 (R2)

1.54 Sponsor-Investigator

- An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.53 Sponsor

- An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

4.1 Investigator’s Qualifications and Agreements

- ***4.1.1*** The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).
- ***4.1.2*** The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator’s Brochure, in the product information and in other information sources provided by the sponsor.
- ***4.1.3*** The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
- ***4.1.4*** The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).
- ***4.1.5*** The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

- **4.2.1** The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
- **4.2.2** The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- **4.2.3** The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- **4.2.4** The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.
- **4.2.5** The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.
- **4.2.6** If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

4.3 Medical Care of Trial Subjects

- ***4.3.1*** A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
- ***4.3.2*** During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.
- ***4.3.3*** It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
- ***4.3.4*** Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

- ***4.4.1*** Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.
- ***4.4.2*** As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.
- ***4.4.3*** During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5 Compliance with Protocol

- ***4.5.1*** The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by theIRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.
- ***4.5.2*** The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).
- ***4.5.3*** The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
- ***4.5.4*** The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:
  - (a) to the IRB/IEC for review and approval/favourable opinion,
  - (b) to the sponsor for agreement and, if required,
  - (c) to the regulatory authority(ies).

4.6 Investigational Product(s)

- ***4.6.1*** Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.
- ***4.6.2*** Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.
- ***4.6.3*** The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.
- ***4.6.4*** The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).
- ***4.6.5*** The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.
- ***4.6.6*** The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

- The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

ICH E6 Good Clinical Practice – Informed Consent

- A process by which a subject voluntarily confirms his/her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participation. Informed consent is documented by means of written, signed and dated informed consent forms.

4.8 Informed Consent of Trial Subjects

- ***4.8.1*** In obtaining and documenting informed consent, the investigator should comply with the **applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki**. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.
- ***4.8.2*** **The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent.** Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.
- ***4.8.3*** **Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.**
- ***4.8.4*** **None of the oral and written information concerning the trial**, including the written informed consent form, **should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights,** or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

- ***4.8.5*** The investigator, or a person designated by the investigator, should **fully inform** the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, **of all pertinent aspects of the trial** including the written information and the approval/ favourable opinion by the IRB/IEC.
- ***4.8.6*** The language used in the oral and written information about the trial, including the written informed consent form, **should be as non-technical as practical and should be understandable** to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
- ***4.8.7*** Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative **ample time and opportunity** to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
- ***4.8.8*** Prior to a subject's participation in the trial, the written informed consent form should be **signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.***
- ***4.8.9*** **If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.** After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8: Informed Consent of Trial Subjects

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a. Trial involves research	k. Anticipated pro-rated payment if any for participation d pro-rated payment if any for participation
b. Trial's purpose	l. Any expenses subject may incur for participating
c. Trial treatments and probabilities for random assignment	m. Freedom to withdraw at any time without penalty or loss of benefits subject is otherwise entitled
d. Trial procedures including all invasive procedures	n. Monitor, IRB, regulatory authorities will have direct access to records
e. Subject's responsibilities	o. Confidentiality limits- who will see the subject's records and the circumstances
f. Experimental aspects of the trial	p. Subject/LAR to be notified in timely manner when new info available that may be relevant to subject's continued willingness to participate in trial..
g. Experimental aspects of the trial	q. Points of contact regarding trial rights & in event of trial related injury
h. Reasonably expected benefits or if there is no intended clinical benefit to subject should be made aware of this	r. Foreseeable circumstances and or reasons under which participation in trial may be terminated.
i. Alternate procedures /courses of treatment that maybe available including their important benefits/risks	s. Expected duration of subject's trial participation
j. Compensation available (and or treatment) for trial related injury	t. Approximate number of subjects involved in the trial

Investigator Responsibilities (ICH GCP 4.0)

- ***4.8.11*** Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
- ***4.8.12*** When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.
- ***4.8.13*** Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8: Informed Consent of Trial Subjects

- ***4.8.14*** Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:
- (a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.
- (b) The foreseeable risks to the subjects are low.
- (c) The negative impact on the subject's well-being is minimized and low.
- (d) The trial is not prohibited by law.
- (e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.
- Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.
- ***4.8.15*** In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

