Clinical Trials 101

ASPIRE webinar 2024

E. Claire Dees, MD
Professor of Medicine
Co-leader Clinical Research Program
UNC Lineberger Comprehensive Cancer Center

Claire_Dees@med.unc.edu

Outline

- What is a clinical trial?
- What are the different phases of clinical trials?
  - A little departure about phase I oncology clinical trials
- What are the important documents pertaining to clinical trials?
- Who is the clinical trial team?
- How is patient safety assessed?
- What are the protections in place for clinical trial participants?
- How can we improve diversity in clinical trial enrollment?
- What are issues and challenges about enrollment, recruitment and trial management and follow up?
- What are some examples of UNC ground-breaking trials?

Why are Clinical Trials important?

- > 1.6 Million new cases of cancer are diagnosed in the US annually
- ~600K people die of cancer each year

- Despite all the recent advances in chemotherapy and treatment, still almost half of all cancer patients die of their disease
- Clearly new treatments are needed!
- Clinical Trials are the way we can evaluate and test new drugs and new approaches in a scientifically and statistically sound way

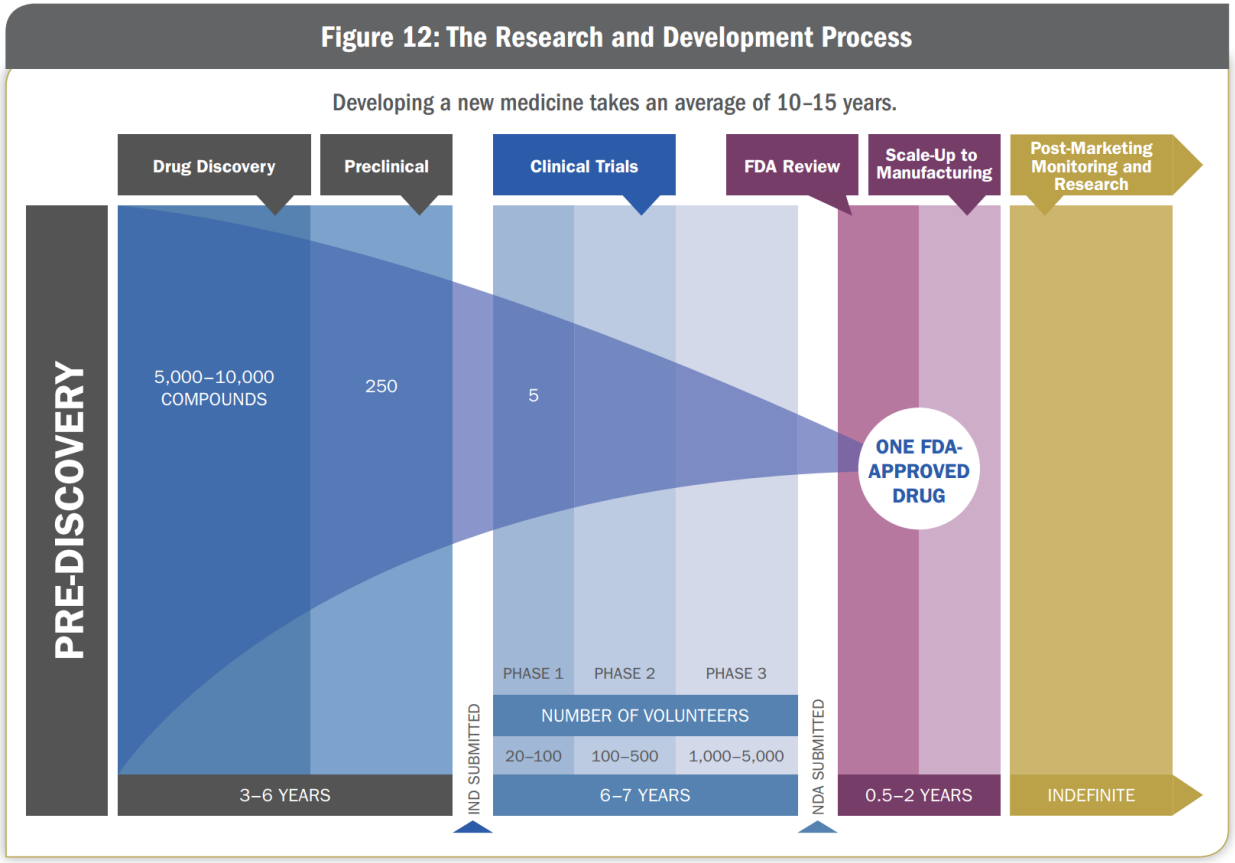
Clinical Trials – NIH definition

- A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about interventions (new drugs, treatments, devices, or new ways of using known drugs, treatments, or devices)
- Clinical trials are used to determine whether new biomedical or behavioral interventions are safe and effective
- Through clinical trials, we can find new ways to improve treatments and the quality of life for people with disease.

Phases of clinical trials

- **Phase 1**
- Purpose:
  - To find a safe dose
