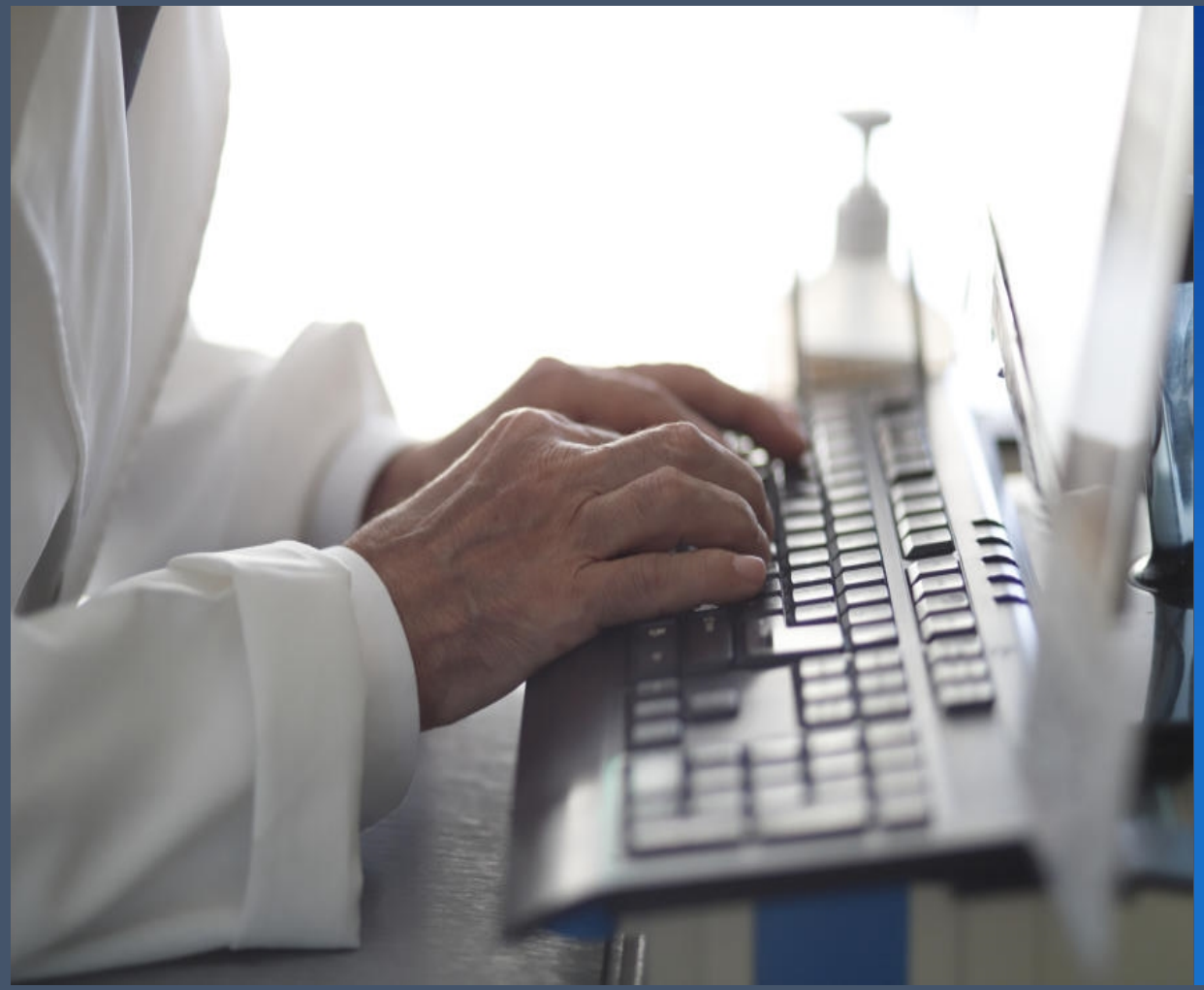
Medical Records, Source, and EDC



Topics

1. Medical and Research Records
2. Electronic Data Capture System
3. Reports: Laboratory, ECG's, Radiographic, Pathology
4. ECG's
5. Sponsor Vendors
6. Physical Examinations
7. Investigational Product
8. Introduction to Side Effects and Adverse Events
9. Introduction to Serious Adverse Events
10. Introduction to The Process of Consent
11. Good Clinical Practices [GCP]
12. Quiz, a 85% pass rate is required to move forward [2 attempts]
13. Conference Call to review

Medical Records

Medical Records are written to record our interactions with our patients. To provide consistent care and for medical/legal purposes.

They may have **some** or **all** the following elements:

1. Identification
2. Medical History
3. Medication Information
4. Progress Notes
5. Family History
6. Treatment History
7. Medical Directives
8. Laboratory Results
9. Consent/Release Forms

Source: Unlike medical records, source documents have an international definition.

The International Council for Harmonisation (ICH) Good Clinical Practice (GCP) requirements ("ICH E6") guidelines define source data and source documents as:

- Source Data (1.51): "All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

- Source Document (1.52): "Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). Original Medical Records (1.43) can also be used to refer to Source Document."

Site Source are all the rain drops that fill the buckets of data for the clinical trial.

Source documentation must be necessary and sufficient to complete the Electronic Data Capture [EDC] system that has been tailored to the clinical trial.

Additional information may be captured in the source that is not in the EDC, the converse is never to occur.

Source Data Verification is the method by which the sponsor will assure that the site has collected and entered correct, valid, reliable data.

In research:
IF IT IS NOT DOCUMENTED IN WRITTING IT DID NOT OCCUR.

Source	Medical Record	Clinical Research
	Name and DOB	Name may or may not be used
	MR number and/or Name of every page	Study number/Site number/Subject Number on every page
	Medical History	Medical History with particular emphasis on clinical trial requirements
	Past Treatment History	Past Treatment History for the clinical trial indication
	Family History	Family History may or may not be included
	Medical Directives	NOT generally part of a research source documents
	Laboratory Results	Laboratory Results
	Progress Notes	Study Visit Notes
	Consent/Release Forms	Informed Consent Forms
		Study Flow Guides
		Investigational Product Accountability Logs

Headers, Footers, and Names

Unlike your office records, names are minimized in source documents.

1. **Never, ever, ever send a document by any means with the name and/or DOB. This would be considered a major deviation.**

1. **In 2010, the European Union added the additional privacy measure of using YOB only.**

Source documents may have headers/footers.

1. **Source pages usually will have the study number, site number and subject number. These may be added by the site or sponsor.**

1. **Completion of headers/footers is mandatory. The monitor or other sponsor representative will take it badly if these are not completed.**

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Chart Notes

In medical practice chart notes are written when a patient comes to the office.

When a patient becomes a participant in a trial, the notes are written at predetermined intervals, the Study Visits.

It is imperative that participants adheres to the study schedule.

If a visit occurs outside of the protocol specified window it is a deviation.

The deviation must be source documented in the participant's source chart.

Chart Notes are termed Source Docs

What occurs and does not occur in a study visit is determined by the protocol and participant safety.

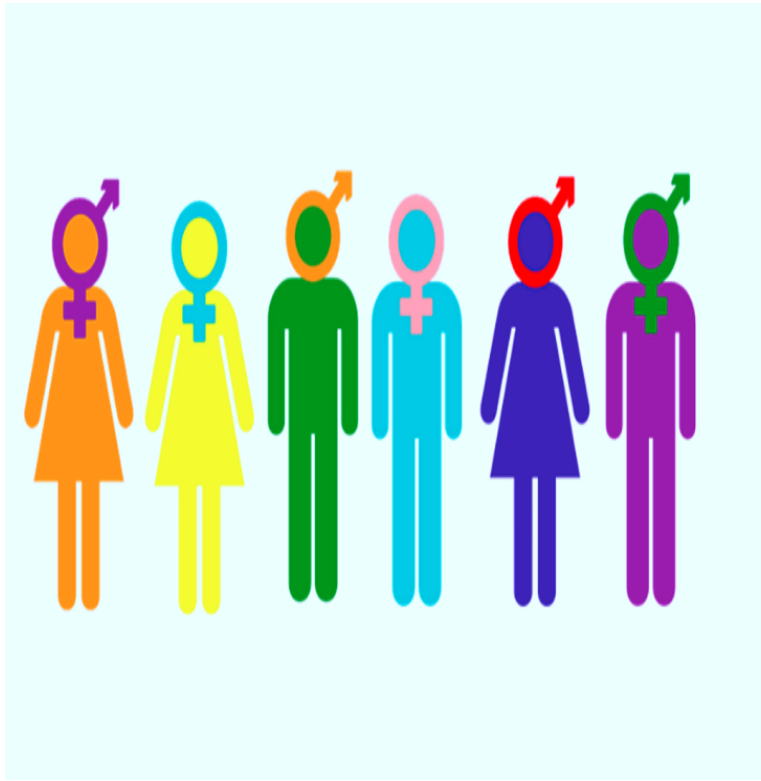
Examples of differences between practice and research:

- **Date – dd MTH YR**
- **Height/Weight – Metric is the standard**
- **Time – 24 hour format, eg 2:00pm = 14:00**
- **BP/P – are taken per protocol requirements, with time in position and time taken source documented**
- **Laboratory, ECGs, Scans, etc – Type and timing is determined by the protocol.**
- **Physical Examinations – type and extent, and timing are determined by the protocol.**

Any variance from what is written in the protocol is considered a deviation.

All deviations must be documented and acknowledged by the PI.

Documentation of Gender in Research



In clinical research we are tasked with determining if a compound is effective, efficacious, and collecting data on any potential side effects [adverse events].

Gender in clinical research is determined by the biology and except for a trial specifically addressing sex chromosome abnormalities there are two genders Male and Female.

Pregnancy is strictly prohibited during clinical research trials unless the trial involves pregnancy itself.

Contraception is mandatory and non-negotiable.

Pregnancy tests serum, urine as per the protocol are just that part of the protocol, they must be performed even if a participant identifies as a male.

If a participant identifies as a gender other than their gender of biology then if they wish to participate in the trial, they must agree to adhere to all gender specified requirements in the protocol.

Documentation of Gender in Research

Source Notes

If you as a physician determine that additional evaluations are necessary for participant safety, then your fist obligation is to the participant.

An emergent telephone call to the medical monitor is well advised prior to performing any procedures unless it is life threatening.

All conversations must be source documented.

The following are usually included for documentation:

a) **Clinical reason as to why additional procedures were deemed necessary**

b) **Documentation of what occurred.**

c) **Documentation of conversation, including print out of all emails, with study team including medical monitor**

d) **Any laboratory, ecg or other results**

   a) **If a local laboratory was used rather than the sponsor's selected laboratory, then documentation of the reason to use the local laboratory.**

      YOU MUST ADD THE LOCAL LAB TO THE 1572!