Short Form – The Players

Participant

- Signs Short Form

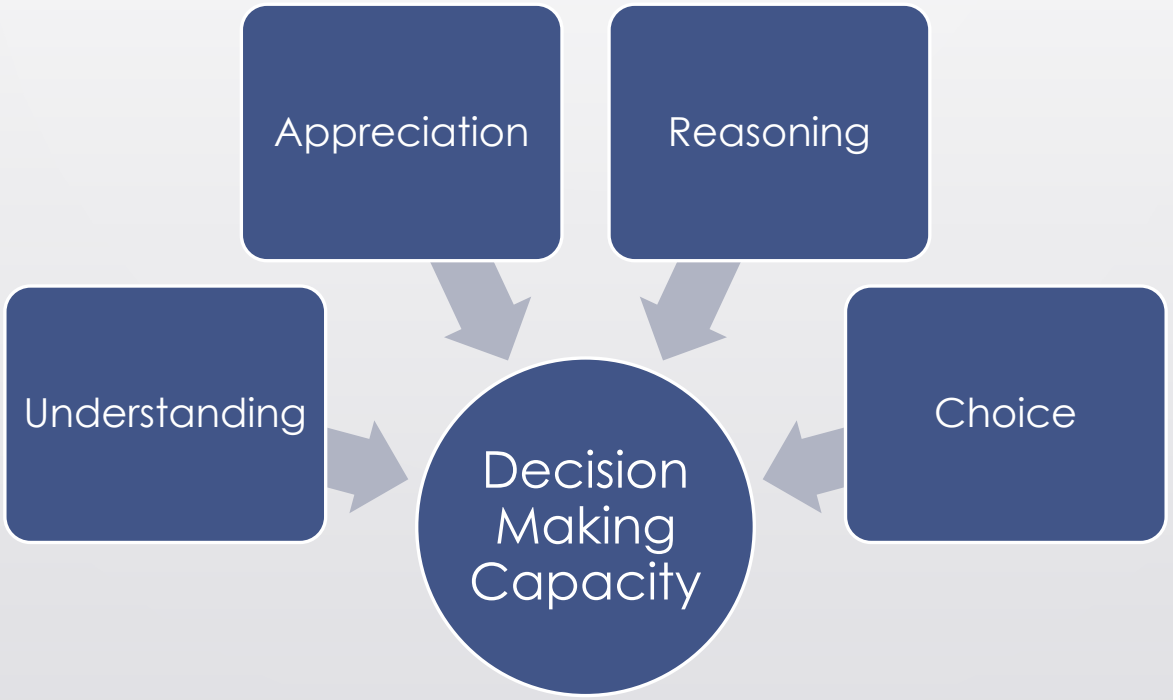
Witness

- Signs Short Form
- Signs "Oral Script" (IRB approved version of consent form)

Researcher

- Signs Short Form
- Signs "Oral Script" (IRB approved version of consent form)

Decisional Capacity



Citation: Appelbaum, P. S., & Grisso, T. (1988). Assessing patients' capacities to consent to treatment. *The New England journal of medicine*, *319*(25), 1635–1638.

Capacity Assessment

- "It is generally agreed that a prospective subject's capacity to decide whether to participate in a particular research project cannot be determined through a general mental status assessment. Instead, investigators must develop and present the specific material relevant to that project and evaluate the prospective subject's understanding and appreciation of that information."

Citation: National Citation: National Bioethics Advisory Commission. Research involving persons with mental disorders that may affect decision-making capacity: report and recommendations, December 1998.

4.9 Records and Reports

- ***4.9.0*** *The investigator/institution should maintain* ***adequate and accurate source documents and trial records*** *that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).*
- ***4.9.1*** The investigator should ensure the **accuracy, completeness, legibility, and timeliness** of the data reported to the sponsor in the CRFs and in all required reports.
- ***4.9.2*** Data reported on the CRF, that are derived from source documents, should be **consistent with the source documents** or the discrepancies should be explained.
- ***4.9.3*** **Any change or correction to a CRF should be dated, initialed, and explained** (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9 Records and Reports

- ***4.9.4*** The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.
- ***4.9.5*** Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. **These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).**
- ***4.9.6*** The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
- ***4.9.7*** Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

