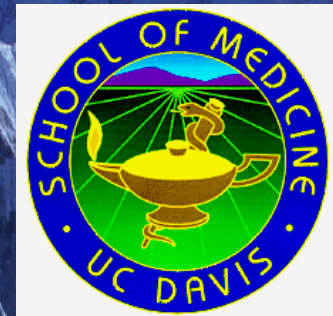


Clinical trials and COHORT

Vicki Wheelock MD

HDSA Center of Excellence at UC Davis

June 6, 2009





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HDSA encourages all attendees to consult with their primary care provider, neurologist or other healthcare provider about any advice, exercise, medication, treatment, nutritional supplement or regimen that may have been mentioned as part of any presentation.

Presenter Disclosures

Dr. Vicki Wheelock

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

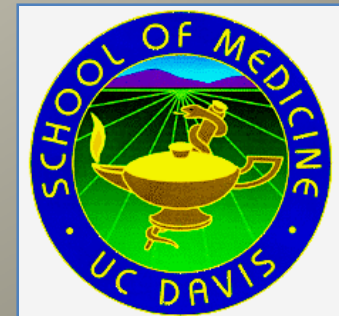
No relationships to disclose or list



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I am the director of the HDSA Center of Excellence at UC Davis, a site investigator for the HSG since 1997, and a member of the HSG Executive Committee.



Questions

- What is a clinical research?
- What is an observational trial?
- Who can participate in research studies?
- How much time does it require?
- What about confidentiality?
- How do people decide whether to volunteer to participate?
- Are we making any progress?
- What HD clinical trials are enrolling right now?

Clinical research studies, especially clinical trials, are how new knowledge is generated, and they help to find new treatments. Being a research participant is not for everyone, but without participants there cannot be new treatments in the future.

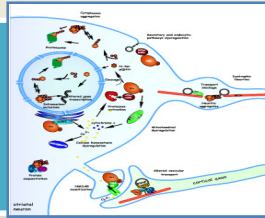
Source: The Huntington Study Group Web Site

HD Clinical research: definition

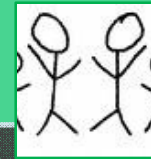
- The goal of clinical research is to study information collected about people enrolled in order to learn about the manifestations of a disease, or to test the safety, benefit, side effects and risks of an intervention designed to help people affected by a disease.
- Types of clinical research:
 - Observational study
 - Clinical trials
 - Double blind, randomized control trials
 - Phase I, II, III

The pathway to finding new drugs

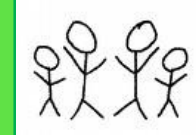
Pre-clinical: models



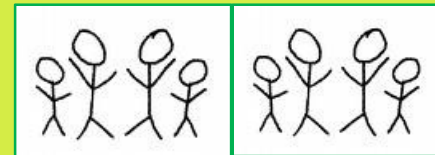
Phase I: test in healthy humans for safety



Phase II: Test in small population with disease for safety and dosing



Phase III: Test in larger population for efficacy



FDA Approval



Who pays for HD clinical research?



National Institutes of Health
Private foundations
Pharmaceutical Companies



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What are observational trials?

- These are studies involving humans that follow research participants over time without making a treatment intervention.
- Observational studies allow researchers to study the progression of HD over time in a number of individuals, and help us to understand the symptoms people experience, the signs noticed by investigators at the sites, the rate of progression, and sometimes markers of HD such as brain scan or blood test changes.

What are double blind, randomized, controlled studies?



- These studies are designed to help prevent judgment or bias by the investigators or research subjects from affecting the study results.
- Double blind: neither the investigator nor the participant can tell if the participant is taking the active drug or a placebo.

What are double blind, randomized, controlled studies?



Randomized: the study participant is assigned randomly to either active drug or placebo

Controlled: The study drug is compared to an known treatment (active control) or to a placebo (inactive compound that appears identical to the active drug).



Who can participate in clinical trials?

- The study protocol is a research plan or roadmap designed to best answer the question posed by the study.
- The protocol includes criteria for who is eligible. This could include:
 - people with HD at early, mid- or late-stage
 - People at 50% risk for the HD CAG expansion
 - Family members who are not at risk for HD, or people who have undergone predictive testing and don't have the HD CAG expansion
 - People with the HD gene expansion who don't yet have symptoms

Who can participate in clinical trials?

- Ability to give informed consent
- Age criteria
- Other medical conditions
 - Safety labs
- Psychiatric conditions
 - Must be stable
- Other medications
 - Some may not be allowed

How much time is required?

- Studies vary in duration, number of activities carried out at study visits
 - Observational studies can last many years
 - Visits are usually just once a year
 - Clinical trials could last 3 months – 5 years
 - Visits are frequent for Phase II trials (every 1-4 weeks)
 - Visits every 1 – 6 months in longer Phase III studies
 - Initial study visits usually last 2 - 3 hours
 - Follow-up visits may take as little as 15 minutes, or as long as several hours
 - Sometimes there may be telephone contacts made between visits

What kinds of activities take place during study visits?

