University of Pittsburgh

History of Human Subject Protections

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Special thanks to Bill Doyle, PhD for content contribution

What is the IRB?

- A committee that has been formally designated to approve, monitor, and review biomedical and behavioral research involving humans.
- Empowered by the FDA, DHHS/OHRP and the University to ensure compliance
- Scientific, ethical, and regulatory oversight

When do you need us?

- Research conducted where University of Pittsburgh faculty, staff or students are *engaged*
  - Regardless of where the research is conducted
- Research conducted in University of Pittsburgh facilities
- Research conducted using the *private* records of the University of Pittsburgh

What is ‘Research’

“A systematic investigation designed to develop or contribute to generalizable knowledge”

What is a ‘human subject’

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or
(2) Identifiable private information.

History of Research Ethics

"The ethics of research were born in scandal and reared in protectionism …You could say that the ethics of human subjects research evolved in a pattern of crisis and response."

Ex-Chair of the Ex-NHRPAC January 2002

Perceived Problem

Journalist:	Amplify, distort, disseminate
Population:	React, complain, demand
Tort Lawyer:	Punish, deter, compensate
Government:	React, enact laws
Panels:	Clarify legal issues
OHRP:	Implement, enforce, punish
IRB:	Change procedures
Researchers:	Modify practice

An Early Experiment: 500 BC

Test us for ten days on a diet of vegetables and water," Daniel said. "At the end of the 10 days, see how we look compared to the other young men who are eating the king's rich food. Then you can decide if to let us continue eating our diet." So the attendant agreed.

At the end of the 10 days, Daniel and his three friends looked healthier and better nourished than the young men who had been eating the food assigned by the king.

So after that, the attendant fed them only vegetables instead of the rich foods and wines.

KING JAMES BIBLE, Daniel 1:8-16

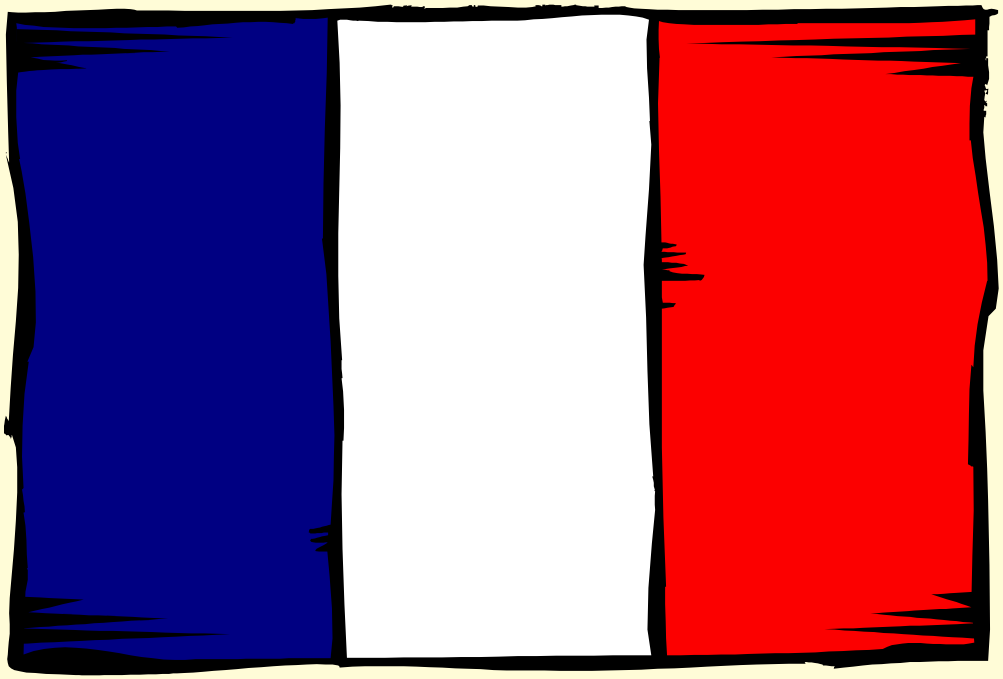
Another Early Experiment – 1 BC

Cleopatra devised an experiment to test the theory that it takes 40 days to fashion a male fetus fully and 80 days to fashion a female fetus.