ALCOA-C+++

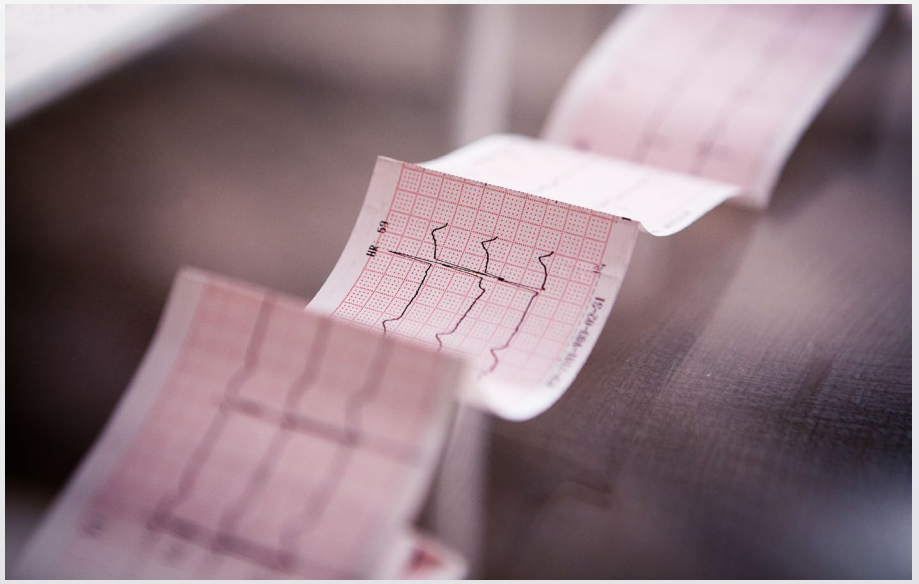
- ❑ Sign/initial and date entries at the time they are made
- ❑ Time of data collection should correspond to time of data entry
- ❑ Data should have a date/time
- ❑ Able to read entry
- ❑ Original records should be preserved
- ❑ Error free data
- ❑ No deletion of data
- ❑ Material used will last
- ❑ Made available for auditors/inspections

Error Correction

- Do not obliterate previous data
- Date the change
- Identify the person making the change
- State the reason for the change
- DO NOT USE WHITEOUT
- Do not change data without knowledge that the change is accurate

Source Documents

- Informed Consent Forms and HIPAA Authorization Forms
- Study visit notes
- E-mail
- IRB correspondence
- Sponsor correspondence
- Lab results
- Test results
- Medical records supplied by the participant
- Questionnaires
- Assessments



If it is not documented, it did not happen

Correspondence

- ✓Include all correspondence with the sponsor regarding study conduct, subject management, protocol deviations and adverse events.
- ✓Documentation may include letters (e.g., site activation), teleconference minutes, newsletters, emails, fax confirmations and shipping receipts.
- ✓Document correspondence in such a manner that the date, persons involved, and relevance to the study are apparent.

All study related documentation (paper & electronic), should be organized, identified and retained so that it can be accurately interpreted without benefit of an interpreter.

- ✓Can I reconstruct what happened?
- ✓Can I identify who did what and when?
- ✓Am I confident in the accuracy and authenticity of the research data?

Investigator Responsibilities (ICH GCP 4.0)

- **4.10 Progress Reports**
  - ***4.10.1*** The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.
  - ***4.10.2*** The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

Investigator Responsibilities (ICH GCP 4.0)

- **4.11 Safety Reporting**
  - ***4.11.1*** All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.
  - ***4.11.2*** Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
  - ***4.11.3*** For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

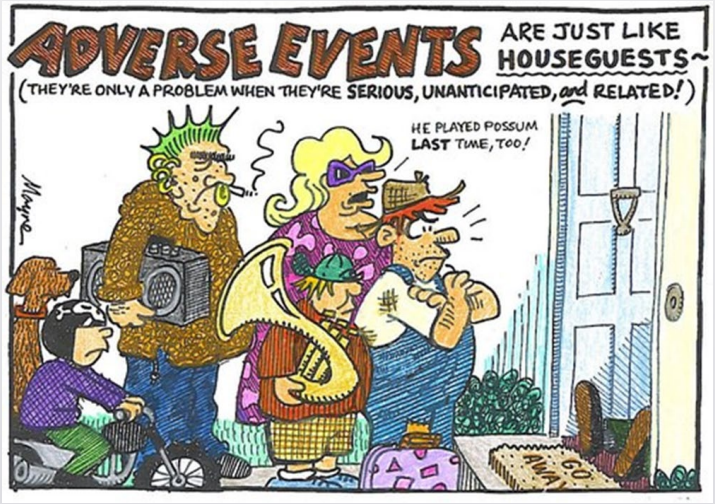
Adverse Event (AE)

Any untoward medical occurrence in a patient administered a pharmaceutical product and which doesn't necessarily have a causal relationship with the treatment.