- Initial visit: informed consent
 - Principles of protection of human subjects require approval of Institutional Review Boards.
 - Informed consent includes a description of the aims of the study, the procedures that will take place, the potential benefits, side effects and risks to participants.
 - Participants are invited ask questions for clarification
 - Often 18 pages long
 - Takes about 45 minutes

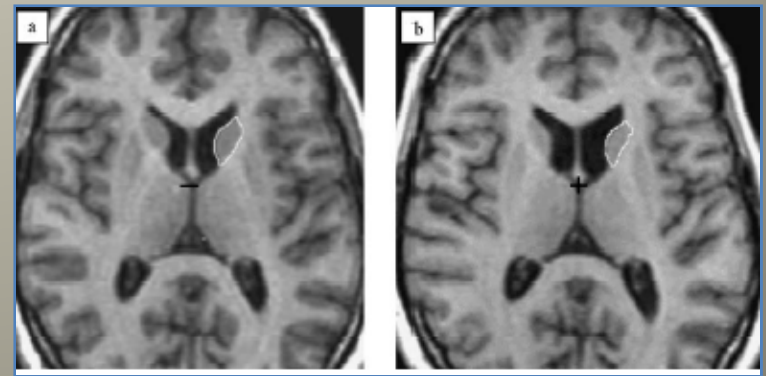
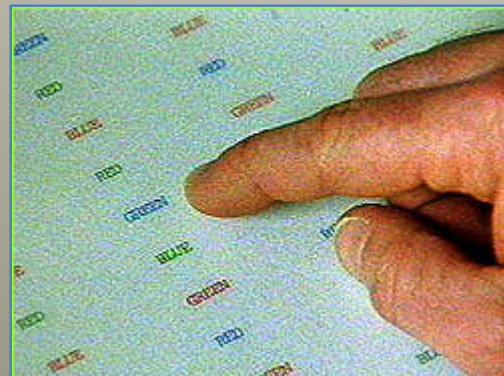
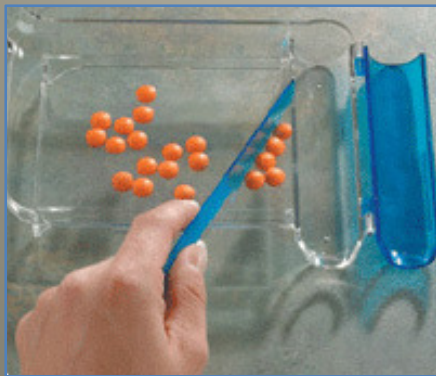
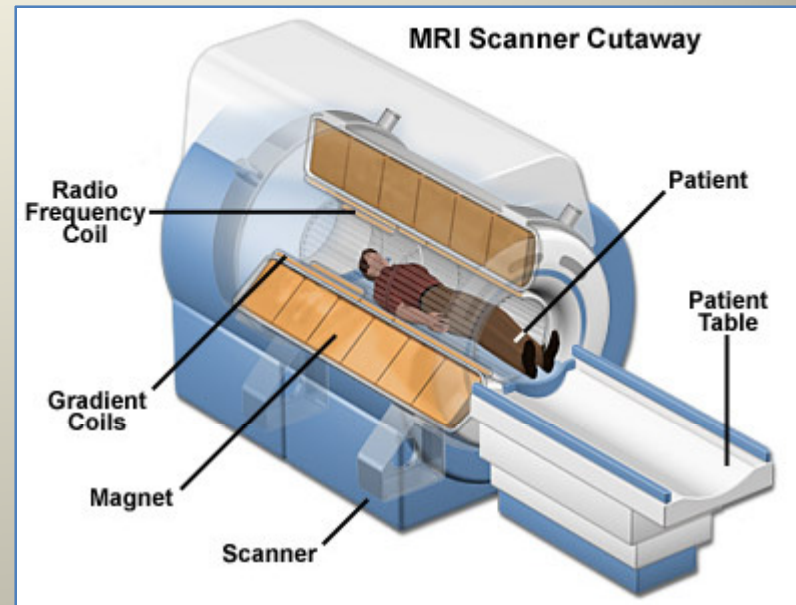
What kinds of activities take place during study visits?

- Measuring “vital signs”: blood pressure, pulse
- Drawing a blood sample(s)
- Meet with site investigator to ask how participant is doing, any health changes, any side effects, possibly physical exam



What kinds of activities take place during study visits?

- Meet with site coordinator to ask about mood or behavior changes, test thinking, turn in empty study medication bottles and count pills
- MRI brain scan
- Neuropsychological tests (memory, thinking, etc)



Read the color of the word out loud

red blue orange purple
orange blue green red
blue purple green red
orange blue red green
purple orange red blue
green red blue purple
orange blue red green
green purple orange red

red white green brown
green red brown white
white brown green red
red white green brown
brown green white red
white brown red green
green white brown red
red brown green white

What about privacy?

- Confidentiality is a prime concern to the HSG
- Participant names and medical information are known to study site personnel, but NOT to anyone else involved in the study
- Participants are assigned an ID code at the sites; all communications with the central site use ID code, not names
- Blood samples are assigned bar codes to further protect privacy
- To date, there have been no inadvertent disclosures of identity or gene status



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What happens after a clinical trial is over?