Requests for Records

As physicians we are accustomed to thinking that the patient's charts are "ours" and that a patient may make a request to see their record and/or have their record sent to whomever they desire so long as a valid release has been signed.

Clinical Research Records do not belong to the PI or site or participant they belong to the sponsor.

Requests for Records

Many sponsors will request that the participant be given the opportunity to inform their primary or specialist of their participation in a trial. If the participant agrees then the site is obligated to notify the PCP or specialist of their patient's participation. This is only a notification that their patient is participating in a clinical trial for the study of XXXX.

You may request background medical records from the PCP or specialist.

This consent does not entitle the PCP, specialist or participant to their entire source document, the chart. The study chart belongs to the sponsor.

Requests for Records

There is an understanding that basic information such as laboratory results that are not unique to the trial, ecg results may be released to the participant's primary or specialists.

It is best that you the PI clarify in writing prior to enrolling participant's that you would like to be able to send routine lab, ecgs, or even basic vital signs [height, weight, BP] to the primary or specialist.

Requests for Records

Beyond the basic information clinical research charts are generally ***not*** released.

If you receive notification for a release to any other than what has been listed, then you should **not** do the following:

- Call the person to whom the information is being released.
- Have your staff contact in any manner the individual.
- Send any records.

You should communicate with the study team the nature of the request in writing by email, and telephone if urgent.

Requests for Records
EMERGENCY

If you are contacted by an emergency room physician and your participant is in the emergency room and if you as the PI deem that the participant's life would be in danger if the trial information was not released, then you may release the information.

Immediately after you ascertain the situation, you must contact by telephone the sponsor's medical monitor. Then you must communicate in writing the discussion with the ED, the rational for your decision, and a synopsis of the call with the medical monitor.

Everything must be source documented with all of the aforementioned information captured, and the emails printed out and filed in the participant's source.

This is an example of a SERIOUS ADVERSE EVENT and will be discussed further later in the lecture.

Record Retention in Clinical Trials

Record retention in medical practice is determined by state law. In clinical research record retention is determined by two parties – the sponsor and the ICH-GCP convention.

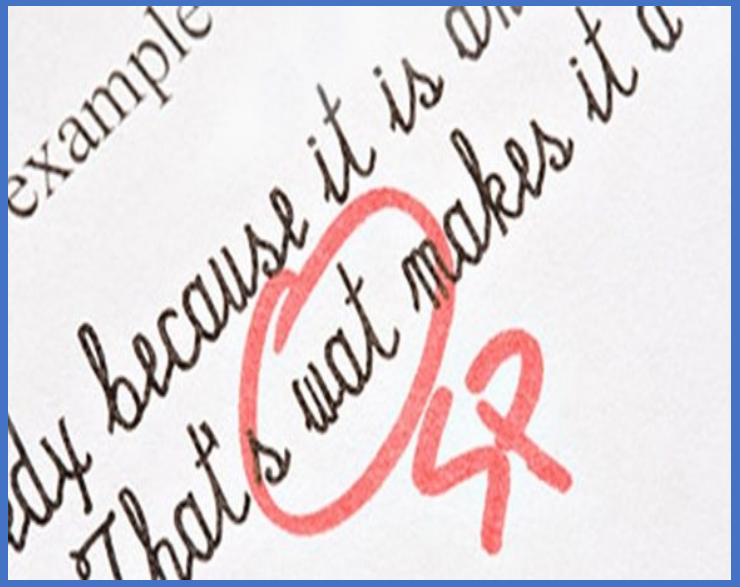
The sponsor may determine how long records should be retained.

If the sponsor does not have a specified time frame all records must be retained at the address listed on the 1572 [your contract with the FDA] for two years beyond the last ICH-GCP participating country files for a NDA [New Drug Application].

Records and all clinical trial materials must be maintained at the specified address given to the sponsor when the study concludes, is closed out.

If the records are moved to a storage area or the records are to be destroyed the sponsor must be notified in writing.

Making Corrections ….



In any source document there will be errors, and corrections will need to be made. We are human, numbers are transposed, dates written in the wrong format, times written in the wrong format. In clinical research it is imperative that any and all corrections are made by a single line through, not obscuring the original data, the correct information is clearly written, and the entire error is dated and initialed by site staff.

Single strike through, correction, date and initial is the ONLY acceptable method of making a correction in a clinical research chart.

Electronic Data Capture Systems

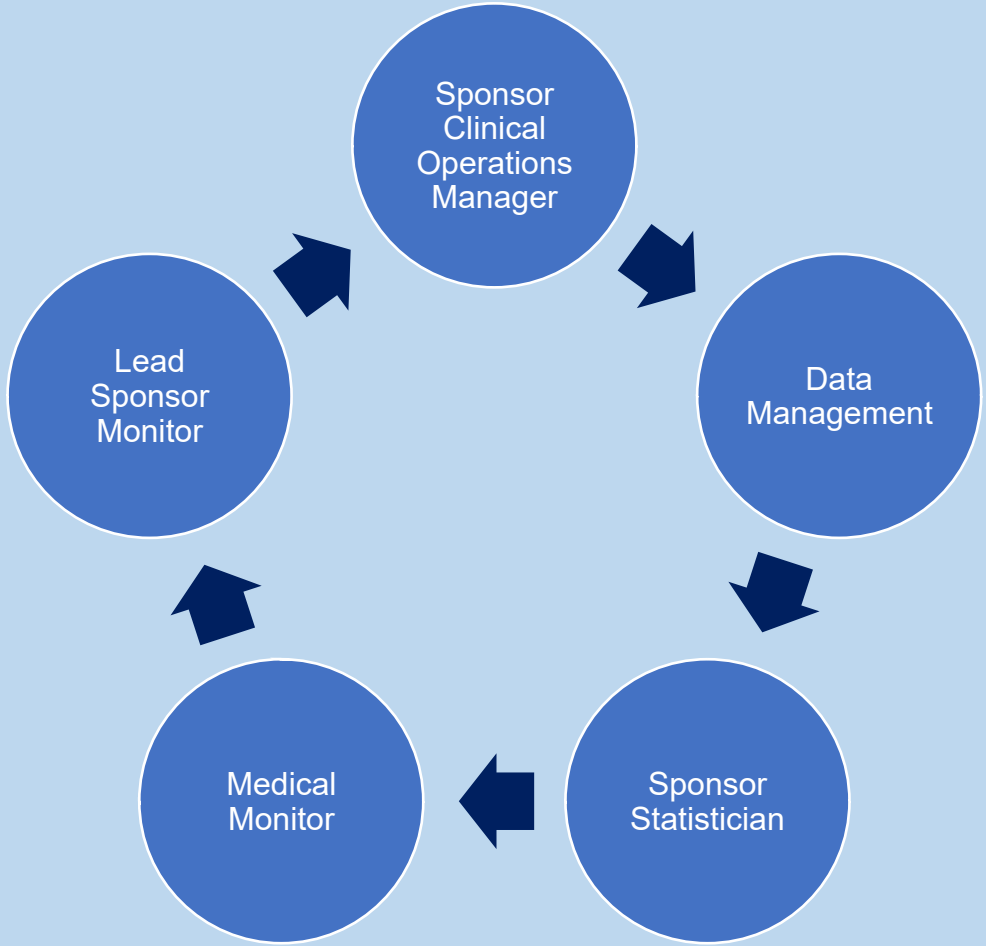
In clinical research our task is to collect data. The original data is the source data. This raw information must be placed into a system where the data may be collated and analyzed.

Prior to the mid 1990's sites would transcribe their site source onto either carbon and then later carbonless paper documents provided by the sponsor. The sponsor's monitor and the site staff would separate the pages, with one page remaining at the site and the other page being sent to the sponsor where the data was entered into the data base for statistical analysis.

Electronic Data Capture systems gradually came into use in the mid 1990's. The site enters their source data into the sponsor provided data base. The systems are built by a team called, Data Management [DM].

Electronic Data Capture Systems

The creation of the EDC for each trial is a detailed process involving multiple teams:



Electronic Data Capture Systems

IBM Clinical Development

There are several steps that must be accomplished prior to the data entry process:

1. The site sends a list of staff names and emails to the EDC Vendor.
2. The EDC Vendor sends a "welcome" email to the site staff.
3. The site staff will enter their username and change their password.
4. Site staff completes any training on the system.
5. EDC vendor will notify the sponsor when the training has been completed.
6. Site staff is granted access to the EDC.
7. The username and password for each site staff is never shared.

Electronic Data Capture Systems

medidata

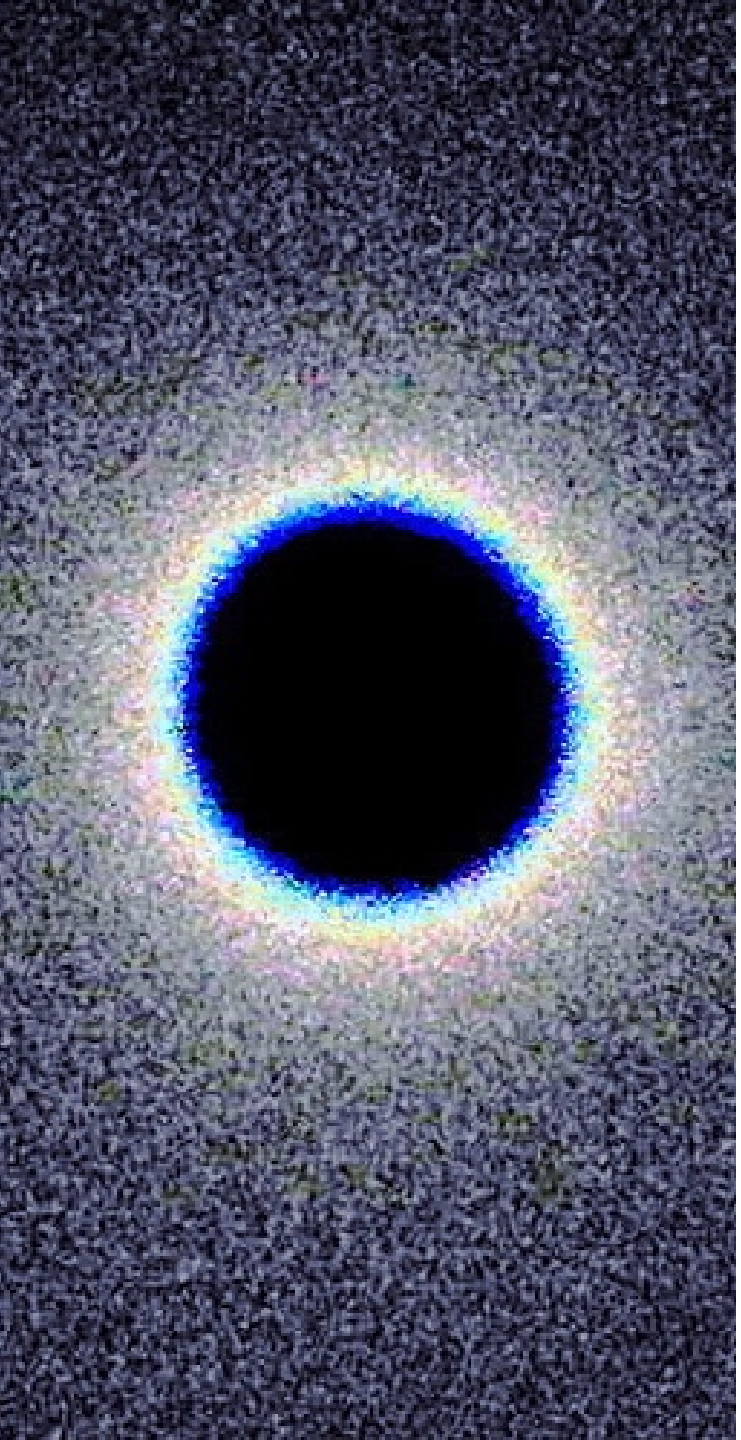
IBM Clinical Development

Clinical ink

OpenClinica

User tasks are separated into the following categories:

