CTI CLINICAL TRIAL & CONSULTING

Celebrating 20 years of life-changing work

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Laying the Foundation for Clinical Research Excellence

Excellence in Clinical Research – Let's See How Far We've Come!

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Introductions

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- Master of Science, Miami University

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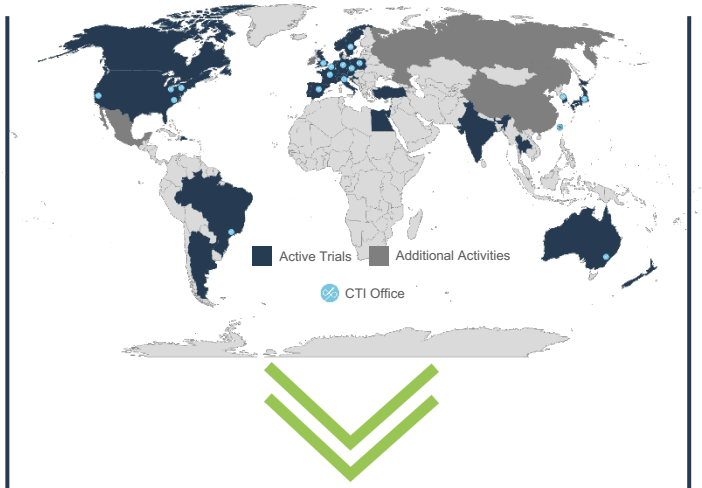
- Bachelor of Science, University of North Carolina at Chapel Hill

Who Is CTI?

CTI is a **FULL SERVICE** **GLOBAL** CRO



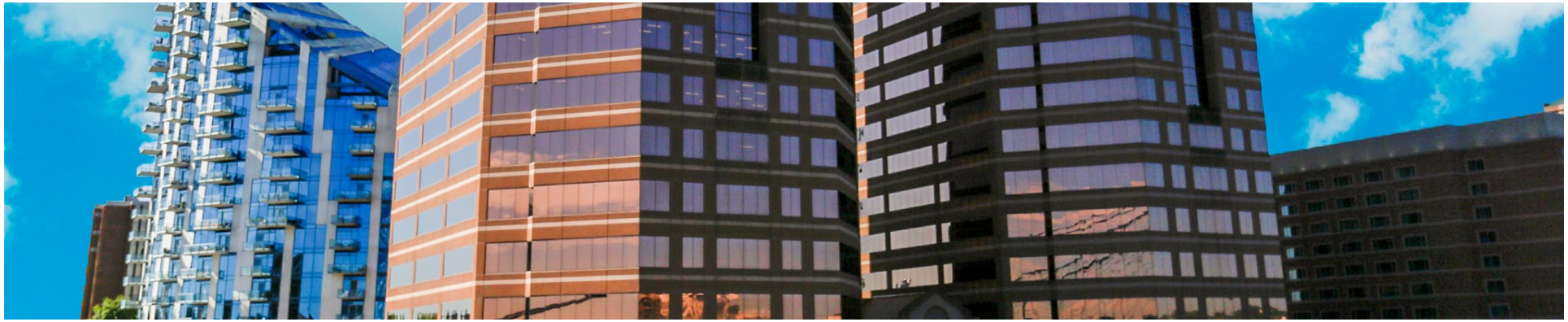
- Associates in more than 35 countries
- Consistent 15% growth rate over the last several years

Specializing in life-changing therapies for **COMPLEX** and **CRITICALLY ILL PATIENT POPULATIONS**

- Rare/Orphan Disease
- Regenerative Medicine
- Gene Therapies
- Immunology
- Transplantation
- Nephrology
- Hematology & Oncology
- Neurology & Sleep Research
- Infectious Diseases
- Hepatology
- Cardiopulmonary
- Pediatric & Neonate Populations
- Devices

CTI Mission Statement

"Our mission is to deliver outstanding customer service, execute high quality projects on-time and on-budget, and conduct trials that benefit the lives of critically and chronically ill patients."



