Pragmatic GCP in Outbreak Situations

Dr Kwaku Poku Asante

25th November 2014

Goals and Objectives

- **To understand:**
  - The affect of Good Clinical Practices on institutions conducting Clinical Research

- **To discuss:**
  - What is GCP
  - Guidelines for GCP
  - Basic principles
  - Practices and strategy for staying compliant with Good Clinical Practices in outbreaks.

What Is GCP?

Good Clinical Practice (GCP) is defined as 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’

Guidelines for GCP 1

- Are mainly focused on the protection of human rights in clinical trial.
- Provide assurance of the safety of the newly developed compounds.
- Ensures rights and safety should prevail over scientific interest
- Provide standards on how clinical trials should be conducted.
- Define the roles and responsibilities of clinical sponsors, clinical research investigators, Clinical Research Associates, and monitors.

Guidelines for GCP 2

- Foreseeable risks/inconveniences and benefit analysis for the individual trial subject and society

- Availability of scientific data: The available non clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial

- Description of detailed trial procedures in a protocol

Guidelines for GCP 3

- Compliance to protocol, local regulation, ethical standards, GCP
- 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

Guidelines for GCP 4

- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks
- Freely given informed consent should be obtained from every subject prior to clinical trial participation
- Data recording, handling, and storage to ensure accurate reporting, interpretation, and verification

Guidelines for GCP 5

- The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements
- 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
- Ensures quality systems

What Happens in a Clinical Trial?

(Continued)

- The trials are conducted in 4 phases.
- GCP Principles are applied through out all these phases

Summary of Phases I-IV

	# Subs.	Length	Purpose	% Drugs Successfully Tested
Phase I	20 – 100	Several months	Mainly Safety	70%
Phase II	Up to several 100	Several months-2 yrs.	Short term safety; mainly effectiveness	33%
Phase III	100s – several 1000	1-4 yrs.	Safety, dosage & effectiveness	25-30%
Phase IV	>10,000	Ongoing post licensure	Safety	

Partners in research

Cholera Outbreak

CDC Home

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

Travelers' Health
All CDC Topics
Choose a topic above
SEARCH

A-Z Index A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

TRAVELERS' HEALTH
TRAVEL SAFE. TRAVEL SMART.

- Home
- Destinations
- Travel Notices
- Cholera in Ghana
- Find a Clinic
- Disease Directory
- Information Centers
- For Travelers
- For Clinicians
- Travel Industry
- Yellow Book
- Mobile Apps
- RSS Feeds

Disease Directory
Learn more about travel-related diseases.

African Sleeping Sickne

Home > Travel Notices

Recommend Tweet Share

Cholera in Ghana

Warning - Level 3, Avoid Nonessential Travel
Alert - Level 2, Practice Enhanced Precautions
Watch - Level 1, Practice Usual Precautions

Updated: November 10, 2014

What is the current situation?

According to the World Health Organization, more than 20,900 cases and 166 deaths from cholera have been reported in Ghana as of October 5, 2014. Many cases have been in the Greater Accra region, including in the districts of Accra Metro and La-Dadekotopon.

CDC recommends that travelers to Ghana protect themselves from cholera by following food and water precautions.

What is cholera?

Print page
Our Twitter
Our Facebook page
Get email updates

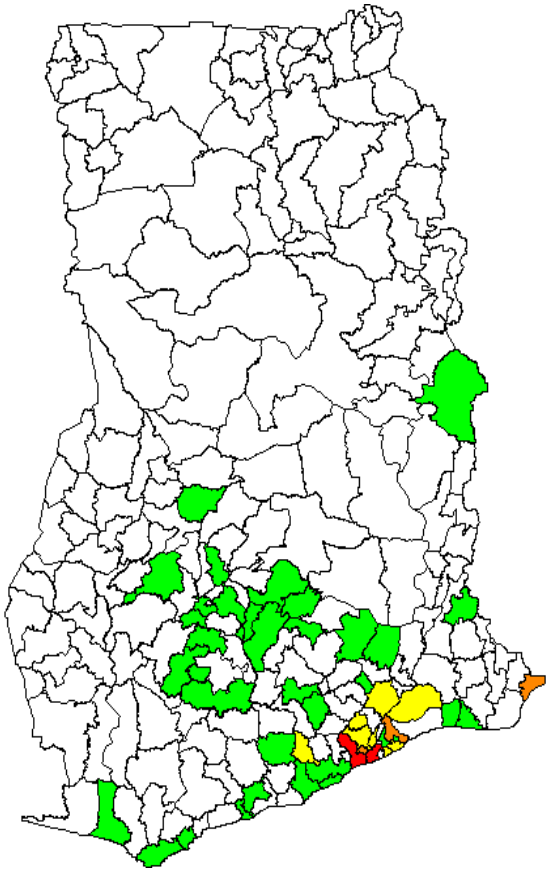
Get email updates
To receive email updates about this page, enter your email address:
What's this? Submit

