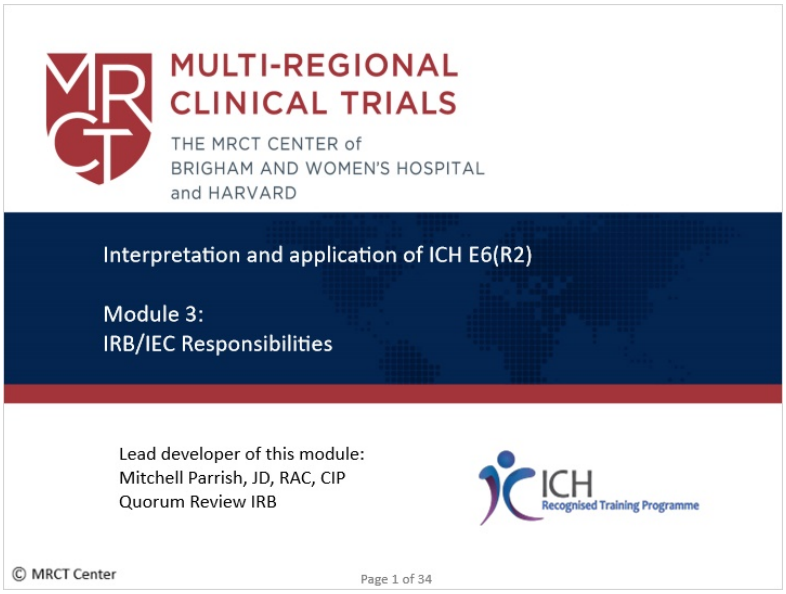
Module 3: IRB/IEC Responsibilities

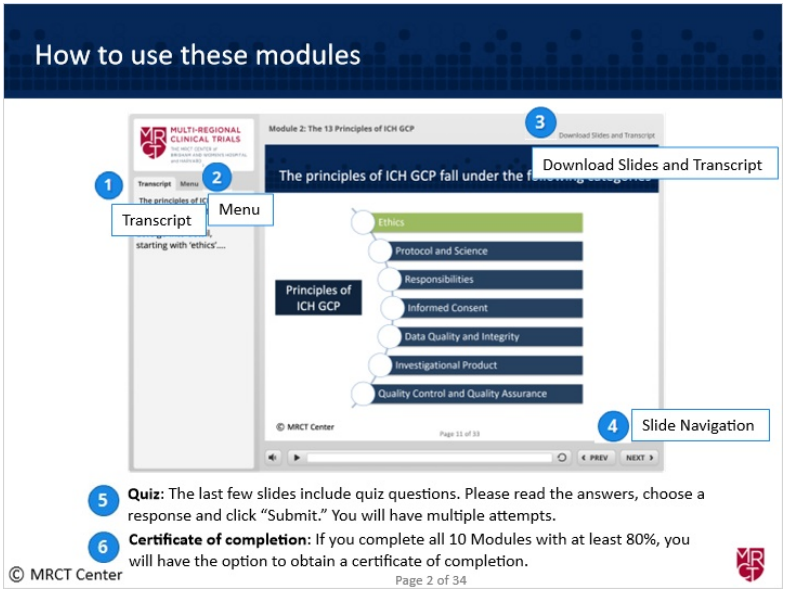
1.1 Interpretation and application of ICH E6(R2)



Notes:

Welcome to Module 3 of this training on the interpretation and application of ICH E6(R2).

1.2 How to use these modules



Notes:

We want to familiarize you with how to use these modules. First, you can click on Transcript on the left side to read along with the audio. Second, if you click on Menu, next to Transcript, you can see where you are in this module. You can also go back to slides that you have previously viewed and listened to.

Third, you can click on the upper right on "Download Slides and Transcript" to view a printable PDF of the slides and transcript of the module. You can also click a link to the Guidelines for Good Clinical Practice.

Fourth, to move to the next slide, click "Next" after you listen to the audio. Click "Prev" to go to the previous slide.

Fifth, the last few slides include quiz questions. Please read the answers, choose a response and click "Submit." You will have multiple chances to answer correctly.

Sixth, if you complete all 10 Modules with at least 80%, you will have the option to obtain a certificate of completion.

1.3 Attribution and Disclaimer

Notes:

Please note that our attribution policy stipulates The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) maintains the copyright to these training materials which were originally developed in English.

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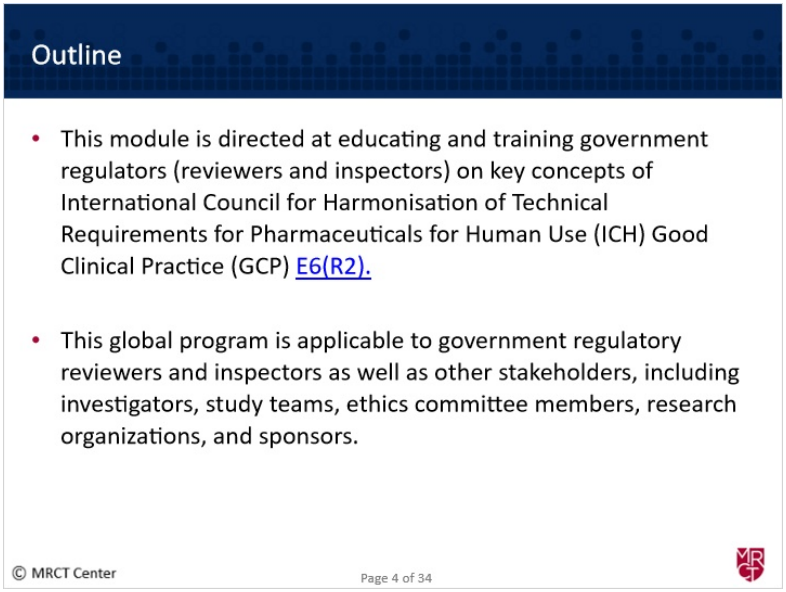
This training programme is recognised by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

This presentation includes the author's views on "Interpretation and application of ICH E6(R2)" theory and practice. The presentation does not represent official guidance or policy of authorities or industry.