What We Will Discuss…

- Clinical Research History and Firsts
- Current Trends in Clinical Research
- Trends for Excellence
- Patient-Focused Research
- Wrap-up
- Questions

Clinical Research History and Firsts

Evolution of Research

- Long History
  - Food to drugs
- Challenges
  - Scientific
  - Ethical
  - Regulatory
- Groundbreaking
- Adaptable
- Regulation and Protection
  - Tragic outcomes

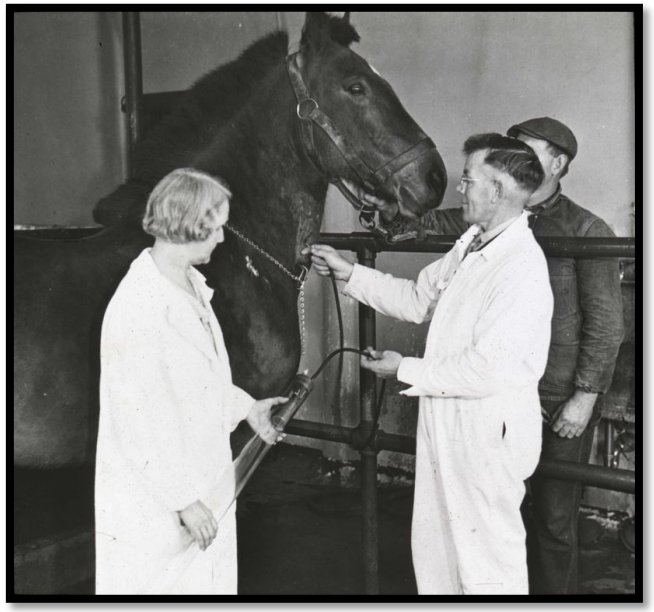
James Lind and Scurvy Trial – 1747

- One of the first clinical experiments in medicine
- James Lind – MD in British Navy
- 1400 / 1900 sailors died of scurvy
- Designed his own experiment
  - 12 sailors divided into 6 groups
  - Each group received different supplement
  - Citrus group had positive effects recovering almost immediately

- Pioneer of naval hygiene
- His work advanced the practice of preventive medicine and improved nutrition

A Horse Named Jim – 1901

- Jim was used to produce serum containing diphtheria antitoxin
- 13 children died after receiving the antitoxin
  - Discovered Jim had contracted tetanus
- Tragedy promoted Congress to pass the **Biologics Control Act of 1902**
  - **Regulatory power over antitoxin and vaccine development**



Food and Drug Act – 1906

- Study conducted on food preservatives and dyes
  - Discovered some were poisonous
- Public outcry
- Act prohibited interstate commerce of misbranded or adulterated food, drug, and drinks
- Mandated truth-in-labeling
  - Monitoring food purity and safety of medicines
- Did not monitor false health claims
- First federal food and drug statute

Food and Drug Administration – 1931

- Increased regulation of food and drug marketing
- Formally called the Bureau of Chemistry and the Food, Drug, Insecticide Administration
- Federal agency of the US Health and Human Services empowered by Congress
- Responsible for protecting and promoting public health through control and supervision of many items in our day-to-day life
- Led by the Commissioner of Food and Drug
  - Reports to Secretary of Health and Human Services
  - Appointed by President (consent of Senate)
  - Headquartered in White Oak, Maryland