  - To explore how the new treatment affects the human body (toxicity) and fights cancer (efficacy)
- Number of people taking part: 15–30
- **Phase 2**
- Purpose:
  - To determine how effective the new treatment is in treating cancer
  - To obtain more information on how the new treatment affects the body and treats cancer
- Number of people taking part: Less than 100
- **Phase 3**
- Purpose:
  - To compare the new treatment (or new use of a treatment) with the current standard treatment (often includes randomization) SOC vs new treatment.
  - Number of people taking part could be >100- 1000s

Timeline of a new cancer therapy



SOURCE: Pharmaceutical Research and Manufacturers of America, Drug Discovery and Development: Understanding the R&D Process, www.innovation.org.

In the modern era of more targeted therapies, sometimes FDA has granted approval based on several phase I trials (Larotrectinib) but that only shortens the timelines by a couple years

What is a Phase I Study?

- First evaluation of a new therapy in humans
  - In oncology – cancer patients
- Objectives:
  - Identify dose-limiting toxicities (DLT)
  - Identify the maximum tolerated dose (MTD)
  - Assess pharmacokinetics (drug metabolism and clearance)
- Schedule based on preclinical profile
  mouse studies
- Dose and escalation scheme are a balance between safety and speed
- Eligibility: patients with advanced malignancy refractory to standard therapy or for which no effective therapy exists

Pharmacokinetics
"what the body does to the drug"

- Mathematical description of the behavior of drug and metabolites
- Provides information on:
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
- Goal is to characterize the drug metabolism and clearance
- Variability within and between patients