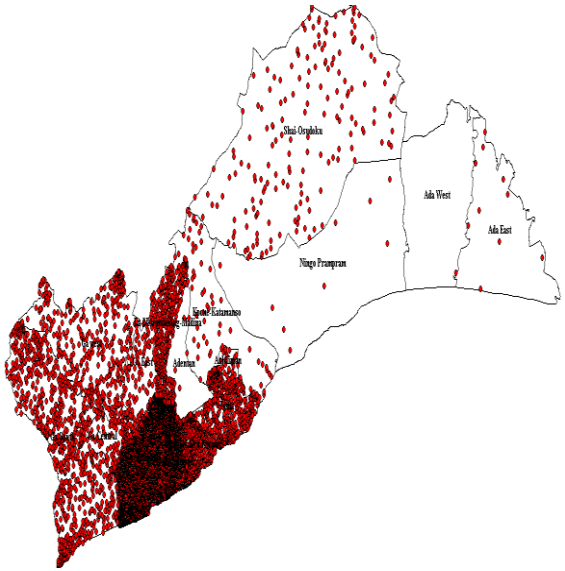
Contact Us:

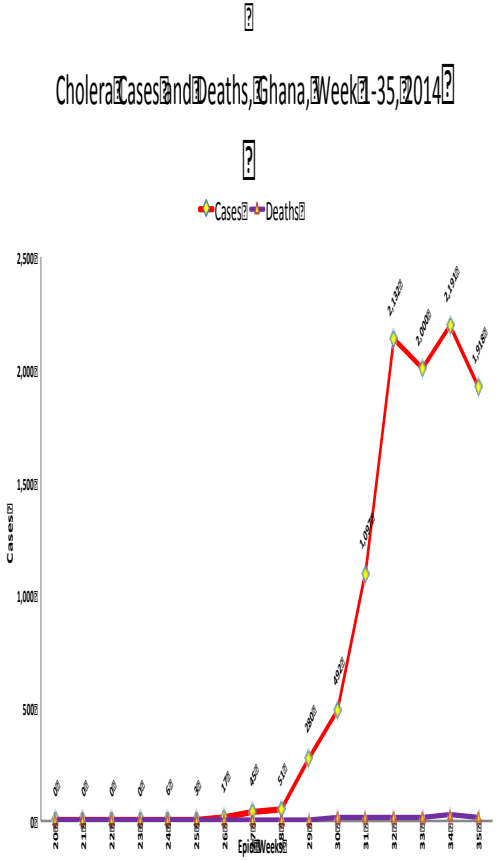
Centers for Disease Control and Prevention
1600 Clifton Rd
Atlanta, GA 30333

800-CDC-INFO
(800-232-4636)
TTY: (888) 232-6348

Cholera Outbreak: Could we have done research







Cholera Outbreak

- Could we have done research?
- Could we have tested whether Choramphenicol treatment in cholera is better than the standard in the outbreak.
- Could we publish the patient hospital records as a researcher during the out break?
- Can a technical officer located in at Amoma health centre conduct a clinical trial because there are cases?
- Could a doctor send patient records to a friend to analyse write a report?

Ethics in Outbreaks

Introduction

- What are out breaks
- What are ethics?
- What are ethical principles
- Ethical business behaviour
- Brief history of evolution of ethics in research
- Ethical principles
- Ethics in research
- Qualitative vs quantitative data

What are ethics?

- Societal norms adopted by a group
  - A conception of conduct that is right or wrong
- Deal with fundamental human relationships
- Are a universal human trait

Ethical Principles – What are they?

