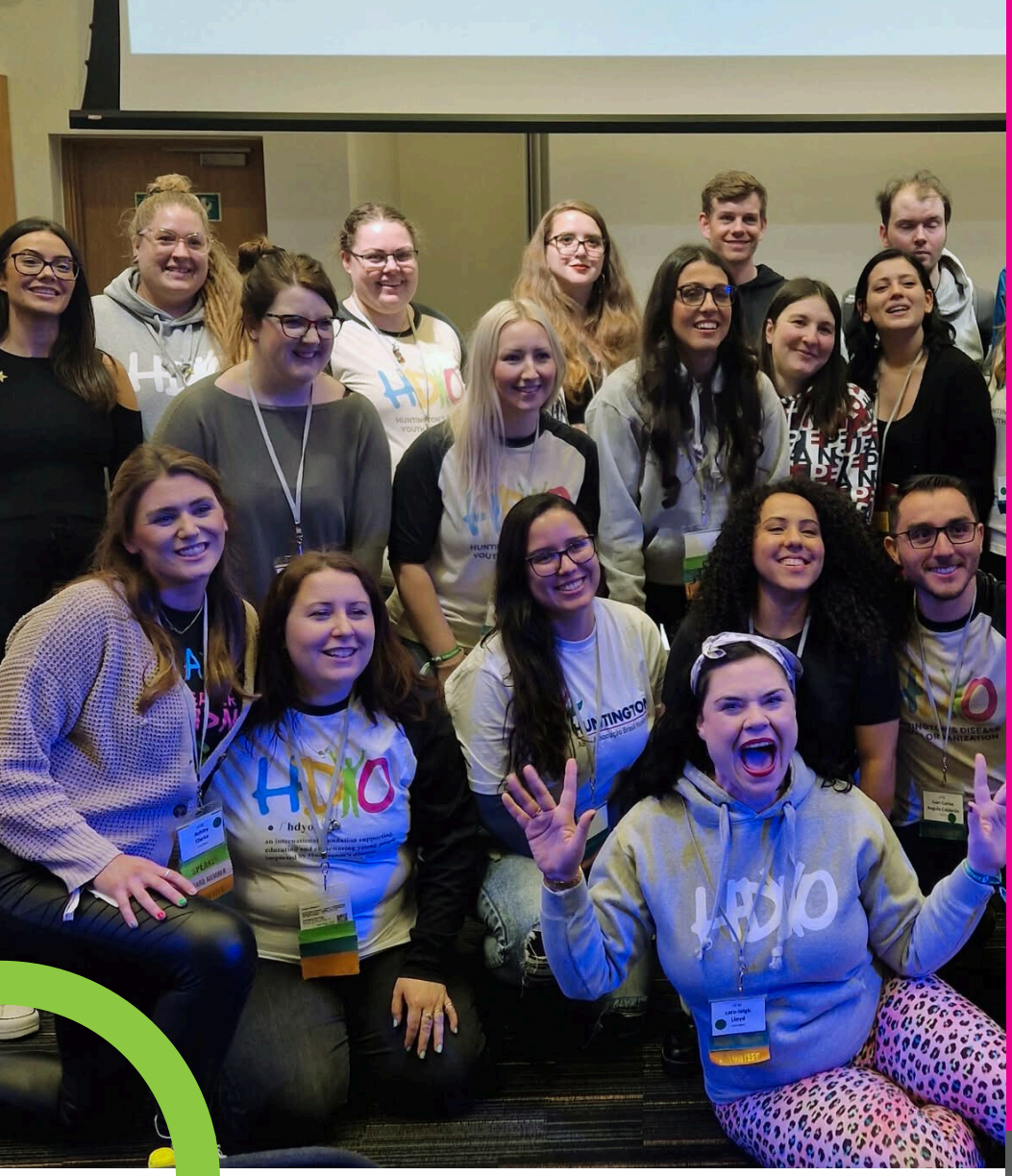

2025

HD RESEARCH TERMINOLOGY

HUNTINGTON'S DISEASE YOUTH ORGANIZATION

TABLE OF CONTENTS

To better understand research, HDYO has created this catalog of terms that are relevant for current clinical trials and research initiatives focused on Huntington's disease. This resource was created in collaboration with the HDYO Research Committee. We hope this resource helps expand your knowledge as you continue your HD journey. To help with navigation, the research terms included in this catalogue have been categorized into the following sections:

HUNTINGTON'S DISEASE YOUTH ORGANIZATION

RESEARCH TERMINOLOGY

BIOLOGY OF HUNTINGTON'S DISEASE

Allele - One copy of two matching genes we inherit - one from each biological parent.