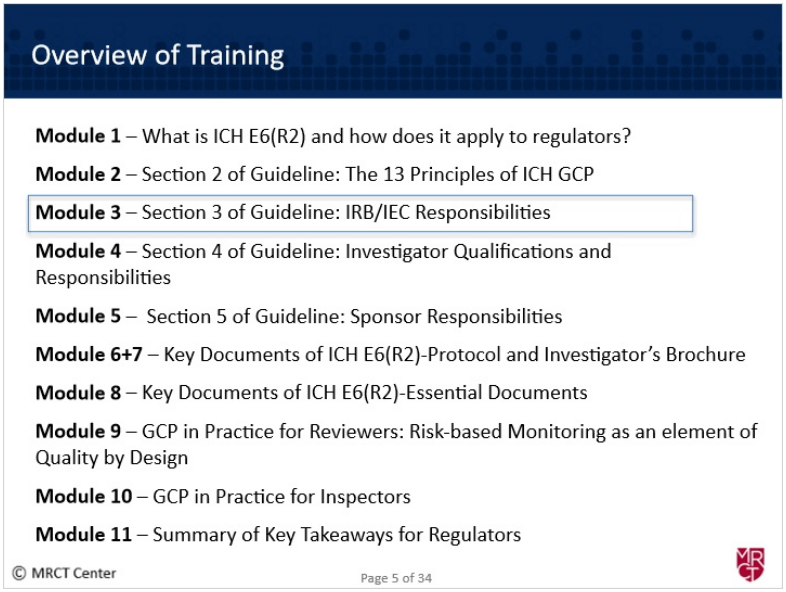
1.4 Outline



Notes:

Overall this training is directed at educating and training government regulatory reviewers and inspectors (as well as other stakeholders including investigators, study teams, ethics committee members, research organizations, and sponsors) on key concepts of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) E6(R2).

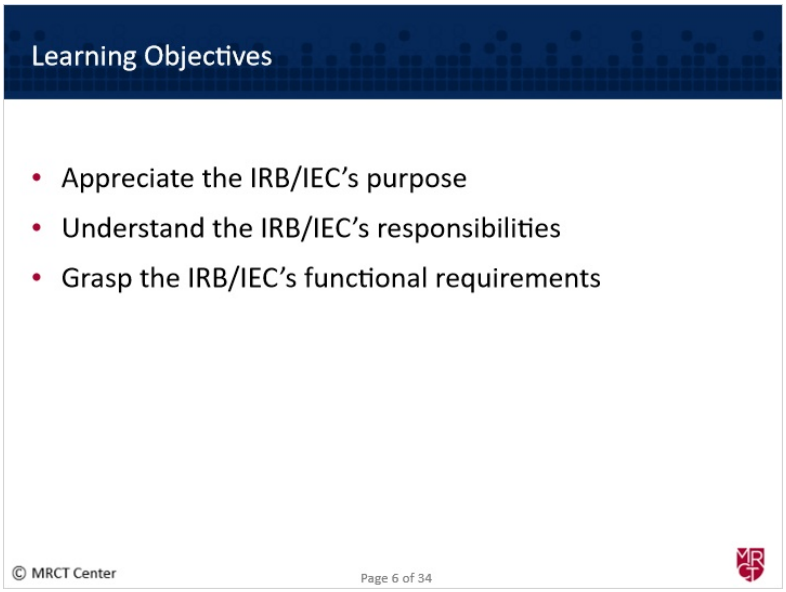
1.5 Overview of Training



Notes:

In Module 3 we will focus on describing the IRB/IEC Responsibilities of ICH GCP as outlined in the guideline

1.6 Learning Objectives



Notes:

We will tackle section 3 today by making sure three objectives are met. Those are 1) appreciate the IRB/IEC's purpose. In other words, why do IRBs/IECs exist? 2) Understand the IRB/IEC's responsibilities. What is the IRB/IEC's role? 3) Grasp the IRB/IEC's functional requirements. How does the IRB/IEC operate?

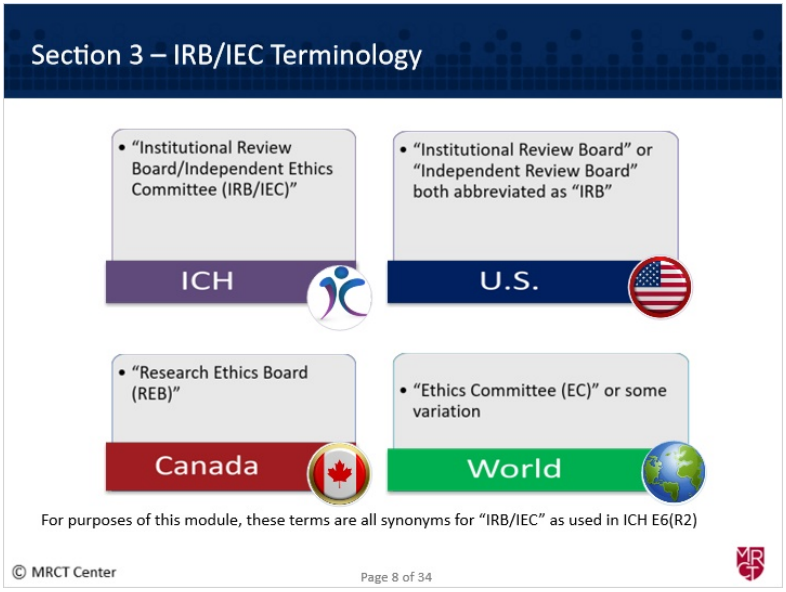
1.7 Background

Notes:

This Module covers institutional review boards or independent ethics committees. No matter your experience with this topic, the intent of this Module is to firm up understanding of this area. Review by IRBs/IECs is not simply an ICH requirement, it is a typical regulatory requirement in numerous countries around the world. Also, these entities can serve as partners in research providing valuable scientific, medical, regulatory, and ethics feedback that moves research forward. Finally, they are ambassadors of research to the population at large. When functioning properly, they help install trust in the ethical research endeavor and provide a level of assurance that research participants are protected and that research is not conducted

in vain.

1.8 Section 3 – IRB Terminology



Notes:

Before we jump into our learning objectives, let's make sure we are all on the same page in a few areas - namely, terminology and any impacts to Section 3 from Revision 2 to the Guideline.

The reason we should discuss terminology is because there are MANY different terms for the same thing depending on the country or even within the same country (as is the case in the USA).

As noted in Module 1, ICH uses two terms for the same thing (in an attempt to cover the most common nomenclature): Institutional Review Board and Independent Ethics Committee.