1. Sponsor Monitor
   a) They do not have the ability to enter data.
   b) They may issue and close queries [questions] regarding data.
2. Sponsor Medical Monitor
   a) They issue medical queries.
   b) They do not enter data.
3. Site staff, research coordinator or data entry
   a) They enter data.
   b) They answer the queries issued by DM, monitor, MM.
4. Principal Investigator
   a) They answer queries, in particular Medical Monitor queries.
   b) They may enter data.
   c) ONLY the PI may electronically sign the EDC records. The electronic signature is legally binding.



Electronic Data Capture: Queries At times a black hole ...

Queries will be issued and may be re-issued throughout the life of the trial.

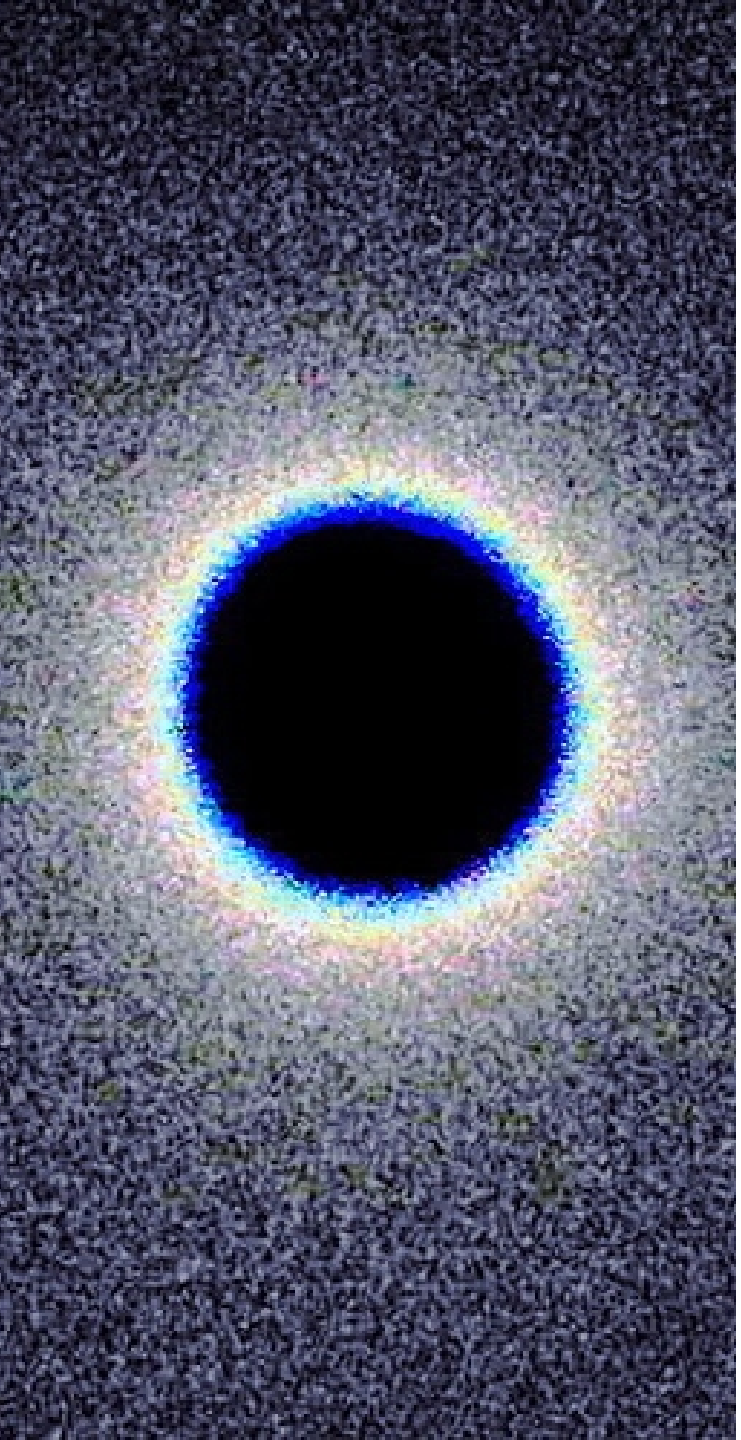
Auto Queries – programmed by DM to catch obvious entry concerns, eg Diastolic BP 20.

Sponsor Monitor Queries – when the monitor is on site they will compare the site source to the data entered in the EDC and issue queries based on missing data, discrepancies between source and EDC entries, inconsistent data, eg weight 55 KG visit 1 and a week later 66 KG, etc.

DM Queries – When the data is being cleaned, that is checked for internal consistency and completeness DM will issue queries.

Clinical Operations – Issue queries based on compliance to the protocol.

Medical Monitor – Issue queries regarding current and past medical history, eligibility, concomitant medication and vital sign queries.

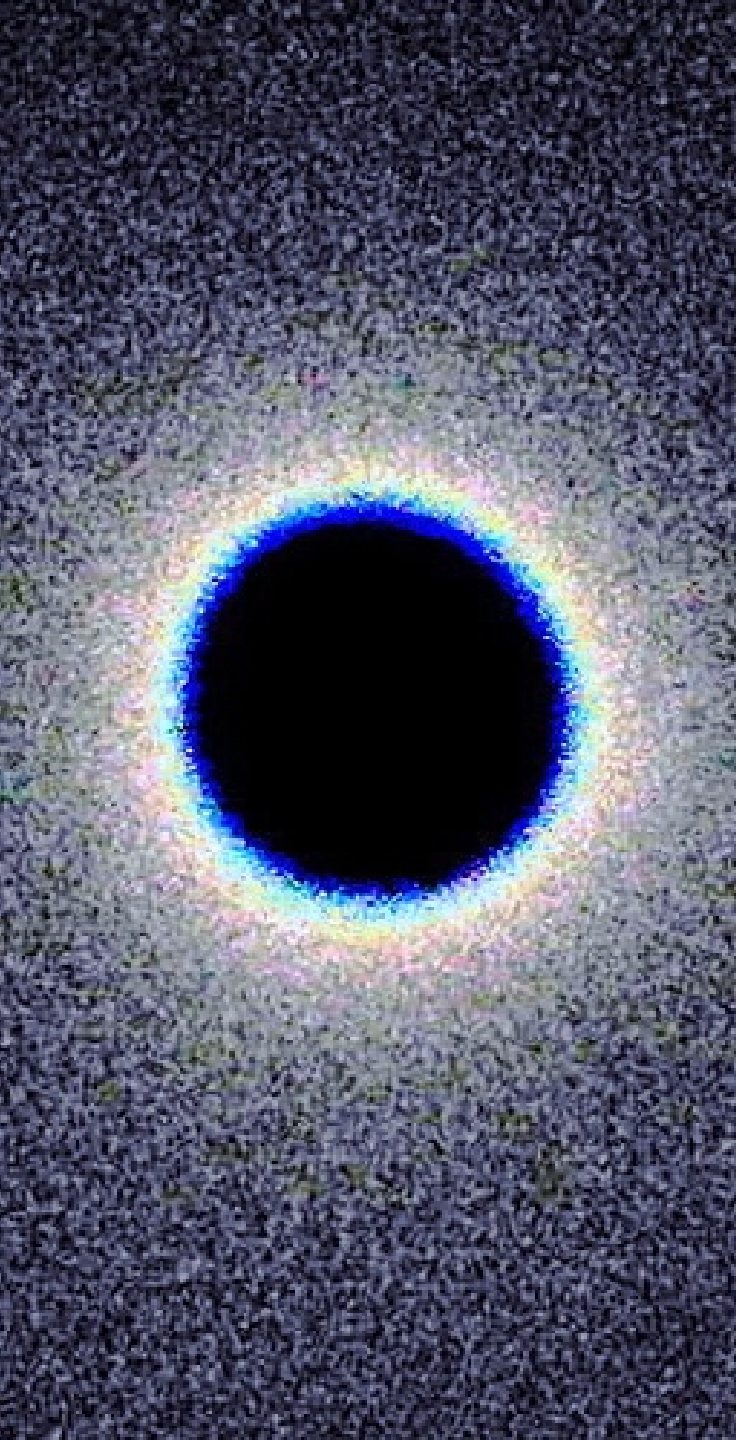


Electronic Data Capture: Queries At times a black hole ...

Sponsors will have clear expectations of timelines for data entry and resolution, answering, of data queries. In general data is expected to be entered within two business days and queries answered in three business days.

As a PI, you are not expected to routinely enter data. That said you are expected to have access to the EDC, have a working knowledge of how to enter the data, and be able to electronically sign the EDC when the data has been cleaned and "locked."

In addition, you are expected to on occasion answer your colleague, the medical monitor, queries. A medical monitor issues queries on a participant's eligibility, signs and symptoms of illness, medications, etc. A PI may delegate this task, but it is imperative that the staff who answers these queries reviews the questions and answers with you and writes in the query that they have reviewed the data with you, the PI.



Electronic Data Capture: Timelines ...

- Data Entry 2 business days
- Data Query Response 2 to 3 business days
- Data Base Lock – Data Queries are expected to be answered in 24 hours

Laboratory, ECG, Radiographic Pathology Reports

All pages for every report must be initialed and dated.