Blood Brain Barrier (BBB) - A natural protective membrane that controls which substances in the blood can reach the brain. Designing treatments that won't be blocked by the BBB or finding ways to temporarily disrupt the BBB is a major challenge for HD drug development.

CAG Repeat - The stretch of DNA at the beginning of the HD gene, which contains the CAG sequence repeated many times. It is abnormally long in people who will develop HD.

Cell - The smallest unit that can live on its own and that makes up all living organisms and the tissues of the body. Different cell types have different functions (e.g. brain cells, blood cells, skin cells).

Complement Proteins - Part of the immune system, complement proteins are involved in clearing damaged cells and are affected in the early stages of HD.

DNA - A molecule that contains genetic information and the blueprint for the development and functioning of an organism.

Dopamine - A signaling chemical (neurotransmitter) involved in movement control, mood, and motivation.

Exon 1 - The first part of the HTT gene that carries the gene mutation.

Gene - Small pieces of DNA, passed from parent to their offspring, that carry information needed to build and maintain different parts of the body. Most genes contain the information for making specific proteins that help you grow and function.

Genetic Modifiers - Genetic variants that can modify the outcome of a disease. Genetic modifiers can increase or decrease the severity of the disease condition but may not be disease-causing themselves.

Genome - The complete set of genetic instructions in DNA that make up a living being.

Huntingtin Protein/Wild Type Huntingtin (HTT) - A protein that plays a role in brain development and neuronal survival. It is the HTT unaffected in HD.

Messenger RNA (mRNA) - Messenger RNA (mRNA) is like a copy of a recipe from a cookbook (DNA). It carries instructions to tiny machines inside the cell, called ribosomes, which read the message and build the protein.

Mutant Huntingtin Protein (mHTT) - A misfolded version of the normal Huntingtin protein (HTT), which is toxic.

Protein - A molecule made up of amino acids that is essential for the human body to function properly. The HD gene has the instructions to make the Huntingtin protein which is important for the development of our nervous system and many other bodily functions.

Sigma 1 Receptor (S1R) - The S1R protein is highly expressed in the brain and spinal cord. It regulates several key processes that are commonly impaired in neurodegenerative diseases.

Single-Nucleotide Polymorphism (SNP) - A tiny change in a single 'letter' of DNA. Scientists study these small differences to see how they might affect things like health, disease risk, and how a person responds to medications.

Somatic Instability/Expansion - This means that over a person's lifetime, the already-expanded HD gene gains even more CAGs in certain cells of the brain and body.

RESEARCH TERMINOLOGY

STUDY TYPES

Clinical Trials/Interventional Studies - A research study that involves human participants to evaluate the safety and effectiveness of new treatments, such as drugs, medical devices, or behavioral interventions.

Observational Studies - Studies that collect information about a population (e.g. people with HD), in the form of surveys, questionnaires, and tasks. Observational studies do not involve any intervention, such as a drug. These studies often include healthy controls (people who do not have the disease) to be able to measure information which might be different in populations with the disease compared to the people without the disease. Observational trials can help discover ways of measuring diseases, such as biomarkers, which can then be used for interventional research.

Registries - A database that collects information about people with a specific condition or disease. Researchers can use registry data for observational studies to answer important health questions.

Surveys - The collection of information from a sample of individuals through their responses to questions.

CURRENT RESEARCH FOCUSED FOR HD

Adeno-Associated Virus (AAV) - A harmless virus that can be used in gene therapy to deliver DNA instructions to cells, so they can make proteins. AAV are often used in brain diseases as they are better at getting into brain cells than other viruses. However, some AAV drugs do not spread very far, so they need to be surgically inserted into the striatum.