When her handmaids were sentenced to death, she had them impregnated and opened their wombs at specific times.

Claude Bernard – Mid 19th Century

"Never perform an experiment which might be harmful to the patient even though highly advantageous to science or the health of others."



Walter Reed, MD - 1900

Exposes 22 Spanish immigrant workers in Cuba with the agent for Yellow Fever

- $100 for contracting disease
- $100 for survival

Final Justification

…remember that no one ever tried to do any good for the world and the people in it, who escaped the harshest criticism from his fellowman! It has always been thus, and doubtless always will be.

The undersigned, Antonio Benino Antonio Benino being more than twenty-five years of age, native of Cerceda, in the province of Corima , the son of Manuel Benino and Josefa Castro here states by these presents, being in the enjoyment and exercise of his own very free will, that he consents to submit himself to experiments for the purpose of determining the methods of transmission of yellow fever, made upon his person by the Commission appointed for this purpose by the Secretary of War of the United States, and that he gives his consent to undergo the said experiments for the reasons and under the conditions below stated.

The undersigned understands perfectly well that in case of the development of yellow fever in him, that he endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay in this island, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service.

It is understood that at the completion of these experiments, within two months from this date, the undersigned will receive the sum of $100 in American gold and that in case of his contracting yellow fever at any time during his residence in this camp, he will receive in addition to that sum a further sum of $100 in American gold, upon his recovery and that in case of his death because of this disease, the Commission will transmit the said sum (two hundred American dollars) to the person whom the undersigned shall designate at his convenience.

The undersigned binds himself not to leave the bounds of this camp during the period of the experiments and will forfeit all right to the benefits named in this contract if he breaks this agreement.

And to bind himself he signs this paper in duplicate, in the Experimental Camp, near Quemados, Cuba, on the 26th day of November nineteen hundred.

The contracting party,
Antonio Benigno

On the part of the Commission:

Walter Reed
Maj. & Surg., U.S.A.

Timeline of “Modern” Protections

- Berlin Code – 1900
- Nazi Codes – 1931
- Nuremberg Code – 1947
- Declaration of Helsinki – 1964, revisions
- National Research Act – 1974
- Belmont Report – 1979
- 21 CFR 50, 21 CFR 56 - 1980
- 45 CFR 46 – 1981

World War II – Nazi Regime

1941: Sterilization experiments at Auschwitz

1941-45: Typhus experiments at Buchenwald/Natzweiler.

1942: High altitude/low pressure experiments at Dachau.

1942-43: Bone regeneration/transplantation experiments at Ravensbrueck.

1942-43: Freezing experiments at Dachau.

1942-43: Coagulation experiments on priests at Dachau.

1942-45: Malaria experiments at Dachau on >1200

1943: Epidemic jaundice experiments at Natzweiler.

1943: Phosphorus burn experiments at Buchenwald.

1944: Seawater experiment on 60 Gypsies at Dachau.

World War II: Japan

- Unit 731 - Epidemic Prevention and Water Purification Department
  - Vivisection without anesthesia, fetal removal
  - Biological weapon testing, mustard gas
  - Germ warfare experiments
  - Amputation, frostbite

Meanwhile, Back on the Ranch…

1906: Dr. Strong of Harvard infects Philippine prisoners with cholera.

1913: 146 PA children were inoculated with syphilis and eyes of 15 children were tested with tuberculin.

1915: PHS induces pellagra in 12 Mississippi prisoners.

1919: Testicular transplant experiments on 500 CA prisoners.

1939: 22 orphans living in Iowa were induced to stutter by Dr. Wendell Johnson.

1941: Dr. Black inoculates a 12 month old with herpes.

1942: Dr. Cohn injects 64 prisoners with beef blood.

1943: Refrigeration experiment conducted on 16 mentally disabled patients at University of Cincinnati.

Wartime “Preparations”

1942-1944: U.S. Chemical Warfare Service conducts mustard gas experiments on thousands of servicemen.

1944: Manhattan Project injection of 4.7 micrograms of plutonium into soldiers.

1944-1946: University of Chicago Medical School professor conducts malaria experiments on more than 400 Illinois prisoners.