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product

Does not have to be related to treatment/drug

- Adverse events may be:
  - symptomatic or asymptomatic
  - clinically detected, radiographically detected
  - abnormal laboratory studies or other assessments (i.e., ECG, ECHO)



FDA (drugs/biologics: 21 CFR 312; ICH GCP E6(R2); ICH E2A; Cartoon Credit: Don Mayne

Serious Adverse Event (SAE)

An Adverse Event that results in any of the following:

- Death
- Persistent or significant disability/incapacity
- Inpatient hospitalization or prolongation of existing hospitalization
- Congenital anomaly or birth defect
- Life threatening event
  - any AE that places the study participant at immediate risk of death from the event or if it is suspected that continued use of the product would result in the participant's death
- Important medical event

Unanticipated Problems Involving Risks to Participants and Others

- Are **unexpected** (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND

- Are **related or possibly related to participation** in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND

- Suggest that the **research places subjects or others at greater risk of harm** (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Participants and Others

- **Physical**
  - Rash
  - Abnormal laboratory finding
  - Worsening of a physical condition
- **Psychological**
  - Altered mental state
  - Suicidality
  - Anxiety
- **Legal**
- **Social**
- **Reputational**
- **Financial**

Example

- A subject is participating in a phase 3, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy agent combined with the current standard chemotherapy regimen, versus placebo combined with the current standard chemotherapy regimen, for the management of multiple myeloma **develops neutropenia and sepsis**.
- The subject **subsequently develops multi-organ failure and dies**. *Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections is a known complication of the chemotherapy regimens being tested in this clinical trial and these risks are described in the IRB-approved protocol and informed consent document.*
- The investigators conclude that the subject's infection and death are directly related to the research interventions. *A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency.*

Unanticipated Problems Involving Risks & Adverse Events Guidance (2007) | HHS.gov

Example

- A subject is participating in a phase 3, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy agent combined with the current standard chemotherapy regimen, versus placebo combined with the current standard chemotherapy regimen, for the management of multiple myeloma **develops neutropenia and sepsis**.
- The subject **subsequently develops multi-organ failure and dies**. *Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections* ***is a known complication*** *of the chemotherapy regimens being tested in this clinical trial and these* ***risks are described in the IRB-approved protocol and informed consent document.***
- The investigators conclude that the subject's infection and death are directly related to the research interventions. *A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency.*
- **This example is not an unanticipated problem because the occurrence of severe infections and death – in terms of nature, severity, and frequency – was expected.**

Unanticipated Problems Involving Risks & Adverse Events Guidance (2007) | HHS.gov

Example

- A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication.
- The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have **severe anemia** (hematocrit decreased from 45% pre-randomization to 20%).
- Hematologic evaluation suggests an **immune-mediated hemolytic anemia**. *The known risk profile of the investigational agent does not include anemia, and the IRB-approved protocol and informed consent document for the study do not identify anemia as a risk of the research.*
- *The investigators determine that the hemolytic anemia is possibly due to the investigational agent.*

Unanticipated Problems Involving Risks & Adverse Events Guidance (2007) | HHS.gov

Example

- A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication.
- The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have severe anemia (hematocrit decreased from 45% pre-randomization to 20%).
- Hematologic evaluation suggests an immune-mediated hemolytic anemia. *The known risk profile of the investigational agent does not include anemia, and the IRB-approved protocol and informed consent document for the study do not identify anemia as a risk of the research*.
- *The investigators determine that the hemolytic anemia is possibly due to the investigational agent.*
- **This is an example of an unanticipated problem that must be reported because the hematologic toxicity was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) serious.**

Unanticipated Problems Involving Risks & Adverse Events Guidance (2007) | HHS.gov

How do we know if an event is an AE?

