From Bench to Bedside

HOW RESEARCH IN A LAB MAKES IT TO A PATIENT’S BEDSIDE

VICTORIA GERMANN, MHS, COT, CCRP AND KIM RILEY, PHD
Outline

- Introductions
- The “Bench”
  - Preclinical Research
- The “Bedside”
  - Types of Human Research
  - How it is Regulated
  - How it is Initiated
  - How it is Conducted
- Next Steps
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Kim Riley

- Clinical Research Coordinator since 2015 at Duke Eye Center
- Coordinate and manage clinical research projects for: Dr. Scott Cousins, Dr. Priyatham Mettu and Dr. Michael Allingham
- Research profile primarily focuses on Macular Degeneration, but some Diabetic Macular Edema as well.
Kim Riley

- Clinical Research Coordinator since 2015 at Duke Eye Center
  - Coordinate and manage clinical research projects for: Dr. Scott Cousins, Dr. Priyatham Mettu and Dr. Michael Allingham

- Earned a bachelor’s from University of North Carolina in 2010

- Earned a doctorate from Vanderbilt University in 2015
  - Research project focused on diabetes
Victoria Germann

- Involved in various research capacities for the last 17 years

- Previous research focused on epidemiology, public health and physical activity research

- Developed a personal interest in ophthalmology and decided to pursue ophthalmic clinical research
Victoria Germann

- Clinical Research Coordinator managing various studies involving retinal diseases
  - Managing start-up and continuation of clinical drug trials as well as prospective and retrospective natural history studies
  - Focus on rare genetic retinal diseases
  - Dry Macular Degeneration
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What do we mean by “the Bench”

- The bench refers to the research bench that experiments are performed at in biomedical research labs.

- These individual labs focus on either one, or several closely-related unsolved questions
  - Usually regarding a particular disease, a protein, an organ or any in between.
At Duke Eye Center, the vast majority of these research spaces are in AERI on the third, fourth and fifth floors.

Several physicians at Duke operate a clinic in addition to managing a research lab.

This is in addition to several PhD’s that solely run their own labs as well.
Who does the Research?

- **Principal Investigator (PI)**
  - The “boss”

- **Research Specialists**
  - Most senior with most experience
  - Usually have no desire for their own lab, or were unable to secure funding for one

- **Post-doctoral Fellows**
  - Those completing training/specialization to become a PI
  - Supposedly 2 years, but this rarely occurs

- **Graduate Students (PhD or Masters)**
  - PhDs- average is 5.5 years
  - Masters- average 2 years

- **Medical Students, Interns or Residents**
  - Research experience is becoming more and more valued to advance

- **Research Assistants and Lab Managers**
  - Keep everything running
Who does the **Human** Research?

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How do research projects get off the ground?

- The PI writes a grant
  - Grants outline a series of experiments/techniques that will be used to answer a question
  - NIH, NEI, Foundations, etc etc
- Grant is reviewed by a panel of anonymous peers
  - Can be accepted and funded (rare)
  - Sent back for revisions with hopes of re-submission and acceptance
  - “Triaged”
- Once funding is obtained, salaries can be paid, equipment/reagents for experiments purchase and research can begin
- Requires an answer within a set time frame-usually 2-3 years.
What’s done at the Bench?

- Research done at the bench is typically referred to as “Pre-Clinical” Research, i.e. research that is done prior to anything reaching clinic or humans.

- It’s highly variable:
  - Pharmacology (developing new compounds or drugs)
  - Genetic manipulation of organisms to mimic human disease states. This could be anywhere from yeast to pigs.
  - What I used in my research with mice
  - Development of devices/robots (surgery or imaging)
  - Any combination therein
What’s done at the Bench?

- All of these techniques and skills are used to answer previously unknown aspects of diseases:
  - How do cancer cells grow so fast?
  - Why do blood vessels start to “leak” in Neovascular AMD?
  - Can we regenerate tissues to cure diseases?

