Informed Consent and Safety Reporting

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Category	Explanation	Examples
Quality (Q) Topics	Those relating to chemical and pharmaceutical quality assurance	Q1A Stability Testing of New Drug Substances and Products; Q3A Impurity in New Drug Substances
Safety (S) Topics	Those relating to *in vitro* and *in vivo* preclinical research	S1 Carcinogenicity Studies; S7A Safety Pharmacology Studies for Human Pharmaceuticals
Efficacy (E) Topics	Those relating to research in human subjects	E4 Dose-Response Information to Support Drug Registration; E6 guideline for Good Clinical Practice
Multidisciplinary (M) Topics	Topics that do not fit uniquely into one of the categories above	M1 Medical Dictionary for Regulatory Activities (MedDRA); M2 Electronic Standards for Transmission of Regulatory Information (ESTRI); M3 Nonclinical Safety; M4 The Common Technical Document (CTD)

Research involving human participants

(sometimes termed “human subjects” in research protocols and reports)

when human beings:

- are exposed to intervention, manipulation, *observation*, or *other interaction* with investigators either directly or through alteration of their environment, or

- become individually identifiable through investigators’ collection, preparation, or use medical or other records or of biological material from human beings.

Ethical framework

- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit evaluation
- Independent review
- Informed consent
- Respect for enrolled subjects

Emanuel E, Wendler D, Grady C. What makes clinical research ethical? *Journal of the American Medical Association* 2000; 283(20):2701-11

What is clinical trial?

- A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. (Ref: WHO Definition)

- Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.

CLINICAL TRIAL

Clinical Trial (also referred to as a clinical investigation or study) is any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), whether approved for marketing or not, and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its efficacy and/or safety.

- **Clinical trial registration** is the practice of documenting clinical trials before they are performed in a **clinical trials registry** so as to combat publication bias and selective reporting.
- Registration of clinical trials is required in some countries and is increasingly being standardized.
- Some top medical journals will only publish the results of trials that have been pre-registered.

Good Clinical Practice (GCP)

- A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

GCP component

- 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.
- 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/favourable 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.

GCP component

- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- 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. This principle applies to all records (paper or electronic) referenced in this guideline.
- 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.

https://www.clinicaltrials.gov/ct2/results?cond=&term=&cntry=MM&state=&city=&dist=

Search

Row	Saved	Status	Study Title	Conditions	Interventions	
1	☐	Recruiting	Causes of Pneumonia in Yangon	• Melioidosis Pneumonia	• Diagnostic Test: InBios® Active Melioidosis DetectTM-Lateral Flow Assay	• Medi Clinic Yang
2	☐	Recruiting	Evaluation of the Performance of a hsRDT Versus cRDT in Reactive Case Detection of Malaria Infections	• Malaria Diagnosis • Malaria,Falciparum	• Diagnostic Test: hsRDT	• Unive (URC Yang
3	☐	Recruiting	Effect of Structured Progressive Task-Oriented Circuit Class Training With Motor Imagery on Gait in Stroke	• Stroke • Gait, Hemiplegic	• Procedure: Motor imagery • Procedure: Health education • Procedure: Task-Oriented Circuit Class Training	• Unive Techn Yang
4	☐	Completed	Empirical ANtibiotic THErapy in Adults Hospitalised With Malaria	• Malaria • Bacteremia • Sepsis		• Insei Yang
5	☐	Completed	Improving Clinical Decision Making Skills for Myanmar Physical Therapists by Series of Workshop	• Cognitive Change	• Other: Clinical Decision Making (CDM) Workshop • Other: Clinical Decision Making (CDM) Workbook	• Unive Techn Yang
6	☐	Terminated	Effectiveness Study of a Treatment to Improve the Mental Health of Children and Adolescents	• Child Mental Disorder • Behavior Problem	• Behavioral: Common Elements Treatment Approach	• Kach Mai K Myitk
7	☐	Completed	Molecular Surveillance of Artemisinin Resistance Malaria in Myanmar	• Drug Resistance • Plasmodium Falciparum Malaria	• Drug: First line antimalarial in Myanmar (artemether-lumefrantrine, dihydroartemisinin-piperaquine, and artesunate-mefloquine)	• Dr. M Yang