- The Huntington Study Group is committed to communicating the results of completed clinical trials to participants
- Timing: as soon as the study data is “locked”
- Mechanism:
 - 1st: conference call with participants
 - HSG website, press releases
- Learning whether participant was assigned to active drug or control group may take weeks – months longer.



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Current observational studies

Study	Number of volunteers	Target participants
PHAROS 1999-2010	1001	people at 50% risk for HD CAG expansion who chose NOT to undergo predictive testing, followed every 9 months for 10 years
PREDICT 2001-2013	1000	people who have undergone testing for the HD CAG expansion, followed annually since 2001
COHORT 2006-	>1800	people who either have manifest HD, are at 50% risk, their family members, spouses who are not at risk , followed annually since 2004



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Examples of recently completed clinical trials

Study	No. of volunteers	Medication	Results
TETRA-HD	84	Tetrabenazine	Positive – FDA approved 2008
TREND-HD	316	Ethyl-EPA (fish oil)	Not effective
DIMOND-B	90	Dimebon	Looks promising; Phase 3 trial planned
DOMINO	100	Minocycline	Not effective



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Basic Research

Preclinical

Phase 1

Phase 2

Phase 3

Available

The HD Pipeline

Source: Marsha Miller, HDSA website

FDA approved

Phase 3

Phase 2

Phase 1

Pre-clinical

NUTRITIONAL SUPPLEMENTS

Creatine (HSR)

CoQ10 (HSG)

Ethyl EPA (Amarin)

DOPAMINE BLOCKERS OR STABILIZERS

Tetrabenazine (Zenelan)

ACER - 116 (Neurosearch)

ANTI-APOPTOSIS

Minocycline (HSG)

TUDCA (HSG)

Methazolamide

Gene Therapy (Neurologix)

GLUTAMATE BLOCKERS OR STABILIZERS

Memantine

Dimebon (Medivation)

BDNF INDUCERS

Galatopram (Celoxa)

Ampakines (Cortex)

Cysteamine (Raptor)

CEP-1347 (Cephalon)

OTHER NEUROTROPHIC FACTORS & MIMETICS

FGF - 2 (Neurobiological Technologies)

Neurturin (Ceregene)

TRO47490 (Trophos)

HDAC INHIBITORS

LVN - 0264 (Envida)

HDACi 4b (Repligen)

ANTIOXIDANTS / ANTI-AGING

CoQ10 analogs (Edison)

Oxygen (Intellect Neurosciences)

Birtan inducers (Birtan)

