Introduction to Clinical Trials

ACTC Conducting Oncology Clinical Trials in Africa II Webinar

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Objectives

- Understand the role of clinical trials in health
- Recognize the cancer epidemic facing Africa
- Learn how oncology clinical trials can help expand cancer care to people of African descent
- Recognize the basic requirements for conducting clinical trials
What Is a Clinical Trial?

A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention.
CLINICAL TRIALS (CTs)

- A CT 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

- To determine:
  - Effectiveness of intervention to treat a disease
  - Safety of a new drug
  - Define dose administration
  - Test drug formulation
  - Explore combination therapies
  - Evaluate effect of therapies on quality of life
In CTs, researchers take the results from basic scientific research and translate them into ways to prevent, treat, or diagnose disease.

From the conduction of the first recorded modern CT by Dr. James Lind in 1747, CTs the driving vehicle for bringing novel agents/device to the public.

Participation in CTs is a way to advance healthcare and improve clinical outcomes.

CTs emerging as an important tool in the arsenal to help mitigate some of the disparities seen in healthcare.
Have CTs improved healthcare?

- Formal record of clinical trials dates back to the “Trialists”:
  - Dr. Van Helmont’s proposal for a therapeutic trial of bloodletting for fevers [1628]
  - Dr. Lind’s, a ship surgeon, trial of oranges & limes for scurvy [1747]

- Historical Highlights of Drug Trials
  - 1909: Paul Ehrlich - Arsphenamine
  - 1929: Alexander Fleming - Penicillin
  - 1935: Gerhard Domagk - Sulfonamide
  - 1944: Schatz/Bugie/Waksman – Streptomycin
  - By 1950, the British Medical Res. Council developed a systematic methodology for studying & evaluating therapeutic interventions
CLINICAL TRIALS

• Per ClinicalTrials.gov, 310,728 trials being conducted worldwide
  – Most CTs conducted in high-resource countries like North America (44%) and Europe (28%).
    • In North America, most trials are conducted in the United States (US, 83%), accounting for ~40% of all CTs conducted globally

• Trend for migration of CTs to developing countries
  – more CTs now conducted in emerging markets of Asia, Latin America and Africa
  – CTs to Africa offers opportunity to address some of the health disparities noted around the globe
Figure 1. Distribution of clinical trials being conducted globally as of June 11, 2019 per ClinicalTrials.gov.

Source: http://ClinicalTrials.gov
Figure 1. Distribution of clinical trials being conducted globally as of June 11, 2019 per ClinicalTrials.gov.

Southeast Asia: 2%
South Asia: 2%
South America: 3%
Pacifica: 2%
North Asia: 2%
North America: 44%
Middle East: 4%
Europe: 28%
Central America: 1%
Africa: 3%
WORLD: 30%

Source: http://ClinicalTrials.gov
CTs in Developing Countries

• Lack of CTs in developing countries such as Africa is problematic
  – many citizens living in poverty

• Citizens bear a high burden of diseases
  • Africa constitutes 20% of the inhabitable earth
  • 1.2 billion people (16.7% of world’s population)
  • world’s poorest inhabited continent
  • life expectancy is <60 years esp SSA
  • average annual income is ~$2,041 USD or $5.60/day
    – This often puts basic healthcare out of the reach of most citizens
Figure 2. Distribution of clinical trials being conducted globally as of June 11, 2019 based upon population, GNP and country.

Source: http://ClinicalTrials.gov
Table 1. Internationally registered clinical trials based upon the WHO international registry ICTRP.