- It takes years to answer a tiny portion of these questions.
  - My doctorate was 4.5 years and the results could be summarized in a paragraph
  - This due to rigorous testing to ensure the validity of the results
Different Stages of Preclinical Research

Early Phase
- Very Basic: Proteins in a tube
  - Their structure, how they work, what happens when they have the wrong structure
- Very Basic Organisms
  - Yeast, bacteria, cell cultures
- “Early” Organisms
  - Worms, fruit flies, zebrafish

Late Phase
- Small Mammals
  - Mice (most common)
  - Gerbils, Rats, Hamsters, Rabbits
- Larger Mammals
  - Pigs, dogs
- Monkeys and Apes

Any experiment done on an animal is reviewed prior to ensure safety for the animal.
Different Stages of Preclinical Research

- A research question will be tested in several models, starting in something less complex (i.e., yeast or fruit fly) before moving on to more complex animals (mice etc).
- The results of these experiments are published in research articles or presented at research conferences (like ARVO).
- Those deemed promising are pursued by pharmaceutical companies for potential human research.
  - These companies have their own “Research and Development” groups that re-validate a lot of the results (safety, safety, safety).
Real Life Example: Elamipretide from Stealth Biotherapeutics, Inc

- Company, Stealth Biotherapeutics, has a drug, Elamipretide that they believe could help in patients with AMD.

- This drug is given to Dr. Cousins to test in his mouse models of Dry AMD (nothing goes straight into humans), it is also tested in cell cultures.

- Several years of research later, positive results are observed (and more importantly believed) and thus they begin to pursue the option of a human trial.
QUESTIONS?
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Types of Human Research Studies

- Retrospective vs Prospective
  - Retrospective: Looking at the past
    - Reviewing medical records
    - Typically used to assess which treatment plan is used for a disease and did patients improve
    - Can be used to compare treatment plans
  - Prospective: Following someone into the future
    - Set plan/treatment
    - Allows for you to control a lot of variables
Types of Human Research Studies:

- **Observational vs. Interventional**
  - **Observational**
    - Only observe the patient on a standard-of-care treatment plan and records the results
  - **Interventional**
    - Provide an intervention (new medication, surgery, non-drug therapy, diagnostic test, imaging, etc) and assess what happens
      - New medication/surgery/non-drug therapy: Does it work? Is it better than alternative?
      - Diagnostic test/Imaging: is it effective? False positives? False Negatives?

- **Natural History:**
  - Combination of the two. No “true” intervention, but long term observation of a subject where set data is collected at set time points.
Types of Human Research Studies:

- MASKED vs UNMASKED
  - Masked:
    - Either all or some of the study personnel, and the subject, are “masked” to:
      1. If they receive any treatment at all (placebo)
      2. What dose of the treatment they receive
      3. How frequently they receive the treatment
    - Done to rule out the “placebo effect” and assess safety
  - Unmasked:
    - Everyone gets the drug and everyone knows about it
    - May include different doses of medication, but everyone is informed about what dose they receive
    - Unmasked trials are usually very early phases
# Clinical Trial Study Phases

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>End Point</th>
<th>Number of Participants</th>
<th>Length of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Safety</td>
<td>~20-80</td>
<td>~few months -1 year</td>
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<tr>
<td>Phase 2</td>
<td>Proof of concept; Efficacy- does it work? (phase 2b)</td>
<td>100-300</td>
<td>~few months-2 years</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Efficacy- is it better than the standard?</td>
<td>300-3000</td>
<td>~1-4 years</td>
</tr>
<tr>
<td>Phase 4/after FDA approval</td>
<td>Efficacy- what are the side effects?</td>
<td>1000+</td>
<td>~1-2 years</td>
</tr>
</tbody>
</table>
Phases of Current Trials

- **Stealth- Phase I**
  - Evaluating safety and feasibility
  - Enrolling approximately 40 participants, all at Duke

- **Apellis- Phase IIB**
  - Evaluating efficacy
  - Duke has 6 participants, however, approximately 240 are enrolled across all study sites

- **Omaspect- Phase III**
  - Just rolled study subjects from a randomized, double-masked, sham-controlled study into open-label
  - Now evaluative long-term safety and tolerability

- **Secondary Studies- Phase I of non-ophthalmic trials assessing ophthalmic safety/side effects**
Governing Bodies - who regulates these trials?