AUTOPHAGY

Venipamil

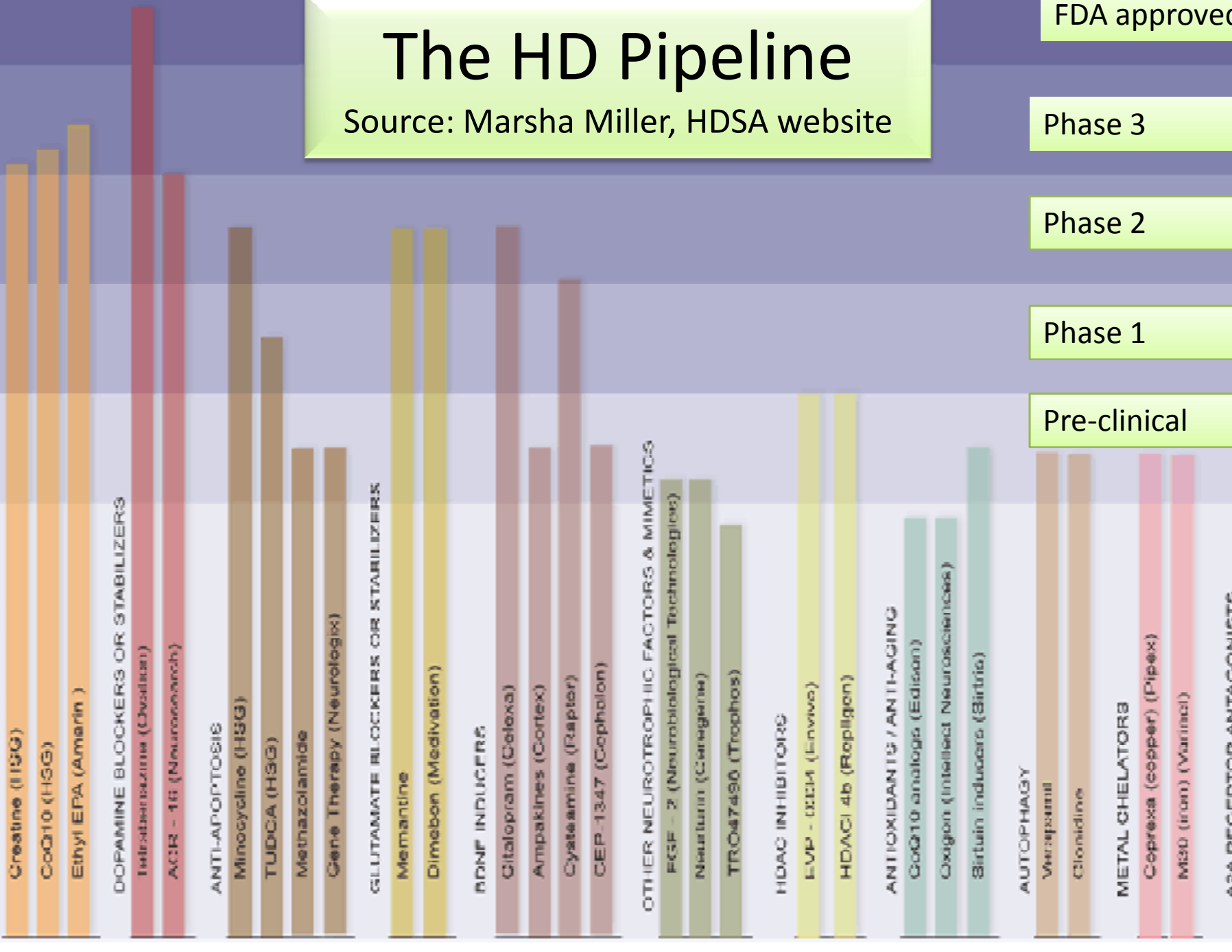
Clonidine

METAL CHELATORS

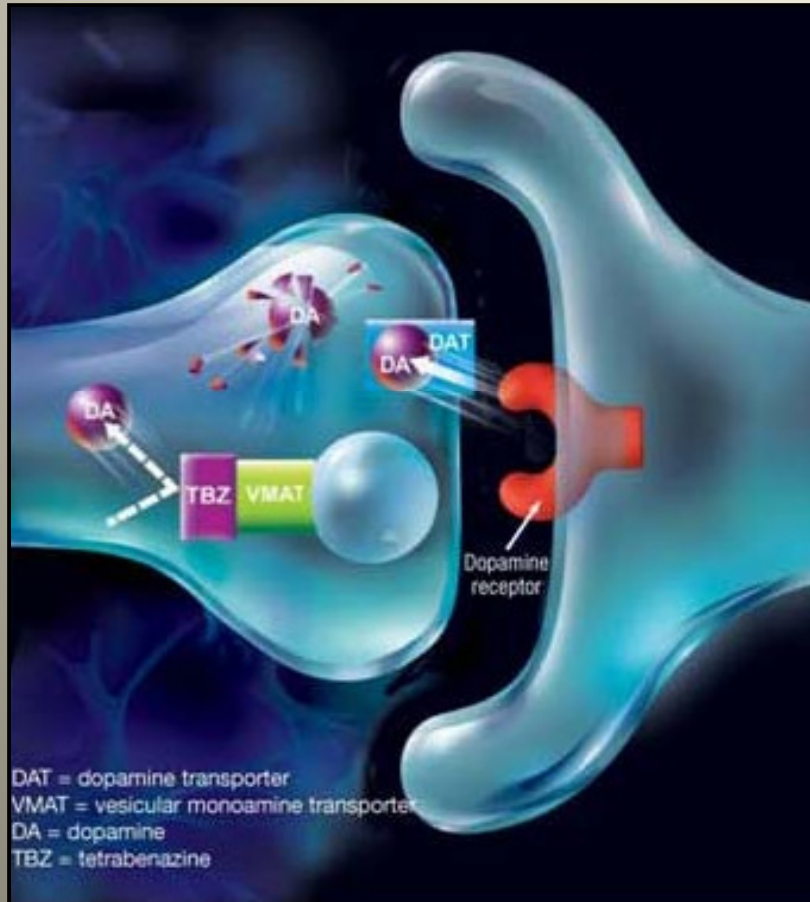
Coprexa (copper) (Pipex)

M30 (iron) (Yannick)