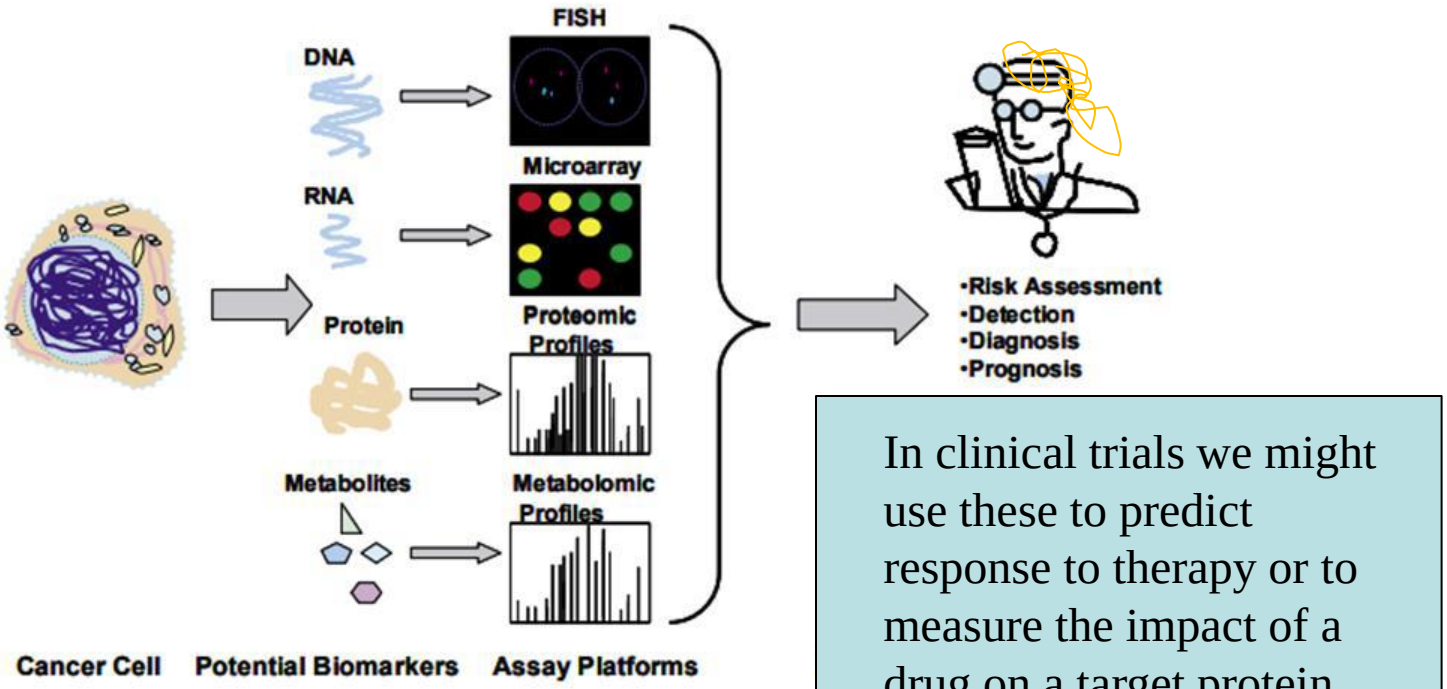
Pharmacodynamics
"what the drug does to the body"

- Both toxic and therapeutic response
- Variables to consider
  - Peak effect, time to effect, duration of effect
  - Response, TTP, survival, serum markers
- PK-PD relationship
  - May be helpful in defining the therapeutic range, choosing the most appropriate schedule

Phase I Trials of Novel Targeted Agents

- MTD may not be the goal of the Phase I trial
  - Targeted agents may not have traditional toxicities
  - Specificity of effect may be lost at MTD
  - Pharmacologic effect may ≠ biologic effect
- Goal: identify optimal biologically effective dose (Not MTD)
- Requires early development and integration of measures of **biologic effect** into Phase I
- **Requires collection of biological specimens to detect drug effect at the cellular level**
- Enrollment may be restricted to those whose tumors have "the target" and thus would be most likely to benefit, even in the phase I trials

What is a biomarker? And why is tissue collection important ?



In clinical trials we might use these to predict response to therapy or to measure the impact of a drug on a target protein

Maruvada, P., Wang, W., Wagner, P. D., & Srivastava, S. (2005). Biomarkers in molecular medicine: cancer detection and diagnosis. BioTechniques, Suppl, 9–15.
Courtesy of Elena Schwartz NCI

Biomarkers, Molecular Diagnostics and Surrogate Endpoints can help us…

- Identify and validate therapeutic targets
- Screen and optimize candidate agents
- Provide proof of concept for agents and models
- Enhance understanding of mechanism and pathways
- Identify optimal target populations
- Predict response, resistance and toxicity
- Rapidly distinguish responders from non-responders

CCR March 2012 “Leveling the playing field: bringing development of biomarkers and molecular diagnostics up to the standards for drug development

However

- **This effort requires considerable**
  - **collaboration across disciplines**
  - **logistical planning**
  - **commitment**
  - **patience**
  - **money**

- **AND of course, contributions by study participants.**

What are the steps to "run a trial"

1. Design the trial.
2. Write the protocol.
3. Shepherd the trial through regulatory approval and contracts.
4. Build a team.
5. Conduct the trial. Analyze the data. Write it up!

Key Clinical Trial Documents/Resources

- Protocol
  - Includes eligibility criteria
  - Schedule of Events
- Informed consent
- Assessment of adverse events (CTCAE)
- Investigator brochure
- IRB application
- IND (if needed)

What is a Protocol?