<table>
<thead>
<tr>
<th>COUNTRY/REGIONS</th>
<th># TRIALS</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td><strong>Globally Registered Clinical Trials by Region</strong></td>
<td></td>
<td></td>
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<tr>
<td>AFRO\textsuperscript{a}</td>
<td>8,687</td>
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<tr>
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<td>SERO\textsuperscript{e}</td>
<td>30,548</td>
<td>6.10</td>
</tr>
<tr>
<td>WRPO\textsuperscript{f}</td>
<td>123,311</td>
<td>24.60</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>501,526</strong></td>
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</table>
Cancer Stats in Africa

• Cancer incidence and mortality rapidly growing worldwide.
  – 17x10^9 new cases in 2018 and 9.5 x10^9 million cancer deaths worldwide.
    • 2nd leading cause of death worldwide, with about 1 in 6 deaths globally due to cancer
      – more than AIDS, TB and malaria combined

• >50% new cases and nearly 75% deaths will occur in Africa and developing countries
  – next 5 years, the annual number of new cases of cancer in Africa >1x10^9 one million with over half a million cancer deaths.
    • These numbers are expected to double by 2040

IARC 2019
Cancer in Africa
Under-representation in CTs

• Lack of CTs in Africa disturbing
  – Has large, ethnically diverse population that bear a high burden of many diseases
  – Populous often poor and can’t afford healthcare
  – Inadequately funded and staffed national, regional and local healthcare entities

• People of African descent under-represented in CTs
  – In US, AA constitutes ~6 of NIH-funded CTs
  – Globally, people of African descent represent <3% of CTs
  – Treatment often given to patients, has not been adequately tested in this patient population
Oncology CTs in Africa

• Increased conduction of oncology CTs in Africa offers benefits for not only the local populace, but the world at large
  – help identify biological underpinnings in cancer contributing to disparity
  – help to identify what cancer treatments are the most beneficial in people of African decent

• Thus, addressing the difficulties encountered in conduction CTs in Africa, could lead to globally impactful and innovative clinical science
Clinical Trial versus ‘Standard of Care’

- **Clinical Trial**
  - Involves human subjects
  - Test an ‘intervention’
    - be it a product, procedure or health care system….in order to improve standard of care!
  - Measures effects over a period of time
  - Most have a comparison CONTROL group
  - Must have method to measure intervention
    - *this is captured in the protocol and this must be stuck to meticulously if the question is to be answered!!*
  - Focuses on unknowns: effect of intervention
  - Must be done before medication is part of standard of care

- **Standard of Care**
  - all about clinical judgement decision/flexibility
  - trials need all to stick with the protocol, no deviation
  - within your clinical judgement
CLINICAL TRIALS

- CTs are a lucrative business
  - estimated at $44.2 billion USD
  - global CT market expected to reach more than $68 billion by 2026

- Cost of bringing a new drug to the market is between $637 million to $1.2 billion per drug
  - ~approximately 40% of drug development costs due to CTs conduction
  - oncology segment expected to experience the fastest growth

- Identifying avenues whereby safe, cost-effective CTs can be performed is a high priority for trial sponsors.
Types of Clinical Trials

- Treatment
  - Test new approaches to treat a disease
- Prevention
  - What approaches can prevent disease
- Early-detection/screening
  - What are new ways to find hidden disease
- Diagnostic
  - How can new tests or procedures ID disease
Timeline Estimate

- Below are some estimates on the amount of time it takes for this process in cancer treatment research.
  - Pre-clinical Trials - 4.5 years
  - Phases I-III - 8.5 years
  - FDA Approval - 1.5 years
  - Phase IV - Ongoing for the duration of the use of the drug

- How long is this whole process?
The Results!

• For approximately every 5,000 to 10,000 compounds that enter preclinical testing, only one is approved for marketing.

• Cost of the failures has to be borne by the price of the one success.
How Are CTs started?

1. Generate idea in a concept protocol
2. Discuss idea with peers and colleagues
3. Protocol review meeting open to all appropriate
4. Submit final protocol or grant application to sponsor
5. Prepare budget and other documents
6. Hire staff, write CRF, SOP’s, laboratory plans, Organise transport, Shipping and ordering. Monitoring plan
7. Ethical Review committees
8. Community engagement DSMB members & charter Source data, training records. Equipment ordering and servicing
9. Study Start!
Research Concepts

• In many studies, the new drug is compared to a **placebo**.

• A **placebo** is a product that looks like the new drug, but it does not have the active ingredient in it. People do not know that they are getting the placebo.