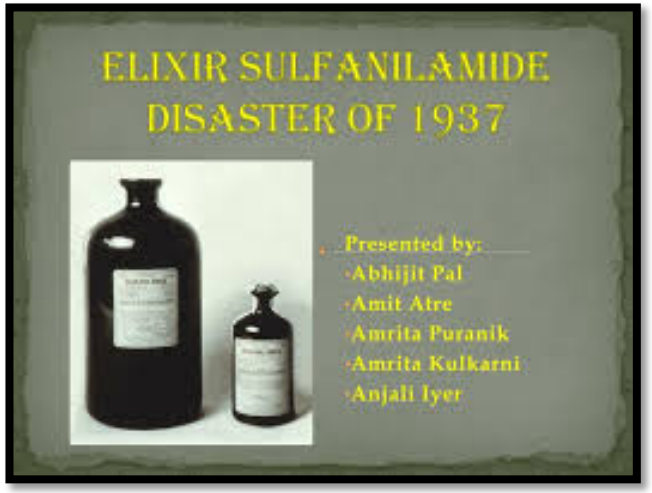
Tuskegee Syphilis Study – 1932

- Infamous, unethical clinical study (1932-1972) – 40 years
- Study to treat “bad blood”, real purpose was to observe natural progression of untreated syphilis
- Rural African American Males from Alabama (airmen)
- Enrolled under false pretenses and not informed
- 431 with syphilis, 169 without
- 1947 penicillin was discovered but subjects were never treated
- Led to the 1979 Belmont Report and establishment of the Office for Human Research Protections (OHRP)

OHRP
OFFICE FOR HUMAN RESEARCH PROTECTIONS

Sulfanilamide Elixir – 1937

- Introduced 2 years earlier to fight bacterial infections
- “Wonder drug” – deadliest mass poisonings of the 20th century
- Drug was produced as a pill – very hard for children to take
- Chemist – Harold Cole Watkins liquefied the drug by dissolving it in diethylene glycol
  - Was not tested (not required at that time)
- Over 100 patients died (mostly children)
- Removed from market due to mislabeling
  - “elixir” – alcohol based
  - Ended up being antifreeze solution



Food, Drug, and Cosmetic Act – 1938

- Followed the Sulfanilamide disaster
- Passed by Congress
  - Requires proof of safety before release of a new drug
  - Adequate directions for safe use of product
  - Extended control to include cosmetics and medical devices
- Extensively amended throughout the years
  - Remains the foundation of FDA regulatory authority to this day
- New Drug Application creation (NDA)

World War II Era – 1939 to 1945

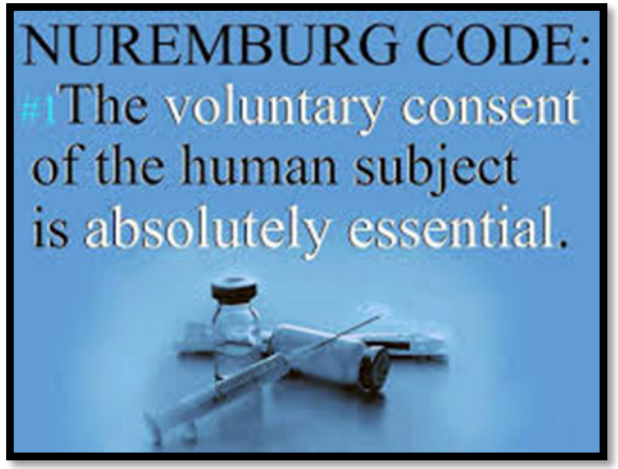
- Experiments performed by Nazi Germany on non-German civilians and prisoners of war
- Conducted without consent
- No benefits
  - Many deaths occurred, trauma, disfigurement
- Included things such as sterilization, euthanasia, temperature / altitude extremes, untested drugs
  - Medical torture
- US led prosecution in the Doctor's Trial

Doctor's Trial – 1946

- 20 German physicians and 3 Nazi officials put on trial for crimes against humanity
- Accused of conducting experiments on prisoners without their consent as well as euthanasia
- 10 ethical principals were drafted known as the **Nuremburg Code**
  - Prototype for future codes to assure human research is conducted in an ethical manner
- 140 days, 85 witnesses, 1500 documents were introduced as evidence
  - 16 out of 23 defendants were found guilty
    7 were executed

Nuremburg Code – 1947

1. Voluntary Consent is essential
2. Results are for the good of society
3. Trials must be based on animal experiments and knowledge of the natural history of the disease or condition
4. Trials must avoid unnecessary physical and mental suffering
5. Trials must not be conducted if injury or death is expected
6. Risks must be less than the importance of the problem
7. Subjects must be protected from harm or injury
8. Trials must be conducted by qualified people
9. Subjects have the freedom to stop at any time
10. Investigators have an obligation to stop if harm occurs