Allele-Selective Huntingtin Lowering - An approach where only the mutant Huntingtin protein is lowered (see also, “Huntingtin Lowering”).

Antisense Oligonucleotide (ASO) - A type of treatment that targets the messenger RNA, (i.e. the part that is responsible for translating the DNA instructions to make a protein). In HD, the goal of the ASOs is to reduce the mRNA from producing the Huntingtin protein. ASOs are delivered into the spine via a lumbar puncture.

Complement Inhibition - A type of immunotherapy that prevents activation of the complement system. The complement system is a part of the body's innate immune system (the body's first line of defense against invading pathogens, such as bacteria, viruses, and parasites) that helps fight infection.

CRISPR (also known as CRISPR/CAS9) - A system for editing DNA in precise ways.

Gene Therapy - Therapies that involve inserting a gene or genetic material (DNA) into the genetic code of a target cell type to manipulate the proteins that those cells produce. In HD, current gene therapy methods aim to limit the production of mutant huntingtin protein by allowing the cells to produce the huntingtin lowering drug itself. This is why the effects of a single treatment could last a very long time.

Huntingtin Lowering - A therapeutic strategy that aims to reduce the amount of mutant huntingtin protein in the body.

RNA Interference - A natural biological process that regulates gene expression by silencing specific messenger RNA molecules.

Signal 1 Receptor Activation - The clearance of toxic proteins may increase energy production and reduces cellular stress and inflammation.

Splicing - An editing process of the messenger RNA (a copy of the DNA) that involves introns (sections of RNA that do not code for a protein), leaving only the protein-coding regions called exons.

RESEARCH TERMINOLOGY

THERAPY DELIVERY METHODS

Gene Therapy Brain Surgery - A surgical procedure typically involving injecting a modified virus, often called an adeno-associated virus (AAV), directly into the brain tissue. This is the most effective way to bypass the blood-brain barrier, which prevents most substances from entering the brain.

Intrathecal Injection - A procedure where medicine is delivered directly into the fluid around the spinal cord (CSF). This helps the medicine reach the brain and nerves more quickly and effectively.

Lumbar Puncture - A procedure used to collect cerebrospinal fluid (CSF) from the lumbar region/spinal canal.

Small Molecule Drug - A drug that can enter cells easily because it is so small. These drugs are typically offered in a capsule or pill form to be administered orally.

OUTCOMES AND MEASUREMENTS

Clinical Outcome - A clinical outcome is a way of measuring symptoms, overall health, ability to function, quality of life, or survival outcomes in a research study.

Symbol Digit Modalities Test (SDMT) - A cognitive task evaluating a person's ability to quickly match symbols to numbers.

Total Motor Score (TMS) - A scale used to assess the motor symptoms of a person with HD.

Composite Unified Huntington's Disease Rating Scale (cUHDRS) - A single score that is calculated based on four scales of the UHDRS: TMS, TFC, SDMT, SWR. This score is sensitive to measuring progression of disease in people with HD.

Meaningful Outcomes/Patient-Centered Outcomes - Patient-Centered Outcomes (PCOs) are comprised of measurable health outcomes that are important, impactful, and/or meaningful to patients. PCOs are comprised of data collected directly from patients, known as patient-reported outcomes (PROs), and through other sources (e.g. caregiver information, biomarkers, research team observation, etc.).

Q-Motor - A series of tasks often utilized in clinical trials of adults with HD to provide quantitative and assessments of motor abilities.

Risk/Benefit Analysis - A comparison between the risks of a situation and its benefits. A risk/benefit analysis is used to calculate whether the benefits of an action are worth the risk of the action.

Stroop Test (SWR) - A cognitive task that measures attention and speed of thinking. In the Stroop test, people are asked to identify colored shapes and/or read the names of words. Finally, they must name the color of ink a word is printed in, often when the word itsef is the name of a different color.

Total Functional Capacity (TFC Score) - A scale used to assess the functional ability of a person with HD.