The U.S., and in particular in the federal regulations of the United States, they use the term Institutional Review Board. However, nearly as common in practice is the term Independent Review Board. The term "Institutional"

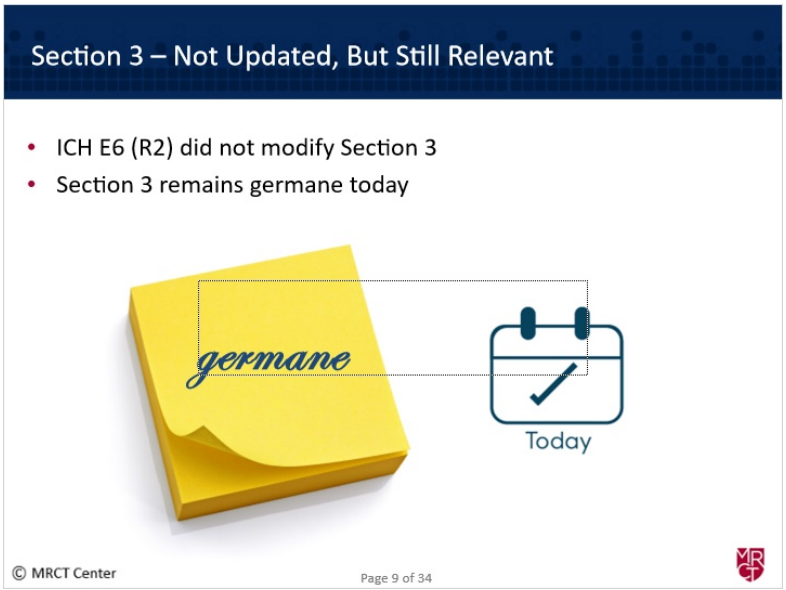
Review Board arose because when these Boards were first created and at the time of creation of the U.S. IRB regulations, nearly all Review Boards were affiliated with an institution (like an academic medical center, hospital system, or research institute). The term “Independent” Review Board gained popularity when it became more commonplace to have a Review Board that was not affiliated with an institution.

Canada uses Research Ethics Board consistently.

Seemingly, the most common term in the EMA and throughout the world, including in developing countries, is “Ethics Committee” or “Research Ethics Committee”

The take away with all these terms is that they all mean THE SAME THING! For consistency throughout this module and from here on out, we use that ICH acronym of “IRB/IEC.”

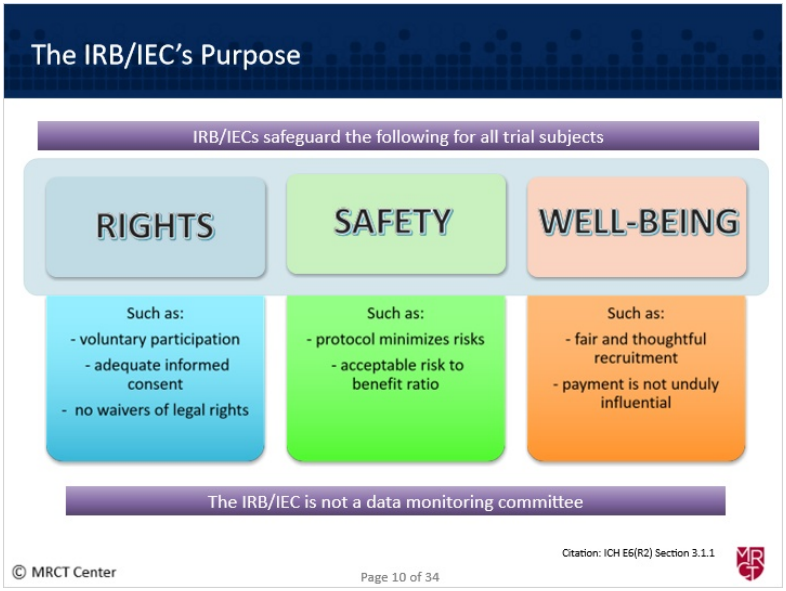
1.9 Section 3 – Not Updated, But Still Relevant



Notes:

In this Module, we are covering Section 3 and IRBs/IECs from ICH GCP E6 (R2). Moreover, we know R2 did not modify Section 3, but we also know that we are not wasting our time with old content - Section 3 is still germane. Now, let's first dive into the IRB's/IEC's purpose.

1.10 The IRB/IEC's Purpose



Notes:

The IRB/IEC's purpose is grounded in three ethical principles, introduced in Module 2, known as respect for persons, beneficence, and justice.

Through their work, IRB/IECs safeguard the rights, safety and well-being of study participants.

For example:

Rights are protected by ensuring participation is voluntary and consent is adequate.

The study is reviewed for **safety** to ensure the protocol minimizes risks and there is an acceptable risk to benefit ratio.

And the **well-being** of participants is considered through fair and thoughtful recruitment and appropriate payment.

In fulfilling their responsibilities, the IRB/IEC is often acting as a form of regulatory body but they are not a regulatory authority and do not review research and research data to determine potential product approval or marketing status like the FDA in the US, Health Canada in Canada, the European Medicines Agency in Europe, and Pharmaceuticals and Medical Devices Agency in Japan.

It is also important to keep in mind that IRB/IECs are not a data monitoring committee.

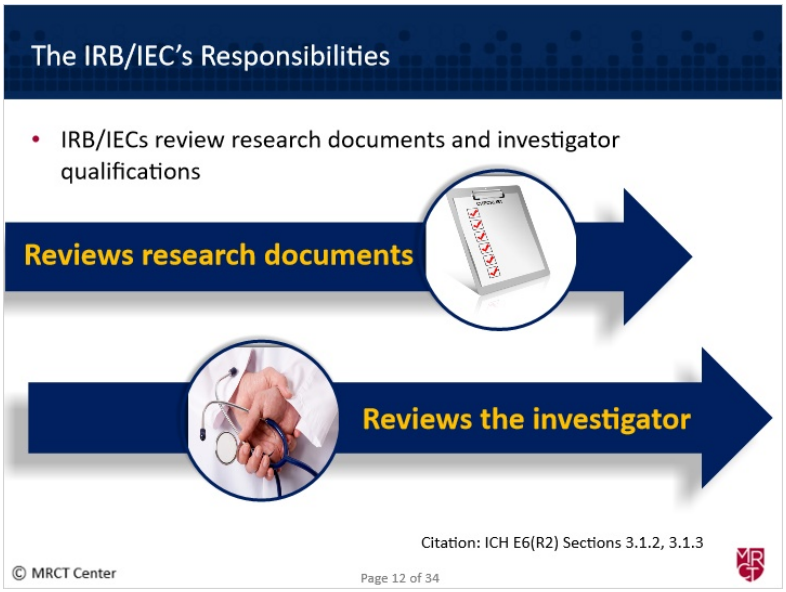
1.11 The IRB/IEC's Purpose

Notes:

We mentioned in the last slide that an IRB/IEC is not a regulatory authority. Nonetheless, IRB/IECs certainly wield a significant amount of influence and control considering that numerous country regulatory authorities around the world mandate that qualifying clinical trials receive IRB/IEC review and approval. To this end, it is important to note that there are checks and balances on the IRB/IEC to make sure it is doing its job.

For example, in-country regulatory authorities may inspect IRB/IECs and audit their work and take action if found out of compliance. Also, IRB/IECs are routinely audited by those research sponsors or institutions who submit their research for review to the IRB/IEC. Finally, in the U.S., there is an accrediting body who does accredit IRB/IECs. This organization is called the Association for the Accreditation of Human Research Protection Programs (AAHRPP) and also accredits outside the United States.