- **Know the participant's medical history**
  - Pre-existing condition diagnosed prior to enrollment is part of the participant's medical history, not an AE

- **Adverse Events may be caused by many things other than the Investigational Product(s)/Device, examples include but are not limited to:**
  - Procedure/assessment related to the trial
  - Change in pre-existing medical conditions, baseline symptoms or previously reported symptom
  - Concomitant medication
  - Accidental injuries

How are AEs Identified?

- During study visits or follow-ups with participants
- Abnormal vitals or laboratory results
- Hospitalization or ER visit
- Abnormal electrocardiograms
- Psychological assessments
- Other?

Challenges identifying and assessing AEs

- Complex protocols involving multiple drugs or therapeutic modalities
- Patients with existing complicated medical history
- Concurrent medical conditions
- Concurrent medications

Reporting Requirements

OHRP
Office for Human
Research Protections

FDA

Pfizer

AMGEN®

Reporting Requirements -IRB

- Policies may vary
- Timeframes may vary
- Most IRB's only want to see Adverse Events that are Unanticipated Problems (UPs)

Reporting Requirements -Sponsor

- **Serious Adverse Events**
  - Reported to Sponsor within 24 hours
  - Follow protocol instructions for reporting
  - Actionable follow up information must be reported within 24 hours of the site being aware of the new information.

Food and Drug Administration

- Any adverse experience associated with the use of the drug that is both serious and unexpected or;

- Any findings from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, and carcinogenicity.

IND Application Reporting: Safety Reports | FDA

FDA Timelines

- Unexpected serious suspected adverse reactions and observations from animal studies suggesting significant risk to human subjects must be reported to FDA as soon as possible but no later than within **15 calendar days** following the sponsor's initial receipt of the information.

- Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than **7 calendar days** following the sponsor's initial receipt of the information.

IND Application Reporting: Safety Reports | FDA

Investigator Responsibilities (ICH GCP 4.0)

- **4.12 Premature Termination or Suspension of a Trial**
  - If the trial is prematurely terminated or suspended for any reason, the investigator/institution should **promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects**, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:
  - ***4.12.1*** If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.
  - ***4.12.2*** If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.
  - ***4.12.3*** If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

Investigator Responsibilities (ICH GCP 4.0)

- **4.13 Final Report(s) by Investigator**
  - Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

8.0 Essential Documents

- Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

- The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial.

- The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.

Regulatory File

A. Study Conduct Documents
   1. Protocol
   2. Informed Consent Form
   3. Advertisements and Subject materials
   4. Sample Case report Forms
   5. Study-Specific Procedures
   6. Laboratory Documents

B. Committee Approvals and Correspondence
   1. IRB Correspondence and Approvals
   2. IRB membership
   3. Other Committee review and Approvals

C. Study Personnel Qualifications and Training
   1. DOA
   2. CV & Licenses
   3. Training Documentation

D. Study Tracking and Monitoring
   1. Subject logs
   2. Specimen Tracking
   3. AE Tracking and Reporting
   4. Deviation Tracking and Reporting
   5. Safety Committee Reports
   6. Sponsor Monitoring

E. Study Correspondence
   1. Sponsor Correspondence
   2. Local Correspondence

F. IND/IDE
   1. Statement of Investigator (i.e. FDA 1572)
   2. Disclosures of Financial Interests
   3. IP Information
   4. IP Accountability
   5. IND Safety Reports