- Any sponsor and/or regulatory agency representative will be checking that ***every*** page is initialed or signed and dated.
- Only individuals with a medical license or if allowed by the protocol a licensed Physician's Assistant or Advanced Nurse are permitted to review and sign/date reports.
  - Any individual designated by the PI with this task must be medically qualified and meet any specific protocol requirements.
- Timeliness is critical in research; sponsors will be expected to see reports signed and dated in a timely manner. In practice this means within 24 to 48 hours of being resulted.

Laboratory, ECG, Radiographic Pathology Reports

All pages for every report must be initialed and dated.

- Ultimately it is the PI's responsibility to review all reports.
  - Even if you have a qualified sub-investigator – MD, DO, NP, DD, PA who is delegated and has met the sponsor's requirements and your state law's requirements you remain responsible for assuring that all laboratory and other results are reviewed and if necessary appropriate action is taken to address any abnormalities.
  - **ALL** abnormal lab values, no matter how insignificant or mundane you clinically view the value MUST be addressed.

Laboratory, ECG, Radiographic Pathology Reports

Management of abnormal findings.

In your clinical practice management of abnormal results is up to your clinical judgement.

This is also true in clinical research with some important caveats:

Certain lab values, ECG parameters, radiographic findings, or pathology findings may be predetermined by the sponsor to be either exclusionary or findings of special interest, also known as “Alert Values.”

These values are determined by the sponsor or requested by a regulatory agency.

Laboratory, ECG, Radiographic Pathology Reports

Management of abnormal findings.

ALL abnormal findings must be commented on by the PI.

If the finding is deemed not clinically significant by the PI and it is not exclusionary or meets other protocol defined criteria for significance, then a simple note on the report stating that it is “NCS” and signed/dated by the PI is sufficient.

Laboratory, ECG, Radiographic Pathology Reports

Management of abnormal findings.

If a value meets exclusion from the trial the comment could be:

Clinically Sig, meets exc or withdrawal criteria, source document and document on report – PI signs/dates both.

If withdrawal criteria is met it is prudent to send an email to the medical monitor documenting the occurrence.

All such emails must be filed in the participant's source.

Laboratory, ECG, Radiographic Pathology Reports

Management of abnormal findings.

If a value is deemed to be clinically significant by you then the following must occur:

1. Clinically Sig, but stable, will monitor, with a note stating such including possible etiology and plan to address abnormality. An email to the medical monitor for further documentation is important.

1. Clinically Sig, and in your medical judgement you wish to withdraw the participant. If possible, it is BEST to contact the medical monitor to review your decision. The decision MUST be source documented with a note by you, and an email to the medical monitor. All correspondence must be filed in the participant's source.

Laboratory, ECG, Radiographic Pathology Reports

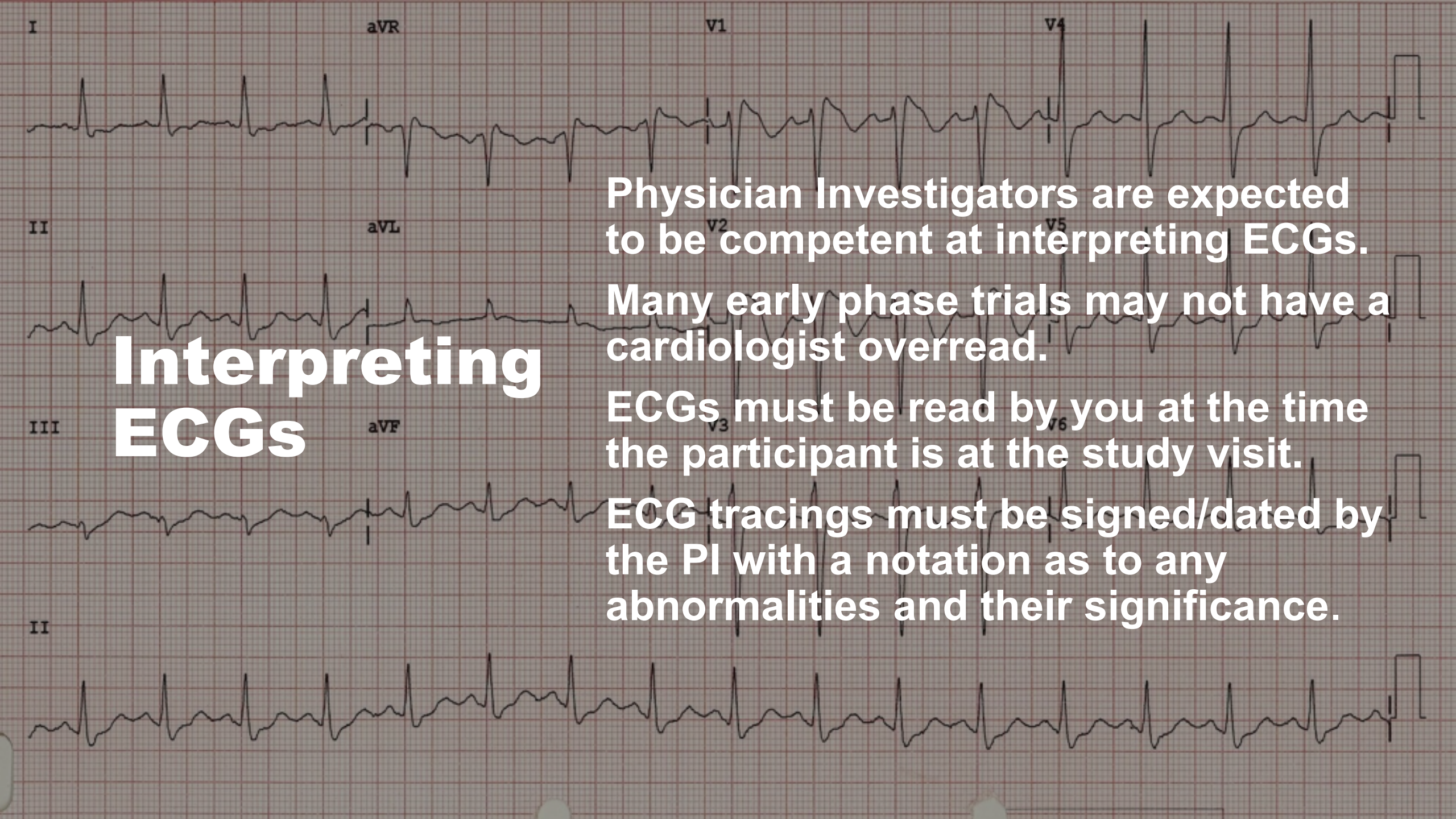
Management of abnormal findings.

If a value meets protocol specified alert criteria, then the following must occur:

1. Acknowledgement of the abnormality
    1. email alerts or other automated alerts must be acknowledged
    2. If there is no auto alert, then the PI must email the medical monitor acknowledging the abnormality.

1. An email must be sent to the study team including the medical monitor with an explanation of possible etiologies.

1. In the email there must be a plan of action to address the issue
    1. The plan must be carried out, and source documented with the findings.



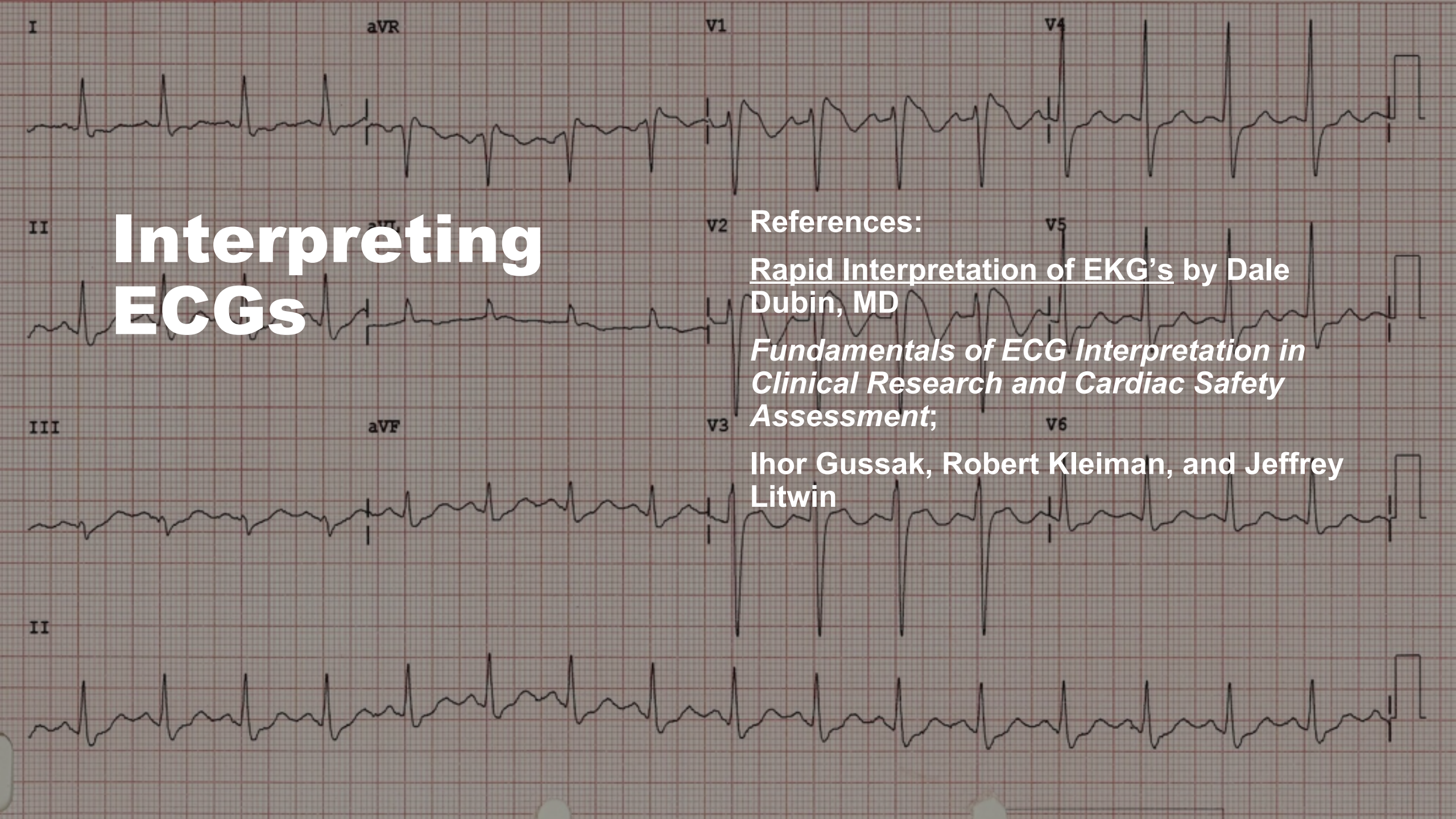
Interpreting ECGs

Physician Investigators are expected to be competent at interpreting ECGs.