• Sometimes the test compares the new treatment against an existing treatment to see if better results can be obtained.
Research Concepts

- **Randomization** is the process by which patients are assigned a group for the Clinical Trial.

- Groups are assigned randomly, not purposefully.

- Some people will receive the new treatment, some may receive an already approved treatment, and some may receive a placebo.

- If one treatment is found superior, the trial is
Research Concepts

- **Blind and Double Blind Trials** are frequently done.

- A **Blind Trial** is a trial in which the patients do not know if they are receiving the treatment or a placebo.

- A **Double Blind Trial** is a trial in which the patients and the researchers do not know who is receiving the treatment.
So where do I start?

• **The protocol.**
  – Establishes the question
  – Ideally has just one and this is the **primary end point**.
  – Common failing is too many end points.
  – The best designed trials keep it simple as this make a clear answer more likely and easier to achieve

• **Secondary objectives**
  – a few related, appropriate secondary questions are normal as long as they do not distract from the primary
  – some might be exploratory

• **Trial is then designed around these objectives**
  – The protocol sets out how the questions will be answered
The Protocol....ALL IN THE TITLE

- Single center, placebo-controlled, etc etc

- Who is conducting the trial, who is sponsoring it, where is it to be conducted and on whom will you be conducting the research

- What are you testing? Is it safe, have the tests been validated? Why is this research needed

- What are the risks, what are the procedures, how will data be collected. How did you calculate how many patients you will need.
Because investigators have multiple legitimate interests, they have potential conflicts of interest.

- Independent review of the protocol minimizes these conflicts.

- Independent review also assures society it will not benefit from abuse of subjects.
Clinical Trials are Done in Phases:

- First, a Pre-Clinical Trial must be done before the Clinical Trial starts.

- **Preclinical trial**
  - research on a new drug or a new medical device or procedure
  - usually done on **animals**
    - learn about mechanisms of action
    - determine how well the treatment works
    - see if it is safe to test on humans
# Phases of Drug Development

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<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Patients</strong></td>
<td>15-30</td>
<td>&lt;100</td>
<td>100 to thousands</td>
<td>Several hundreds to several thousands</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>First in humans, Find safe dose</td>
<td>Determine efficacy</td>
<td>Compare new agent with standard treatment</td>
<td>Post – market, Long-term safety and efficacy</td>
</tr>
</tbody>
</table>
Phase I:

- Researchers test an experimental drug or treatment in a small group of people (approximately 20-80) for the first time.

- The purpose is to evaluate its safety and identify side effects. If this is a veterinary study, it is conducted in animals.
Phase II:

- The experimental drug or treatment is administered to a larger group of people/animals (approximately 100-300)

- To determine its **effectiveness** and to further evaluate its **safety**.
Phase III:

- The experimental drug or treatment is administered to a large group of people/animals (300-3,000 or more)
- To confirm its effectiveness
- To monitor side effects
- Compare it with standard or equivalent treatments.
Approval

• Once a drug has proven satisfactory after Phase III trials, the trial results are usually combined into a large document called IND:
  – a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life.

• This collection of information makes up the "regulatory submission":
  – provided for review to the appropriate regulatory authorities like the U.S. FDA
  – If approved, then sponsor can market the drug, device or treatment.
Phase IV:

- After a drug is licensed (approved by the FDA) or treatment is launched

- Researchers track its safety, seeking more information about a drug or treatment’s risks, benefits, and optimal use.

- These long-term studies involve large groups of participants
  - designed to reveal if any unexpected side effects occur in a small percentage of individuals.
Where do the people come from?

- Clinical Trials require people to volunteer to be tested! They are often paid.

- Would you volunteer to be a subject in a Clinical Trial?

- What if it meant you received a treatment for a disease that wasn’t available to anyone else?
Human Research is Highly Regulated

- Code of Federal Regulations (CFR)
  - Title 21- Food and Drugs
    - Part 50  Informed Consent
    - Part 56  IRB
    - Part 312  IND
    - Part 314  NDA
    - Part 600, 6001  Biologics
    - Part 812, 813, 814  Medical Devices

- Title 45- Public Welfare
  - Part 46 (subparts B, C, D)  DHHS, Protection of Human subjects
Why is Human Research Highly Regulated?