ASA RECEPTOR ANTAGONISTS

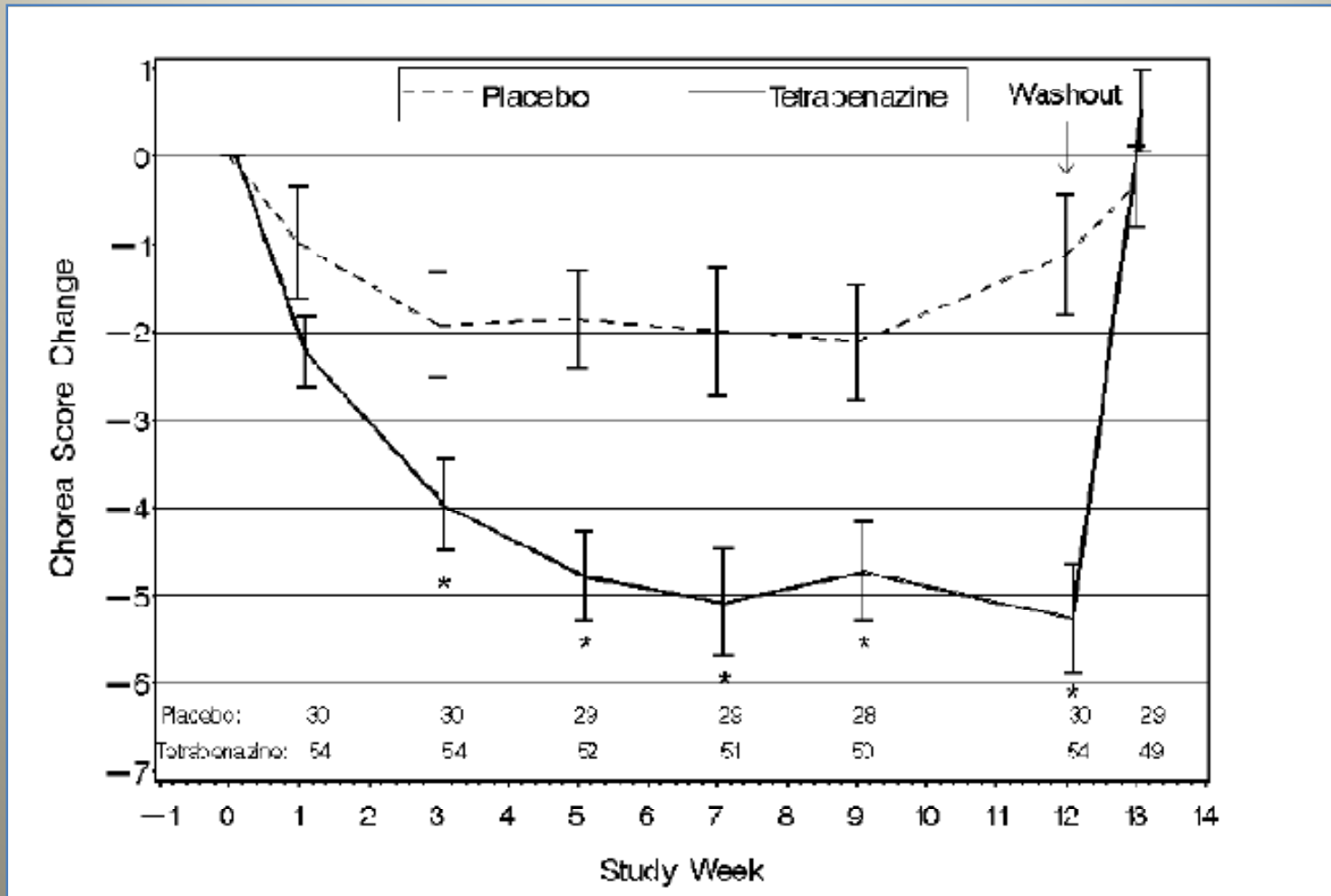


2008: First drug approved by FDA for HD Tetrabenazine (*TETRA study*)



- Double-blind, placebo-controlled study of tetrabenazine in manifest HD
- 84 people with HD, randomized 2:1 to TBZ or placebo for 12 weeks
- Primary endpoint: chorea score

Results: Tetrabenazine

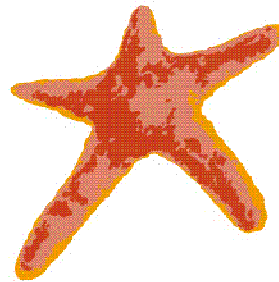


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Tetrabenazine: Xenazine



Lundbeck



Getting involved in research: Five good reasons for participating

from Terry Tempkin

- You've always wanted to help
- You want to contribute to the efforts for a cure
- You have the time
- You care about HD research and future generations
- Participating in research makes you feel good about helping to advance treatment and find a cure

Reasons for NOT participating in clinical research

- I don't have enough time
 - Work, school, family activities
 - Caregiving for family members
- I'm concerned about my privacy.
- It's too stressful to think about HD.
- I don't want to have physical exams, or thinking tests; I'm already worried enough.
- I hate having blood tests!
- It's too far to drive to the nearest study site.
- I don't want to be on a placebo.

There are reasons for and against
volunteering for clinical research.....

You must decide
what's best for YOU



Active HD studies



STUDY	Length of study	No. of visits	Participants		
			Age	Number	HD status
COHORT	Ongoing	annual	15+	>1800	All members of a family with HD; can also participate in other studies
PREDICT	Ongoing	annual	18+	1000	People who have tested and know their CAG repeat length
HART	4 months	7	18+	220	People with early-mod HD
2CARE	5 years	14	16+	600	People with early HD
CREST-E*	3 years	16	18+	650	People with early HD
PREQUEL*	5 months	7	18+	90	People with the HD CAG expansion who don't have symptoms