- Document that provides road map to your study
- The reason for doing the trial
- Who can join the trial (called “eligibility criteria”)
- How many people are needed for the trial
- Any drugs or other treatments that will be given, how they will be given, the dose, and how often
- What medical tests will be done and how often
- What types of information will be collected about the people taking part
- Ensures study is conducted appropriately and consistently across team members and sites
- Ensures safety of study subjects and integrity of data generated

Schedule of Events

Table 7-2 Multiple Dose/Dose Escalation Treatment Time and Events Schedule Cycle 1

	Dose-Escalation Phase								Follow-up
	Multiple-Dose Treatment (28-day Cycle) Visit Day (window)								EOS/ Early Withdrawal[b]
Study Procedure	**1[a]**	**2**	**4 (± 2 days)**	**10 (± 2 days)**	**16 (± 2 days)**	**17 (± 2 days)**	**24 (± 2 days)**	**28 (± 2 days)**	**Variable**
Assess vital signs[h, j]	X	X	X	X	X	X	X	X	X
Abbreviated physical examination[i]	X				X			X	X
Clinical laboratory sample collection[c]	X	X	X	X	X		X	X	X
Obtain 12-lead (supine) electrocardiogram[j]	X								X
Ophthalmologic Evaluation[k]	X								X
Urine pregnancy test	X								X
Collect peripheral blood pharmacodynamic samples[g]	X								X
Review concomitant medications and adverse events	X	X	X	X	X	X	X	X	X
Administer [redacted]n clinic[d]	X				X	X			
Collect blood pharmacokinetic samples[f]	X	X			X	X			
Collect blood samples for metabolic profiling	X	X			X	X			
Drug accountability[e]	X				X			X	X
Urinalysis									X

Abbreviations: EOS = End-of-Study; PK = pharmacokinetic;

a. Subjects will be leave after the 8 hour PK blood sample is taken. Subjects will return the following day for the 24 hour PK blood sample.

b. The Follow-Up Period will consist of an EOS/Early Withdrawal visit to occur within ~2 weeks after the last dose of study drug or as soon as possible after early withdrawal for those subjects who discontinue.

c. Approximately 10 mL of blood will be collected for safety laboratory tests. Hematology: white blood cell count with differential, hemoglobin, hematocrit, platelet count, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration; Serum Chemistry: albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, bicarbonate, calcium (albumin corrected), chloride, creatinine, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, magnesium, uric acid, and total protein.

d. Study drug will be administered by study site staff after predose procedures have been completed.

Adverse Events

- Definition: any change in patient's condition from the day protocol treatment began, regardless of cause
- Protocol includes specifics on dose modifications based on specific adverse events and how severe the adverse events are
- Use CTCAE (Common Terminology Criteria for Adverse Events) as standard to grade severity of side effects.
- CTCAE is organized by organ system.
- Determine relationship to study treatment (unrelated, unlikely, possible, probably, definitely) and clinical significance (did you have to take action?)

CTCAE

- Grade 1 Mild
- Grade 2 Moderate
- Grade 3 Severe or medically significant but not immediately life-threatening
- Grade 4 Life-threatening consequences
- Grade 5 Death related to AE

Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements. **Navigational Note:** -					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors. **Navigational Note:** -					
Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-	-
Definition: A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood. **Navigational Note:** -					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of	Life-threatening consequences; urgent intervention indicated	Death

Common Terminology Criteria for Adverse Events

Clinical Trial Team – Principal Investigator

- Principal Investigator (PI) has ultimate responsibility for the team's performance on the:
  - Science
  - Integrity of the research
  - Business operations
- Understands and follows the protocol as approved by the IRB
- Follows all applicable federal, state and institutional regulation
- PI responsibilities are stated in the FDA regulations
- PI can delegate responsibilities to clinical trials study team
  - Study team does day-to-day functions involved in a clinical trial
  - PI ultimately is responsible for the research and actions of the study team

Who are the other players?