Recruitment status

- **Not yet recruiting:** The study has not started recruiting participants.
- **Recruiting:** The study is currently recruiting participants.
- **Enrolling by invitation:** The study is selecting its participants from a population, or group of people, decided on by the researchers in advance. These studies are not open to everyone who meets the eligibility criteria but only to people in that particular population, who are specifically invited to participate.
- **Active, not recruiting:** The study is ongoing, and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled.
- **Suspended:** The study has stopped early but may start again.
- **Terminated:** The study has stopped early and will not start again. Participants are no longer being examined or treated.
- **Completed:** The study has ended normally, and participants are no longer being examined or treated (that is, the last participant's last visit has occurred).
- **Withdrawn:** The study stopped early, before enrolling its first participant.
- **Unknown:** A study on ClinicalTrials.gov whose last known status was recruiting; not yet recruiting; or active, not recruiting but that has passed its completion date, and the status has not been last verified within the past 2 years.

Healthy Volunteers Needed For a Research Study of Hand Movements

Earn $10/hour playing computer games

The laboratory of Dr. Krakauer
is seeking healthy volunteers aged 18-40 years
for a
All studies are

IRB: NA_00048918, A Study

JOHNS HOPKINS
Approved April 16, 2012

Want to participate in a research study on a contraceptive vaginal ring?

If you are a healthy woman between the ages of 18 and 39 and have regular menstrual cycles, you may be eligible for a research study of a method of birth control.

This study will evaluate the effects of receiving two birth control hormones in a vaginal ring.

- Multiple, frequent study visits over an eight month period
- Visits will occur at Johns Hopkins Bayview
- Participants should be using a non-hormonal method of contraception, or not be at risk for pregnancy
- Compensation for participation and travel

Please call **410 550 3060** or email whrap@jhmi.edu

PI: Anne E. Burke, MD, MPH
Study Number: NA_00068632

IRB number 00002388; February 17, 2011; version 2

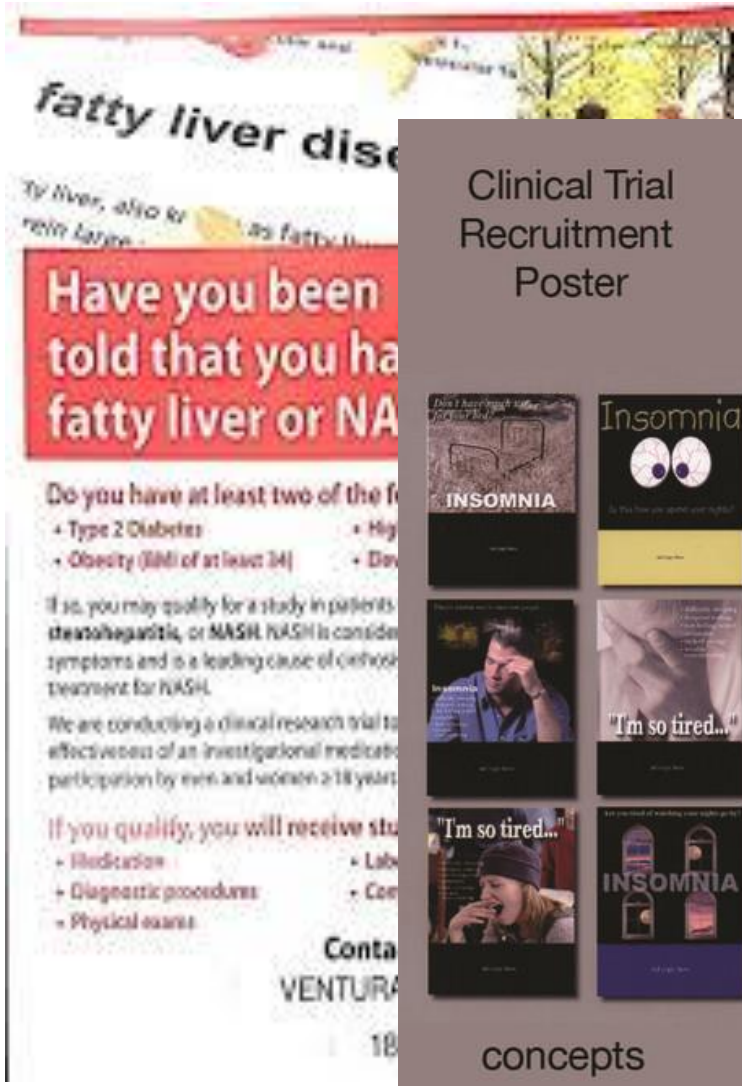
Are you interested in a study about how patients talk with doctors?