- FDA
  - Based on International Harmonization Guidelines
  - Federal Regulations
  - Federal Guidelines
- Duke University
  - Duke Office of Clinical Research (DOCR)
    - Institutional Review Board
      - Based on ICH, GCP, CFR
  - Duke School of Medicine/Medical Center Policy and Procedures
    - Research standards held by Duke which reflect their mission
The FDA

- Protection of rights, safety and welfare of people who volunteer to participate
- Belmont Report
- Good Clinical Practice (GCP)
- Federal Regulations and Guidelines
The Belmont Report

- History- Developed in 1978 (some say 1979)
- Outlines ethical principles and guidelines for protection of human research subjects
- 3 core principles
  - 1. Respect for Persons- courtesy, respect, protection, informed consent
  - 2. Beneficence- Do No Harm- max benefits, min risks
  - 3. Justice- fair distribution, costs/benefits, equally
Good Clinical Practice (GCP)

- International quality standard
  - Developed by the International Conference on Harmonization
  - Design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials/studies
- Addresses ethics and quality data
- 13 principles in a nutshell
  - Ethical
  - Scientifically sound
  - Qualified staff
  - Informed consent
  - Data Quality/Integrity
Code of Federal Regulation (CFR) and Guidelines

- Code of Federal Regulation (CFR)
  - General and permanent rules set forth by governing agencies

- Guidelines
  - Reflect the agency’s (FDA) current thinking on GCP conduct
  - A bit more fluid
Duke Clinical Research

- Duke has its own set of standards, which differ from other universities, private practices and industry standards
- Duke Institutional Review Board (IRB)
  - Study/Protocol Application
  - Informed Consent forms (Duke standard language)
  - Anything that a research participant may see, MUST have their approval
- Duke School of Medicine/Medical Center Policy and Procedures
  - Research standards held by Duke
  - Example: No cold calling
Duke Clinical Research in the news...

- Regulations and governing bodies can fail to an extent
- 2011 - Anil Potti
  - Oncogenomics fabrication scandal
  - Altered data sets to improve the accuracy of predictors for response to treatments
  - Reported false data in several publications
  - Publications retracted
  - Settled outside of court
- Currently practicing oncology in North Dakota
Show Me The Money!

- Who pays for all of this? Funding is vital.
  - Industry funded
  - Physician Initiated/Grant funded
  - Foundational Funding

- The Rub - we are dependent on industry/grant/foundational support
  - No grants/studies, no job and we get sacked
  - Research actually pays the clinic for their resources when needed
What does the money go to?

- Personnel
  - PI’s
  - Clinical Research Coordinators
  - Clinical Trial Assistants
  - Administrative Staff

- Covering study practices

- Covering subject compensation
  - We love valet
Where are we in the process?

- FDA has agreed to the research
- Duke has agreed to let us carry out our research study
- Funding has been acquired so that we have staff, building, equipment in order conduct the research...

What now?
The Players

- Sponsor
  - The Pharmaceutical/Biotherapeutic company that owns the drug/device involved in the trial.
  - The ones that pay the bills
- CRO- Contract Research Office
  - The “managers” of the trial. Ensure everything we’ve discussed so far occurs on schedule
  - Handle the coordination of all sites and issues that arise
- The Site
  - “Boots on the Ground” portion of the study
The Players: The Site continued

- **PI’s**
  - Principal and Sub
  - Injectors

- **Clinical Research Coordinators (CRCs)**
  - Manage the day-to-day coordination of the trial
  - Perform the consent
  - Liaison between the PI’s, Sponsor and CRO

- **Clinical Trial Assistants (CTAs)**
  - Perform the study activities
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The PROTOCOL

What is it?
- Our guidebook, map and law of how we will conduct the study

Why do we need it?
- What we are approved to do
- Ensures human research subject protection
- Addresses data integrity so that our data and results can be analyzed and actually mean sometime

Who develops it?
- Depending on who is funding the research
  - Industry, Physician (research team), Foundation