Subject File

Informed Consent

Eligibility and Enrollment

Study Assessments

- Source Documents
- Case Report Forms

Study Treatment

Adverse Events

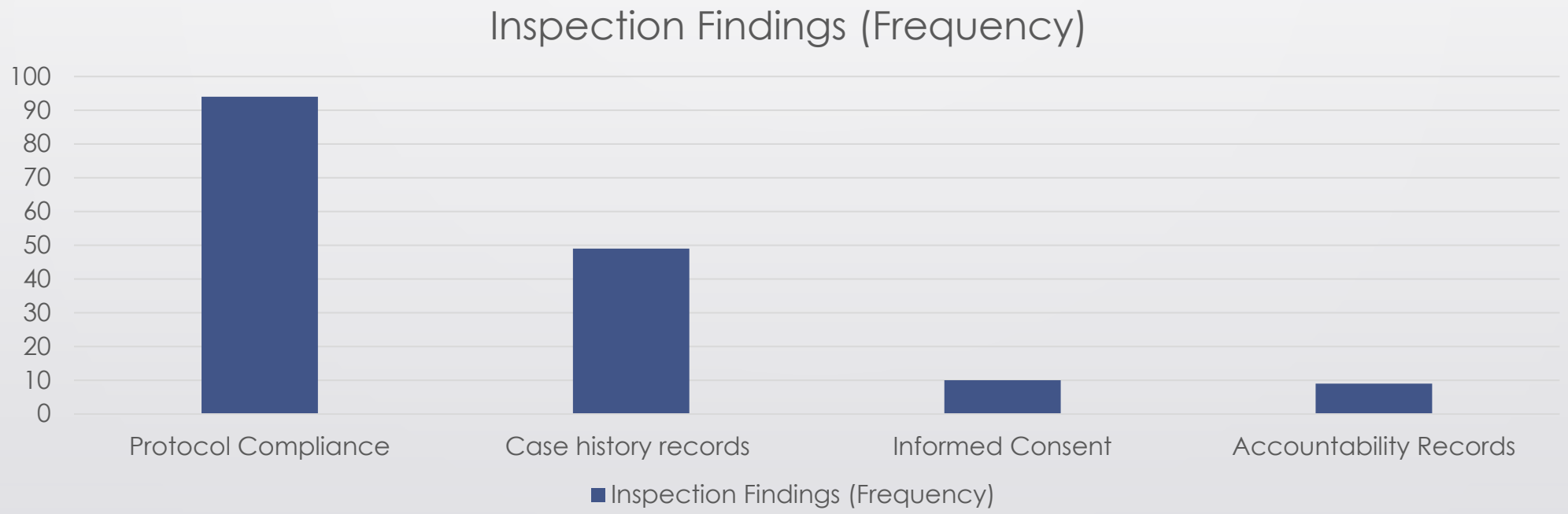
- ✓ All study documents should be stored in a secure location, whether they are maintained in a paper or in electronic format. If any documents are stored separately from the main file(s), a Note-To-File should be used to indicate where the information is located.
- ✓ Information that should *not* be kept in regulatory and subject files includes: grant application, clinical trial agreement (contract), budget information, subject payments, and quality assurance documents. In addition, the regulatory file should not include documents with patient names.

Why Do I Care?

- Ensure the data generated are accurate, verifiable, and reproducible
- Provides public assurance that the rights, safety, well-being of participants and others are protected
- Ensure treatments are safe and effective

Warning Letters | FDA

Food and Drug Administration Inspections Findings 2023 – Bioresearch Monitoring



Inspection Observations | FDA

Common Inspection Findings

- Failure to follow the investigational plan and/or regulations
- Inadequate recordkeeping
- Inadequate accountability of investigational product

You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, you are required to e
conducted in accordance with the investigation
Protocols **(b)(4)** and **(b)(4)** required you to e
before enrollment in the studies. Specifically, b
you to exclude subjects on current or recent (w
antidepressants, antipsychotics, or mood stabi
participate in the studies and undergo a medic
antidepressants but had not responded to an a
weeks at a therapeutic dose) at the time of thei
required these subjects to be tapered off their c
remain off medication for 5 elimination half-liv
failed to adhere to these requirements.

You failed to take adequate precautions to prevent theft or diversion of an investigational drug that is subject to the Controlled Substances Act [21 CFR 312.69], and you failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, when handling an investigational drug that is subject to the Controlled Substances Act, you are required to take adequate precautions to prevent theft or diversion of the controlled substance into illegal channels of distribution. These precautions include the storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited. In addition, as a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol **(b)(4)** required you to ensure that all clinical drug supplies were stored in a secured, monitored, and limited-access area, in accordance with labeled storage conditions. Additionally, the protocol required the clinical investigator to limit access to the study drug to the named subinvestigators, or to other appropriately designated study personnel or monitoring personnel.

Warning Letters | FDA

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol **(b)(4)** included three main treatment phases: (1) Remission Induction (and Early Intensification); (2) Consolidation; and (3) Continuation Treatment, during which subjects were assigned to treatment based on risk group [low-risk, standard-risk, and high-risk **(b)(4)**] and cell type (**(b)(4)**).