1.12 The IRB/IEC's Responsibilities



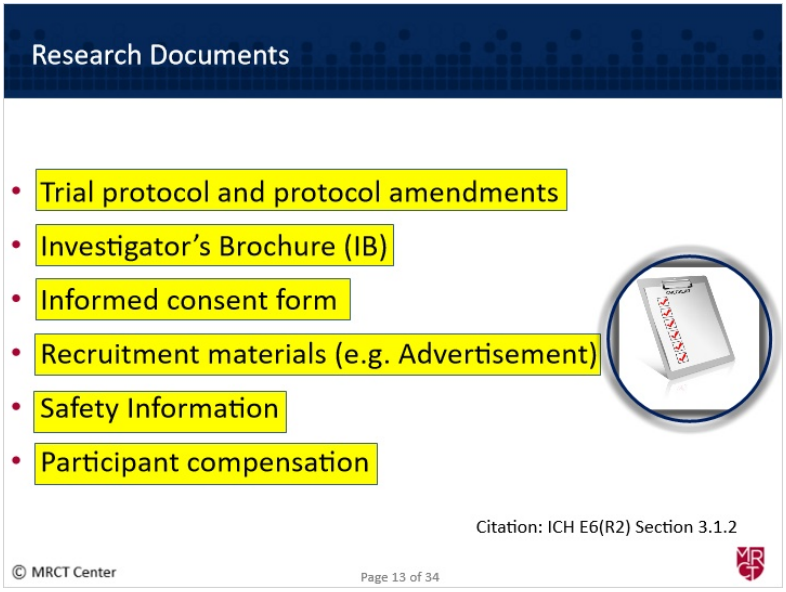
Notes:

The IRB/IEC is charged with reviewing both research documents and the investigator. This slide purposefully depicts the review of research documents and the investigator as two separate activities. Often, the IRB/IEC will first review the research protocol and all related documents, essentially "the research." Then, the IRB/IEC will review the qualifications of the investigator or investigators who will conduct the research.

Let's go a little further now and break down first what IRB/IEC responsibilities are with respect to reviewing research documents and then with respect to

reviewing investigators.

1.13 The IRB/IEC's Responsibilities – Research Documents



Notes:

In order to approve the research an IRB/IEC must review.

-Trial protocol and protocol amendments

-Investigator's Brochure (IB)

-Informed consent form

-Safety Information

-Participant Compensation

-Recruitment Material (e.g., Advertisements)

It is not simply that the IRB/IEC must check off the fact that it has seen and reviewed these documents. There is quite a bit more to it. To determine what the IRB/IEC is to actually review for each of these documents you do have to look outside of ICH GCP Section 3.

For the trial protocol and amendments, the IRB/IEC must consider all information at ICH E6(R2) section 6. For example, the summary of nonclinical studies, risks and benefits, trial population, trial design, and more.

The IB is a key document for the IRB/IEC to review in order to understand the investigational product.

For the informed consent form or forms, the IRB/IEC must ensure the consent form is understandable to participants and includes all those elements of consent outlined at ICH E6(R2) section 4.8.10. For example, trial explanation, risks and benefits, trial alternatives, confidentiality considerations, and more.

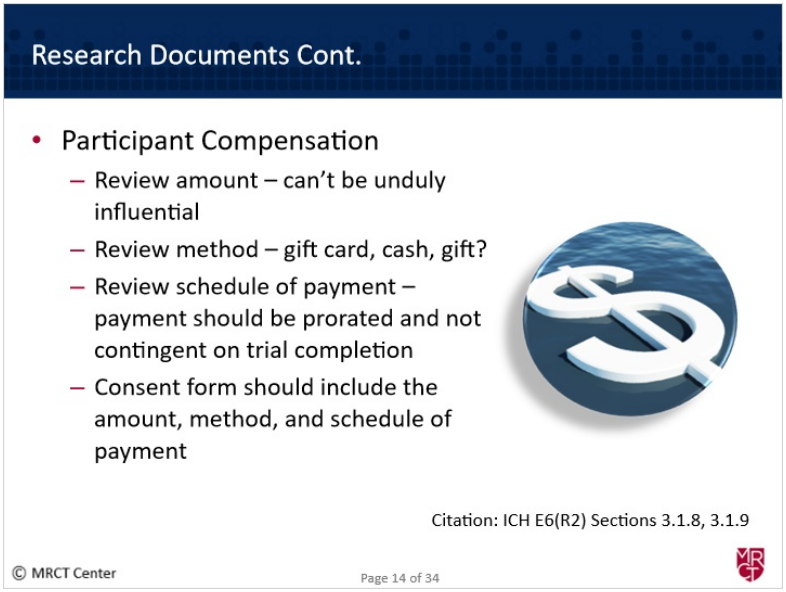
Study-specific recruitment materials and advertisements are also considered part of the informed consent process and thus require IRB/IEC review.

Other key documents to review are those documents related to safety information that would impact the IRB/IEC's decision about whether to approve the research and/or impact a participant's decision to participate in the trial. We will cover safety information more in depth later in this Module.

Finally, the IRB/IEC must review participant compensation to ensure it is appropriate and not unduly influential.

Only after considering all of these research documents and information can the IRB/IEC decide if it can approve the clinical trial.

1.14 The IRB/IEC's Responsibilities – Research Documents Cont.



Notes:

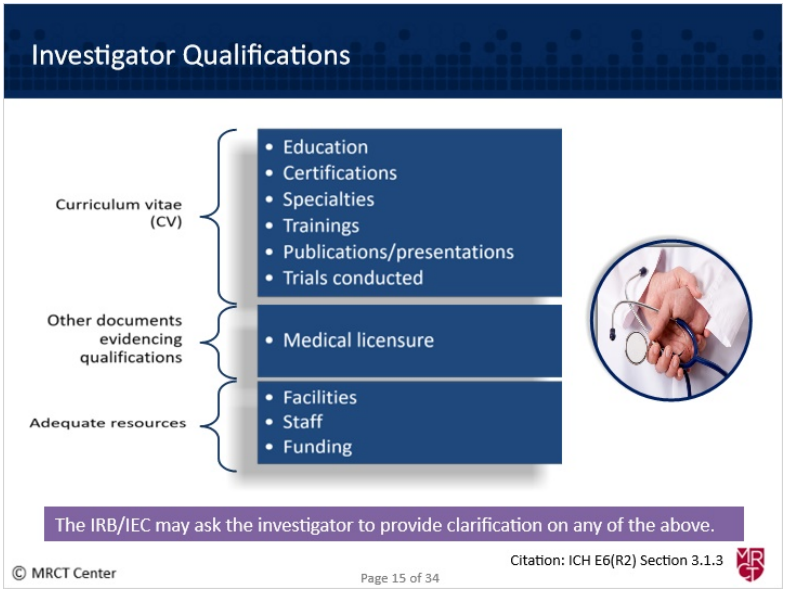
Before moving onto the IRB/IEC's review of investigator qualifications, let's look closer at that participant compensation issue noted in the last slide. It is important to first check local laws whether participant compensation is allowed.