1945: Manhattan Project injection of plutonium into 3 patients at University of Chicago.

1946-1953: AEC sponsored study conducted at the Fernald school in MA. Residents were fed Quaker Oats cereal containing radioactive tracers

Nuremberg Trials

During the Nuremberg War Crimes Trials, 23 German doctors were charged with crimes against humanity for “performing medical experiments upon concentration camp inmates another living human subjects without their consent…..”

NUREMBURG CODE - 1947

- As a result of these trials, rules were adopted that are now know as the “Nuremberg Code”
  - Voluntary Consent is Essential
  - Capacity to Consent
  - Freedom from Coercion
  - Comprehension of Potential Risks/Benefits
  - Freedom to Withdraw At Any Time
- Minimization of Potential Risks/Harm
- Favorable Benefit/Risk Ratio
- Qualified Investigators/Appropriate Research Design

Basic elements of informed consent

1. A clear statement that it is a research study, purposes and the expected duration, procedures to be followed, and identification of any procedures which are experimental;
2. A description of any risks or discomforts to the subject;
3. A description of any benefits to the subject or to others;
4. Alternative procedures or courses of treatment
5. A statement describing how confidentiality will be maintained;
6. For research involving more than minimal risk, compensation for injury;
7. Research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
8. A statement that participation is voluntary

Declaration of Helsinki - 1964

Upholds Nuremberg Code and goes further:

- The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize impact on physical and mental integrity and personality.

- In publication of his or her research, the physician is obliged to preserve the accuracy of the results.

- The research protocol should always contain a statement of the ethical considerations involved and that these principles were complied with

Willowbrook Hepatitis Studies-1950s

- Purpose-understanding of natural history of infectious hepatitis
- All newly admitted patients at extended care facility ("mentally defective persons") deliberately infected with strain of hepatitis
- Parents gave their written informed consent**

  **Parents were told that unless they agreed to allow child to participate, the child could not be enrolled into the institution

Jewish Chronic Disease Hospital Studies – 1960s

- 22 chronically ill, debilitated non-cancer patients 'enrolled'
  - Live cancer injected into bloodstream
  - Determine whether cancer cells lived longer in debilitated non-cancer patients than in those with cancer
  - Patients were not given the opportunity to provide consent

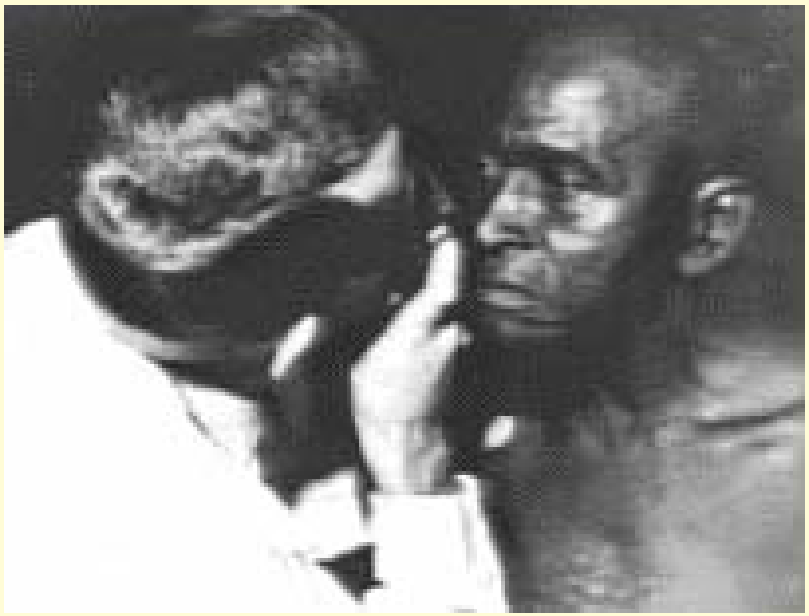
Milgram Research on Obedience 1960s

- Understand acts of genocide that occurred during the Holocaust (why people follow directions of authority figures even when things are cruel or unethical)
- Involved overt deception, lack of adequate informed consent, and psychological harm
- Experiment on obedience to and defiance of authority
- Subjects administered a memory test and were told to shock the respondent if answers were wrong

Tuskegee Syphilis Study

- Funded by US Public Health Service
- Study to evaluate untreated syphilis in humans
- No effective tx when study commenced
- Subjects-African-American sharecroppers in Alabama
- Perception-receiving beneficial care

The Tuskegee Syphilis Study



- Conducted from 1932-1972
- In the 1940s when penicillin, known to be effective in the treatment of syphilis became available, these men were neither informed of this nor given the antibiotic.