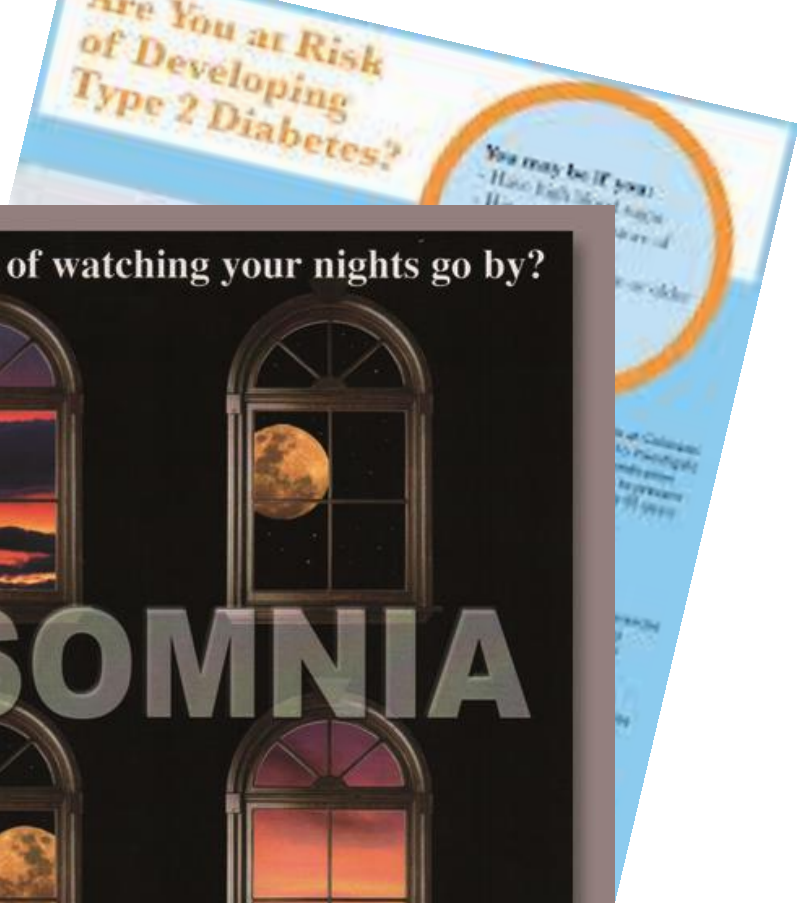
Researchers at Johns Hopkins need volunteers over 21 years of age for a research study to improve the way doctors and patients talk about depression, feelings and emotions. The main researcher is Debra Roter, DrPH.

You will watch two short videotapes of a doctor conducting a medical visit and imagine that the doctor is talking directly to you. You will be asked to respond to the video doctor in your own words as you would to a real doctor. You will also be asked to answer questions about your reaction to the video tape.

Your participation in the study should take approximately 1 ½ hours. You will be paid for your time and effort.

If you are interested, please call Rita Johnson at 410-502-4129 for more information





Clinical Trial Recruitment Poster

concepts

finished product

What Is Informed Consent?