If it is, IRB/IECs are to review participant compensation to ensure it is not coercive or unduly influential. Regarding unduly influential, this determination comes down to the following question: Is the payment amount, method, or timing/schedule of payment such that it would make a participant act against their own best health interest?

Payment should be prorated (For example, broken down by study visit).

And the consent form should include details of how the participant will be paid, for example, the method and the schedule of payment.

1.15 The IRB/IEC's Responsibilities – Investigator Qualifications



Notes:

As to the review of investigator qualifications, here are those things that the IRB/IEC must assess:

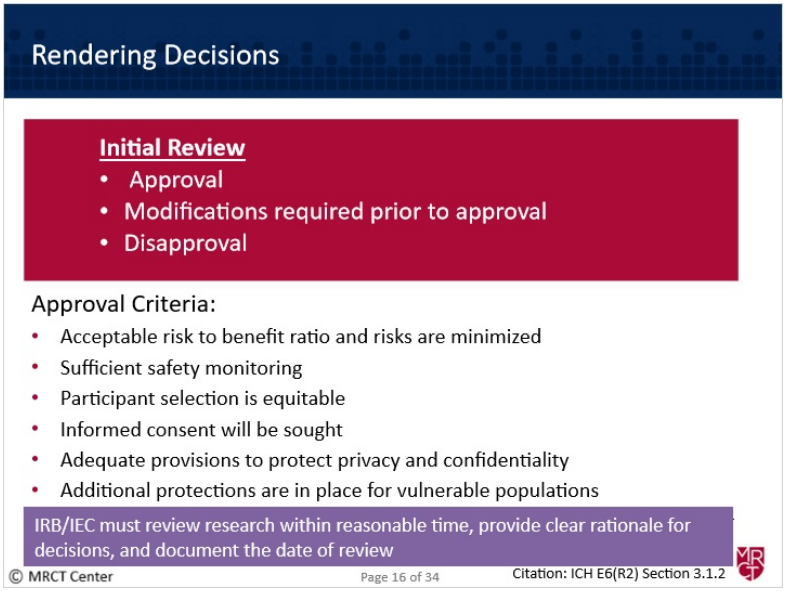
The investigator's CV, which should include, at a minimum, Education, Certifications, Specialties, Trainings, Publications and presentations, and Trials conducted.

The investigator's applicable licensure with the most obvious licensure being one's medical license.

And, the investigator's resources available to conduct research. This includes the investigator's facilities and staff. Ultimately, the IRB/IEC needs to know that the investigator has the infrastructure and capacity to provide appropriate oversight and that such oversight will not disappear overnight. How this looks in practice is IRB/IECs will often ask investigators to provide information on how many active studies they are currently running and how many support staff (e.g. research coordinators, sub-investigators, etc.) they have. If there are a significant number of interventional trials and say, just 1

or two research coordinators and no sub-investigators, the IRB/IEC may require the investigator to provide clarification on how they will adequately oversee and support their trials.

1.16 The IRB/IEC's Responsibilities – Rendering Decisions



Notes:

In terms of the IRB/IEC's main responsibility, this really comes down to determining whether research should be approved, modified, or disapproved. The criteria used to assess whether to approve research is generally:

-An acceptable risk to benefit ratio

-Sufficient safety monitoring

-Participant selection is equitable

-Informed consent will be sought

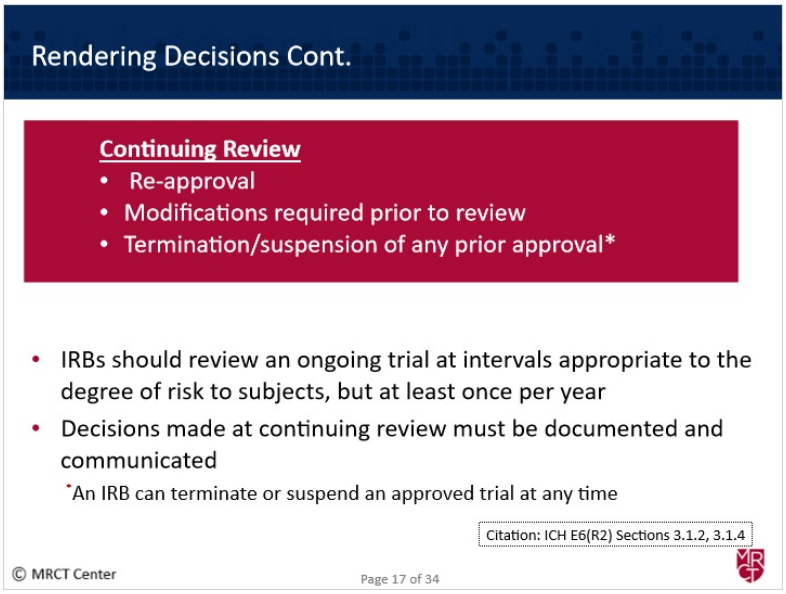
-Adequate provisions to protect privacy and confidentiality

-Additional protections are in place for vulnerable populations.

I will touch more on vulnerable populations in just a minute.

The IRB/IEC must review research within a reasonable time, provide clear rationale for decisions, and document the date of review and documents reviewed. Document of such review is generally captured via meeting minutes.

1.17 The IRB/IEC's Responsibilities – Rendering Decisions Cont.



Notes:

An IRB/IEC's role does not stop at initial review. In addition to maintaining appropriate oversight, the IRB/IEC must perform a continuing review of the research at least once per year. The criteria to determine either required modifications, or termination or suspension of approval are the same as initial review. Again, any decisions made at continuing review must be documented and accurately communicated.