During the Continuation Treatment phase, subjects at standard risk or high risk with either a **(b)(4)**. Subjects at low risk were to stop **(b)(4)** pulses after Week 49 of Continuation Treatment.

You failed to adhere to these requirements. Specifically, Subject **(b)(6)** was a pediatric subject (6 years old) with **(b)(4)** Continuation Treatment. However, this subject continued to receive **(b)(4)** treatment through Week 61. As a result, this subject received three additional doses of **(b)(4)**, on Week 53 (**(b)(6)**), Week 57 (**(b)(6)**), and Week 61 (**(b)(6)**), and three additional five-day cycles of **(b)(4)** during Weeks 53, 57, and 61. Subjects administered **(b)(4)** are exposed to a risk of certain serious toxicities, including but not limited to neurologic and hematologic toxicity. Since Subject **(b)(6)** received additional doses of **(b)(4)** that were not required by the protocol, this subject was exposed to an increased risk of these toxicities.

In your October 27, 2022, written response to the Form FDA 483, you acknowledged that the subject received additional study treatments of **(b)(4)**. You stated that these additional treatments occurred because a physician subinvestigator misinterpreted the drug administration plan. You stated that the Institutional Review Board (IRB) was notified of this occurrence within the time frame specified by the IRB policy.

Warning Letters | FDA

You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol **(b)(4)** required you to ensure that subjects met all eligibility requirements before their enrollment into the study. Specifically, Protocol **(b)(4)** required you to ensure that subjects had a laboratory-confirmed **(b)(4)** at the local study laboratory, to be eligible for inclusion in the study. In addition, the protocol required the subject to be within **(b)(4)** test result from the local study lab at the time of study randomization, to be eligible for inclusion in the study.

You failed to adhere to this requirement. Examples of this failure include, but are not limited to, the following:

1. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization. In fact, this subject had a **(b)(4)** test result on **(b)(6)**.

2. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization. In fact, this subject had a negative **(b)(4)** test result on **(b)(6)**.

3. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization.

4. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization.

5. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization. In fact, this subject had a **(b)(4)** test result on **(b)(6)**.

6. Subject **(b)(6)** was randomized into the study and dispensed investigational drug on **(b)(6)**, without a laboratory-confirmed **(b)(4)** of randomization. In fact, this subject had a **(b)(4)** test result on **(b)(6)**.

Warning Letters | FDA

FDA Approves First Cellular Therapy to Treat Patients with Unresectable or Metastatic Melanoma

For Immediate Release: February 16, 2024

Today, the U.S. Food and Drug Administration approved Amtagvi (lifileucel), the first cellular therapy indicated for the treatment of adult patients with a type of skin cancer (melanoma) that is unable to be removed with surgery (unresectable) or has spread to other parts of the body (metastatic) that previously has been treated with other therapies (a PD-1 blocking antibody, and if *BRAF* V600 mutation positive, a *BRAF* inhibitor with or without a MEK inhibitor).

"Unresectable or metastatic melanoma is an aggressive form of cancer that can be fatal," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research (CBER). "The approval of Amtagvi represents the culmination of scientific and clinical research efforts leading to a novel T cell immunotherapy for patients with limited treatment options."

Melanoma is a form of skin cancer that is often caused by exposure to ultraviolet light, which can come from sunlight or indoor tanning. Although melanomas only represent approximately 1% of all skin cancers, they account for a significant number of cancer-related deaths. Melanoma can spread to other parts of the body if not detected and treated early, resulting in metastatic disease.

Treatment for unresectable or metastatic melanoma may include immunotherapy using PD-1 inhibitors, which are antibodies targeting certain proteins in the body to help the immune system fight off cancer cells. In addition, drugs targeting the *BRAF* gene, which helps with managing the growth and functioning of cells, may be used for treating melanoma associated with *BRAF* gene mutations. Those patients whose melanoma has progressed with these therapies have a high unmet medical need.

Thank you to my partners for getting down with GCP

Several slides were courtesy of or influenced by:

- Linda Coleman
- Alyssa Gateman
- Laura Holtz

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