- Past transgressions lead to the need for laws that protect the rights and welfare of human subjects.
  - Nuremberg Doctors Trial of 1946 (Nuremberg Code)
  - Thalidomide Tragedy (Kefauver-Harris Amendment)
  - Tuskegee Experiments (Belmont Report)
  - Human Radiation Experiments
  - Gene Transfer Experiment
Timeline Of Events

- Landmark events
  - Tuskegee Syphilis Study (1932-72)- alternative treatments were not made known
  - Nazi experiments on cold water survival- (1933-45) is it ethical to publish or use the data?
  - Willowbrook hepatitis studies (1956-72)- vulnerable subjects infected with hepatitis with no consent
  - Jewish Chronic Disease Hospital studies of cancer cell injection (1963)-vulnerable subjects, no consent
Timeline Of Response: Ethics Lag Behind

Tuskegee 1932
Nazi 1933
Tuskegee 1947
Nuremberg

Jewish Chronic Disease Hosp 1956
Willowbrook 1963

Nazi 1979
Willowbrook

Helsinki 1964
Belmont 1979
Codes Of Research Ethics

- Nuremberg Code (1947)
  - Informed voluntary consent, societal value, risk to be taken should never exceed that determined by the social or humanitarian importance of the problem to be solved by the experiment
  - Risk benefit not addressed
Codes Of Research Ethics

• Declaration of Helsinki (orig. 1964 and revised 5 times, latest 2000)
  – Respect for the individual
  – Right to self determination
  – Right to make informed decisions (informed consent)
  – Needs of subject always comes before needs of society
  – Written protocol, independent review
• Clinical research should be based on animal and laboratory experiments.

• Clinical research should be conducted and supervised only by qualified medical workers.

• Clinical research should be preceded by a careful assessment of risks and benefits to the patient.

• Human beings should be fully informed and must freely consent to the research.
Tuskegee Study

- Time Frame: Began in 1932 – *Ended in 1972*
  - 399 African American men joined the study with the US PHS for free medical service
  - Their disease was followed without treatment
  - The subjects were not informed of what was being studied or of the treatment alternatives available.
  - Penicillin – was available to the public in 1947

Outcomes:
- 28 men had died of syphilis
- 100 others were dead of related complications
- At least 40 wives had been infected
- 19 children had contracted the disease at birth
Belmont Report (1979)

- **Respect for Persons**
  - individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection

- **Beneficence**
  - Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being.

- **Justice**
  - An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed.
Ethical Challenge: Need for international guidelines for CTs

• The most frequently sited reason for lack of CT conduction sited was ethics
  – Due to conduction of several questionable CTs in Africa, the international research community not eager for migration
  – Thus, must make sure CTs in Africa are conducted according to international guidelines

• Agreement between countries that there needed to be a global standard by which all trial are conducted
  – This is Good Clinical Practice (GCP)
  – protects those in a trial, but also those who’s treatment will depend on the data
What About International Regulation?

• E6 Good Clinical Practice (GCP): Consolidated Guidance
  - International ethical and scientific quality standard for designing, conducting, recording and reporting trial results.
  - Essentially ensures that the rights of the patient are protected and by all those given a drug or intervention in the future based upon that data.
Ethical Challenge: Definition of ICH-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.”

Drafted by the International Council of Harmonisation (ICH GCP)
Informed Consent (IC)

- IC ensures individuals decide whether they enroll in research and whether research fits with their own values, interests, and goals.
  - For those who cannot consent, ie children & mentally impaired, must be sure research fits with their interests.

- Is dynamic process that adapts to new information discovered by investigators during the course of the trial
  - whether from the trial or other sources.

- Updating of informed consent is often required during the course of a clinical trial.
Informed Consent

The Federal regulations require 8 elements be included in each informed consent form.