Why is it SO important?
- It allows to collect quality data, in the same way, across multiple sites - i.e. the McDonalds Policy (remember all of the regulations for both study subjects and data?)
Objectives, Endpoints and Data Integrity

- Objectives- the hypothesis or purpose of the study
  - Will differ based on type and phase of study

- Endpoints- Main measurements the company wants to collect
  - Also differ based on study (drug trial or natural history?)
    - Primary
      - Primary Efficacy
      - Primary Safety
    - Secondary

- Data Integrity
Study Objectives & Endpoint Examples

- Assess the safety, tolerability and evidence of activity of multiple IVT injections of drug X
- Evaluate the long-term safety and tolerability of IVT injections of drug X
- Assess different treatment options: Eylea alone vs. Eylea+New Drug
- Characterize a population
- Measure, test-retest variability
- Estimate rates of progression of clinical parameters
- Investigate structure-function relationships for insights into the mechanisms of retinal degeneration
- Is something a “Biomarker” i.e. a predictor that a disease will occur?
- Is one type of photography superior to another at diagnostic ability?
Can You Change a Protocol?

- New information
  - Must submit an “Amendment” which may need to go through the full review process (IRB)
  - Originates from the sponsor of the study (industry, physician, foundation)
  - Must be the same across all sites

- Approval from governing boards ensures protection, integrity of the study and study participants

- Can take MONTHS
  - Vital that all information is submitted correctly the first time or can cause a significant delay in the study
Training and Certifications

- Integrity of data collection
- Ensures knowledge on the part of the staff
- Documents responsibility and understanding of the protocol
- Manual of Procedures (MOP)
  - Ophthalmic Examination
  - Imaging
  - Drug preparation
  - Etc etc
Ophthalmic Certifications

- Visual Acuity
  - Standard of Care
  - Research Gold Standard
- Exam Lane certifications
  - Length, equipment, lighting
- Examiner certifications
  - Trial frame refractions
  - Documentation/measurement
    - ETDRS (Early Treatment Diabetic Retinopathy Study)- number of letters as opposed to the smallest line with less than 2 errors
CRC’s and CTA’s are very adaptable and resourceful.

Additional certifications that may be needed and obtained:
- Phlebotomy
- Pregnancy testing
- ECG’s
- Microperimetry
- Biological Specimen Processing
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Congratulations: Your Study has been APPROVED

- Now we can begin recruiting.
  - Have to consult the protocol for all “Inclusion” and “Exclusion” Criteria

- But how do we find participants?
  - Database searches (DEDUCE and DESCERN)
  - Endless spreadsheets and logs

- Remember... no cold calling
  - Clinic plays a vital role in research and participation
  - Possible study participants are in clinic
    - Physicians and Fellows can provide the introduction for research staff
      - This is why we are constantly stalking your clinics
Enrollment into a Study: The Informed Consent

- In order to enroll someone into a study, they must go through the “Informed Consent” process
  - This is the backbone of human research, few things are more sacred to us than the idea of informed consent
  - The study, with all its risks and benefits, is explained to the potential subject in a private room with no interruptions from other staff
  - Potential subject is encouraged to share the document with family members, friends and other physicians
  - It is NOT a contract, and the subject can withdraw at any time with no bearing on their medical care
- This process must occur prior to ANY study related test or procedure
Enrollment into a Study: The Informed Consent

- Who can undertake the process varies by the type of study:
  - Retrospective studies (medical record reviews) can have waivers where consent is not required
  - Simple observational studies can have a CTA administer consent
  - Everything else necessitates a CRC or PI

- Once a consent form is signed, the subject is officially enrolled in the study
You have your first patient-time to get to work!