"Consent given by a competent individual who

- Has received the necessary information
- Has adequately understood the information
- After considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation"

Source: Council of International Organizations of Medical Sciences (CIOMS) Ethical Guidelines

3 fundamental aspects of Informed consent

- **Disclosure**(o kaw o et aju mift 7mrsm;u kH o dy;_cif)

  This disclosure must be made in such a way that it provides a reasonable person the information she or he would need in order to make an informed decision.

- **Comprehension**(o kaw o et aju mift 7mrsm;u kHm;v n fb ab maygu fcif)

  Individuals must have the mental or decisional capacity to understand the information presented to them in order to make an informed decision about participation in research.

- **Voluntariness(** o kaw o ew Gfygoifefv Gfv yfbGaq kzwfcif)

  Individuals' decisions about participation in research should not be influenced by anyone involved in conducting the research: "...consent must be freely given or truly voluntary."

Informed Consent

A process by which a subject voluntarily confirms his or 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 participate. (1.28, ICH GCP 2016)

Informed consent is documented by means of a written, signed and dated informed consent form.

General Requirements

When obtaining consent from subjects for participation in clinical trials, the investigator must ensure that the following requirements are satisfied:

- Consent must be legally effective.
- The language used to obtain consent must be understandable to the subject (or the subject's LAR).
- Consent must be obtained under circumstances that allow the subject (or the subject's LAR) sufficient time to decide whether or not to participate.
- Consent must be obtained without undue influence or coercion.

Timing of Consent

- Once a subject is identified and agrees to participate in a trial, consent must be obtained. It is important that consent is obtained and documented before the subject's participation in the trial begins.

- However, procedures that are to be performed as part of the subject's medical care, and which would be done whether or not the participation in the trial were being considered, may be completed, without first obtaining informed consent from the subject.

Creation of Informed Consent

- Use local language
- Write to appropriate reading level
- Illustrate with appropriate concepts and images
- Perform a translation and back-translation
- Pilot-test

Documenting consent

- When the subject agrees to participate (or the subject's LAR agrees to the subject's participation) in the trial, consent is documented by having the subject (or the subject's LAR) personally sign and date the consent form.
- It is important that the person obtaining consent use the most current IRB/ERC approved version of the consent form.

- The FDA regulations require the subject (or subject's LAR) receive a copy of the consent form.
- ICH (2016) E6 Section 4.8.11 also requires that the subject (or subject's LAR) be given a copy of the signed and dated consent form.

Obtaining Consent Without Obtaining a Signature on a Consent Form

- In limited circumstances, the FDA allows an investigator to obtain consent verbally without obtaining a signature on the consent form (21 CFR 56.109[c][1] .
- The IRB must approve this consent process, which is referred to as a **"waiver of documentation of consent."**
- The IRB can approve this type of waiver only when study participation presents minimal risk to the subject.
- The IRB may require the investigator to provide the subject with written materials about the research.
- **ICH E6 does not include a similar provision for waiving the requirement for a signature on the consent form.**

Signature by Person Conducting the Consent Discussion

- **ICH (2016) E6 Section 4.8.8** states that "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."
- **The FDA regulations at** 21 CFR 50.27(a) (Protection of Human Subjects 2016) only require the signature of the subject and the date the subject signed the consent form.
- To assure compliance with the ICH requirement, the consent form should include a signature line labeled "person conducting informed consent discussion."
- This line should **not** be labeled "Investigator's Signature," unless the investigator is always the person who obtains consent.

During the trial

- As the clinical trial progresses, the protocol might be revised or new information may be obtained.
- The consent document should be revised whenever there are changes or new information that might affect the subject's willingness to continue to participate

When ICF is revised

- When the consent document is revised, IRB approval of the revised document must be obtained.
- The revisions should be discussed with the subject (or subject's LAR).
- If the subject (or subject's LAR) consents to continue participation, the subject (or subject's LAR) should sign and date the revised document, and they should be given a copy of the signed and dated document.