- **Sponsor**: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
- **Investigator**: A person responsible for the conduct of the clinical trial at a trial site.
- **Sponsor-investigator**: An individual who both initiates and conducts, alone or with others, a clinical trial.
- **Clinical Research Nurse/ Coordinator** helping to introduce the trial and the details, reviewing the consent and the requirementshelp with the day to day, talking to patients, documenting AEs, doing drug reconcilliation, contacting patients once off trial for survival follow-up; **Study Coordinator**
- **Data manager or CRA-** enters data into databases, working with pharma sponsors and monitors, sometimes lab collections
- **Regulatory team** makes sure all study documents are up to date, amendments are reviewed by IRB/reviewed by study personell/told to patients, training by study staff is done

Different types of trial sponsors

- Investigator initiated trials (IIT or IST)
  - Could be funded by grants or pharma
  - Usually needs an IND or IND exemption
- Pharma sponsored trials
  - In these, you are the site PI. Maybe you are one of the steering committee or leadership who helped design it.
  - Need to beware of COI issues . Draw a line between consulting and PI roles.
  - Some are big pharma with CROs to operationalize the trial. And some are small pharma like G1Therapeutics or Meryx for example
- NCI sponsored cooperative group trials – eg: ALLIANCE, ECOG, NRG, ETCTN
  - Often investigators have a leadership role in design
  - Many of us are on committees at COOP groups
  - Funding is poor but national rep and career opportunity
  - LAPS credit

Regulatory and Administrative Requirements

Multiple Levels of Review

- PRC (Scientific Review Committee)
- NC TRACS/ GCRC (General Clinical Research Center)
- IRB (Institutional Review Board)
- NIH Office of Extramural Research
- FDA - IND
- Institutional Administrative Review
  - Financial, legal, logistical

What protections are in place for clinical trial participants?

- Every NCI designated cancer center needs to have a scientific review committee for their trials. Ours is called **PRC**
  - to ensure the proposed research has solid science and will improve scientific knowledge for this cancer
- The **IRB** (OHRE) - primary role is to protect the rights and welfare of research participants to ensure the risks to patients are minimized.
  - IRBs must review and approve research studies that involve people.
  - The IRB is a committee of scientists and non-scientists, as well as people that live in the community.
  - The IRB has it's own application which is different from(but includes some of the same information as) the clinical trial protocol.
- **Data and Safety Monitoring Board** –
  - most therapeutic trials have one- either internal or external
  - The board is made up of experts who review the results and safety of the study.
  - If they determine that the experimental treatment is not working or is harming participants, they can stop the trial early.

https://research.unc.edu/human-research-ethics/participants/
https://research.unc.edu/human-research-ethics/training-and-education-resources/

Informed Consent

- One of the most important duties of the PI is to ensure adequate informed consent.
- Informed consent is an essential process through which the research team explains the trial to you before you decide whether to take part. The research team explains the trial's purpose, procedures, and possible risks and benefits. You have the right to ask questions and learn about all that is involved in the trial, including all your treatment options, details about treatment, tests, and possible risks and benefits. They will also discuss other rights, including your rights to decide to take part in and to leave the study at any time. You have the right to both hear and read the information in language you can understand.

The Importance of Diversity in Clinical Trials Participants

- Do the participants enrolled on clinical trials mirror the patient population?

- Participants in trials should represent the populations that are impacted by the disease, including racial and ethnic minorities, all ages and genders.

- Why does this matter?
  - Equity
  - Access to novel/ investigational therapies
  - Drugs may have different pharmacokinetics and different tox in different populations (eg: women clear gemcitabine differently than men, older patients may be more predisposed to neutropenia)
  - How can we extrapolate trial findings to the typical cancer population

Lack of Diversity in Clinical Trials

- Historically oncology clinical trials participants have been overwhelmingly white and young.
- FDA summary report of clinical trials between 2015 and 2019 shows that non-Hispanic white populations compose 78 percent of participants enrolled in U.S. trial sites, though they comprise 61 percent of the country's population.
- Majority of women participating in clinical trials in the United States are white (78 percent)
- While cancer incidence increases with age, patients over 65 are underrepresented in cancer clinical trials.