- This is where the Protocol becomes your Holy Book of choice:
  - Each protocol has a Schedule of Events-outlines what must occur on what day of each visit of the study.
  - Any item that is not collected when it should results in a “Protocol Deviation”
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### Monthly Groups Visit Schedule

<table>
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<th>Visit #</th>
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<td>Blood Draw – Safety Labs</td>
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<td>Urine Sample Collection</td>
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<td>Blood Draw – Genotyping (if applicable)</td>
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<td>Digital Color Fundus Photographs (DCFP)</td>
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<td>Fundus Fluorescein Angiograms (FFA)</td>
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<td>Study Eye Determination</td>
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<td>Randomisation</td>
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<td>APL2 administration or Sham Injection</td>
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<td>Post-Injection Assessment</td>
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<td>Concomitant Medication / Adverse Events</td>
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- Values: SE = Study eye only.
<table>
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<tr>
<th>Evaluation*</th>
<th>Screening Days -60 to -1</th>
<th>Baseline Day 1 (&lt;3 days)</th>
<th>Study Month (≥15 Days)</th>
<th>End of Study/Early Termination (≥15 Days)</th>
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<td>Prescreen</td>
<td>Screening</td>
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<td>Informed Consent*</td>
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<td>Genotyping*</td>
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<td>Eligibility Criteria*</td>
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<td>Demographics</td>
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<td>Medical History/Review of Systems*</td>
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<td>NEI VFQ-25 plus its additional items*</td>
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<td>PGLS*</td>
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<td>Diet and Light Exposure Questionnaire</td>
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<td>Adverse Event Assessment</td>
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<td>Medications/Nutritional Supplements/Therapies/Procedures Assessment</td>
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<td>Alcohol, Tobacco, and Substance Use Assessment</td>
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<td>Vision-related Family History</td>
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<td>Physical Examination*</td>
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<td>Vital Signs*</td>
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<td>Pregnancy Assessment</td>
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<td>Refraction and BCVA</td>
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<td>Intraocular Pressure Assessment</td>
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<td>Visual Field Assessments (Kinetic and Static)</td>
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<td>sDOCT – EZ Width and EZ Area Measurement</td>
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<td>Clinical Ophthalmic Examination*</td>
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<td>Rod Visual Field</td>
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<td>ERG (Dark- and Light-adapted)*</td>
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Study Windows

timing is everything

Two different types

1. Study Schedules
   - Sometimes only a 5 day window to get the study subject seen
   - Difficulties- clinic space, physician time, staffing

2. Visit day study windows
   - Ex- vitals need to be taken an hour before study drug dosing and again 30 minutes after dosing
     - Reconstitution of study drug needs to be at least an hour before dosing but then is only good for 4 hours- seems like a lot of time, but is it?
     - Work-up, imaging, blood draws…
Data Collection

- Remember the regulations and international standards?
  - Human Subject Protection AND Data Integrity

- Quality of data is vital to the integrity of the study
  - The Quality of the data is determined by:
    - Amount of planning before the study begins
    - Precise, accurate execution
    - Ability to analyze
  - If any of these areas are inadequate the quality of the data is greatly lessened
  - Quality must be maintained throughout the life of the study
Data Collection

- Data collection is VITAL to the results of the study
  - Inaccurate data collection, meaningless results

- Unacceptable data collection corner cutting
  - But this way was quicker
  - But I wasn’t paying attention
  - But I still got the same result I would have
What Data Should Be Collected

- Team Approach (researchers, data management team, IT, etc.)
  - What is the hypothesis?
    - Determines what needs to be collected
  - How can it be measured in a way that is meaningful?
    - Determines testing and units
    - Endpoints of the study are determined
  - How can it be collected?
    - This is when the protocol begins development
How is the Data Collected?

- This is the vital role that the CTA performs
- Must be able to collect data via the ophthalmic gold standard
  - Goldmann Applanation
  - Trial Frame Refractions
  - ETDRS Visual Acuity testing
- Due to the protocol and gold standard of collection testing can take lengthy amounts of time
  - Visually impaired study subjects
  - Multiple testing required
  - Detailed documentation and timing
Data Collection- Adverse Events

- Besides the standard required collection of data outline in the Protocol, Adverse events must also be collected by CRC.
- Adverse Events (AEs) can be thought of as the “side effects”.
- Can range from serious to completely benign.
  - IOP increase
  - Hospitalization
  - Sinus infection
- The PI decides if the AE is related to the study treatment or not.
- All must be reported in a quick manner. If serious enough, may shut down a study.
Data Management

- **What Is It?**
  - Managing the Data of a research study over its entire life cycle
    - How it is collected
    - How it is managed
    - How it is protected
    - How it is destroyed

