Clinical Trials: What Every Patient Should Know

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Personal Perspective
The FDA

- Upton Sinclair’s 1906 book “The Jungle” revealed food adulteration and unsanitary practices in the meat production industry
- Public outrage prompted Congress to assume federal responsibility for public health and welfare
- The Pure Food and Drug Act and Meat Inspection Act were passed by Congress in 1906 empowering the USDA Bureau of Chemistry to enforce these laws
The FDA

- In 1927 the Bureau of Chemistry’s regulatory powers were reorganized under the USDA’s new “Food, Drug and Insecticide Administration”
- Name shortened to “Food and Drug Administration” in 1930
- Federal Food, Drug & Cosmetic Act of 1938 required a physician prescription for certain drugs

Bill Leading to the Pure Food and Drug Act
The FDA

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- Following the thalidomide catastrophe a 1962 amendment to the FD&C Act led to a formal FDA drug approval process
- Safety and efficacy to be determined through a clinical trials process regulated by the agency
Emergency Use Authorization

vs

Standard FDA Approval Process
EMERGENCY USE
AUTHORIZATION
Emergency Use Authorization

- established in 2004 after the September 11 terrorist attacks
- rules created to fast-track development of drugs and vaccines during a public health emergency
- safety and efficacy data required but over shorter period than is standard
- data reviewed by outside advisory committee
- companies given EUA must continue performing clinical trials to ensure more longterm data
- FDA expects that companies will also file for standard approval
How long it took to develop other notable vaccines

- **Polio**: 7 years (1948-1955)
- **Measles**: 9 years (1954-1963)
- **Chickenpox**: 34 years (1954-1988)
- **Mumps**: 4 years (1963-1967)
- **HPV**: 15 years (1991-2006)
- **Coronavirus (Pfizer/BioNTech)**: 11 months (2020)

Average vaccine development: 10.7 years

Sources: Center for Infection and Immunity; National Institutes of Health; Centers for Disease Control and Prevention

* during COVID PHE 4 monoclonal therapies, 3 oral antivirals & remdesovir were all granted EUA status
The standard drug approval process is rigorous and....

• slow - from pre-clinical testing of a drug to getting to market takes 12 years on average

• expensive - “the entire cost (of new drug development) may be in excess of 1 billion dollars”

Van Norman, G; Drugs, Devices and the FDA; JACC: Basic to Translational Science Vol. 1, No. 3, 2016 April 2016:170–9
FDA Approval Process

- Slow, methodical and expensive
- All approvals require a clinical trials program
- Even after an FDA approval there is often additional testing or investigation needed
- The standard process is the focus of today’s presentation
• Clinical trials are the means by which we evaluate a new drug or device for a particular disease or medical problem; or an old drug or device for a new application (e.g. methotrexate)

• New treatments are evaluated for safety and efficacy

• Data generated by a clinical trial provides the FDA with information necessary to determine if a drug should be approved

• Upon a drug’s approval, *Prescribing Information* and patient labeling documents are generated that outline dosing and safety guidance

• Every step of this process is regulated by the FDA
Stages of Clinical Trials

- **Pre-clinical**: in the laboratory with animal subjects
- **Phase 1**: healthy volunteers to determine “pharmacology” of a drug
- **Phase 2**: to prove an effect, find the right dose and evaluate safety
- **Phase 3**: to generate more meaningful data on safety and efficacy
- **Phase 4**: primarily performed to evaluate long term safety
Randomised
Double-blind
Controlled
New Drug - Pill “A” is Compared to Something Else
• itself in a different dose, or
• a drug with a known effect, and/or
• a placebo or “dummy pill” that has no expected effect
Randomized
Double-Blind
Double-Blind

• the patient is blinded to their treatment group assignment to lessen the chance that a preconception will affect outcome

• the clinician investigator is unaware of what the patient is getting to minimize bias which might influence results
Other Clinical Trial Jargon

• Dose finding

• Single or double-blind

• Placebo controlled *crossover* Open label

• Open label

• Long term follow-up - usually open label
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Current Sjögren’s Trials
Getting Involved in Clinical Trials

• Why participate?
• How do I get started?
• Am I eligible?
• Is it safe?
• What happens at my visits?
Why Participate?

• to gain access to a promising treatment not available elsewhere

• to obtain care at no cost or receive treatments that would otherwise be unaffordable

• to gain a better understanding of your disease

• to feel empowered and gain a sense of control of your disease

• to be involved in the development of a new treatment to help you and others who have your illness

• to contribute to scientific and medical knowledge
Why Participate?

Frequently stated patient concerns

• “I don’t want to be a guinea pig”
• time commitment
• complicated science and complicated protocols
• uncertainty about getting the active treatment
• trust
Why Participate?

Frequently stated physician investigator concerns

What’s the potential benefit for the patient?

• is the duration of the study sufficient to provide a meaningful result to the patient

• is there a stipend for the patient if the study requires travel and significant inconvenience

• what percentage of patients will get the active treatment

• is there an opportunity for a long term open label extension
How Do I Get Started?