COHORT



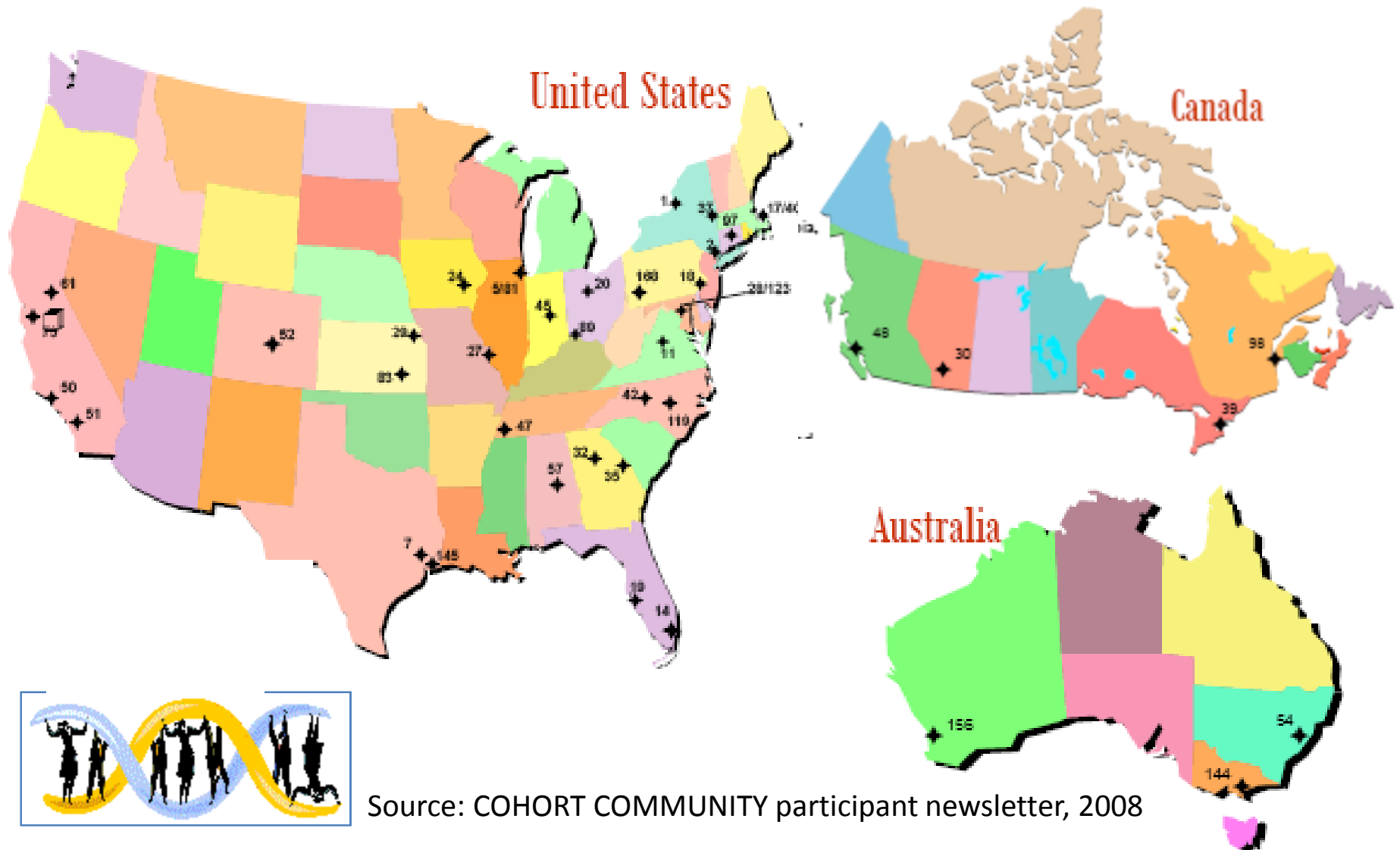
- **Cooperative Huntington's Research Trial**
- Long-term observational trial with annual visits
- Sponsor: CHDI
- **Goal:** to learn more about the clinical features of HD in order to plan future research studies aimed at delaying onset or slowing progression of HD
- Annual visit
- Currently > 40 sites in US, Canada and Australia; ~1800 participants enrolled.
- Includes: clinical exam, collecting blood for genetic testing, collecting family history, and collecting and storing blood and urine for future research.

COHORT



- Who's eligible? People with the HD CAG expansion with or without symptoms, their parents, spouse, siblings, children or grandchildren > 18 years.
- *New: People who have undergone testing but don't have the HD CAG expansion.*
- *New: extension to adolescents age 15-17*
 - *Eligible if a parent at-risk or with CAG gene expansion is enrolled in COHORT*
 - *Give informed consent*
 - *Consent to blood draw for CAG repeat length*
 - *Optional to consent for collection of additional blood samples*

COHORT: Where are we?



Source: COHORT COMMUNITY participant newsletter, 2008

PREDICT study



- Sponsor: NIH, CHDI
- Trial type: Observational
- Goals:
 - To determine what the earliest signs of HD are and when they begin
 - To determine what the most accurate tests are that clinicians can use in detecting the onset of HD
 - To determine what factors influence the age at which a person carrying the HD gene develops the illness
- Who's eligible?
 - People who know their gene status and have no symptoms of HD