Many early phase trials may not have a cardiologist overread.

ECGs must be read by you at the time the participant is at the study visit.

ECG tracings must be signed/dated by the PI with a notation as to any abnormalities and their significance.



Interpreting ECGs

References:

<u>Rapid Interpretation of EKG's</u> by Dale Dubin, MD

Fundamentals of ECG Interpretation in Clinical Research and Cardiac Safety Assessment;

Ihor Gussak, Robert Kleiman, and Jeffrey Litwin

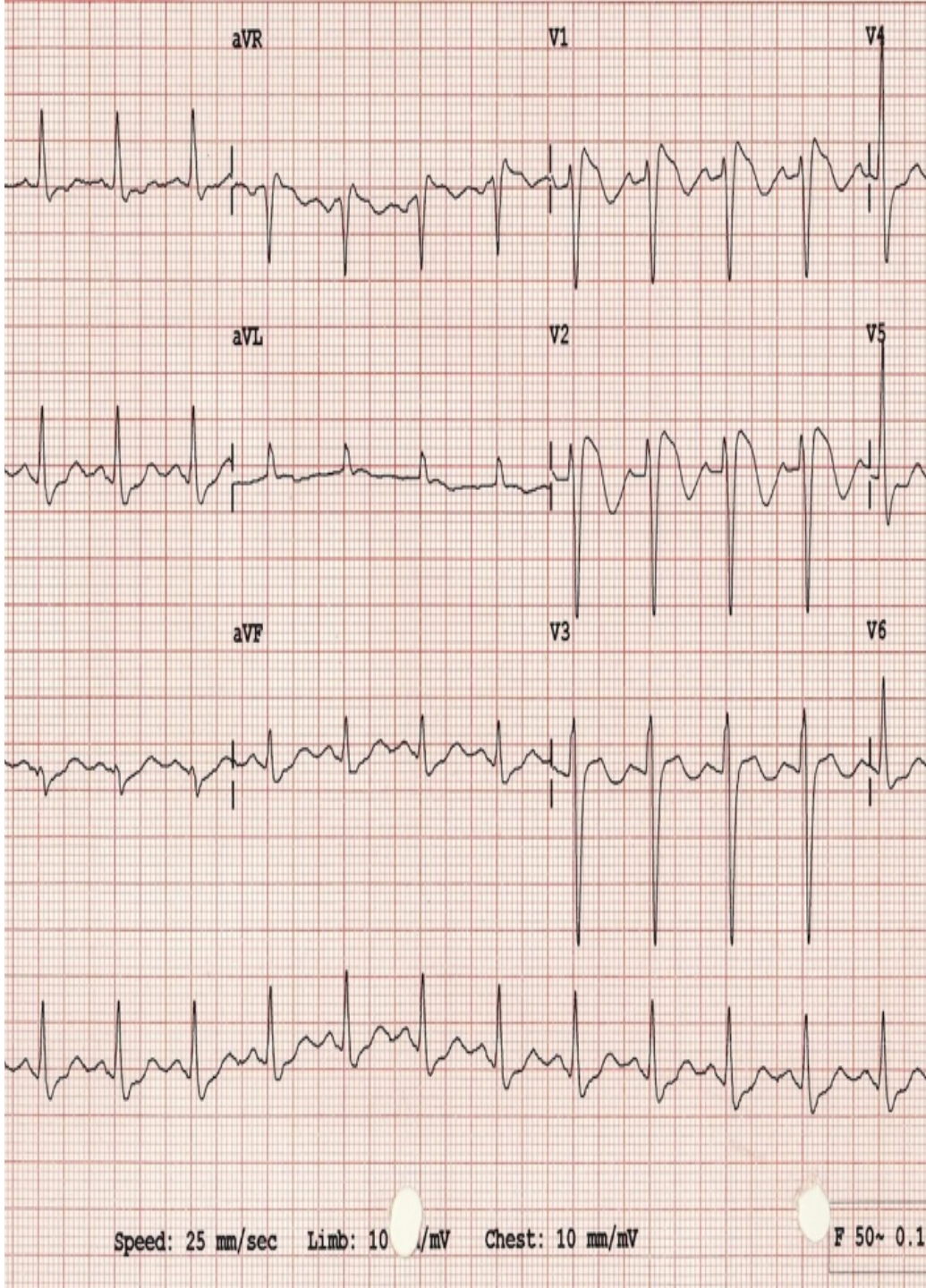
Interpreting ECGs

It is common in clinical trials to have exclusionary or alert values for the following ECG paramatres:

1. **Rate <50 or >110 beats per minute**
2. **Wolf Parkinson White Syndrome**
3. **QTcF**
   a) **> 450 mSec for males and > 470 mSec for females**
4. **Any Left sided block even if it is incomplete**
   a. **Left hemiblock**
   b. **Left anterior fascicular block**

When there is a central overread, then usually the cardiologist's reading will be the deciding read.

Even when there is a cardiologist overread, it is imperative that you the PI carefully interpret the ECG, it is not appropriate nor prudent to depend on the machine read. As the physician in charge of the study you must determine the PR, QRS, QTcF, QTcB, Ventricular Rate, and if there are any arrhythmias.



Interpreting ECGs

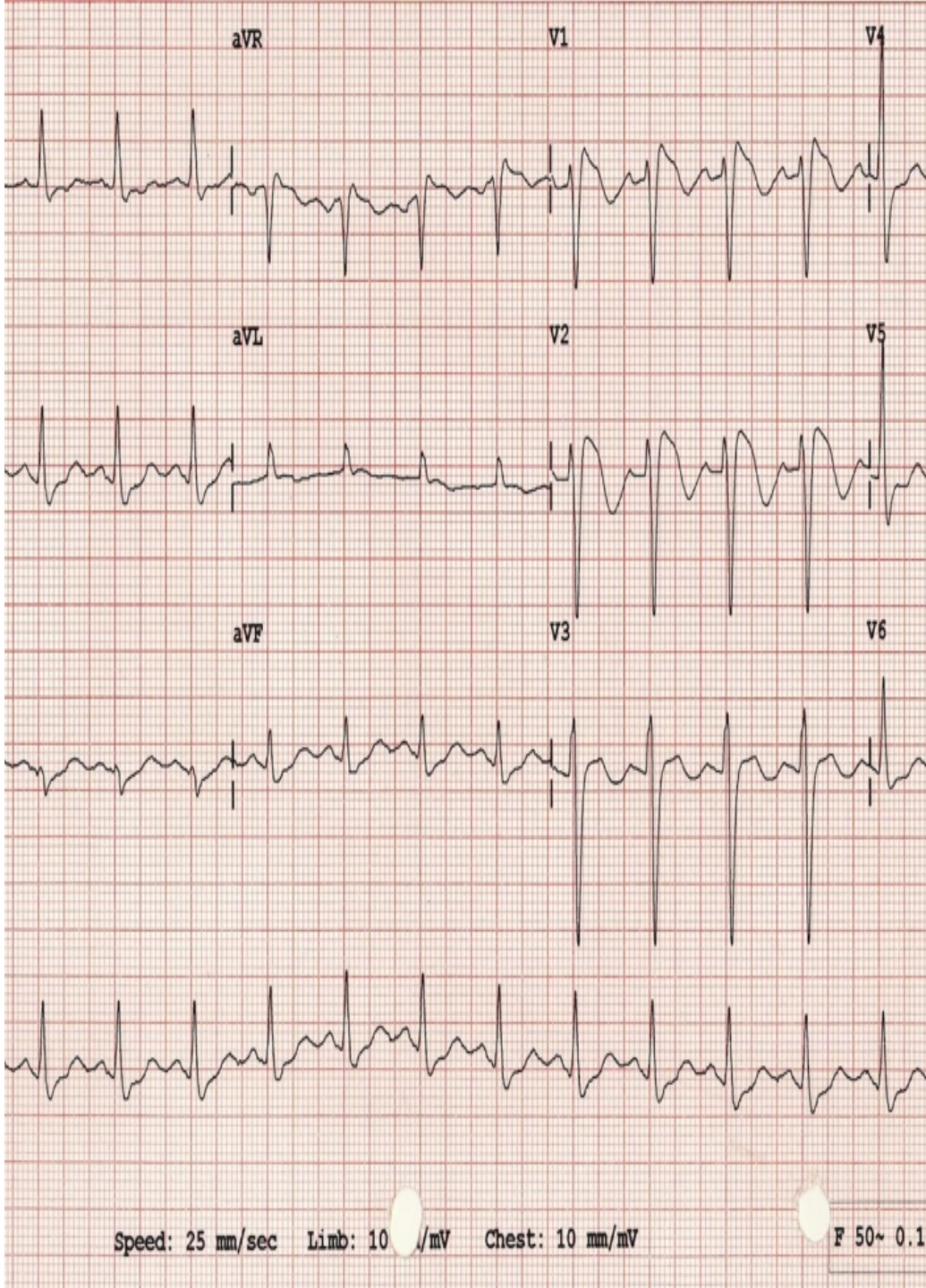
If you receive an alert from the sponsor's ECG vendor, it must be acknowledged, usually by email.