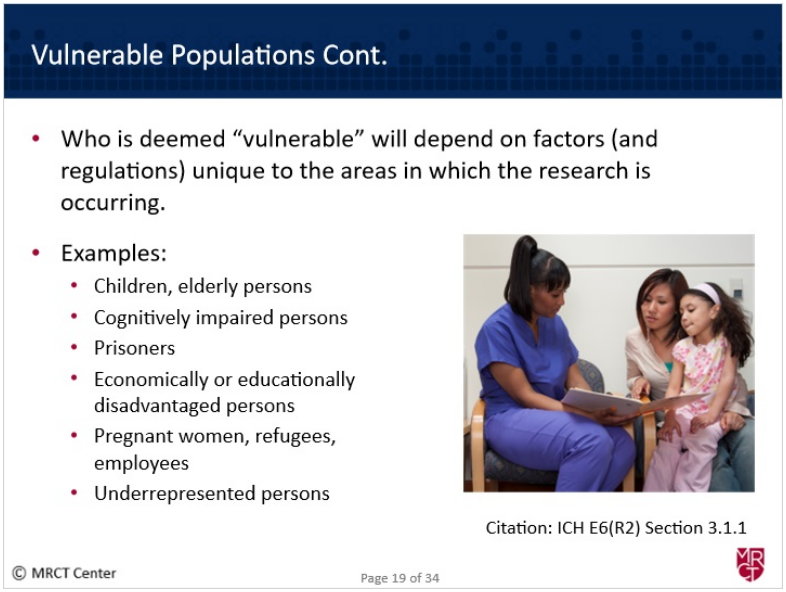
1.18 The IRB/IEC's Responsibilities – Vulnerable Populations

Notes:

We mentioned vulnerable populations and additional protections with respect to the IRB/IEC's role during initial review and which carries into continuing review. We are now going to spend some time on this topic.

It is important to realize that the definition or concept of "vulnerable" depends on local context, culture, and other factors. A population that may be deemed vulnerable in one country may not be considered vulnerable in another. For example, some countries consider economically disadvantaged individuals to be "vulnerable." And, within those countries what is perceived as economically disadvantaged will change depending on if the study is conducted in a historically poor rural community as opposed to a historically affluent urban center.

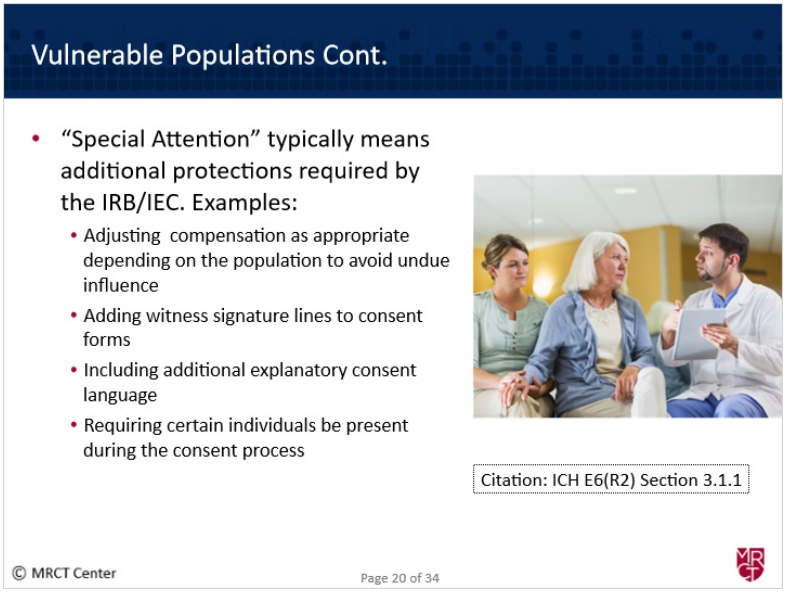
1.19 The IRB/IEC's Responsibilities – Vulnerable Populations Cont.



Notes:

Moreover, some country regulations actually define certain populations as vulnerable where others do not. An example list of populations that are often found vulnerable include: children, elderly persons, cognitively impaired persons, prisoners, economically or educationally disadvantaged persons, pregnant women, refugees, employees, and underrepresented persons.

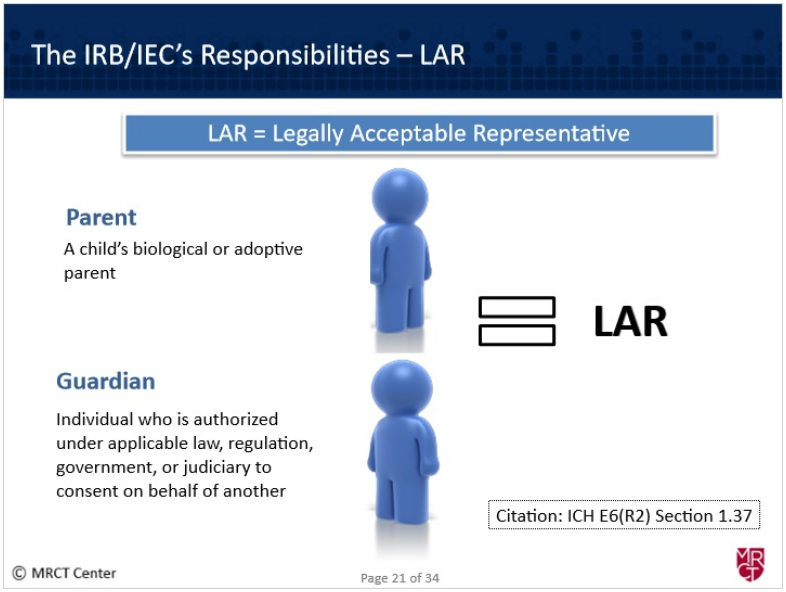
1.20 The IRB/IEC's Responsibilities – Vulnerable Populations Cont.



Notes:

For populations that are deemed vulnerable, a few examples of additional protections, or "special attention" as ICH GCP E6(R2) calls it, may include adjusting compensation as appropriate depending on the population to avoid undue influence, or adding witness signature lines to consent forms, including additional explanatory consent language, or requiring certain individuals be present during the consent process (like both parents, if there are two, for certain pediatric studies).

1.21 The IRB/IEC's Responsibilities – LAR



Notes:

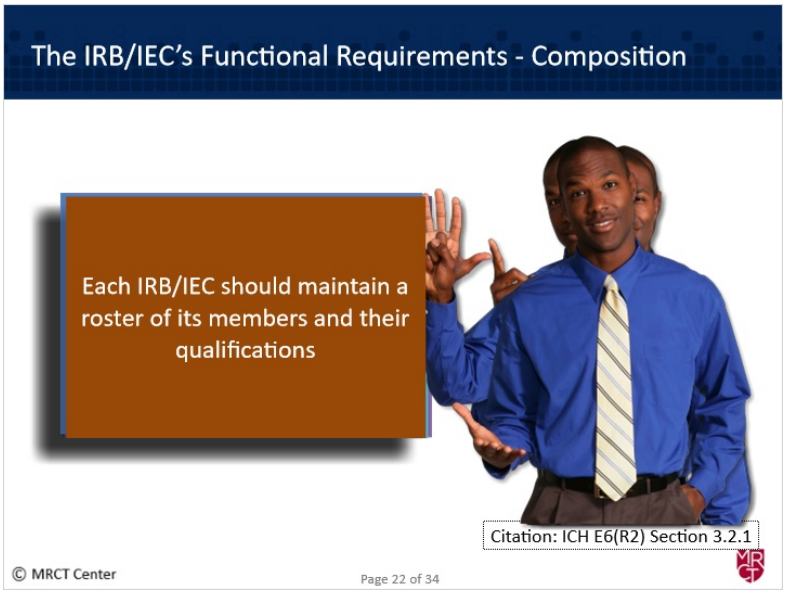
When talking about vulnerable populations, some of these populations will require obtaining consent from an Legally Authorized Representative. The most common populations are children or those who are cognitively impaired. Let's define and talk about this term.