Thalidomide – late 1950's

- Sleep and morning sickness drug marketed in Europe
- German manufacturer claimed it was non-addictive, no hang-over and was safe for pregnant women
- Sold over-the-counter in Germany (1957) and then broader is EU, South America, Canada, etc
- 10 years later, German physician noticed an increased number of babies with birth defects
  - German health authorities traced the defects back to Thalidomide and it was pulled from market, other countries followed
- US – not approved but was being used in research with women ~ 1000 physicians
  - No requirement to notify FDA of investigational use

Declaration of Helsinki – 1964

- Expands on the principals of Nuremberg Code
  - Worldwide recommendations to guide physicians on conducting biomedical research involving humans
- Developed by the World Medical Associate
- Cornerstone of human research ethics
- 6 revisions to date (major revision in 2008)
- Focus is on research subjects right to determine their participation and their right to make informed decisions
- Powerful statements
  - Rights of human subjects should never be compromised for the sake of science

Declaration of Helsinki – 1964 *continued*

- Duty of physicians to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information
- Medical research involving humans must conform to generally accepted scientific principals, and be based on thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation
  - Welfare of animals used for research must be respected
- Caution must be exercised in the conduct of medical research that may harm the environment
- Protocol described for the first time – protocol considerations must be clearly described
  - Funding, sponsor, affiliations, conflicts of interest, incentives, compensation for injury

Declaration of Helsinki – 1964 *continued*

- Submission of protocol to ethics for review prior to study start
  - Independent review, free from undue influence
  - Governed by laws and regulations of the country/ies and follow international norms and standards
  - Committee can continue to monitor ongoing for safety
  - No change to research protocol can be made without considerations and approval by the committee
- Human studies conducted by qualified individuals with appropriate scientific training – must protect subjects
- Vulnerable populations or communities justified only if the research is responsive to the health needs and priorities of this population or community or they stand to benefit from the research results
- Risk assessment (benefits outweigh the risk)
- Research is publically registered prior to 1st subject recruited
- Stop research if risks outweigh benefits at any time, or when there is conclusive proof of positive and beneficial results

Declaration of Helsinki – 1964 *continued*

- Informed consent must be voluntary and contain essential elements (written / verbal in some cases)
  - Assent
  - Legally authorized representative
- Confidentiality of participation and privacy protection

- Publication (authors, editors, and publishers) also have ethical obligations to make public the results and it must be complete and accurate
  - Includes sources of funding, institutional affiliations, and conflicts of interest
  - Report negative, positive, and inconclusive results
- Section C – combining medical research and medical care

National Research Act – 1974

- In response to the Tuskegee study and other unethical trials
- Signed into law in 1974
- Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Over 5 years, several reports were commissioned and identified principals related to research involving
  - Fetuses
  - Prisoners
  - Children
  - Mentally infirmed subjects
- Issued the Belmont Report in 1979

Belmont Report – 1979

- A statement of basic ethical principals and guidelines for the protection of human subjects
- Timeless and foundation of what we do today
- Contains guiding principals, analytical framework, and helps to resolve ethical problems related to research
- Part B – 3 basic principals
  - **Respect for Persons** – respect for the decisions of autonomous individuals and protection of those with diminished autonomy
  - **Beneficence** – obligation to do NO harm – maximize benefits, minimize harm – Hippocratic Oath references
  - **Justice** – fair and equal distribution of clinical research burdens and benefits

Early 80s and 90s

- Orphan Drug Act – 1983
- Food and Drug Administration became part of the Department of Health and Human Services
  - Commissioner – appointed by President
- Safe Medical Devices Act – 1990
- International Conference on Harmonisation (ICH) – 1990
  - EU, Japan, and US – plans to harmonize globally regulatory requirements to reduce duplication, save time, and decrease costs for processes / procedures to market products internationally
  - Ensure quality, safety, and efficacy