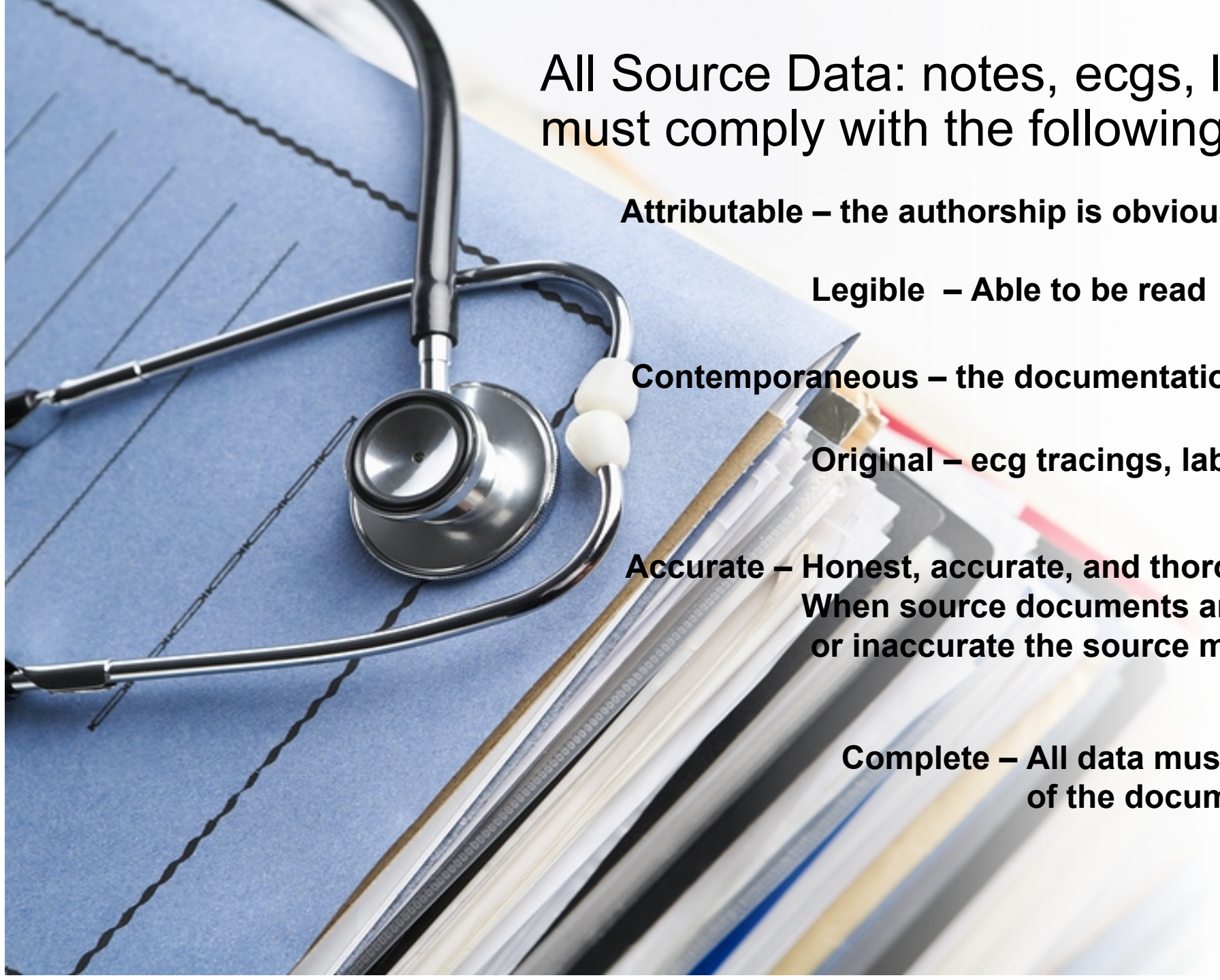
Any action needed as per protocol must be taken, such as withdrawing the participant from the trial, repeating the ECG if permitted by the protocol, and a plan of action regarding the abnormal findings must be source documented.

If the PI has designated the duty of interpreting ECGs, then that person MUST have a medical license, be a Physician's Assistant, or an Advance Practice Nurse.

In addition, to state licensing requirements individual protocols may have their own criteria, such as only a licensed physician may interpret and sign/date ECGs.

In the event the PI has designated a site staff to read the ECGs, you, the PI, continues to be responsible for the interpretation.





All Source Data: notes, ecgs, laboratory results, etc must comply with the following ALCOA with a C….

Attributable – the authorship is obvious, signature/initials and date

Legible – Able to be read

Contemporaneous – the documentation is done in a timely manner

Original – ecg tracings, lab results, source notes

Accurate – Honest, accurate, and thorough.
When source documents are incomplete, inconsistent, or inaccurate the source must be documented as such.

Complete – All data must be retained from the creation of the documentation.

“Vendors”

In medical practice you may select what laboratories, radiology centers, or cardiologist you choose to send your patients.

In clinical research the sponsor may choose to have a central laboratory, ecg center, or scan center. Collectively they are termed, “Vendors.”

Some well known vendors are:

- ACM – laboratory
- Q2 – laboratory
- Labcorp – laboratory
- Clario - ecg

“Vendors”

The advantage to a central vendor is that the laboratory samples will be analyzed with the same reagents on the same instruments and the data will be stored in one location.

The central lab selected by the sponsor shall provide the necessary requisitions, draw and transfer tubes, shipping supplies and invoices.

The site is responsible for:

1. Obtaining the samples
2. Processing the samples
3. Shipping the samples
4. Retrieving laboratory results
5. Ordering supplies

Each central laboratory will supply the site with a laboratory manual.

The manual may be updated throughout the study. The site must archive the predecessor manuals.

“Vendors”

Likewise, for an ECG vendor the advantages are that each ECG will be obtained on a sponsor approved device, transmitted electronically to the vendor and read by a group of cardiologists selected by the sponsor.

ECG machines will be programmed by the vendor with the study specifics including:

1. Sponsor
2. Study Number
3. Site number – to be entered by site
4. Subject number – to be entered by site
5. Visit type/number – this may be entered by the site or pre-programmed by the vendor

“Vendors”

Frequently the ECG vendor will send the device in specially designed boxes. It behooves the site to carefully label and store the packing supplies.

ECG devices are to be returned at the conclusion of the trial. Sponsors take a dim view on sites that routinely lose their return shipping supplies.

ECG vendors will furnish the site with an ECG reference manual detailing how and when to perform ECGs. The manual will have details on trouble shooting, and usually a help desk number/email.

“Vendors”

Retrieving your results:

Laboratory results, ECG overread by cardiologists, and any other centralized reports are retrieved on the vendor portals.

A unique username and password will be assigned to each staff member who is delegated by you to receive access the portals.

Sharing your username/password is STRICTLY FORBIDDEN.

“Vendors”

Retrieving your results:

You may certainly delegate study staff to retrieve results from the various online portals; however, it is your responsibility to assure that all the results are retrieved and that you, the PI, are aware of the workings of the various portals.

A sponsor representative may request that you demonstrate a working knowledge of the portal, or a regulatory agency may ask you directly how you obtain your results.

What if we made an entry error?

Errors occur and the vendors will issue a DATA CLARIFICATION FORM or QUERY.

These corrections are made in the online portal for the vendor. There are vendors that will not notify a site that there is an issue.

In this case, it is the site's responsibility, in *other words yours*, to realize that you have not received a result and check the portal.

Some vendors will send an email to the site stating that there is an issue.

What if we made an entry error?

TIMELINESS is imperative in clinical research.

If a query is not responded to in sufficient time the screening window will close, and the participant will not be able to proceed with the trial.

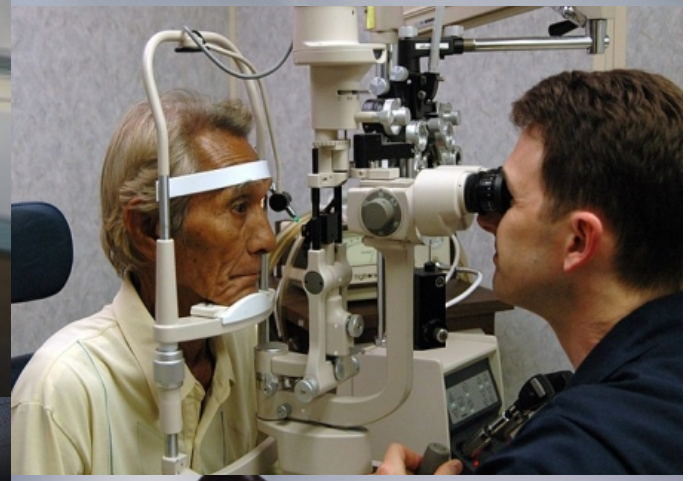
A query may occur if the result triggers an alert, usually a significantly abnormal finding. Failure to address the query may *jeopardize participant safety.*

What if we made an entry error?

Sponsors routinely receive reports on the timeliness of query response and the type of query [a site always enters unscheduled rather than screening]. If a site is delinquent or the there is a repetition of errors the following may occur:

- Screening Hold – no further participants are allowed to be screened.
- Sponsor Audit
- Regulatory Inspection

To avoid these dire consequences correctly completing the lab, ecg and other vendor requisitions and answering the vendor queries within two business days is imperative.



- **Post operative pain trials by definition involve operations. Sponsors will approve the hospital and staff for the surgical procedures.**

- **A variety of scans or other specialty examinations may be obtained as part of a clinical trial.**

In these instances, the site or the sponsor will select a local center to perform the procedures. The sponsor must approve the center.

There are two options for results:

a. **The center agreed upon by the site and sponsor has a specialist approved by the sponsor who will send the results to the site.**

b. **The scans or other data will be sent to a central vendor, selected by the sponsor. The results will be sent to the site.**

Physical Examinations

Many clinical trials will require at least one PE and most will have regularly scheduled examinations. The extent and elements of the examination will be delineated in the protocol.

If you as the physician deem any additional elements are necessary, then they may be performed. Your reasoning behind your decision must be source documented.

As a physician you will be expected to perform physical examinations as per protocol requirements.

Neurologic examinations including AIMS, BARS, SAS, ESRS movement disorders examinations are nearly always including in CNS trials.

A PI may delegate the performing of physical examinations; however, you remain responsible for assuring that they are conducted as per protocol and the person delegated meets not only state license requirements but protocol requirements.

Investigational Product

IP is dispensed by the site at set intervals as per protocol.

The protocol will state how the IP is to be stored, and how it is to be administered it is critical that the protocol be adhered.

If there is non-adherence it must be source documented.

Non-adherence is a protocol deviation and will need to be documented.

Investigational Web Response System:

IWRS

Sponsor's will usually select a vendor who will package, ship, and receive IP back to the depot at the close of the trial.

When IP arrives at your site, it must be immediately unpacked, the IP reconciled with the shipping invoice, and the registered in the sponsor's vendor.

The general name of these vendors are termed, IWRS, Investigational Web Response System.

