FRDA CLINICAL TRIALS

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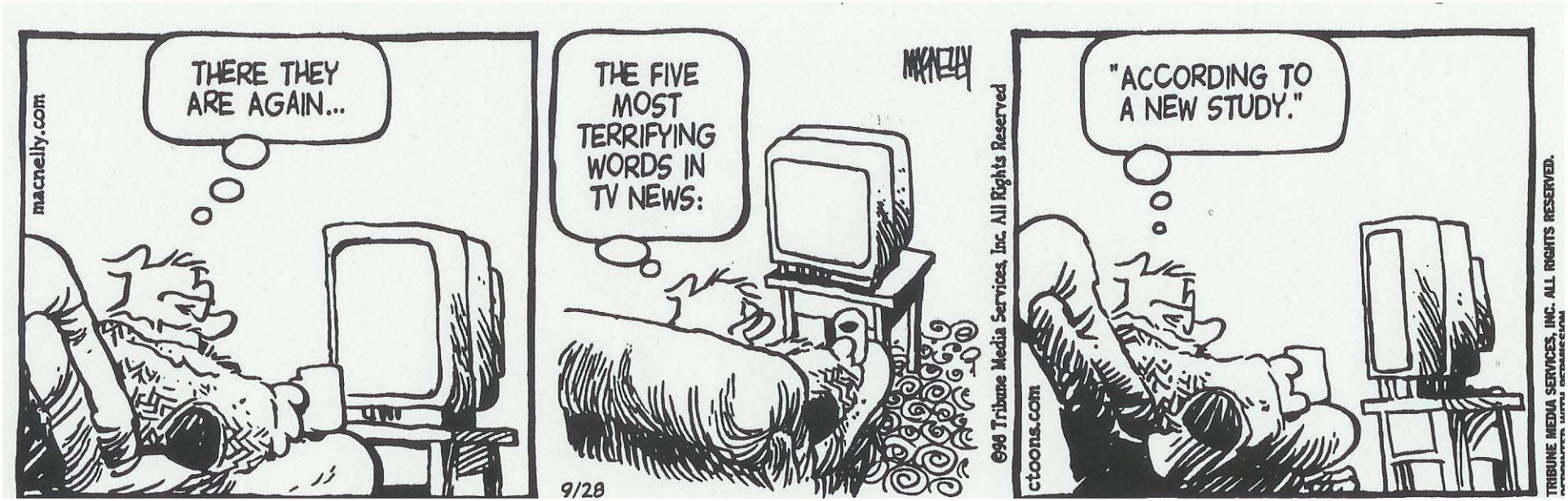