- Guides to moral behavior
  - Good: honesty, keeping promises, helping others, respective rights of others
  - Bad: lying, stealing, deceiving, harming others

- Universality of ethical principles: should apply in the same manner in all countries, cultures, communities

- Relativity of ethical principles: vary from country to country, community to community

Ethical Relativism

- Defined by
  - Various periods of time in history
  - A society's traditions
  - The special circumstances of the moment
  - Personal opinion

- Meaning given to ethics are relative to time, place, circumstance, and the person involved

Nuremberg

- During the Nuremberg War Crimes Trials, 23 German doctors were charged with crimes against humanity for:

- “performing medical experiments upon concentration camp inmates and other living human subjects, without their consent, in the course of which experiments the defendants committed the murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts.”

The Nuremberg Code (1947)

As part of the verdict, the Court enumerated some rules for "Permissible Medical Experiments", now known as the “Nuremberg Code”. These rules include:

- **voluntary consent**
- **benefits outweigh risks**
- **ability of the subject to terminate participation**

Tuskegee Syphilis Study

- American medical research conducted by the U.S. Public Health Service from 1932 to 1972.
- examined the natural course of untreated syphilis in black American men.
- They were not told that they had syphilis, nor were they offered effective treatment.

Tampa Tribune 3/11/00

- TAMPA - A lawsuit accusing USF doctors of experimenting on pregnant women without their consent is settled for $3.8 million…. The experiment wasn't considered risky and no adverse effects were documented, plaintiffs in the suit agree.
- However, the failure to inform … as many as 3,000 ... pregnant women of various experiments conducted between 1986 and 1990 has cost Tampa General Hospital, USF and the state $3.8 million.

Several others

- Thalidomide (late 1950s)
- Declaration of Helsinki (1964)
- Tearoom Trade (1960s)
- Milgram (1963)

Beecher Article

- 22 published medical studies presenting risk to subjects without their knowledge or approval
- Published in some of the most prestigious journals and conducted at some of the most prestigious institutions

Henry K. Beecher “Ethics and clinical research”
New Engl J Med 274 (1966):1354-60

Mechanisms of Protection

- Ethical regulations or guidelines
  - Ethics committees
- Law
- Universal principles of human rights

Ethical Principles

- In research, ethical principles help to make and to justify decisions
- They are abstract and difficult to implement in practical situations
- But key phrases are important:
  - Voluntary participation
  - Informed consent
  - Risk of harm
  - Confidentiality
  - Anonymity

Ethical Principles Guiding Research

- Respect for human dignity
- Respect for free and informed consent
- Respect for vulnerable persons
- Respect for privacy and confidentiality
- Respect for justice and inclusiveness
- Balancing harms and benefits
- Minimizing harm
- Maximizing benefit

1. Human Dignity

- **Cardinal Principle**
- Basis of ethical obligations
- Two essential components
  - The selection and achievement of morally acceptable ends
  - The morally acceptable means to those ends

Protect the multiple and interdependent interests of the person (bodily, psychological, cultural integrity)

2. Consent

- Presumption that individuals have capacity and right to make free and informed decisions
- In research = dialogue, process, rights, duties, requirements for free and informed consent by the research subject
- Your research **cannot** proceed without consent
- Consent **must be** maintained throughout

3. Vulnerable Persons

- Ethical obligations towards vulnerable persons
  - Diminished competence
  - Diminished decision-making capacity
- Entitled to special protection, special procedures to protect their interests
- Entitlement (based on grounds of human dignity, caring, solidarity, fairness) to special protection against abuse, exploitation, discrimination

4. Privacy & Confidentiality

- Fundamental to human dignity
- Standards protect the access, control, dissemination of personal information
- Helps to protect mental, psychological integrity

5. Harms and Benefits

- Balance critical to ethics of human research
- Foreseeable harms should not outweigh anticipated benefits
- Harms-benefits analysis affects welfare and rights of subjects

6. Justice and Inclusiveness

- i.e., fairness and equity
- Procedural justice
  - Application process
- Distributive justice
  - Harms and benefits

7. Non-malfeasance

- Duty to avoid, prevent or minimize harm
- No unnecessary risk of harm
- Participation must be essential to achieving scientifically and societally important aims that cannot be realized without the participation of human subjects
- Minimizing harm requires smallest number of human subjects that will ensure valid data

