HDBuzz

Huntington's disease research news. In plain language. Written by scientists. For the global HD community.

HDBuzz primer: Clinical trial designs and phases

HDBuzz untangles hope from hype in clinical trial announcements

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The last few years have been full of announcements about the results of clinical trials for HD drugs, but it can be surprisingly hard to understand what these results actually mean. What seems like a simple question – did a drug work or not – turns out to be more complicated than you'd expect. HDBuzz is here to help HD families untangle hope from hype when it comes to clinical trial announcements.

The path to success: How new drugs get approved

A drug's life begins long before that drug ever appears on the shelf in the pharmacy or your doctor's office – on average, about twelve *years* before. So, what exactly happens during all the time it takes for a new drug to get to market? Because new drugs are unproven chemicals that could be dangerous to humans, much of this time is spent in testing. New drugs have to be approved as safe and effective by government regulators before they're used in the clinic. This approval process involves a tremendous amount of work - and thus a tremendous amount of time.

Worldwide, each country has its own legally specified path toward drug approval. We'll focus in this article on what happens in the US, but similar drug approval pathways exist all around the world.

The path toward drug approval requires rigorous testing to prove that a drug candidate is safe and effective in humans.
Image credit: freeimages

In the US, the Food and Drug Administration (FDA) is responsible for approving new drugs. A company with a new drug candidate, for example one that might help in Huntington's disease, starts the approval process by giving the FDA three types of information about their drug candidate: animal studies proving that it is not toxic, manufacturing information showing that it is being made properly, and clinical plans to test it in people.

After receiving this information, the FDA can give the company the green light to start testing the drug candidate in people. Surprisingly, at this early stage, the FDA **does not** make the company prove that their drug candidate is beneficial – just that it is expected to be safe in humans.

Once the FDA grants a drug company permission to test its drug candidate in people, the real work begins. The company now has to prove that the drug candidate safely and effectively fights human disease, which it does by running clinical trials (which we'll focus on for the rest of this article). Only after successfully completing many clinical trials do drugs get approved for human use.

Clinical trials 101: Design

Clinical trials form the cornerstone of the drug approval process, so knowing how these trials are done is important. In this section, we'll talk about some key fundamentals that apply to all clinical trials – including those for HD drugs.

What are clinical trials?

In essence, clinical trials are **very carefully planned** experiments designed to answer specific questions about how a drug affects human beings. Clinical trials typically address one, or both, of the following questions: *is the drug safe* and *does the drug work*.

Answering the first question – is the drug safe – involves monitoring the people who take the drug for unexpected, unpleasant, or dangerous side-effects. The FDA wants to keep dangerous drugs off the market, so it requires drug companies to look for these side-effects very carefully. Because we can't tell the future, though, we don't know ahead of time what types of side-effects a drug might have. Clinical trials participants therefore undergo lots of tests and questioning to detect a broad range of potential drug-related side-effects.

The second type of question that clinical trials ask is whether a drug improves some aspect of a disease. Answering this question can be hard, because human diseases – and brain diseases in particular – are complex. For example, all HD families know that HD affects every part of a person's life: patients have mood problems, thinking problems, movement problems, and ultimately die very young. An effective HD drug might improve **any** of these things, and so drug companies must design their clinical trials very carefully to detect drug-related disease improvements.

What makes a clinical trial successful?

The FDA has a very clear definition of what constitutes success in a clinical trial. This definition centers around something called a **primary endpoint**.

> "From the FDA's perspective, the primary endpoint is the **only** outcome of a trial that matters for declaring that trial a success or failure."

A primary endpoint is the main question asked in a clinical trial - the one for which the drug company most wants to find an answer. In a trial for an HD drug, for example, the primary endpoint might be whether the drug is safe, reduces movements, makes thinking symptoms better, or even delays the onset of the disease. You can think of a trial's primary endpoint as the specific end goal of drug treatment – the thing we hope the drug does.

The FDA makes drug companies define their primary endpoints, as well as exactly how many participants they need to test those endpoints, ahead of time *before* a trial starts. This requirement prevents the misinterpretation or overinterpretation of the trial's results. If a drug achieves its pre-defined goal (and thus works the way the drug company anticipated), we say that the trial "met" its primary endpoint.