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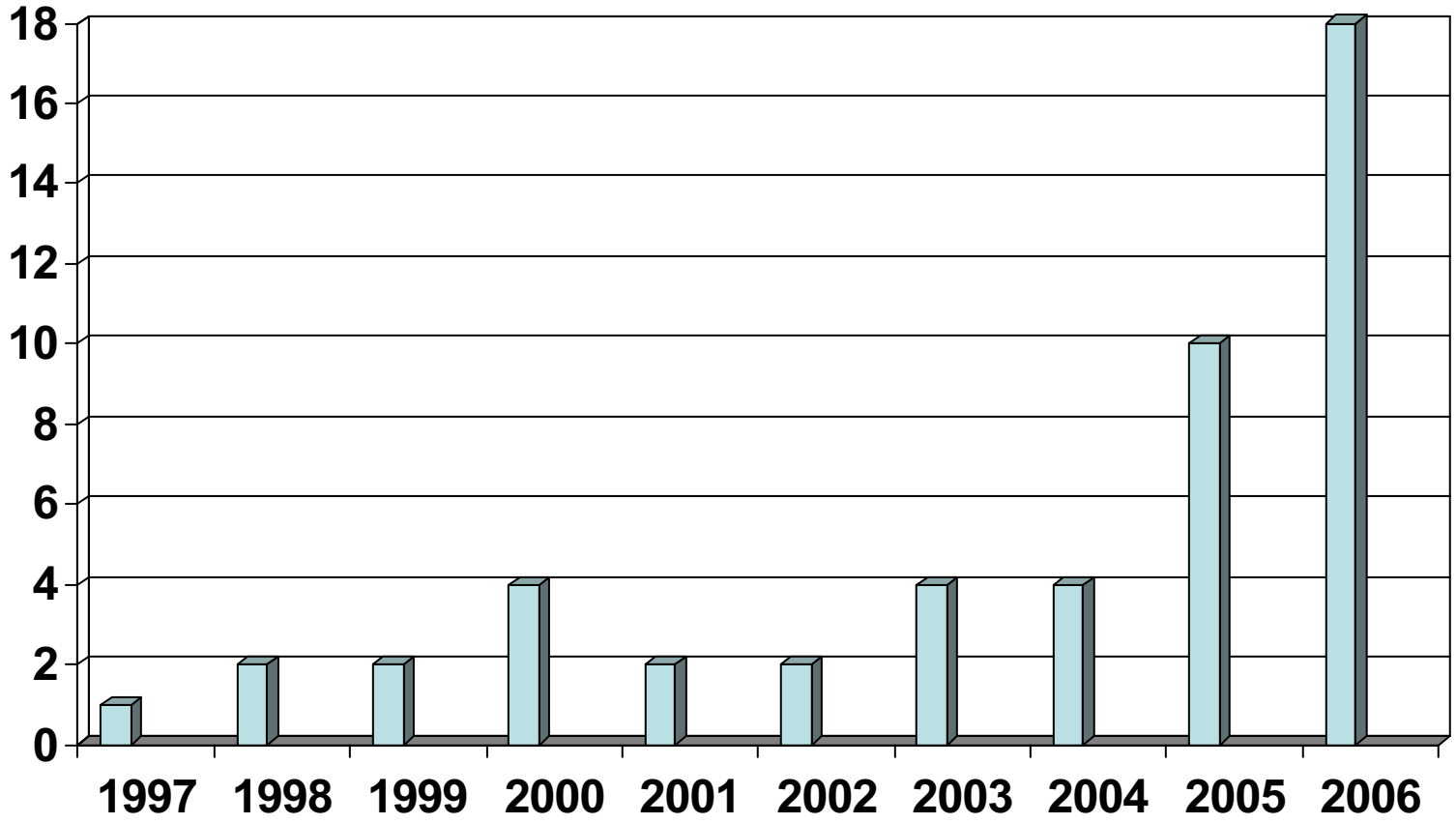
US STUDIES FUNDED BY FARA, MDA, NAF, AND NIH FOR FA



Clinical Trials Questions

- How do drugs get chosen for testing?
- What about “N of One” Trials?
- If it’s a safe enough drug for testing, why all the focus on protecting the participant?
- If it’s a good drug, why doesn’t everyone respond the same?
- Is it fair to exclude some patients from clinical trials?

PRO'S AND CON'S OF CANDIDATE DRUGS FOR HUMAN TRIALS

- **Rationale--do we expect it to work?** Basic Science
- **Efficacy-has it worked in animal or pilot human trials (even "N of One" trials)?**
- **Safety**
- **Do the anticipated benefits outweigh the risks?**
- **Availability--designer drugs vs. already available ones. What's in it for the drug company?**
- **Cost (and where to get the money from)**

EFFICACY--CAN WE SHOW THAT THE DRUG ACTUALLY MAKES A DIFFERENCE?