Early 80s and 90s *continued*

- Pediatric Rule – 1997
- FDA Modernization Act (FDAMA) – 1997
- ICH E6 Good Clinical Practice (GCP) Consolidate Guidance – 1997
  - Effective guideline to ensure proper conduct of clinical research
  - Allows outside US clinical study data to be accepted by FDA if performed under ICH guidelines

ICH GCP Guidelines – 1997

- FDA adopted a number of these including E6 (1997) – Good Clinical Practice (GCP)
- Guidelines are recommendations on how clinical research should be conducted
  - Ongoing guidance documents written by FDA
    - FDA's current thinking on a topic (known as information sheets)
    - Can be found at www.fda.gov
- ICH E6 has been adopted for trials conducted in US
- International standards to promote greater harmonization of technical guidelines
- Completely or fully adopted by many countries

Good Clinical Practice (GCP)

- Standards for conducting clinical research studies
- Goal is to protect public health and the rights, welfare, and confidentiality of research participants
- Ensure all data and reported results are credible and accurate
- Includes
  - Regulations enforceable by law
  - Guidelines that are a generally accepted practice but not enforceable by law
  - Local laws affecting a specific region, city, state

2000s to Now

- Privacy Rule – implement requirements for HIPAA – 2000
- Best Pharmaceuticals for Children Act – 2002
- Pediatric Research Equity Act – 2003
- Public Registry of Clinical Trial Data – 2005
- FDA Amendments Act – 2007
  - Clinicaltrials.gov
- NIH Public Access Policy – 2008
- **ICH E6 R2 – 2016**

Improving Clinical Research through Experience

- Transition from paper files to electronic Trial Master File (eTMF)
- Introduction of emergency medical record (EMR) at sites
- Paper case report forms (CRFs) to electronic data capture (EDC)
- Clinical Trial Management System (CTMS)
- Remote monitoring
- Trial and error

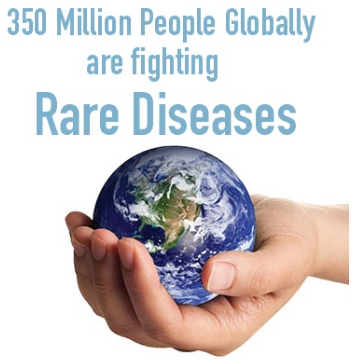
Where Are We Now?
Current Trends in Clinical Research

Medical Device

- Organ Perfusion
  - Ex Vivo Lung Perfusion – perfusing “trash” lungs to determine if fit for transplant
  - Saving lives by increasing number of donor organs
  - Xenotransplantation – pig organs repurposed for human transplant
- AV Grafts
  - Improving kidney dialysis graft survival by introducing new materials and methods
  - Patient quality of life (QoL) may be drastically improved
  - In some instances, greater risk but can have greater patient outcomes

Rare Disease

- Definition of Rare Disease
  - US: A disease or disorder that affects fewer than 200,000 Americans at any given time
  - EU: A disease or disorder that affects fewer than 1 in 2000
- Some Facts
  - 80% of rare diseases have identified genetic origins
  - Others are the result of infections (bacterial or viral), allergies and environmental causes, or are degenerative and proliferative
  - 50% of rare diseases touch children
  - It is estimated that there are 6000 to 7000 rare disease affecting approximately 350 million patients globally (25-30 million in US)
  - Typically these diseases are serious, progressive, and often life-threatening
  - Most do not have treatment options
  - Government policies and incentives have lead pharmaceutical companies to the development of orphan drugs, leading to many new trials in the rare disease space



Cell and Gene Therapy

- First approved gene therapy clinical research in the US took place on 14 Sep 1990
  - National Institutes of Health (NIH), under the direction of William French Anderson
  - 4-year-old Ashanti DeSilva received treatment for a genetic defect that left her with ADA-SCID, a severe immune system deficiency
- Hunter Syndrome – Mucopolysaccharidosis (MPS) II
  - Rare genetic disease – affects less than 500 boys in the US
  - Missing an enzyme used to break down cellular waste; waste builds up, and leads to progressive damage throughout their bodies
  - Some never develop speech, but some boys learn like a typical child then begin losing skills and what they've learned at a young age
  - Eventually lose the ability to walk, talk and eat; most do not live to see their teen years