First, LAR can mean "legally authorized representative" or "legally acceptable representative," which is the term found in ICH GCP E6(R2). Second, LAR is an overarching term that encompasses other terms that further define the type of LAR. So, know that an LAR may be a child's biological or adopted parent. An LAR may also be a person's guardian by way of law or court order. For example, via an advanced medical directive.

When an LAR is used to consent an individual into a clinical trial, this is significant because, if you recall from earlier in this Module, one of the key things an IRB/IEC is safeguarding is an individual's rights and one of those rights is the right for an individual to choose or, "consent to", whether or not they want to participate in the trial. When an LAR is the one providing the consent you take away the individual's right to decide for herself or himself whether or not they want to participate and place that choice in someone

else's hands. This is why ICH E6(R2) emphasizes that for trials using LARs, the IRB/IEC must consider ethical concerns and consider regulatory requirements in terms of 1) any restrictions a country may have on the use of LARs in clinical trials and 2) those laws or regulations that may define who an LAR is and the LAR's authority.

1.22 The IRB/IEC's Functional Requirements - Composition



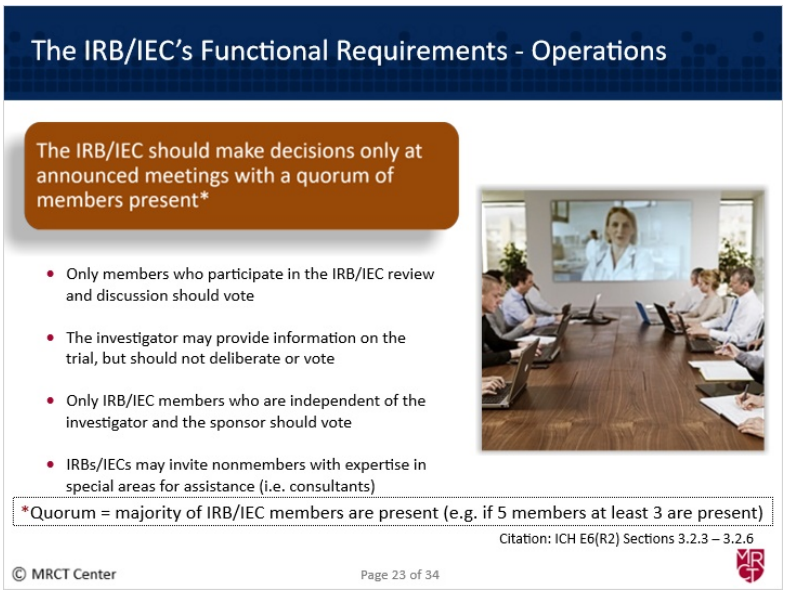
Notes:

In the last section of this Module we cover the IRB/IEC's functional requirements. In other words, what comprises an IRB/IEC and what are its required procedures?

An IRB/IEC should have at least five board members. At least one of those five members should be "nonscientific." This means not trained in a scientific discipline. One of the five members should also be independent ("not affiliated") with the IRB/IEC reviewing the research or the research site conducting the research. Typically "independent" means *not employed by*. Finally, the IRB/IEC members should collectively have the right qualifications and experience to evaluate the science, medical aspects, and ethics of each clinical trial reviewed.

Each IRB/IEC should maintain a roster of its members and their qualifications and make such roster available to any requesting regulatory agency or sponsor, CRO, institution, or researcher the IRB/IEC reviews studies for.

1.23 The IRB/IEC's Functional Requirements - Operations



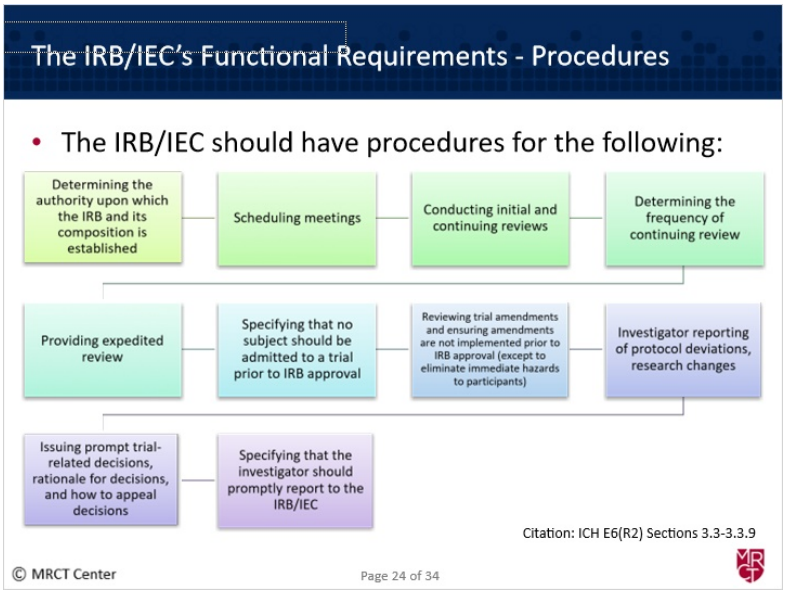
Notes:

We just discussed the IRB/IEC's composition, let's now discuss the IRB/IEC's functioning and operations, which really means let's discuss an IRB/IEC's deliberations and voting.

The IRB/IEC should make decisions only at announced meetings and upon which a quorum is present. A "quorum" is a majority of the IRB/IEC members on the IRB/IEC roster. If there are five members on an IRB/IEC, a quorum is at least three. Only members who participate in the IRB/IEC review and discussion should vote. In other words, only informed members should vote. The investigator may provide information to the IRB/IEC about the trial, but should not deliberate or vote. Only IRB/IEC members who are independent of the investigator and the sponsor should vote. Finally, IRBs/IECs may invite nonmembers with expertise in special areas for assistance. This means the

IRB/IEC can rely on consultants to ensure the IRB/IEC is sufficiently informed such that it can evaluate the clinical trial's science, medical aspects, and ethics.

1.24 The IRB/IEC's Functional Requirements - Procedures



Notes:

Switching gears from IRB/IEC operations, this slide focuses on IRB/IEC written procedures.

The IRB/IEC should have procedures for the following:

-Determining the authority upon which the IRB/IEC and its composition is established

-Scheduling meetings

-Conducting initial and continuing reviews

-Determining the frequency of continuing review

-Providing expedited review (IRBs/IECs may utilize something called "expedited review" per 3.3.5.)