Unified Huntington's Disease Rating Scale (UHDRS) - A tool developed as a scale to assess four domains of clinical performance and capacity in HD: motor function, cognitive function, behavioral abnormalities, and functional capacity. The TFC, TMS, and SDMT are all scales within the UHDRS.

RESEARCH TERMINOLOGY

BIOMARKERS

Biomarker - A test of any kind - including blood tests, thinking tests, and brain scans - that can measure or predict the progression of a disease. Biomarkers may make clinical trials of new drugs quicker and more reliable.

Atrophy - Loss of volume (i.e. size) in specific regions or across the whole brain due to cell death.

CAP Score - A commonly used measure used to estimate how much a person has been exposed to the HD mutation over time. The CAP Score helps predict the progression of the disease and related health changes.

Caudate - A small region, deep in the brain, impacted by HD very early in the disease course. Along with the putamen, this region is part of a cluster called the striatum, which connects to almost every part of the brain. Atrophy in the striatum can affect all areas of function: thinking, movement, and emotions.

Cerebrospinal Fluid (CSF) - A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

Chorea/Motor/Movement Symptoms - Symptoms relating to how someone moves and/or their ability to control movement. In HD, there is often an impact on movement. Erratic movements are called chorea. There can also be changes to how someone walks, speaks, and swallows.

Cognition/Mind - The mental process of acquiring knowledge and understanding through thought, experience, and the senses.

Inflammation - The response from our immune system to injury or infection. Diseases like HD can cause too much inflammation over a long time which might be bad. Some treatments try to reduce inflammation.

Integrated Staging System (HD-ISS) - A research tool for classifying disease progression in HD. Stages range from 0 (gene positive with no symptoms) to 3 (gene positive with functional decline including difficulty with daily activities).

MRI - Images used to visualize the structure and function of the body, including the brain, using very strong magnets.

Neurodegenerative Disease - A disease caused by progressive malfunctioning and death of brain cells (neurons and glia).

Neurofilament Light (Nfl) - Neurofilament light (NfL) protein in blood and CSF has been proposed as a biomarker of neurodegeneration in a number of conditions, including HD. When brain cells are injured, NfL levels increase.

Putamen - A small region, deep in the brain and close to the caudate, impacted by HD very early on in the disease course. Along with the caudate, the putamen is part of the striatum, which connects to almost every part of the brain. Atrophy in the striatum can affect all areas of function: thinking, movement, and emotions.

Striatum - A cluster of small regions, deep in the brain, that is affected early on in HD. It connects to almost every part of the brain. Atrophy in the striatum can affect all areas of function: thinking, movement, and emotions.

Synapse Loss - The loss of connections between neurons in the brain. Synapse loss is an early feature of many neurodegenerative diseases.

Ventricles - Fluid-filled cavities inside the brain. Ventricles contain CSF fluid which nourishes and cleanses the brain. The lateral ventricles are two of the four ventricles commonly measured in HD. As the disease progresses, or in the presence of inflammation, the ventricles expand.

Volume - The size of a brain region measured usually using MRI.

RESEARCH TERMINOLOGY

CLINICAL TRIALS

Adverse Event - Any unfavorable or unintended medical occurrence that happens to a participant in a study.

Blinded Study - A study where participants or researchers don't know which treatment a participant is receiving. Blinding prevents bias and helps ensure that the results are based on the treatment being tested, not on other factors.

- Single-Blind - Only the researcher knows which treatment the participant is receiving.
- Double-Blind - Neither the participant nor the researchers know which treatment the participant is receiving.
- Triple-Blind - Participants, researchers, and the people analyzing the data don't know which treatment the participant is receiving.

Dosing - Refers to the administration of a pre-specified amount of therapy given to clinical trial participants to determine what is safe and effective.

Data Safety Monitoring Board (DSMB) - An independent group of experts that monitors the safety of participants and the efficacy of treatments during a clinical trial.

Efficacy - A measure of whether a treatment meets its intended goal.