Investigational Web Response System:

IWRS

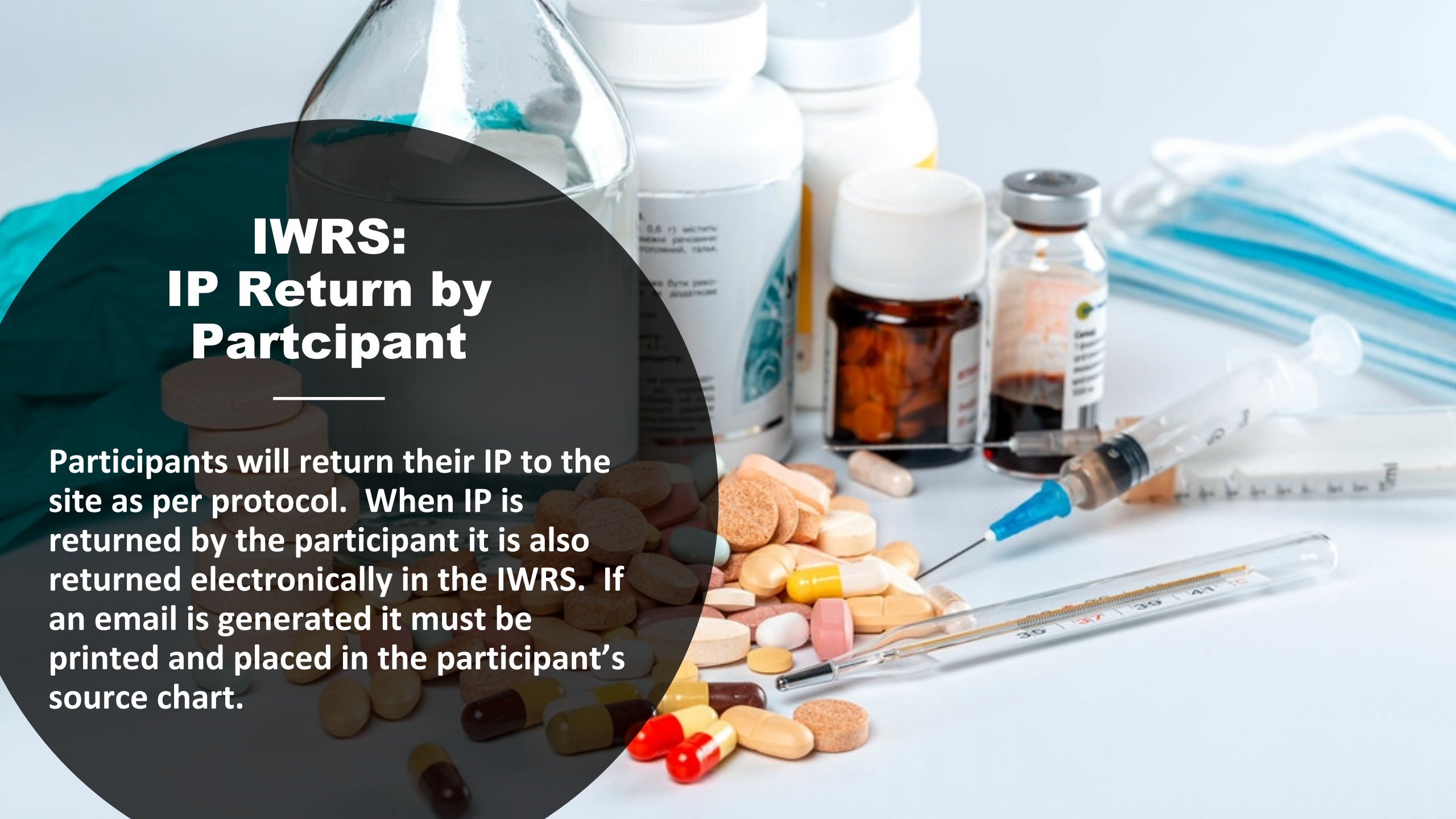
To gain access to the IWRS system, the site submits staff names and emails to the selected system. The individual will receive a “welcome email” with the username/temporary password. That person will go into the portal, change their password, complete any training, then another email will be sent to the individual giving access to the portal.

Username and Passwords are NEVER to be shared.

IWRS: Receipt and Dispense

Usually once an IP shipment is received or IP is assigned to a participant whomever is listed on the IWRS system for a site will receive a confirmation email.

These emails are to be printed and filed either in the IP file and/or participant source files.



IWRS: IP Return by Partcipant

Participants will return their IP to the site as per protocol. When IP is returned by the participant it is also returned electronically in the IWRS. If an email is generated it must be printed and placed in the participant's source chart.

IWRS: Reconciliation

IP reconciliation for the entire site inventory is done at least at the conclusion of the trial.

IP that has not been dispense, IP that has been returned and registered, and IP that has been lost or damaged is reconciled in the IWRS.

The assigned site staff and the sponsor representative both work on the reconciliation. A final IP accountability is completed, printed, signed/dated by site staff, PI, and sponsor representative.

The IP is either returned to the depot or destroyed on site.

The final IP reconciliation is copied and filed at the site, a copy is sent with the IP to the depot, and a copy is maintained by the sponsor.

Investigational Product

Accountability for IP is performed as per protocol.

Generally, IP is accounted for when it is dispensed and then when it is returned by the participant.

The individual units of IP are counted, eg 2 cc per day x 10 days = 20 cc, 30 cc was dispensed at visit 1 and 10 cc returned at visit 2, compliance was 100%.

Each time the IP is dispensed and returned this calculation must be made and recorded in the participant's source. This entry must have site staff signature, and/or initial and always a date.

Investigational Product

NONcompliance with IP is a major concern in clinical research.

If a participant is noncompliant on more than one occasion or has “lost IP” communication with the study monitor from the sponsor is strongly advisable.

Investigational Product

At various time points in a study IP reconciliation will occur. The sponsor's monitor will count, measure, or otherwise determine if the site's IP logs per participant and for IP received at the site are in order.

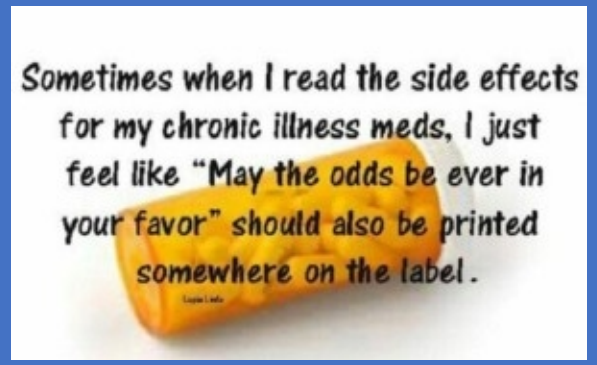
When IP is returned to the sponsor's selected vendor depot all IP records are usually signed by the PI or designated site staff.

Even if this task has been delegated to a site staff the PI is ultimately responsible for the receipt, storage, and administration of the IP including individual participant records.

Investigational Product

Although the PI may not receive the IP at the site, or even perform the initial counts of IP packages the PI is responsible for the chain of custody of the IP including assuring that all compliance records are correct and documented.

Side Effects and Adverse Events



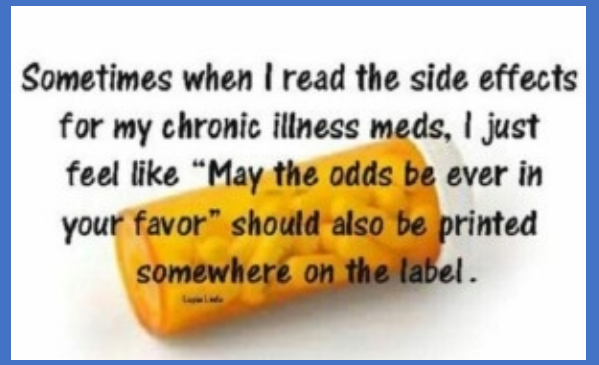
In medicine we are accustomed reading a package insert, and other information on medications that we prescribe regarding side effects.

In clinical research we help write the package insert. For IP there is not a comprehensive list of known side effects. Through the process of clinical research, we develop an understanding and listing of untoward medical occurrences that eventually are compiled into the package insert. During a trial these medical occurrences are termed Adverse Events.

The definition of an Adverse Event by the FDA:

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or. laboratory finding), symptom, or disease, temporally associated with the subject's receipt of a test article [IP]

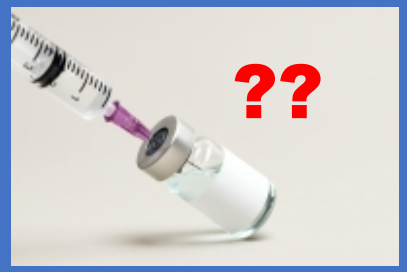
Side Effects and Adverse Events

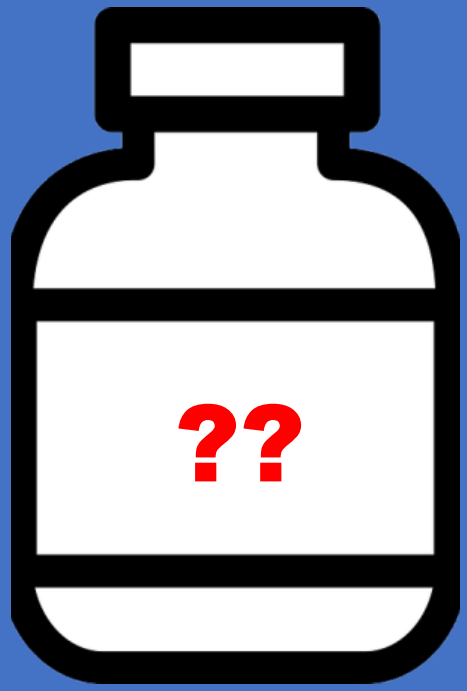


Depending on the stage of development, we may know very little about the potential untoward reactions or interactions of the IP or we may know a great deal.

In a Phase I trial there is virtually no knowledge of untoward medical occurrences, the metabolism, distribution, excretion or maximal tolerated dose. If an IP reaches Phase IV we will know the metabolism, distribution, excretion and most commonly occurring medical occurrences.

The unknown …





In double blind placebo-controlled trials neither the participant nor the site staff know what the participant is receiving. As physicians we are aware that patients may have side effects to even inert substances. Participants in trials who are on placebo may well have many "adverse events."

Your task in the trial is to collect the information from the time of FIRST dose of IP to the Follow Up visit or as stipulated in the protocol.

Degree of severity of AE

Mild – little to no medical consequence and no treatment is required.

- **Example – mild facial sunburn**

Moderate – some level of symptomatology, and treatment may be required.

- **Example – Sprained ankle requiring immobilization and NSAIDs.**

Severe – significant impairment, medical treatment required.

- **Example – Fractured arm requiring casting, physical therapy follow up, narcotic medication for pain management and may require outpatient surgery.**

Start/Stop Dates

Timelines and timeliness is important in documentation of AE's. This is the second part of documentation.

The start date/time is the time the participant became symptomatic.

The stop date/time is the time the event has resolved. It may be ongoing so there would not be a stop date, the documentation is "ongoing."

related?

The final part of documented an IP is determining if it is related or NOT related to the IP.

The two basic classifications are:

NOT RELATED to IP

RELATED to IP

Further granularity may be requested by the study team:

Unlikely to be related to IP

Possibly related to IP

Probably related to IP

Definitely related to IP

ONLY THE PI CAN MAKE THIS DETERMINATION.

AE Example: Mild

AE Term: Headache, bilateral, nonmigraine

AE Intensity: Mild

Treatment: none

Start date: 3 May 2022 at 0800

Stop date: 3 May 2022 at 0900

Related to IP: Not related

AE Example: Moderate

AE Term: Headache, bilateral, migraine

Pertinent information, participant has a history of migraines

AE Intensity: Moderate

Treatment: Zomig 1mg SL at 0815, Zomig 1mg at 1200

Start date: 3 May 2022 at 0800

Stop date: 3 May 2022 at 1400

Related to IP: Not related

AE Example: Severe

AE Term: Gastroenteritis {use the correct medical term, but list the symptoms in your source – nausea, vomiting, diarrhea, fever, chills}

AE Intensity: Severe

Treatment: IV hydration 2 Liters over four hours, Phenergan 75mg IM

Start date: 3 May 2022 at 0700

Stop date: 3 May 2022 at 1800

Related to IP: Related. “Subject became acutely ill after receiving first dose of IP at 0630. No family members or acquaintances are ill.”