Challenges when obtaining consent from research subjects

Language issues

The consent process should be conducted in the language spoken by the subject, and the consent form should be translated into that language. An IRB may require independent confirmation of the accuracy of the translation.

Not able to read ICF

If a subject (or subject's LAR) is unable to read, an **impartial witness** should be present and personally sign and date the consent form as an indication that the information in the consent form and any other written information was accurately explained to

Subject (or Subject's LAR) in a Different Locale

In some instances, it might be difficult to obtain consent because the subject (or the subject's LAR) is not physically present during the consent discussion. The FDA has indicated in guidance that it is acceptable to conduct the consent discussion by phone and satisfy the requirement for a signed consent document by having the signed and dated consent form returned by facsimile (fax).

Cultural Issues

- In some cultures it may be considered rude to ask questions of an investigator or researcher, or rude to decline what is perceived of as a request for a favor.

- In these circumstances, it is important that the person obtaining consent understands the cultural issues, designs/conducts a consent process that is sensitive to those issues, and ensures that the subject understands that participating is completely voluntary.

understanding of trial purpose

- ranged from 10% of US males who understood the purpose of a variety of trials they were participating in to 62% of Canadian participants who understood the purpose of a neuro-oncology trial.

- Understanding of trial purpose in developing country studies also varied, ranging from 26% of Malian parents who understood the purpose of a malaria trial for their children to 90% of mothers with children in a paediatric influenza trial in The Gambia.

- Understanding of trial nature, assessed by participants' understanding that they were participating in research and of the investigational and experimental nature of research interventions, varied from 31% of participants in a US phase 1 oncology trial to almost 100% of participants in both a Swedish and a Finnish trial,and from 47% of women in a Bangladeshi nutritional trial for iron supplements to 100% of women in an HIV trial in Côte d'Ivoire.

Understanding of randomisation

- Understanding of randomisation was low compared to understanding of other aspects of a trial.
- In developed country studies, understanding of randomisation appeared to vary according to how close to actual consent it was measured.
- For example, 68% of parents understood randomisation when asked within 48h of consent in US paediatric oncology trials, and as many as 79% understood randomisation in an HIV vaccine trial when assessed immediately after disclosure.
- Yet fewer than half of the participants were reported to comprehend randomisation in six developed country studies in which understanding was assessed months or years after consent. *(Ref: J Med Ethics 2012;38:356e365. doi:10.1136/medethics-2011-100178)*

When prior consent not possible

- Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations)

Study documents

- Refers to the type of documents that the study sponsor or principal investigator may add to their study record.
- These include a study protocol, statistical analysis plan, and informed consent form.

Case study

- Dr. Apsen is the clinical investigator for a phase II trial of CMX23, an investigational drug intended for treatment of nerve pain resulting from complications of diabetes.
- Dr. Apsen enrolled five (5) subjects in the trial, and each subject received two (2) doses of the study drug. Before he enrolls his sixth subject, he receives a communication from the sponsor informing him that 223 subjects are currently enrolled in the trial and six (6) percent of those enrolled have developed elevated liver enzymes.
- The sponsor also reports that one subject developed liver failure. The sponsor reports that the episodes of increased liver enzymes and of liver failure are probably related to CMX23 and represent a new risk of CMX23. What should Dr. Apsen do?

Ref: https://www.citiprogram.org

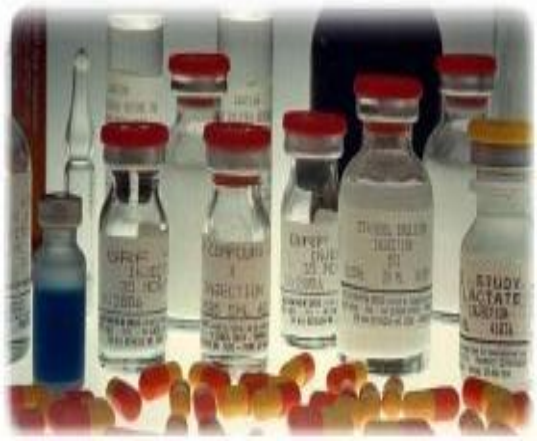
- Dr. Apsen must report the information to the IRB according to the IRB's reporting requirements.
- The IRB will consider whether the risk to benefit relationship of this trial remains reasonable and whether any revisions should be made to minimize risks.
- The IRB will require the consent document to be revised, because this is a newly identified foreseeable risk
- Dr. Apsen should not enroll any new subjects until the consent document includes information about this risk and he should advise currently enrolled study subjects about this new risk as soon as possible.