- Recent examples: 3 pivotal trials published in NEJM
  - KATHERINE study (adjuvant TDM1 in HER2 + breast cancer) 71% white, 8.6% Asian, 2.6% black
  - KN522 study (adding pembrolizumab to chemo in preoperative therapy for TNBC) 90% were < 65 years old and racial breakdown not reported (?)
  - Sacituzumab phase III trial in metastatic TNBC 80% white, 12% black

Why is there a lack of diversity in clinical trials?

- Lack of information about clinical trials
- Mistrust
- Provider assumptions-Are the trials offered/ presented?
- Lack of comfort with trial process
- Time and resource constraints associated with participation
- Lack of awareness about the existence/importance of clinical trials
- Restrictive eligibility criteria

- For older adults in particular, participation is diminished due to eligibility criteria, concern for toxicity/patient age, transportation limitations, patient knowledge limitations, burden of time with participation

Efforts to Improve Diversity in Clinical Trials

FDA has issued recommendations for enhancing diversity in trials

- Scrutiny regarding eligibility criteria
  - Don't use template eligibility
  - Consider allowing mild organ dysfunction (heart function)
  - As excretory/metabolic pathways, DDI become available, expand eligibility with less exclusions related to conmeds/comorbidities
- Note that ASCO has also come out with a publication about eligibility criteria
- Identify drug metabolism/excretion across different populations early in development
- Make participation less burdensome (virtual visits, health tools at home)
- Engage with patient advocacy groups early on in drug development
- Varying recruitment techniques (social media, social groups)

What are we doing here at UNC LCCC to enhance recruitment and increase diversity in clinical trials participants?

- Clinical Trials Navigation program and Clinical Trials Interpreter
- Clinical Trials information and QR code links in exam rooms and waiting rooms
- CTO initiated an accrual think tank and implementation group
- Research 4 me - a public engagement website developed by the North Carolina Translational and Clinical Sciences Institute . This patient-friendly platform includes basic information on clinical trial participation, available clinical trials, and key eligibility criteria. QR code to the Research for Me website is now featured on infusion waiting room TVs and the after-visit summaries for all ambulatory visits.
- All providers can also review available clinical trials through Microsoft Teams and a QR code was placed in provider work rooms.
- Weekly “ trial highlights” are sent by email to internal and external oncologists which summarize trial eligibility and contact info for the study team

UNC LCCC efforts to increase the reach and representation of our clinical trials

- With the support of a V Foundation grant, Carrie Lee, MD, MPH, and Marjory Charlot, MD have developed a multi-media educational approach with an emphasis on minority participants (including a video and printed educational materials that will be for clinic waiting rooms as well as MyChart after visit summaries) to enhance equity in clinical trial participation.

- Dr. Charlot launched a clinical trial navigator program that reached 127 patients in 2023, 90% of whom identified as Black or African American. The clinical trial navigation efforts are aimed at reducing barriers to trial participation identified by patient survey including: lack of trial awareness, transportation, financial, family/caregiver support and food insecurity.
- UNC CTO leadership has engaged in a catchment area tour of UNC Health Network sites across the state to undertake a needs assessment and readiness for research evaluation with emphasis on hybrid decentralized trials.

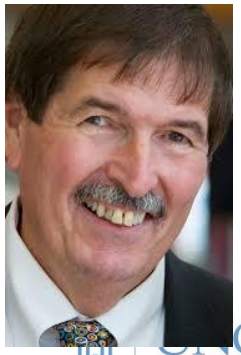
History of Medicine:
Some LCCC Drug Development Highlights

Bob Orlowski + Proscript
PS-341
First response in a patient on the UNC phase I trial
Led to the approval of VELCADE

Serody lab developed Dendritic cell therapy for breast cancer
LCCC first in human trials

Bae-Jump lab studies metformin in endometrial cancer. Then LCCC trial. Then GOG trial

Earp and Frye develop oral MER kinase inhibitor. Now in phase I clinical trial here



Thanks and Acknowlegements

- Phase I trials group at UNC
- UNC Breast Cancer group
- Clinical trials mentors and colleagues
- Patients and advocates
- Carrie Lee, Marjory Charlot, Kaitlin Morrison, Carley Emerson, Lisa Carey, Patty Spears