Reaction: Tuskegee

Journalist:	Front page of NYT 1972
Population:	Disbelief, distrust, demand
Tort Lawyer:	Lawsuit, awards $37,500/per
Government:	Closed study, National Research Act, 45 CFR 46, Presidential Apology 1997
Panels:	Syphilis study panel, National Commission, Presidential Commissions
IRB:	REQUIRED

National Research Act - 1974

- Established the IRB system for regulating research
- Created the National Commission for the Protection of Human subjects of Biomedical and Behavioral Research
    - Charged with identifying basic principles that should underlie research conduct and recommending guidelines to ensure these principles (Belmont Report)

Belmont Report

- Written in 1978 by the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research
- Explains the three principles that are the main tools to evaluate the ethics of research protocols:
  - Respect for Persons = informed consent
  - Beneficence = risk/benefit analysis
  - Justice = equitable selection of subjects

Belmont Report

- Boundaries Between Practice and Research
  - distinguish between biomedical and behavioral research and the practice of accepted therapy in order to know what activities ought to undergo review for the protection of human subjects of research.

The Principle of Respect for Persons

- Acknowledges the dignity and autonomy of individuals
- Requires that subjects give informed consent to participate in research
- Provides for additional protections of individuals who are not capable of self-determination
  - Children; prisoners; mentally disabled
- Promotes the concepts of privacy and confidentiality

Guatemala Syphilis Study

-Overseen by former Dean of Pitt's GSPH, Dr. John Cutler

-Supported by U.S. Public Health Service

-Guatemala, mid-1940's

-Participants not informed or consented

-Deliberately infected ~1500 prisoners, mental patients & orphans with Venereal Disease to test penicillin

-Vulnerable populations

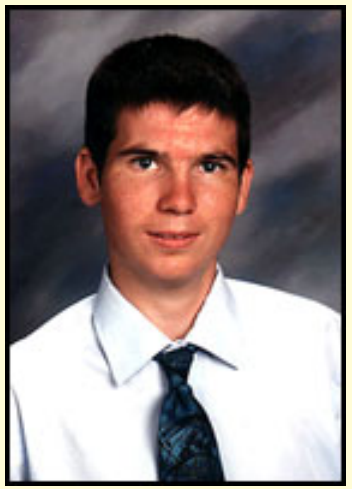
-Poor scientific documentation & methodology

The Principle of Beneficence

- Requires that the study be carefully designed so that benefits be maximized and any potential harm be minimized
- Requires that the risks of the research are justified by the potential benefits
- Requires that conflicts of interests be managed

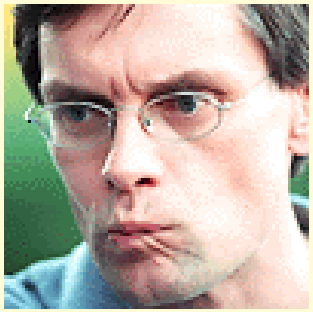
The Washington Post
washingtonpost.com

FDA Halts Gene Experiments at University of Pennsylvania



By Rick Weiss and Deborah Nelson
Washington Post Staff Writers
Saturday, January 22, 2000; Page A1

The federal government yesterday halted all human gene therapy experiments involving a prominent researcher at the University of Pennsylvania, saying an investigation into the September death of a teenager there found the school's prestigious program in serious disarray.