Endpoints

- Primary Endpoint - The main result(s) that will be used at the end of a study to determine if the study met its aims (e.g. to see if a given treatment is safe and effective or if there is a significant difference between the treatment group and the control group). Primary endpoints must be defined before a trial starts and are required by regulators for drug approval.
- Secondary Endpoint - May provide supportive information about a therapy's effect or demonstrate additional effects on the disease or condition. Secondary endpoints must be defined before a trial starts and supports regulatory decision making.
- Surrogate Endpoint - A biomarker or test that can be used as a substitute for a clinical endpoint, because it has a strong predictive link. For example, if a drug can slow atrophy in the brain, it might eventually slow worsening of symptoms. A surrogate endpoint can be used as evidence for drug efficacy, in the absence of clinical improvement.
- Exploratory Endpoint - May provide supportive information about a therapy's effect, mechanism, or demonstrate additional effects on the disease or condition. There can be multiple exploratory endpoints that contribute to understanding treatment effects and can help guide future trials of a given treatment. These endpoints don't need to be pre-defined.

Healthy Control - A person without the studied disease or condition who is used in a comparison group for a scientific study.

Inclusion/Exclusion Criteria - A set of characteristics that define which participants can and cannot be included in a research study.

Longitudinal Study - A study where each participant is evaluated multiple times over the study period. This is different from a cross-sectional study, where each participant is evaluated only once.

Open Label Trial or Extension - A part of the trial in which everyone receives the treatment. Everyone, including sponsors, participants, and researchers, all know that participants have been treated with the study drug. Open label trials are susceptible to bias through placebo effects, but are useful in certain cases (e.g. where it's unethical to have a placebo group, or to enable continued trial participation after the end of the blinded treatment period).

RESEARCH TERMINOLOGY

CLINICAL TRIAL CONTINUED

Phases

- Phase 1 Trial - A small trial (20-50 people) primarily testing safety and collecting exploratory information about the treatment effects.
- Phase 2 Trial - A medium sized trial (50-200 people) testing safety and effects of the drug.
- Phase 3 Trial - A large trial (e.g. 200-1000 people) testing whether the drug helps with symptoms or slow disease progression.

Placebo - A placebo is a dummy medicine containing no active ingredients. The placebo effect is a psychological effect that causes people to feel better even if they're taking a pill that doesn't have an active ingredient.

Post Hoc Analysis - A statistical analysis that examines data after a study is complete. Post hoc analyses are data driven rather than pre-specified, hypothesis driven, and can therefore be biased.

Protocol - A document that outlines the details of a study, including how it will be conducted, what will be done, and why.

ACCESS

Early Access Program - A potential pathway for patients diagnosed with a serious and/or life-threatening disease or condition to gain access to an investigational product for treatment. This is outside of a clinical trial when no comparable or satisfactory alternative therapy options are available.

Accelerated Approval - In the U.S., the FDA allows early approval of some therapies if evidence supports their safety but definitive evidence of clinical benefit is still limited (e.g. a biomarker that strongly predicts clinical benefit, shows a positive signal). The approval is conditional, pending the collection of definitive evidence. If subsequent results are positive, the therapy receives full approval. If the results are negative, the therapy will be withdrawn.

Post Market Surveillance - Once a treatment is approved and available to the wider population, additional evidence of the safety and efficacy of the drug will continue to be collected by hospitals and clinics. This is important for ensuring the drug is safe and effective for everyone and any unknown effects are recorded.

Regenerative Medicine Advanced Therapy (RMAT) - Designation given by the Food and Drug Administration to drug candidates intended to treat serious or life-threatening conditions. This allows for accelerated approval based surrogate or intermediate endpoints.

Regulatory Bodies - The regulatory bodies (e.g. FDA (USA), EMA (EU), MHRA (UK)) are government bodies, responsible for reviewing new drugs/devices/interventions or changes to the label of existing drugs/devices/interventions and approving or rejecting them. No drugs/devices/interventions is allowed to be sold and prescribed in a country without approval from a regulatory body.

HDYO Breaking Down Barriers YouTube Playlists

- **An Insight Into Drug Development & Clinical Trials**
- **Access to Research**
- **What is a Biomarker**
- **Somatic Instability**
- **Casual Conversations about Trials**
- **More**