Clinical research in HD

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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

Dr. Wheelock is 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 trial?
• What is an observational trial?
• Who can participate in research studies?
• How much time does it require?
• What about confidentiality?
• Why do people volunteer to participate in research?
• Why do people decide not to volunteer?
• 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
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
The study team

• Site investigator
• Site coordinator
• Research assistants: handling blood samples, data entry
What kinds of activities take place during study visits?

• Initial visit: informed consent
  – 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 to 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
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.
What happens after a clinical trial is over?

• The Huntington Study Group is committed to communicating the results of completed clinical trials to participants
• Mechanism:
  – 1st: conference call with participants
  – HSG website, press releases
• Timing: as soon as the study data is “locked”
• Learning whether participant was assigned to active drug or control group may take weeks – months longer.
<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHAROS</td>
<td>1001</td>
<td>people at 50% risk for HD CAG expansion who chose NOT to undergo predictive testing, followed every 9 months for 10 years</td>
</tr>
<tr>
<td>PREDICT</td>
<td>1000</td>
<td>people who have undergone testing for the HD CAG expansion, followed annually since 2001</td>
</tr>
<tr>
<td>COHORT</td>
<td>1800</td>
<td>people who either have manifest HD, are at 50% risk, their family members, spouses who are not at risk, followed annually since 2004</td>
</tr>
</tbody>
</table>
### Examples of recently completed clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Medication</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TETRA-HD</td>
<td>84</td>
<td>Tetrabenazine</td>
<td>Positive – FDA approved 2008</td>
</tr>
<tr>
<td>TREND-HD</td>
<td>316</td>
<td>Ethyl-EPA (fish oil)</td>
<td>Not effective</td>
</tr>
<tr>
<td>DIMOND-B</td>
<td>90</td>
<td>Dimebon</td>
<td>Looks promising; Phase 3 trial planned</td>
</tr>
<tr>
<td>DOMINO</td>
<td>100</td>
<td>Minocycline</td>
<td>Not effective</td>
</tr>
</tbody>
</table>
The HD Pipeline
Source: Marsha Miller, HDSA website

<table>
<thead>
<tr>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>FDA approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUTRITIONAL SUPPLEMENTS</td>
<td>CREATINE (H4G)</td>
<td>COQ10 (H4G)</td>
<td>ETHYL EPA (Armarin)</td>
<td>Dopamine Blockers OR STABILIZERS</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Nicotinic Acetylcholine Receptor Agonists</td>
<td>Nicotine</td>
<td>Cholinergic</td>
<td>Cholinergic</td>
</tr>
<tr>
<td>Memantine</td>
<td>Dimeboxane (Medivation)</td>
<td>Citalopram (Coca)</td>
<td>Ritaline (Rapiser)</td>
<td>TRC-4180 (Tranora)</td>
</tr>
<tr>
<td>Neurotransmitters</td>
<td>Neurotransmitters</td>
<td>Neurotransmitters</td>
<td>Neurotransmitters</td>
<td>Neurotransmitters</td>
</tr>
<tr>
<td>GABAergic</td>
<td>GABAergic</td>
<td>GABAergic</td>
<td>GABAergic</td>
<td>GABAergic</td>
</tr>
</tbody>
</table>

Basic Research

Other Neurotrophic Factors & Mimetics

PDGF -2 (Neurotrophin Biological Techniques)

Neurturin

BRAIN BIOLOGY

Autophagy

Metal-Chelators

Cu, Zn SOD (CuZnSOD)
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
Tetrabenazine: Xenazine
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

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Length of study</th>
<th>Number of visits</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>COHORT</td>
<td>Ongoing</td>
<td>1</td>
<td>All members of a family with HD; can also participate in other studies</td>
</tr>
<tr>
<td>PREDICT</td>
<td>Ongoing</td>
<td>1</td>
<td>People who have tested and know their CAG repeat length</td>
</tr>
<tr>
<td>HART</td>
<td>4 months</td>
<td>7</td>
<td>People with early-mod HD</td>
</tr>
<tr>
<td>2CARE</td>
<td>5 years</td>
<td>14</td>
<td>People with early HD</td>
</tr>
<tr>
<td>CREST-E*</td>
<td>3 years</td>
<td>16</td>
<td>People with early HD</td>
</tr>
<tr>
<td>PREQUEL*</td>
<td>5 months</td>
<td>7</td>
<td>People with the HD CAG expansion who don’t have symptoms</td>
</tr>
</tbody>
</table>
COHORT

• *Cooperative Huntington’s Research Trial*
• Long-term observational trial with annual visits
• **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 and Canada; ~1800 participants enrolled.
COHORT

• Includes: clinical exam, collecting blood for genetic testing, collecting family history, and collecting and storing blood and urine for future research.

• Who’s eligible? People with the HD CAG expansion with or without symptoms, their parents, spouse, siblings, children or grandchildren > 18 years.

• New: extension to adolescents age 15-17
PREDICT study

- Sponsor: NIH
- 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
Figure 1. Intervention model for adult-onset disease. Downward-pointing arrow indicates administration of an effective prophylactic neuroprotective agent in a treated individual; upward-pointing arrow, clinical diagnosis of an untreated individual.
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
2CARE study update

- 39/43 sites approved
- Enrollment: near 300 (plan for 608), which is slower than predicted
- 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
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
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.

H · S · G
Huntington · Study · Group
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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The Cure

Research & treatments

HDSA

1993: the gene

Mt. Everest

Chdi

Lundbeck

NeuroSearch

NATIONAL INSTITUTES OF HEALTH

Medivation

Hereditary Disease Foundation