The Principle of Justice

- Requires that all subjects be treated fairly

- Requires that there must be equity in subject selection to insure that certain individuals or classes of individuals are not systematically selected or excluded unless there are scientifically or ethically valid reasons for doing so

Justice

- Willowbrook study
- San Antonio contraceptive study
- Randomization of military personnel to penicillin or placebo for treatment of strep pharyngitis on development of rheumatic fever or nephritis

And yet…

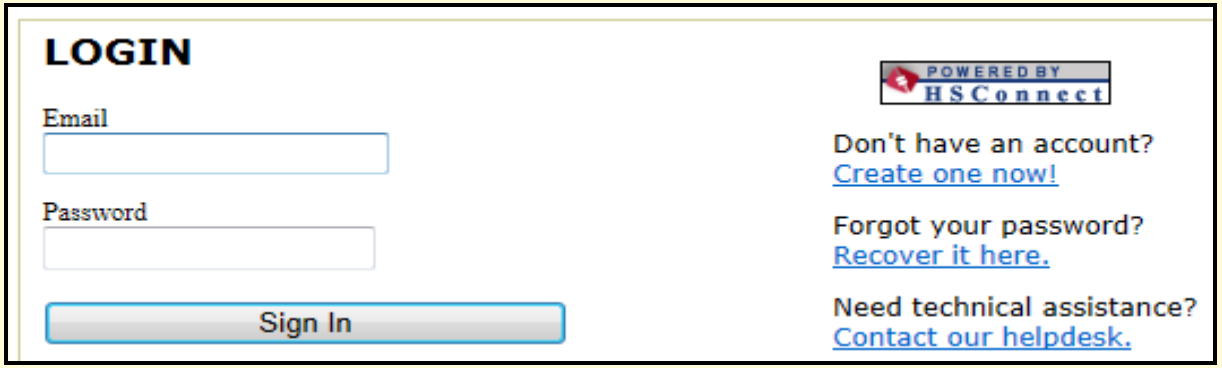
1991: Tony LaMadrid commits suicide in study on relapse of schizophrenics withdrawn from medication at UCLA, **1993**: Kathryn Hamilton dies after participating in breast cancer experiment at Fred Hutchinson Center, **1995**: 19-year-old Nicole Wan dies after being paid $150 to participate in MIT experiment to test pollutants, **1999**: 9 month-old Gage Stevens dies at CHP during Propulsid clinical trial for infant acid reflux. **1999**: 18-year-old Jesse Gelsinger dies after being injected with adenovirus in gene therapy experiment. **2001**: Ellen Roche, a healthy 27-year old volunteer, dies in challenge study at Johns Hopkins University. **2001**: April 4, Elaine Holden-Able dies after drinking orange juice that had been mixed with a dietary supplement. **1999**: Veterans Administration shuts down all research at West Los Angeles Medical Center after allegations of medical research performed on patients who did not consent. **1999**: OPRR shuts down research at Duke University because of inadequate IRB supervision of human subject experiments. **2000**: University of Oklahoma melanoma trial halted for failure to follow government regulations and protocol. **2001**: Biotec, a company in PA asks the FDA for permission to conduct placebo trials on infants in Latin America born with serious lung disease though would be illegal in U.S. **2003**: FDA reports that, for the past four years, experiments on cancer patients were conducted at Stratton Veterans Affairs Medical Center by Paul Kornak who had no valid medical license and who repeatedly altered data and committed numerous violations of the protocols. **2011**: Duke U sued over cancer trials conducted under false credentials.

Getting started on submission

Investigator Requirements

- Responsible Conduct of Research
- Research with Human Subjects
  - Biomedical researcher (includes health sciences students)
  - Social and behavioral researcher
  - Undergraduate student research (must be minimal risk)
- Good Clinical Practice (if the study involves an IND or IDE)
  - Recommended for any clinical research study

Login Using Pitt CITI Portal



Add a course or update your learner groups for *University of Pittsburgh*

Select Curriculum - University of Pittsburgh

Review the *University of Pittsburgh* Instructions page.