PREDICT-HD Study Activities

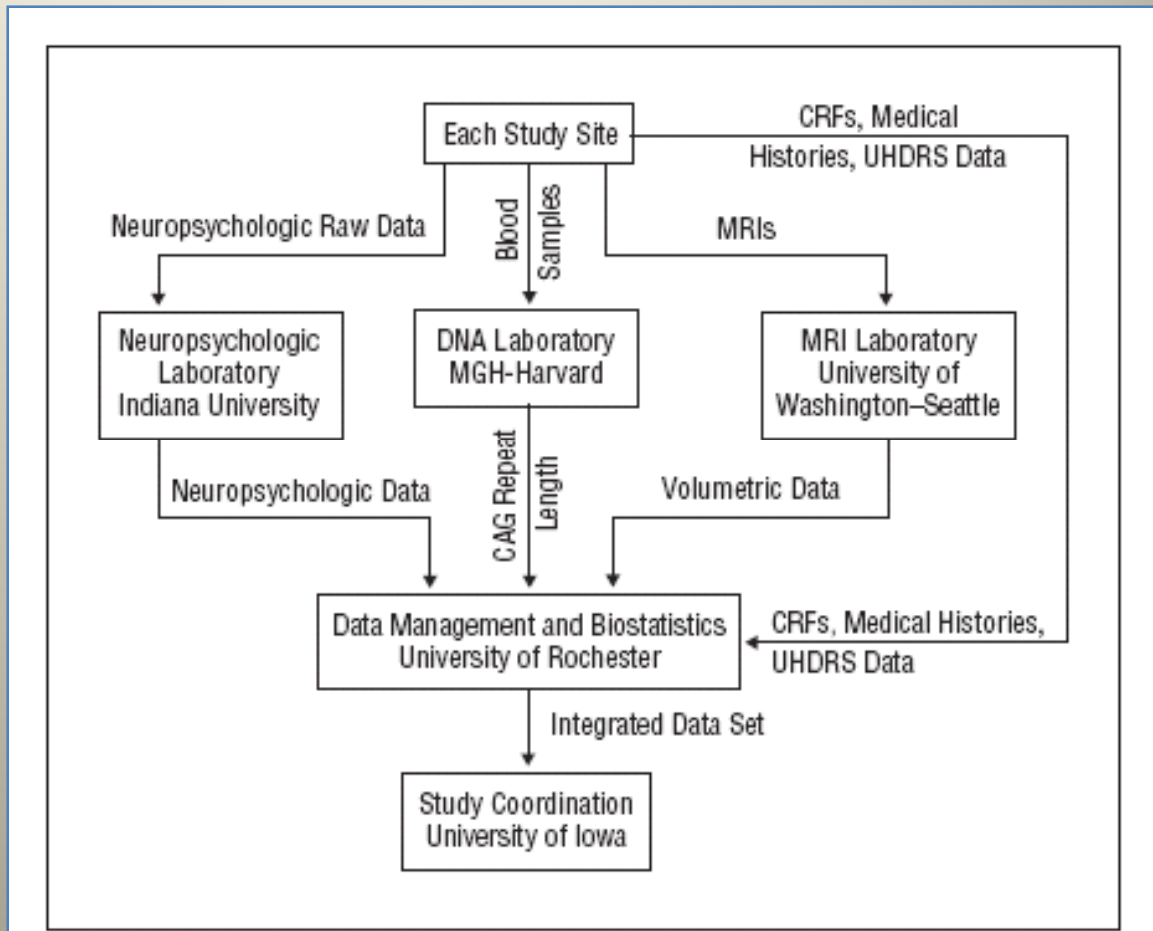
Questionnaires

Neuro exam

Blood test

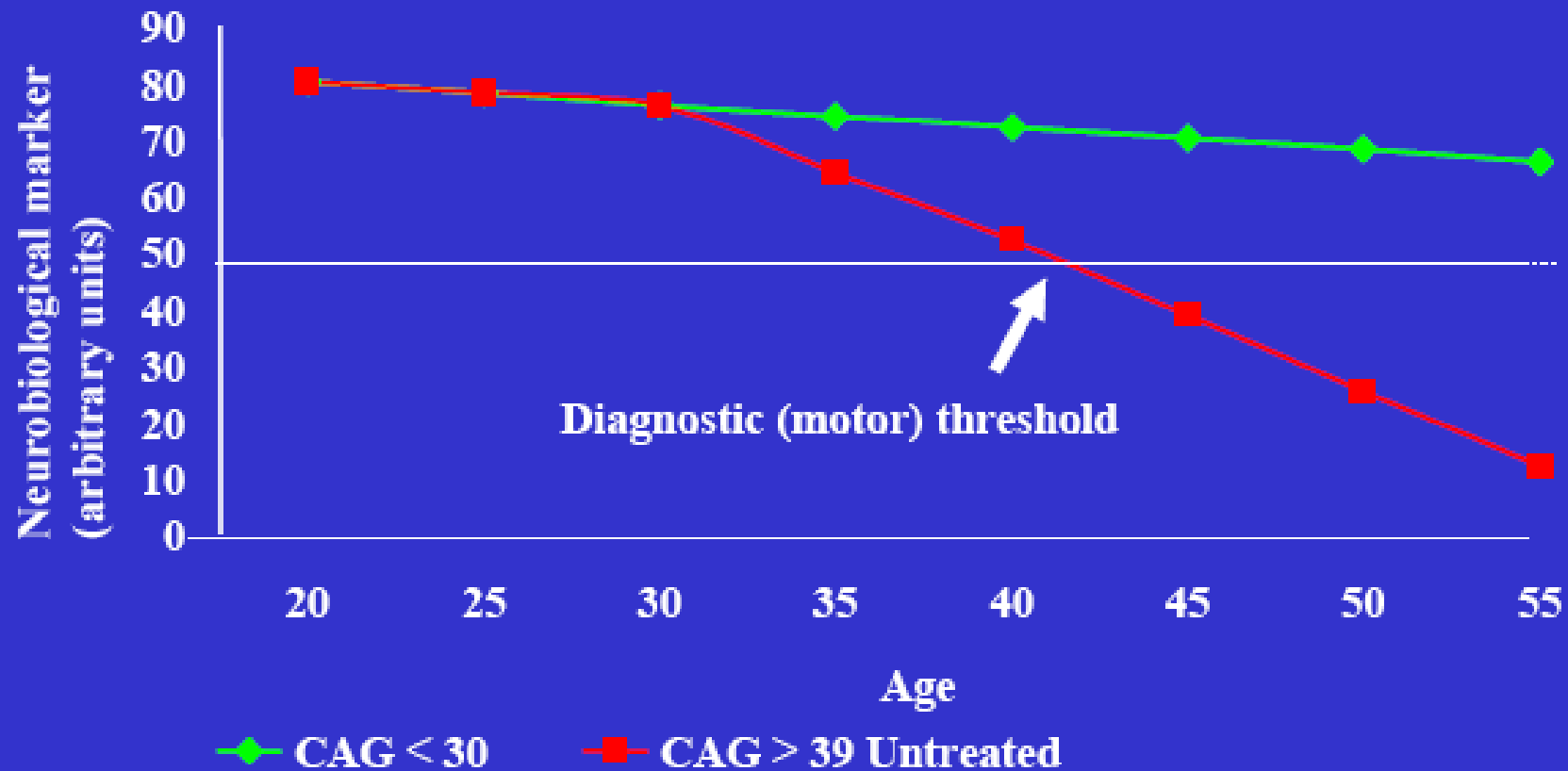
Brain MRI

Neuropsychological tests



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HD Over the Lifetime



Paulsen JS, Hayden M, Stout JC and the PREDICT-HD Investigators.
Preparing for clinical trials: The PREDICT-HD study. *Arch Neurol* 2006;63:883-890



2CARE Study



- Sponsor: NIH, Phase III
- Drug: Coenzyme Q10 2400 mg/day for 5 years
- Trial type: Double-blind, randomized, placebo controlled
- Previous trials:
 - CARE-HD (CoQ10 600 mg/d) suggested slowing of disease progression
 - Pre-2CARE assessed safety and tolerability of different doses
- Primary endpoint: slowing in rate of worsening of HD



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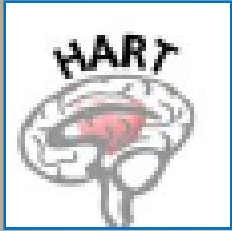


2CARE study update

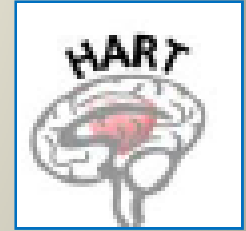


- 41 sites active
 - US: 37
 - Canada: 3
 - Australia: 1
- Enrollment: near 300 (plan for 608), which is slower than predicted
- We need more participants!!
- Data Safety Monitoring Board meets regularly





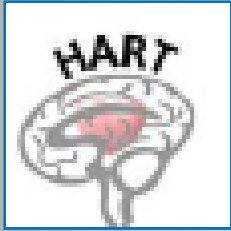
HART trial



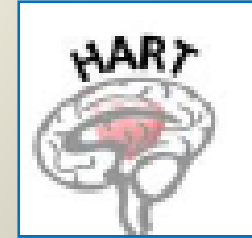
- Sponsor: Neurosearch, Sweden
- Compound: ACR16
- Mechanism: Dopamine stabilizer
- Trial type: IIb
- Previous trials: Phase II in 28 patients with HD for one month showed improvement in voluntary movement and gait



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HART trial



- Design: 3 different doses vs placebo in 220 participants
- Duration: 3 months