1) Purpose and duration of participation
2) Risks
3) Alternatives
4) Benefits
5) Confidentiality of records
6) Compensation for injuries
7) Person to contact for answers to questions
8) Voluntariness and right to withdraw
Risk:Benefit Information for IC

• The consent form should have language that an adult with a 10th grade education would understand and describes **why?** the research will be conducted and **how?**

• The **risks and potential benefits** should be clearly described to the subject/patient in language and reasoning he/she can understand.
Risk/Benefit Balance

- Risks could include drug toxicity, lack of efficacy, risk of biopsies, risk of imaging technology
- Potential complications of therapy including hospitalization or even death
- Time, anxiety, financial costs
Consent

• Once the risks and benefits have been described the subject/patient should be as free as possible from coercion from any source.

• The subject/patient should be aware of accepted alternatives to the clinical trial.
Probability of Efficacy

• Even though we don’t know whether there is clinical efficacy, there’s a probability based on preclinical and clinical data that the intervention could have some efficacy

• Freedom to make choices
Risk/Benefit Balance

- To approve a study, the IRB must find that
  - “risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result”

45 CFR 46.111(a)(2)
Ethical Requirements

• Ethical guidance is needed to prevent exploitation of subjects in research

• Use a systematic approach to determine whether a study is ethical

• Balancing of principles when applied to particular trials can be complex

• Clarity about conflicts of interest can help investigators navigate this difficult issue
Subject Data Collection

- Data is collected on case report forms (CRF)

- Much of clinical data is taken from the subjects medical record (source documents)

- Pharmaceutical and device trials, data is verified by multiple players
The Case Record Form

• Turns the protocol into your data capture system

• Should only collect data listed in the protocol and nothing else... i.e unless you will use ‘weight’ and have set out to do so, no need to record. Often far too long and collects data that is not used.

• Differs from the source data - patient notes and lab reports. This is a central concept in GCP that data is always verifiable

• Data taken from here and entered into a database and then exported to statistical package. Important to keep CRFs to allow you to go back and resolve data queries
Database and Statistics

• Need stats advice right at the start
  – Helps you decide on the all important ‘n’
  – How will you randomize--maybe you don’t need 1:1.
  – Time, cost and ethics – but you still need to answer the question

• Protocol needs to explain statistical objectives of your trial
  – it is the report and analysis plan sets out how you will analysis the data.
  – Must be finalized before database close to avoid risk of manipulating the data

• Database should be secure and have an audit trial
  – Currently difficult in non-commercial trials
Adverse Event (AE) Reporting

• Any untoward medical occurrence in a patient who receives either an investigation agent or takes place in an investigational procedure or test.

• An adverse event does not always show relationship to the research investigation. It could be due to concurrent illness.

• Serious adverse events (SAE’s) are those that include the following:
  – Events resulting in death
  – Life threatening events
  – Permanently disabling events
  – Events requiring hospitalization
  – Events resulting in persistent disability or incapacity
Clinical Trial End Product

- Ideal: Unambiguous conclusion regarding the clinical outcome of the test treatment/device.

- Always strive for the ideal, but in most cases have to settle for the best comprise.
Basic of conducting a CTs

• Write a good protocol - Weigh risks vs. benefits
• Obtain IRB/IEC approvals
• Protect the subjects –
  – Obtain Informed Consent,
  – Ensure safety, rights & confidentiality
• Use qualified study team
• Handle investigational products appropriately
• Implement quality systems
• Record and analyze information appropriately
• Follow the protocol and trial SOP’s!!!!
CONCLUSION

• Multinational cancer trials in Africa is a imperative from a scientific, logistical, economical, and moral viewpoint.
  – balance between all stakeholders
    • sponsor and government provisions, institutional requirements, and ethics makes the relation between business, science, and healthcare complex

• Critical for participation of local investigators in the design and management of CTs and publishing of results
  – way to safeguard the intricate pathway towards good research, equity in access to cancer care, and improved patient outcomes worldwide.
References

NCI website on Ethics in Clinical Trials
http://clinicalcenter.nih.gov/recruit/ethics.html

Clinicaltrials.gov

https://www.who.int/ictrp

http://worldpopulationreview.com