Based on this idea, the FDA defines clinical trial success in a black-and-white way: a trial that meets its primary endpoint is a success; otherwise, it's a failure. From the FDA's perspective, then, **the primary endpoint is the only outcome of a trial that matters** for that trial's success.

Beyond the primary endpoint

Of course, a drug company running a clinical trial very well might want to ask more questions than simply the one specified in the primary endpoint. These other questions are called **secondary endpoints**.

Secondary endpoints are meant to help companies look at treated patients as broadly as they can to determine the effects of a drug. For example, if an HD drug was expected as its primary endpoint to improve movement symptoms, a secondary endpoint might be whether the drug helps patients control their emotions better. Drug companies can have as many secondary endpoints as they like in a clinical trial – often there are several, and sometimes there can be dozens.

Unlike primary endpoints, secondary endpoints aren't the be-all-end-all for whether the FDA calls a trial successful. **Even if a secondary endpoint works out, it's not sufficient on its own to consider the trial successful** – because, as we talked about already, success in a clinical trial depends on that trial's *primary* endpoint.

Nevertheless, secondary endpoints do give us some very important information. They let us detect potentially unexpected ways that a drug improves a disease, thereby giving us a better feel for how drugs work in humans. Thus, secondary endpoints are informative because they tell us what sorts of effects to focus on in trials down the road.

Dealing with multiple endpoints

If primary endpoints are what the FDA really cares about, though, why not just call *every* question – primary endpoints, secondary endpoints, the whole kitchen sink – a primary endpoint so that they all matter to the FDA? Wouldn't this give a drug the best chance of success?

Adding endpoints to a clinical trial actually makes it harder for that trial to succeed.
Image credit: freeimages.com

Well, not really. To understand the problem with this kitchen-sink approach, let's use an analogy.

Imagine that a teacher was explaining the laws of probability to a class full of students, each of whom had a coin. If the teacher had a single student flip the coin 5 times, what are the chances that student would get

heads (or tails) all 5 times? Some simple math tells us that there is a 1 in 32 chance such a thing would happen. So, if there's just one student doing this "experiment", it's pretty unlikely that we'd successfully see 5 heads in a row.

But, imagine the teacher had all 32 students in the class do the experiment at the same time. Now what? With a 1 in 32 chance of success, it's pretty good odds that someone would be lucky enough to get 5 heads in a row when the whole class was doing the experiment.

In exactly the same way, **each additional endpoint in a clinical trial is basically adding another kid to the class flipping coins**. More endpoints gives an experimental drug more chances for "success", just by chance.

When scientists analyze clinical trial results, they have to take endpoints from studies with lots of them with a grain of salt. If we measure lots of endpoints, we have to have a higher standard for how impressive any positive effect we see.

Scientists do careful math to account for multiple comparisons when they report clinical trial results to scientific journals or the FDA. However, HD scientists have not always been so careful in press releases and news reports, which is often the source of information for patients and families.

Do multiple comparisons really matter?

To convince you that drawing false conclusions this way really does matter, let's look at example of what can go wrong when we ignore this problem of multiple comparisons.

Way back in 2005, scientists tested a drug called ethyl-EPA in an HD clinical trial. Ethyl-EPA stabilizes the powerhouses that give brain cells energy and improves brain cell health, so there was reason to believe it might help in HD. The trial's primary endpoint asked whether ethyl-EPA treatment could improve motor symptoms in HD patients, and its secondary endpoints focused on changes in other symptoms and patient subgroups.

Ignoring multiple comparisons is dangerous because it can lead to false conclusions about a clinical trial's success.
Image credit: freeimages.com

Unfortunately, the trial didn't meet its primary endpoint: ethyl-EPA didn't improve motor symptoms in HD patients any more than a dummy drug. Based on the FDA's black-and-white definition of success, the trial failed.

However, the math folks analyzing the trial noticed something. Even though the primary endpoint didn't work out, the trial did meet a *secondary* endpoint asking if ethyl-EPA improved motor symptoms in patients with relatively mild HD mutations. Therefore, it seemed like ethyl-EPA might actually work – but only for patients in this specific group.

Remember, though, that symptom improvement in this patient subgroup **was not** the trial's primary endpoint and that we can't interpret trial success from a secondary endpoint. Doing so runs us full force into the problem of multiple comparisons. The trial wasn't *designed* to deal with multiple endpoints, so treating it like it was puts us in the statistical danger-zone - **where our conclusions may be false**.