Question 1 **If you are required to complete the Conflict Of Interest (COI) Training Course for PHS-funded researchers, select this CITI COI course. Investigators who do not work on PHS-funded research can complete either the CITI COI course or the University of Pittsburgh Internet-based Studies in Education and Research (ISER) COI Training module available at https://cme.hs.pitt.edu.**

Choose one answer

- ○ Yes
- ◉ **No, not at this time**

Question 2 **Based on your research/teaching interests, select the most appropriate course in *Responsible Conduct of Research* if you are required to complete this training. All individuals conducting human subjects research are required to complete either the Biomedical or Social/Behavioral course.**

Choose one answer

- ◉ **Biomedical** Responsible Conduct of Research Course
- ○ Responsible Conduct of Research for **Engineers**
- ○ **Humanities** Responsible Conduct of Research Course
- ○ **Physical Science** Responsible Conduct of Research Course
- ○ **Social and Behavioral** Responsible Conduct of Research Course
- ○ **No, not at this time**

Question 3 **If you are conducting research with human subjects, select one of the following courses (Note: if you conduct biomedical *and* social/behavioral research, select the course of greatest interest to you).**

Choose one answer

- ◉ Biomedical Research (includes all health science students)
- ○ Social & Behavioral Research
- ○ Undergraduate Student Research (Note: not more than minimal risk research)
- ○ **No, not at this time**

University of Pittsburgh **OSIRIS** Login

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Full AAHRPP Accreditation

IRB Mailing List

Receive the latest updates regarding regulatory information and other news of concern to the research community.

Click here to sign up. You may unsubscribe at any time.

Home

Welcome to the University of Pittsburgh Institutional Review Board (IRB) online submission process, also known as **OSIRIS** (**O**nline **S**ubmission for **I**nstitutional **R**ev**i**ew**s**)!

For general information about the University of Pittsburgh IRB, please go to http://www.irb.pitt.edu.

For general information about **OSIRIS**, please go to http://www.irb.pitt.edu/osiris/.

To log on to OSIRIS, you will need a username and password from HSConnect. If you need to create an account, go to www.hsconnect.pitt.edu. University of Pittsburgh and UPMC-affiliated researchers can use their usernames and passwords from the Internet-based Studies in Education and Research training they must take prior to completing an online submission.

If you need more information about obtaining your username and/or password or other IRB related questions, please review the **General Information** page, available from the link on the left-hand side of this page, or contact us at irb@pitt.edu.

Thank you for using OSIRIS!

Changes in Training Requirements for All Faculty, Students, and Staff Conducting Research with Human Subjects at the University of Pittsburgh or UPMC

The University of Pittsburgh IRB is migrating to a new human subjects training program that has been developed by Collaborative Institutional Training Institute (CITI). Effective March 5, 2012, this program will replace the previously required "Module 1 –Research Integrity" and "Module 2 – Human Subjects Research".

Click here for an overview and timetable information.

Click here to access the Pitt CITI portal and more information.

Submission of New Studies

- **OSIRIS** (electronic submission process)
  - Pre IRB reviews
  - Series of questions and answers to build application
  - All attachments (grant, consent form, multi-center protocol) included in one online location

Ancillary Reviews

- Fiscal Review
- Scientific Review
- Research Protocols Involving Human Subject or Patient Exposure to Ionizing Radiation: Radioactive Drug Research Committee
- Gene Transfer Research: University of Pittsburgh Institutional Biosafety (rDNA) Committee (IBC-rDNA)
- Conflict of Interest

Types of Review

- **Exempt (determination made by IRB)**
  - Limited, very restricted categories of research that are exempt from many of the Federal research regulations
- **Expedited ("Administrative") Review**
  - Minimal risk research that falls into certain categories
- **Full Board Review**
  - More than minimal risk research, or research that cannot be expedited

Current IRB Timelines (Mean)

- Exempt determinations
  - 2 days until review
  - 3 days until approval issued

- Expedited projects
  - 8 days until review
  - 20 days until approval issued

If you don't hear from the IRB in 10 business days, contact the reviewer

Current IRB Timelines (Mean)

- Full Board
  - Assignment to Committee Meeting
  - Generation of Meeting Minutes
  - Correspondence to Investigators
  - Review of Responses to Comments
- Submission to Approval – 54 days

The IRB Is At Your Service…

- askirb@pitt.edu
  - ✓ Consultations
  - ✓ Pre-reviews
  - ✓ General questions
  - ✓ IRB Makes House Calls! Request on-site training

- www.irb.pitt.edu
  - ✓ Click on Calendar of Events
- irb@pitt.edu
  - ✓ OSIRIS training/support
  - ✓ CITI training/support
  - ✓ IT questions