- Outcome measure: primary is motor function, secondary measures are cognition and psychiatric function
- We need more participants!!



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CREST-E study



- Sponsor: NIH, Phase III
- Drug: Creatine 5 to 40 gm/day*
- Trial type: Double-blind, randomized, placebo controlled
- Previous trials: Creatine in HD
- Primary endpoint: slowing in rate of progression of HD

**Must have medical supervision at high doses to avoid toxicity.*



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PREQUEL: coming soon



- Sponsor: NIH
- Drug: Coenzyme Q10
- Participants: 110 people with the HD CAG expansion with no motor findings of HD
- Design: all groups on active treatment
 - 600, 1200, 2400 mg CoQ10
- Planned launch: summer 2009



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Coming soon.....

- Sponsor: Medivation
- Study Conduct: HSG and Euro HD Network (EHDN)
- Drug: Dimebon
- Design: Phase III trial, double-blind, randomized controlled design
 - Duration: 6 months
- Participants: early to mid-stage manifest HD

Are we making progress?

- The HD community and scientists are partners in working together to find the cure
- Nearly 4000 people are in observational studies
- More than 1000 people are in clinical treatment trials or have recently participated, and we will need another 1500 participants for current and upcoming clinical trials
- The first drug for HD has been approved and is available to patients.

What do we need?



WE NEED YOU!





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The Cure



HDSA



1993: the gene

NEUROSEARCH



Mt. Everest



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