Nevertheless, based on the "success" of this secondary endpoint, a new clinical trial was designed to test ethyl-EPA in HD. This time, the primary endpoint asked if ethyl-EPA improved motor symptoms *specifically* in patients with mild HD mutations. Unfortunately, just as in the original trial, ethyl-EPA *still* didn't improve motor symptoms, even for these specific patients.

Therein lies the danger of ignoring multiple comparisons – and interpreting secondary endpoints like primary endpoints – in clinical trials. When we don't correct for multiple comparisons, the conclusions we draw about a trial are often mistaken. Such false conclusions raise our hopes about a drug, only to dash them when subsequent trials fail.

The bottom line is that if a company, researcher, or news story is talking about clinical trial results, it's important to know whether they've corrected for multiple comparisons. If they haven't, you'd better take their conclusions with a grain of salt.

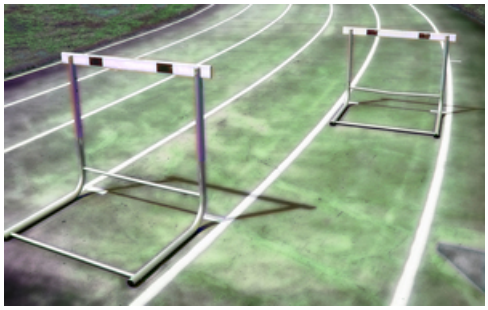
Clinical trials 102: Phases

Now that we've covered the fundamentals of clinical trial design – and why accurately understanding these fundamentals is important for interpreting trial results – we can talk in more detail about the types of clinical trials a drug candidate undergoes on the path to FDA approval.

You can think of clinical trials like a system of hurdles that every drug candidate must clear before being approved for human use. These hurdles sometimes make the path toward available treatments seem long, but they're actually critical for protecting people from exposure to potentially dangerous – or just plain ineffective – drugs.

Phase 1: Is this drug safe?

The first hurdle a drug candidate has to pass involves proving that it's safe in humans. Traditionally, this is established in a phase 1 clinical trial, in which a small number of healthy volunteers take the drug to see if it has unexpected dangers.



Clinical trials are like a system of hurdles that every drug candidate must clear before being approved for human use.
Image credit: freeimages.com

Because their primary endpoint is **safety**, phase 1 trials are successful only if the new drug can be given without causing unacceptable side-effects.

The people who participate in phase 1 clinical trials are often the first humans to receive a new drug, so these trials are normally done in (brave!) healthy volunteers rather than in vulnerable patients. However, some phase 1 trials – those posing risks that are ethically unacceptable to ask healthy individuals to take – do assess safety in patients.

For example, phase 1 trials of cancer chemotherapy drugs are commonly done in cancer patients because of these drugs' severe toxicity and side-effects.

Similarly, phase 1 trials of HD drugs are sometimes done in HD patients rather than healthy volunteers because of ethical concerns. One such trial, the 2015 Isis trial of huntingtin-silencing drugs, is assessing safety in HD patients because it would be unethical to ask healthy volunteers to undergo the trial's invasive drug-administration procedures.

Regardless of who the participants in phase 1 clinical trials are, though, the thing to know about these trials is that **they are only interested in whether a drug is toxic** – *not* whether it actually benefits patients. If you read a news story about a new HD drug clearing a phase 1 hurdle, therefore, remember that the drug still has a lot more hurdles to clear before we'd know whether it could help in HD.

Phase 2: Is this drug useful?

Of course, the end goal of clinical trials is to prove that new drugs *do* help in HD. Moving in this direction, a drug candidate that clears the phase 1 safety hurdle can graduate to **more focused safety and efficacy testing** in a phase 2 trial. Phase 2 clinical trials usually have a larger number of patients than phase 1 trials (from dozens to hundreds), and they are done primarily in people with the disease that the drug is intended to treat.

Surprisingly, some phase 2 trials are designed with safety as their primary endpoint – just like phase 1 trials. In HD, such safety-focused phase 2 trials have included Prequel, Reach2HD, DIMOND, Omeros' OMS824 study, and Pre-CREST. Most of these trials also included a number of secondary endpoints looking at HD symptoms in treated patients, but their ultimate success or failure was dependent *only* on the safety of the drugs they tested.