- **Symptomatic benefit vs. disease-modifying**
- **Is the candidate drug strong and specific?**
- **How much does the disease change over how much time? Natural history.**
- **How accurately can this change be measured? Rating scales, QOL measures.**
- **Can biomarkers show clinically meaningful change quicker? 1° vs. 2° outcome measure.**
- **Can enough researchers and patients be found? Research centers and registries.**

FOR EXAMPLE: UMBILICAL STEM CELL TRANSPLANTATION FOR BRAIN DISEASE

- **Symptomatic benefit vs. disease-modifying**

NO ATTEMPT TO CONTROL FOR OTHER TREATMENTS, OTHER EFFECTS.

- **Is the candidate drug strong and specific?**

NO EVIDENCE AS TO WHAT ITS REAL EFFECT IS.

- **How much does the disease change over how much time? Natural history.**

TIMELINE WRONG FOR TRUE DISEASE-MODIFYING EFFECT.

- **How accurately can this change be measured? Rating scales, QOL measures.**

HAVE BEGUN TO USE VALIDATED MEASURES.

- **Can biomarkers show clinically meaningful change quicker? 1° vs. 2° outcome measure.**

NO BIOMARKERS USED TO MONITOR EFFECTS.

- **Can enough researchers and patients be found? Research centers and registries**

HIGH INTEREST IN MANY COMMUNITIES BUT FEW ETHICAL CONTROLS.

FOR EXAMPLE: LITHIUM FOR ATAXIA

- **"Lithium Carbonate and Choline Chloride in Cerebellar Ataxia."**
- **10 patients (3 FA, ILOCA 3, 2 Etoh, 1 AHC, 1MS)**
- **Partial improvement with CC, marked with both**
- **1984!**
- **How did this miss getting into the pipeline?**
- **I was involved with a clinical drug trial for ataxia then**
- **I knew about choline**
- **This article was published in the Indian Journal of Pharmacology and there was no PubMed back then**
- **There were no patients on the Internet.**

TYPES OF CLINICAL TRIALS

TYPE	# SUBJECTS	LENGTH	AIM OF STUDY
N of 1	1	Ongoing	Do I get better or stop getting worse on this drug?
Pilot	Up to 20 All get drug	Weeks to months	Is a larger study worth doing, will there be problems?
Phase 1	20-80 normal or patient in groups of 3	2 years	Escalating doses to learn side effects, safety, best dose
Phase 2	20-300 Control and drug groups	2 years	To assess potential for good effects, as well as side effects. Also designed as "futility" study—to show a drug doesn't not work(fewer subjects, less$)
Phase 3	300-3000 Control and drug groups	3-5 years	To prove efficacy May include crossover design or open extension trial
Phase 4	100's-1000's Open drug use	Ongoing	To find out more about the effects of an approved drug.

The Pathway to Approval of a New Drug Goes Through the FDA

- If it's a safe enough drug for testing, why all the focus on protecting the participant?

Well-designed safety studies in animals and people are required by the FDA.

People cannot be unfairly coerced into participation.

- If it's a good drug, why doesn't everyone respond the same?

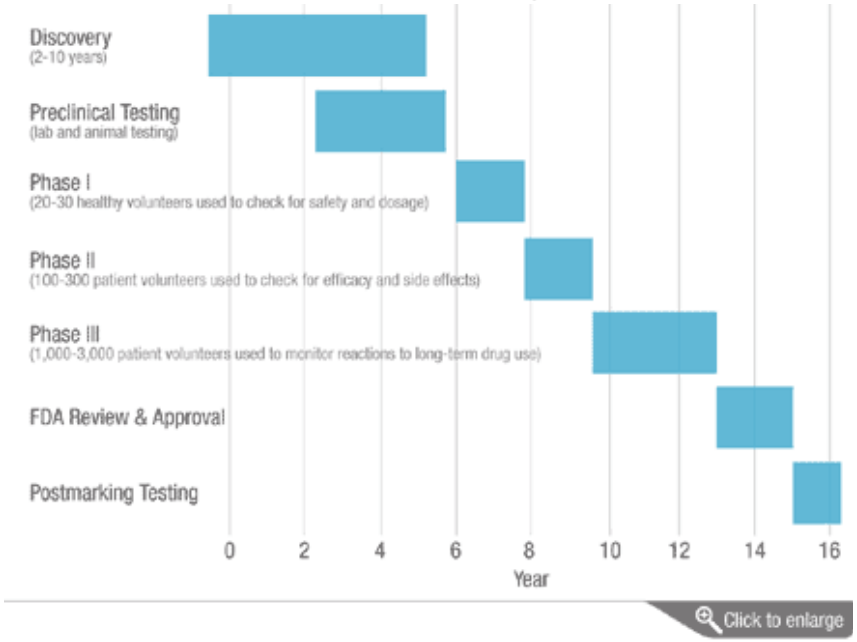
Well-designed Phase I, II, and III trials are required, with placebo controls, to be absolutely certain that the drug is responsible for observed good effects. The placebo effect is very real.