- Dr. Apsen reports the risk information to the IRB

- The IRB requires Dr. Apsen to include a description of this new risk information in a revised consent form and submit the form to the IRB for approval.

- Dr. Apsen has a new subject ready to enroll. He has not yet submitted the revised consent document to the IRB for approval. What should Dr. Apsen do with respect to the new subject?

- Dr. Apsen must obtain consent from the subject with an IRB-approved consent document that includes all of the foreseeable risks.
- The currently approved consent document does not include all reasonably foreseeable risks.
- He should not enroll the subject until the IRB approves a consent document that includes this new risk



Safety Reporting

Adverse event

An unfavorable change in the health of a participant, including abnormal laboratory findings, that happens during a clinical study or within a certain amount of time after the study has ended.

This change may or may not be caused by the intervention/treatment being studied.

Adverse Event

- Any untoward medical occurrence in a patient or subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
- An adverse event (AE) can therefore be any unfavourable 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 (1.2, ICH GCP 2016).

Serious adverse event

- An adverse event that results in death, is life-threatening, requires inpatient hospitalization or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect.

  (1.50, ICH-GCP 2016)

Safety reporting

- All serious adverse events (SAEs) should be reported immediately to the sponsor
- 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 regulatory requirement(s) and report to regulatory authority(ies) and the IRB/IEC.

- Sponsor-investigators must notify regulatory authorities and all participating investigators in writing of events that are both unexpected and serious, and are associated with the use of drugs as soon as possible, but no later than fifteen (15) calendar days after the sponsor-investigator determines that information received must be reported. I
- Reports. Adverse reactions that are unexpected, fatal, or life threatening must be reported no later than seven (7) calendar days after the sponsor-investigator receives the information.

Ref

- International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 2016. "International Council for Harmonisation (ICH) Harmonized Guideline: Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2)."

- U.S. Food and Drug Administration (FDA). 2017. "IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects." July.

- CIOMS guideline

e-Learning Courses

ICH Good Clinical Practice E6 (R2)

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2017 Ethical and Regulatory Aspects of Clinical Research Course Fall: Registration Confirmation

Current Registration Details

Yin Thet Nu Oo

Location

Registration Item

DMR Myanmar ERC

- Sessions
- Date and Time Session
- 10/04/2017 8:30 AM IRBs, the Common Rule, and Subject Selection
- 10/11/2017 8:30 AM Risks and Benefits, Research with Pregnant Women, and Research Participant Panel
- 10/18/2017 8:30 AM Informed Consent, Research with those with Impaired Capacity for Consent, and Conflicts of Interest
- 10/25/2017 8:30 AM Ethics of Research with Children, Randomized Clinical Trials, and Pragmatic Trials
- 11/01/2017 8:30 AM Ethical issues in International Research and Mock IRB
- 11/08/2017 8:30 AM Stored Tissue, Big Data, and Incidental Findings