If you've been paying attention, you probably want to know why drug companies would ever run phase 2 trials with safety as a primary endpoint. What do they get from clearing this hurdle that they wouldn't already have from a phase 1 trial?

First, like many things in life, the answer comes partly down to money. Running human clinical trials is incredibly expensive. Many companies running HD trials simply don't have the resources to run efficacy-focused phase 2 trials. A successful safety-focused phase 2 trial, though, might bring in funding for later trials to test whether a drug works. Second, as noted above, safety-focused phase 2 trials almost always have additional *secondary* endpoints focused on efficacy. These endpoints look at the effects of the drug on a whole host of signs of disease – without running the risk of trial failure if some endpoints don't work out. This information helps companies design later efficacy-focused trials that are centered on the right endpoints and have a

Remember: saying that a phase 2 trial succeeded is meaningful **only** when you know what that trial's primary endpoint was.

greater chance of success.

Some phase 2 trials do ask directly whether the drug under study affects the disease it's intended to treat. Efficacy-focused phase 2 trials use measures of symptoms as their primary endpoints. In HD, such efficacy-focused phase 2 trials include the Amaryllis, Legato, and Pride-HD trials. If you hear that one of these trials met its primary endpoint, you'll know that the drug being tested actually affected HD symptoms.

The take-home message about phase 2 clinical trials is that both safety- and efficacy-focused trials move potential new HD drugs toward the clinic. For practical purposes, however, remember that **saying that a phase 2 trial succeeded is only meaningful when you know what the primary endpoint of that trial was**. No matter how exciting the results are, a phase 2 trial focused on safety alone is not sufficient to get drug approval.

Phase 3: Does this drug really work?

Drug candidates that successfully complete phase 2 clinical trials can move onto the final hurdle in the long journey toward drug approval – testing in phase 3 clinical trials.

Phase 3 clinical trials are very large, expensive, and typically long trials that carefully examine the effects of a drug on disease symptoms. Phase 3 trials often have from hundreds to thousands of patients in them, and they can take years to complete. These trials take so long both because they have so many participants and because they monitor these participants for long periods to prove that a drug really is safe and effective.

Phase 3 clinical trials always have **efficacy** as their primary endpoint. A successful phase 3 clinical trial lets us say, with confidence, that the drug being tested improves a specific aspect of the disease in question. Thus, these trials are the ones that really get us excited when we're thinking about HD treatments.

A number of phase 3 trials of HD drugs have been run to date, including 2Care, CREST-E, HART, MermaiHD and First-HD. In each case, the hope was that the trial would definitively demonstrate that the drug under investigation helped HD symptoms. Only one recent HD phase 3 trial, First-HD, succeeded in meeting its primary endpoint.

This high rate of phase 3 trial failure is not uncommon and is in line with what happens in trials for many other diseases. It certainly doesn't mean that future phase 3 clinical trials of HD drugs are doomed to failure. Instead, the high failure rate just serves as a reminder that finding drugs to treat HD is a hard problem – but one that there are a lot of really smart, dedicated people working to solve.

The take-home message

Everyone working in HD – researchers, physicians, and families – wants nothing more than the development of effective therapies for the disease. To get there, we need successful phase 3 trials of effective therapies.

Along the way to this goal, lots of phase 1 and 2 trials are going to be done. Keeping a clear head when reading about these early trials - and their bewildering array of endpoints - is a good strategy for avoiding disappointment. Remember, **it's the primary endpoint of a trial that really counts**, so knowing what that endpoint is will help you sort out hope from hype in clinical trial announcements.

Finally, many new trials are on the horizon, and the trend certainly seems to be towards bigger and better trials – so we're hopeful that in the near future, we'll have new results from phase 1, 2, and 3 clinical trials for you to read about on HDBuzz.

The original version of this story mistakenly described the state of Phase 3 studies in HD. This information has been corrected in the current version.

The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...

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Glossary

Food and Drug Administration The government regulatory authority in the US responsible for approving new drugs

secondary endpoints Additional questions asked in a clinical trial that help scientists look at treated patients as broadly as they can to determine the effects of a drug

primary endpoint The main question asked in a clinical trial

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

efficacy A measure of whether a treatment works or not