8. Beneficence

- The duty to benefit others
- The duty to maximize net benefits
- Produce benefits for subjects themselves, other individuals
- Produce benefits for society as a whole and for the advancement of knowledge (usually the primary benefit)

Being Pragmatic as a researcher in outbreaks

- Follow code of ethics
  - Objectivity
  - No misrepresentation
  - Preserve anonymity and confidentiality
  - Competing research proposals

Rights & Obligations of Subject

- A consensus on the following
  - Right to informed consent
  - Obligation to be truthful
  - Right to privacy
  - Right to confidentiality
  - Right to no harm
  - Right to be informed
  - Do not mis-represent data
  - Privacy
  - Commitment to research
  - Pseudo-pilot studies (understanding of Ebola)
  - Advocacy

Ethical issues in Ebola Outbreak

- Vaccines
  - Two vaccines

    Chimpanzee adenovirus serotype 3 (ChAD3-ZEBOV) and Recombinant vesicular stomatitis virus (rVSV-ZEBOV)
  - number of countries in Europe, in the US, Canada, Kenya, Gabon and Mali to test for safety and efficacy.

Experimental Ebola therapies raise ethical questions

Karen Weintraub, Special for USA TODAY 7:13 p.m. EDT August 7, 2014

(Photo: David Goldman, AP)

Two Americans with Ebola received at least half of the world's supply of a drug that might be able to change the course of the deadly virus.

Some people are asking how to allocate additional doses of this drug and whether it was ethical to give those drugs to American missionaries when they weren't available to West Africans suffering from or fighting the outbreak.

The World Health Organization will convene a panel of medical ethicists early next week to discuss the use of such experimental treatments. The group will probably decide how to allocate medications should more become available.

The use of the drugs for the Americans alone has struck a nerve for some in Africa.

The health minister of Nigeria, one of the four countries where Ebola has broken out,

Context

- All medicines are to be tested in clinical trials before approval for use in humans.
- Two health workers infected with the Ebola virus with experimental medicine that has never been tested and shown to be safe in humans

Key ethical questions

- Is it ethical to use unregistered interventions with unknown adverse effects for possible treatment or prophylaxis.
- If it is, what criteria and conditions need to be satisfied before they can be used?
- If it is ethical to use these unregistered interventions in the circumstances mentioned above, then what criteria should guide the choice of the intervention and who should receive priority for treatment or prevention?

WHO panel recommendation - 11 August 2014

- “the panel agreed unanimously that, in the exceptional situation of the current Ebola outbreak, there is an ethical imperative to offer the available experimental interventions that have shown promising results in the laboratory and in relevant animal models to patients and people at high risk of developing the disease, with the proviso that the conditions listed below are met”.

Conclusion

In the particular context of the current Ebola outbreak in West Africa, it is ethically acceptable to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention.

Ethical, scientific and pragmatic criteria must guide the provision of such interventions. The ethical criteria include transparency about all aspects of care, so that the maximum information is obtained about the effects of the interventions, fairness, promotion of cosmopolitan solidarity, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity, involvement of the community and risk–benefit assessment.

If and when unproven interventions that have not yet been evaluated for safety and efficacy in humans but have shown promising results in the laboratory and in animal models are used to treat patients, those involved have a moral obligation to collect and share all the scientifically relevant data generated, including from treatments provided for "compassionate use".

Researchers have a moral duty to evaluate these interventions (for treatment or prevention) in clinical trials that are of the best possible design in the current exceptional circumstances of the West African Ebola outbreak, in order to establish the safety and efficacy of the interventions or to provide evidence to stop their use. Continuous evaluation should guide future interventions.

Key issues in CT

- Regulatory requirements
  - Urgent requests
  - Expedited review
- Urgent measures to improve readiness for clinical trials and vaccines
  - Funding
  - Identify good and experienced investigators
- Liability
  - Group liability –WHO, funders, country

Key issues in CT

- **WHO 2014**
- “The meeting concluded that neither affected countries nor industry should be left alone to bear the burden should lawsuits arise following possible adverse reactions to an Ebola vaccine. To respond to this potential problem, a proposal was made to establish a “club” of donors, in collaboration with the World Bank”