Serious Adverse Event
Defined by the Code of Federal Regulations, CFR 21

- Fatal
- Immediately Life Threatening
- Results in disability or permanent damage
- Requires hospitalization
- Prolongation of existing hospitalization
- Congenital anomaly or birth defect
- Is medically significant

Serious Adverse Event

The duty to report to the sponsor is regulated by the FDA.

1. 24 hours from the time you learn of the event to report on sponsor provided form
2. Basic elements are:
    a) Nature of event
    b) Treatment required
    c) **Related or not related**
    d) Date/time of onset and resolution if known.

Serious Adverse Event

Nature of event

- If the event was death, then the cause of death must be included
- Use medical diagnosis. There is a narrative section to give clinical signs, symptoms, course of event.

Treatment Required

- If you cannot obtain the medical records within the initial mandatory 24 hour time frame, enter records requested.

Related or not related

- This is VERY important. This is only the provenance of the PI and consultation with the sponsor medical monitor is strongly encouraged.

Date/time of onset and resolution if known

- The date of onset is the minimal data required
- Very frequently the event will be ongoing and follow up reports are the norm.
- if the event was death then the cause of death is the event.

SAE Example

AE Term: Gastroenteritis {use the correct medical term, but list the symptoms in your source – nausea, vomiting, diarrhea, fever, chills}

AE Intensity: Severe

Treatment: IV hydration 2 Liters over four hours, Phenergan 75mg IM, admitted to Gen Med Unit for observation, ECG normal, Hospital DC pending reciept

Start date: 3 May 2022 at 0700

Stop date: 3 May 2022 at 1800

Related to IP: Related. "Subject became acutely ill after receiving first dose of IP at 0630. No family members or acquaintances are ill."

This even qualifies for being a SERIOUS ADVERSE EVENT due to hospitalisation. The PI determines the severity of the event.

SAE Example

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Consenting: It is a process.

In medicine we frequently obtain consents for blood transfusions, surgical procedures, administration of certain medications, etc. These are legal documents and must be signed by the physician.

Usually, medical procedure consents are a one and done.

Participating in a clinical trial may involve multiple procedures, agreeing to receive an unknown/unproven compound with no expectation of benefit, and participation may extend over years.

Consenting: It is a process

Obtaining consent is the first step in a clinical trial.

Consent MUST be obtained prior to ANY other procedures.

Consenting: It is a process

Obtaining consent for a participant to engage in a clinical trial is a legal process.

You as the PI may delegate this duty, but not the responsibility of assuring that the subject and any ancillary individuals who are considering the trial are duly informed of the process, the risks and the medical alternatives and assuring that all questions by the patient and/or any ancillary parties, eg caregivers, parents, relatives are answered to their satisfaction.

The sponsor and regulatory authorities expect that you, the PI, are actively engaged in the consent process and have thoroughly vetted each and every participant.

Consenting: It is a process

Consents may be periodically updated by the sponsor or at the request of a regulatory agency throughout the life of the trial.

Consents are updated due to additional information regarding the IP, new safety concerns or improved safety of the IP, addition of procedures, decrease/increase in the number of visits, etc.

Each time an updated consent is issued by the sponsor and approved by the IRB the PI, you, are obligated to reconsent the participant prior to any further clinical trial procedures.

Failure to re-consent participants is considered a major protocol deviation.

Consenting: It is a process.

The consent process must be source documented and signed/dated by the person who conducted the consent procedure.

Included in the documentation must be the following verbiage as per the Code of Federal Regulations:

The main Informed Consent Document (ICD), relevant sub study ICD(s) [such as but not limited to pharmacogenetic sampling], and any applicable Assent Document(s) were reviewed with subject & if applicable the parent/guardian. All questions were addressed to the subject's/parent's/guardian's satisfaction. The subject has been informed that the trial is posted on www.clinicaltrials.gov as required by law and may be viewed at anytime by the subject. Each party who signed a document received a signed/dated copy prior to proceeding with any study related procedures. The original signed and dated document is maintained in the patient/subject's source.

Regulations

Clinical Research is even more regulated and scrutinized than clinical practice. In subsequent lectures we will review the FDA, Institutional Review Boards [IRB].

The FDA is the overarching regulatory body for all clinical trials conducted in the US. It does not have authority ex US, but an FDA inspector may conduct an inspection of a site in another country when the trial is being conducted in the US. Likewise, a US based site may be subject to an audit [the European term for a regulatory inspection] by EU authorities.

The Code of Federal Regulations are the rules that govern all clinical research in the United States.

Please review the FDA slide deck, “Structure and Mandate” and “Informed Consent and Ethical Considerations” after completing the quiz.

The next few slides give a brief historical background on the evolution of our field.

Good Clinical Practices: A brief historical background

1945 – The Nuremberg Code

- From the absence of ethical conduct of German physicians in WWII the first research guidelines were developed.

1945 – World Medical Association

- Created shortly after the Nuremberg Code as many viewed the code only in terms of war crimes and not applicable to practice.

1964 – The Declaration of Helsinki in its introduction contained a binding statement for physicians: “The health of my patient will be my first consideration”. The declaration was viewed by some as weakening the intent of the Nuremberg Code.

1964 to 1996 – International Conference of Harmonization of Good Clinical Practices.
Increasing concerns were expressed regarding the use of placebo-controlled trials and natural history trials when there were known effective treatments. In 1996 the first round of what is now known as ICH-GCP were published.

Nuremberg Code
The Doctor's Trial

The following are the essentials of the first codification of research:

- The voluntary consent of the human subject is absolutely essential."
- No coercion in informed consent
- Subjects must be free to stop at any time.
- Prior animal data
- Scientific value
- Anticipated results justify the risks
- Favorable risk/benefit ratio
- Suffering by subjects should be avoided
- No expectation of death/disability

Declaration of Helsinki

The Declaration of Helsinki was adopted by the WMA June 1964, and has been modified numerous times reflecting the evolution of clinical research, public views, and the practice of medicine.

The first general principle is:

“The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

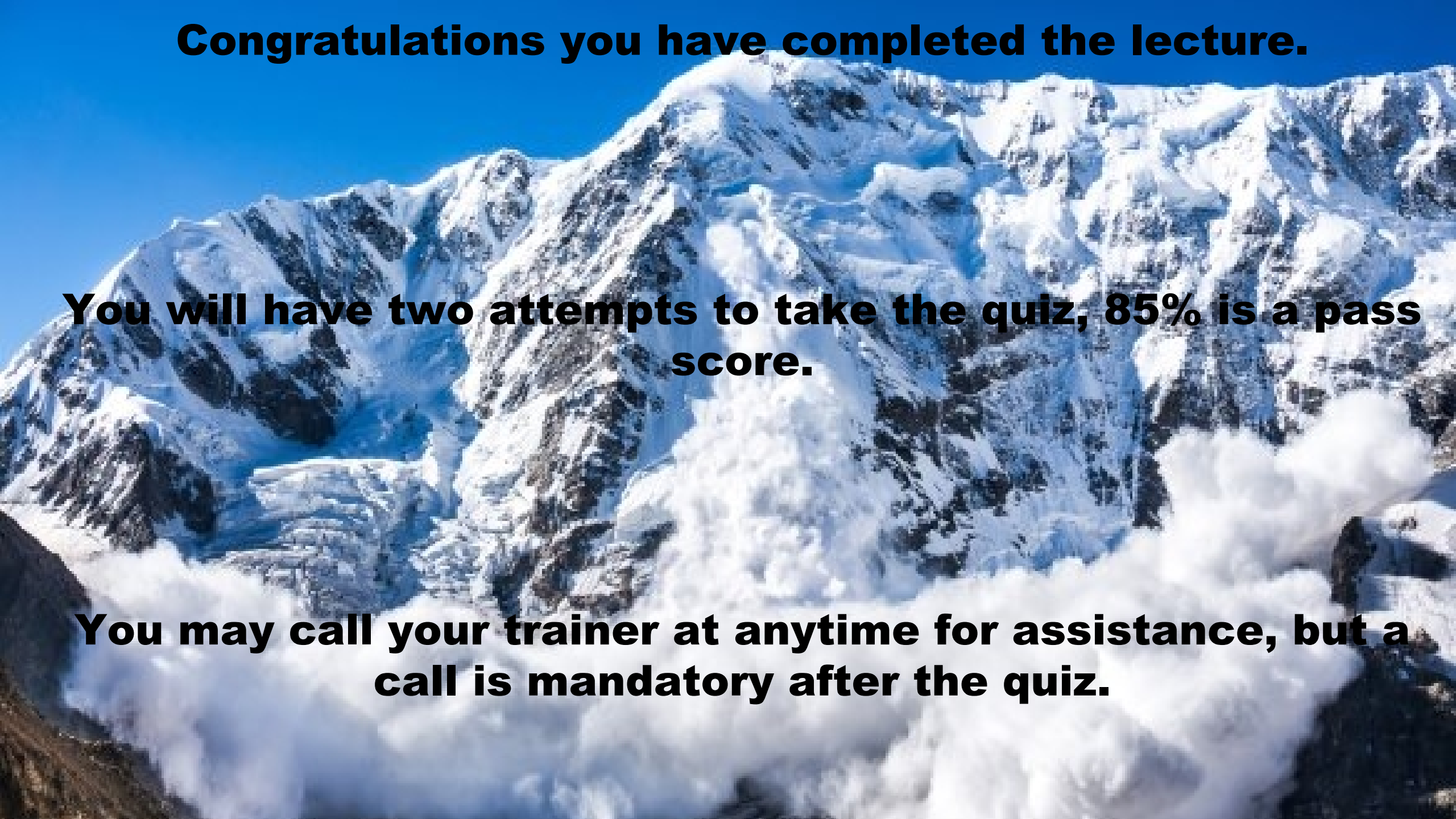
From 1964 onward there has been a growing awareness that clinical research is imperative to medical progress, but those of us in research have particular ethical dilemma’s that must be discussed, understood, and any infringement on patient’s well being shall not be tolerated.

ICH-GCP Initiated 2008

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO). This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.


Congratulations you have completed the lecture.
You will have two attempts to take the quiz, 85% is a pass score.
You may call your trainer at anytime for assistance, but a call is mandatory after the quiz.