NATIONAL INSTITUTES OF HEALTH

certifies that

Yin Thet Nu Oo, MD or equivalent

has participated in the educational activity titled

"Ethical and Regulatory Aspects of Clinical Research"

at

THE NATIONAL INSTITUTES OF HEALTH
CLINICAL CENTER, DEPARTMENT OF BIOETHICS

Bethesda, Maryland

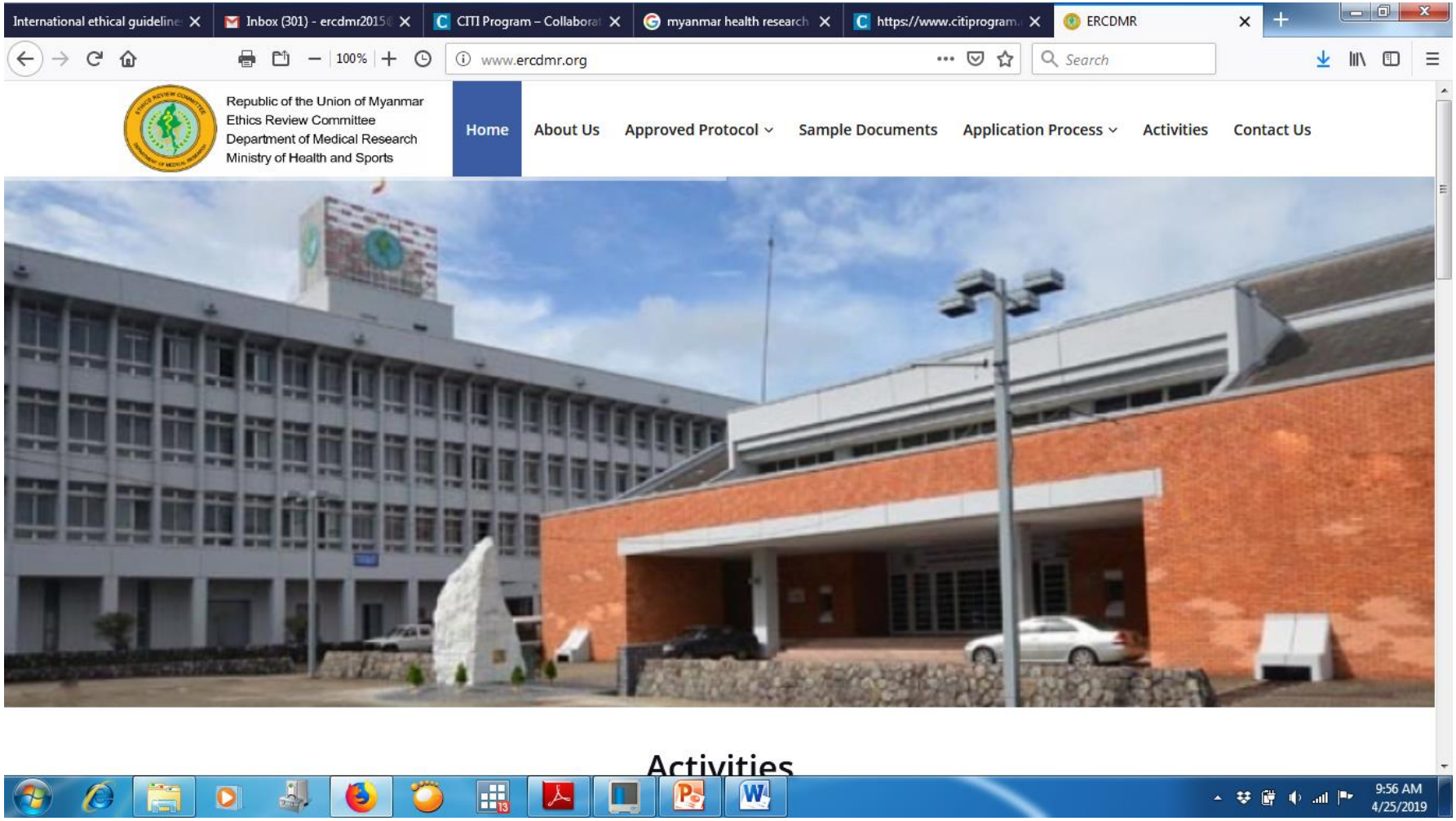
September 27, 2017 through November 8, 2017
and has attended 5.00 of 7 sessions

Christine Grady RN PhD

Christine Grady, RN, PhD
Chief

November 8, 2017
Date

www.irbdmr.gov.mm




Thank You