• it may come up at a visit with your physician

• you may see an advertisement on line, in your newspaper or on local or national broadcast media

• you may seek opportunities on www.clinicaltrials.gov
Am I Eligible?

• clinical trials are performed according to a plan design called a protocol which is unique to each project

• protocols define eligibility criteria such as age, gender, duration of illness, prior therapies, other medications you may be taking

• eligibility criteria fall into 2 categories:
  • inclusion: clinical and laboratory characteristics of your illness
  • exclusion: co-existent illness, prior treatments, history of allergy, etc
Is it Safe?

There is a significant, layered, complex infrastructure specifically developed to assure safe conduct of clinical trials in the United States.
Is it Safe?

• physicians and their coordinators are trained in “good clinical practice” principles (GCPs) and coordinators are likely certified

• before conducting a study the site must have the protocol reviewed by an Institutional Review Board (IRB); which then requires regular reporting of the site

• an independent data safety monitoring board is designated by the study sponsor to review all adverse events with the power to stop the study

• FDA regulations and auditing authority

• The informed consent
Informed Consent

“A process by which a subject voluntarily confirms…willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.”

-International Conference on Harmonization - Good Clinical Practice
Elements of Informed Consent

1. Description of the clinical trial
2. Potential risks and discomforts
3. Potential benefits
4. Alternative treatments available
5. Confidentiality
6. Compensation and medical treatment in event of injury
7. Contact information at the investigative site
8. Voluntary nature of participation and the right to withdraw
Is it Safe?

• has the drug been tested before or is it new

• has it been used in other diseases but is now being applied to your illness

• what is the safety of similar drugs in its class

• known risks should be spelled out in the informed consent
What Happens at My Visits?

• initially your clinical research coordinator will explain the nature of the program

• at a screening visit, the coordinator and investigator will provide you with the informed consent form, give you ample time to review it and answer any questions

• if all inclusion and exclusion criteria are met, randomization and treatment will begin at the baseline visit
What Happens at My Visits?

• thereafter, the clinical research coordinator and investigator will closely monitor your progress at every visit

• you may be asked to fill out questionnaires to assess how you feel and determine your progress - your input is essential to this process

• the study team meticulously takes notes, records measurements and explains what is happening all along the way
What Happens at My Visits?

- physical examinations will be performed at predetermined intervals

- testing will typically be required: blood work, x-rays, MRI's if part of the study design

- some studies in Sjogren’s require measurements of tear or saliva production

- parotid ultrasound studies may be required in others

- care will be at no cost to you
What Happens at My Visits?

• your safety is of paramount importance

• your compliance is critical to a good study outcome

• you may or may not notice improvement in the condition being treated

• some studies may have “open-label” extension periods and others “cross-over designs”
Trial Design in Sjögren’s
Candidate Selection

• primary Sjögren’s vs secondary
• early vs late disease
• specific symptom-focused
  • dry eye
  • dry mouth
  • fatigue
  • arthritis
• systemic disease-focused
  • e.g. hematologic, lung or kidney involvement
  • quality of life
  • outcome measures (ESSPRI, ESSDAI, SSI, PROFAD)
Trial Design in Sjögren’s Outcome Measures

- PROFAD - Profile of Fatigue and Discomfort
- SSI - Sicca Symptoms Inventory
- ESSPRI- EULAR Sjögren’s Syndrome Patients Reported Index
- ESSDAI - EULAR Sjögren’s Syndrome Disease Activity Index
Clinical Trials

You may have heard about Clinical Trials and would like to learn more. This section offers information on what a Clinical Trial is, what is involved in a Clinical Trial and how participating in a Clinical Trial may benefit you. Also, you will be directed to a current listing of active Clinical Trials in Sjögren’s.

Everyday research is being conducted to unveil new medications, therapies and diagnostic tools for Sjögren’s. By participating in a clinical trial, you will be helping to potentially uncover breakthroughs that will help Sjögren’s patients worldwide.

Clinical trials are designed to add to medical knowledge and most importantly, the results of these trials can make a difference in the care and treatment of Sjögren’s patients. A clinical trial is important because it contributes to the advancement of science.
Clinical Trials and This Practicing Rheumatologist

by Herbert S. Baraf, MD, FACP, MACR
Arthritis and Rheumatism Associates, P.C., Wheaton, Maryland

With a career spanning almost forty years, it’s time for me to look back upon those things that have given me professional satisfaction and draw advice from those experiences to pass on to my younger colleagues.

I have worked in a private practice setting since completing a rheumatic disease fellowship at Duke University in 1978. Duke, a premier center for basic and clinical research for decades, was a great place to be. As a fellow, however, my goal was to take care of patients, eventually in a community practice setting, and not to

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“From a humble start… I have participated in the struggle to make my patients’ lives better one at a time. By being part of the clinical trials process, a clinician’s reach extends beyond the lives of their patients to the lives of all patients with rheumatic disease.”

—personal statement In Sjogren’s Quarterly Summer 2017