- **When does the process begin?**
  - Before the protocol is developed

- **Why is the integrity of the data important?**
  - Bad data, worthless research, time and information lost
Endpoints

- Represents the clinical outcome of interest
  - Examples from current studies
    - Number and severity of local and systemic treatment emergent adverse events (investigational drug study)
    - Change from baseline in: EZ width, visual fields, ERG, BCVA
    - Geographic Atrophy area progression as measured by fundus autofluorescence
    - Rate of Side Effects or the tolerability receiving treatment
    - Increase of letters in different lighting
    - How often intravitreal injections are required
How Is It Collected?

- Principle of how to collect good data:
  - Gather the most specific data possible
    - Most detailed unit of measurement (whenever possible, collect continuous data, can later create ordinal/nominal values)
    - Do not leave room for ambiguity or interpretation
  - Which is better for collecting a patient's blood pressure?
    - High, Low, Average
    - Diastolic_____/Systolic_____
  - Ophthalmic collection:
    - BCVA via Snellen
    - Number of letters correctly read on ETDRS chart
Where does it live?

- So, so, so, so many binders

- Most studies require all data to be collected on paper or a “Case Report Form” (CRF). This is referred to as “source”
  - Source is sacred

- Most also require entry of information into an “electronic data capture” system
  - Allows for monitoring remotely
  - Also easier to compare results in real-time across all sites (Safety)
How Is It Managed?

- Monitors- Neutral Third Parties from CROs (the middle men) come in a double check the source against the EDC.
  - They also review medical records, confirm eligibility
  - Ensure no missed AEs
  - Ensure sites are up to code

- Monitors are the necessary evil of clinical research
  - Great asset to your research
  - Can also be a great pain in your….
    - Queries
How Is It Protected?

- **Access**
  - Not everyone needs access to everything!

- **Security**
  - Locked in a locked space
  - Firewalls

- **Audit Trials/Tracking (paper and electronic trails)**
  - Initialing, dating, verifying
  - Electronic systems are increasing the ability to track every change or access point

- **Back-up of back-ups of back-ups**
How Is It Destroyed?

- The Protocol (again)
  - Determines how long the information will be retained
  - Spells out how destruction of the data will occur
- Informed Consent also documents how long we keep the data
  - Study subjects sign off on how long data is kept
  - Biorepository- sometimes this is for longer than the study subject would be expected to live
Study Close-Out

- What happens when a study ends?
  - Why did it end?
    - Sponsor discontinued funding
    - Results were proving to be negative and showed increased risk
    - All subjects completed (natural history)
    - Results were positive!
  - What happens at the end of the study is determined by:
    - Study phase
    - Study results
Current Study Examples

- **Stealth**
  - Option 1: Repeat as phase II with larger population
  - Option 2: Reformulate drug- different way to administer? Different dose?
  - Option 3: Sell off drug to other company and drop it all together

- **Proxima**
  - Natural history study that did not enroll any subjects due to screen failure
  - Close study

- **Omaspect**
  - Phase III, currently under review by the FDA to see if the results are proving it is better than the current standard treatment (which is observation)
  - If approved will go to market and be available in clinics where appropriate
Long Term Path of a Study

- **Option 1: Rare**
  - Works it way up the phases, deemed safe, deemed effective
  - Approved by FDA
  - Goes to Market and is prescribed

- **Option 2: Common**
  - Works it way up the phases, issues arise and is sent back for further testing or is sold to another company who may test it in another disease state or human population

- **Option 3: Common**
  - During some aspect of a study it is deemed either unsafe or ineffective and is killed
Long Road to Approval

- On average it takes over a decade for a drug to get to the market
  - Preclinical research
  - Phase 1
  - Phase 2
  - Phase 3
  - Phase 4

- This is why some medications are so incredibly expensive, companies have to recoup money spent on development in order to put it towards the next drug. They also have to recoup their losses on several failed drugs.
Conclusions

- Clinical Research is a beast
- Research a lot of regulations
- Research is intensive
- Research can improve quality of life
QUESTIONS?