-Specifying that no subject should be admitted to a trial prior to IRB/IEC approval

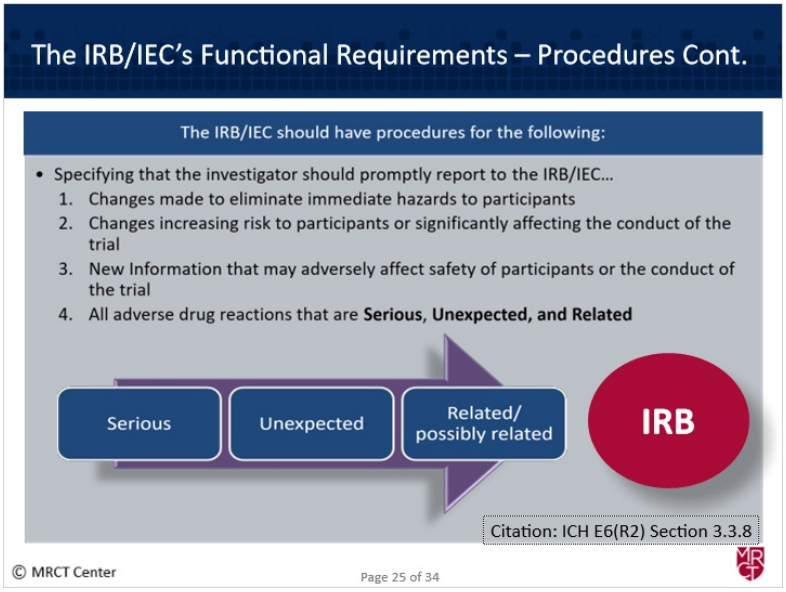
-Reviewing trial amendments and ensuring amendments are not implemented prior to IRB/IEC approval (except to eliminate immediate hazards to participants)

-Investigator reporting of protocol deviations, research changes

-Issuing prompt trial-related decisions, rationale for decisions, and how to appeal decisions

-Specifying that the investigator should promptly report to the IRB/IEC four things . . . (See next slide)

1.25 The IRB/IEC's Functional Requirements – Procedures Cont.



Notes:

The four things that investigators should promptly report to the IRB include:

1)Changes made to eliminate immediate hazards to participants

2)Changes increasing risk to participants or significantly affecting the conduct of the trial

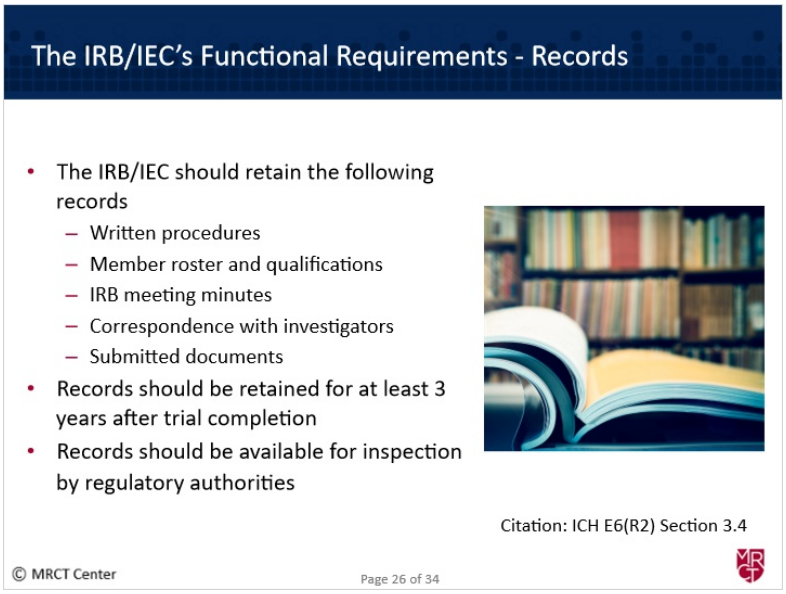
3)New Information that may adversely affect safety of participants or the

conduct of the trial

4)All adverse drug reactions that are **Serious**, **Unexpected, and Related or Possibly Related.**

Note to presenter, if wanted could take a deep dive into explaining Adverse Event reporting requirements in each country and how all are generally the same. With respect to U.S., could discuss UP, SUSAR, UADE, SAE, AE etc. Nonetheless, this is a more complicated topic and could take considerable time.

1.26 The IRB/IEC's Functional Requirements - Records



Notes:

Lastly, ICH E6(R2) sets out IRB/IEC records requirements.

The IRB/IEC should retain, for three years after trial completion, the following records:

-Written procedures

-Member roster and qualifications

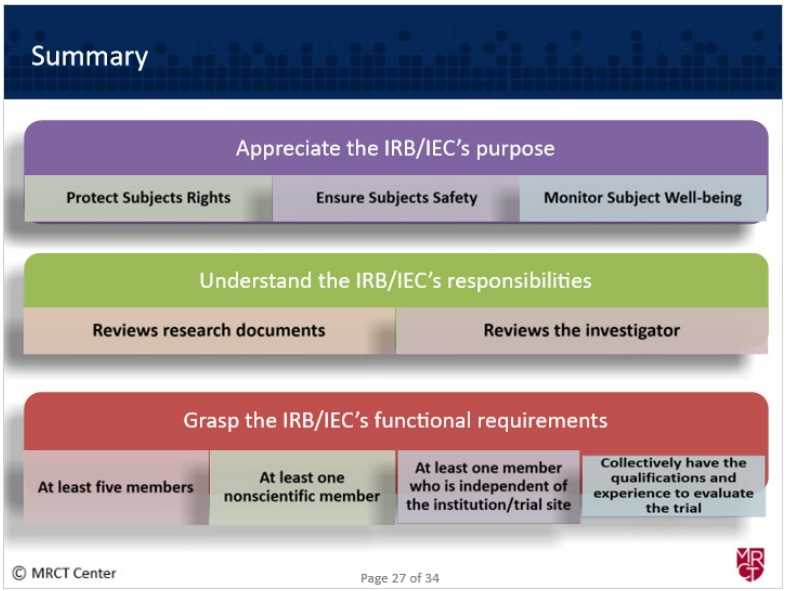
-IRB/IEC meeting minutes, which should capture documents reviewed, members presenting and voting, any controverted deliberations, and decisions

-Correspondence with investigators

-Submitted documents to the IRB/IEC

Records should be available for inspection by regulatory authorities.

1.27 Summary



Notes:

In conclusion, we set out to appreciate the IRB/IEC's purpose, its responsibilities, and functional requirements.

To wrap up this educational Module, let's put our new found (or reaffirmed!) knowledge to the test with a case study and discussion questions as well as a few quiz questions.