Project Alive – Hunter Syndrome

- Researchers are in the final stages of developing the first gene therapy clinical trial for boys with Hunter Syndrome
- One-time delivery of a normal copy of the defective gene which ideally causes the body to naturally produce the missing enzyme
- Considered an orphan-drug
- In development at Nationwide Children's in Columbus, Ohio
- Project Alive founded by parents working to fund a cure

Trends for Excellence

The Backbone – Clinical Research Coordinators

- Communication
  - Effective and often
- Collaboration
  - PI and Investigators
  - Sponsor and CRO partners
- Connection
  - Empowered
  - Accountable
- Commitment
  - Resourceful
  - Patient experience always in mind
- Coordination
  - Patients, protocol, data

https://acrpnet.org/2018/08/14/the-anatomy-of-a-great-clinical-research-coordinator/

Clinical Research Organizations (CROs)

- Provides support to the pharmaceutical, biotechnology, and medical device industries
- Services outsourced on a contracted basis
- Grew when Pharma companies needed to decrease overhead
- Opted for outsourcing solutions – transfer of services to outside vendors (Clinical Monitoring, Safety, Data, Regulatory)
- Range from large, international full-service organizations to small, niche specialty CROs

Sponsors

- Oversees, funds, and collects and analyzes the data for a clinical trial
- Manages quality and risk control
  - Selects the Investigator(s)
    - Provides Investigator(s) with the required information to conduct the clinical trial
  - Ensures proper monitoring of the clinical study
  - Ensures all the necessary ethic review(s) and approval(s) are obtained
    - Ensures any reviewing ethics board and regulatory agencies are promptly informed of any significant new information
  - Prepares and submits to the appropriate regulatory agencies
  - Ensures compliance with labeling, reporting, and record-keeping requirements
  - Ensured the clinical study is conducted in accordance with Good Clinical Practice (GCP)

Investigators

- Importance of understanding responsibilities
  - Protect the rights, safety, and welfare of subjects
  - Ensure subjects provide informed consent prior to participation
  - Ensure compliance with all requirements of the protocol
  - Ensure all colleagues are informed and trained in their study responsibilities
  - Control drug / device under investigation
  - Maintain adequate records
  - Ensure Institutional Review Board (IRB) / Ethics Committee (EC) review and approval
- Pass along research knowledge through training and mentoring

Responsibilities in Clinical Trials

Improvement
in Patient Care

Success Requires:

- Partnerships
- Collaboration
- Teamwork
- Commitment

Excellence in Training

- “Do It Right the First Time”
- Shortage of experienced staff
- Mentoring
  - Right knowledge and the right attitude
- Delegation of Authority
  - Role-based training
  - PI oversight

Standardization and Processes

- Principal Investigator (PI) Oversight Plans
  - Involvement and availability
- Challenges in Global Standardization
  - Communication
  - Global Standard Operating Procedures (GSOPs)

Remembering Our Purpose . . . the Patient

- Cures vs Quality of Life (QoL) improvement therapies
- Patient experience should remain the focus of research and its processes
- Research evolving to aid in rare diseases and smaller populations with novel therapies in cell and gene therapy
  - MPS II
  - Ex Vivo Lung Perfusion (EVLP)

Wrapping Up…

- The idea of research started with a **desire to help!**
- Clinical research history is not without its share of unfortunate outcomes and mistakes…many **lessons learned**
- **Regulation** and improvements in systems and processes
- **Experience** has led to improved research processes, practices, and patient outcomes
- **Excellence** is found when all parties own their responsibilities, and collaborate and communicate
- Common goal should always be improving the quality of life and delivering cures to our **PATIENTS!**

Questions?

THANK YOU!