DO WE REALLY NEED PLACEBOS?

- **Gold Standard for Phase III clinical trials is the double–blind, placebo-controlled, randomized study.**
- **The "placebo effect" is very real and accounts for all the other effects not related to the drug directly.**
- **Dramatic differences between the placebo and drug groups will usually result in all subjects being placed on drug before the end of the trial. Open extension studies are usually done.**
- **If it would be dangerous for a potential subject to end up on placebo, that subject would not be enrolled in the study. This includes the subject having to stop other medications to enter the study.**
- **Active placebos may be used once the first drug is approved.**
- **Use of historical controls or subject acting as own control may require a longer study to prove benefit of drug.**

OFFICIAL PIPELINE FOR NEW DRUGS

Up to 15 years and $500-700million to get to market



- **Discovery—clinicians and scientists working out the cause of the disease, the "dominos" that fall over, and targeted candidate drugs.**
- **Preclinical testing—test tube and animal studies.**
- **Phase I—dosing, safety**
- **Phase II—safety, possible efficacy**
- **Phase III—efficacy**
- **FDA Approval**
- **Phase IV--Post-marketing studies for long-term side-effects and good effects.**

- **To help with promising drugs for serious diseases with unmet needs:**
- **NIH—Rapid Access to Intervention Development (RAID)**
- **FDA—Orphan Drug Status**

FUNDING
A PUBLIC-PRIVATE PARTNERSHIP

- **Discovery—clinicians and scientists working out the cause of the disease, the "dominos" that fall over, and targeted candidate drugs.**
  $25-80,000 per yr over many years

- **Preclinical testing—test tube and animal studies.**
  $100,000 per year for at least 2 yr

- **Phase I and Phase II--**
  $500-700,000 per year for 4 yr

$2-4 million to get to this point

- **Phase III—$4-5 million ($10K/subject)**
- **FDA Approval**
- **Post-marketing studies for long-term side-effects and good effects and possible other uses of the drug.**

- **Government**
  Private research foundations

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Is it fair to exclude some patients from clinical trials?

- **The number of patients and the type of patients (age, level of disability) chosen for a clinical trial are determined in order to achieve the best results in the shortest time with the least cost.**
- **But, the drug when approved will certainly be used by all ages and all levels of disability.**
- **A compromise with the drug company and the FDA might be in order.**

REGISTRIES

- FA
  http://www.faresearchalliance.org/registry

- FA, SCA, SPORADIC ATAXIA
  http://cooperative-ataxia-group.org/register.htm

THANK YOU

- **National Ataxia Foundation—**
  sponsor of grants for our internal database, our DNA bank, and our web-based database project.

- **Muscular Dystrophy Association and**
- **Friedreich's Ataxia Research Alliance—**
  sponsors of our grant for the collaborative project on "Clinical Outcome Measures in Friedreich's Ataxia".

- **The Smith Family Foundation**

- **Dr. David Lynch and the CCRN**

- **And to our patients and their families for their willingness to work with us and to share with us their ideas and hopes.**
- **Clinical trials won't work without you!**