

# Clinical trials explained

## Typical for new treatments and diagnostic tests

### Stages in the clinical trial journey to research new treatments

In most clinical trials, some participants will receive the treatment being investigated and others will receive a placebo (a 'dummy' treatment that has no known physical effect on the body).

This is so researchers can tell which effects are likely due to the investigational treatment, and which are due to chance.

#### Phase 1 – is this new treatment tolerated in humans?

Phase 1 or Phase I trials are usually very small. They typically include ~20-80 'healthy' volunteers (unless in rare diseases or oncology) – people who do not have the disease or condition in question. Phase 1 trials evaluate the safety (side effects) of a new treatment in humans over several months, and what the ideal dose (amount) of drug is.

#### Phase 2 – is this new treatment useful?

Phase 2 or Phase II trials typically include a few hundred people who have the disease or condition in question. They look for signs of how effective the new treatment is, and continue monitoring any side effects over several months to 2 years. Phase 2 trials usually include a placebo and help to identify the dose (amount) of drug that results in the most favourable outcomes.

#### Phase 3 – does this new treatment really work?

Phase 3 or Phase III trials are big studies that typically include more than 300 people with the disease or condition and take place over 1–4 years. Typically, approval of a new treatment for use in patients only happens after a Phase 3 trial is complete. They explore how the new treatment impacts different types of patients and, if there is already treatment available for the disease or condition, how the new treatment compares to 'standard treatment'. Phase 3 trials usually include a placebo and, due to their size, continue to look for any less common side effect.

Normally, trials must go through the same progression of Phases 1 to 3 before a treatment is submitted for a licence to allow the treatment to be made available outside of a trial setting.

Trials may be described as 'blind' when the participant, or 'double-blind' when the participant and the investigator, do not know which participant is receiving the treatment being investigated or the placebo. This is to keep the study objective.

The results will only be 'unblinded' once the trial has ended. Because different people join a trial at different times, the results may only be 'unblinded' long after a participant has completed their own involvement in the trial.

## Other types of studies that can form a 'trial programme'

- 1. Natural History Study** – natural history studies look at how a medical condition develops over time either without treatment, or with standard treatment, by following and observing people who live with the disease or condition. This study can therefore act as a benchmark to how well a new, investigational treatment works. As treatments are not evaluated in a natural history study, a placebo is not required.
- 2. Pharmacokinetic Study** – pharmacokinetic studies are typically small trials that look at how the human body deals with a drug, in terms of how it is absorbed, circulates and exits the body. The study usually happens as part of a Phase 1 trial, or before.
- 3. Open-Label Extension** – open-label extensions are studies that take place after the Phase 1–3 trials and often before the treatment is licensed for use in patients. The reason it's called 'open-label' is because everyone knows the treatment that they are receiving; no participant is receiving placebo. The purpose is to gather more information about how well a treatment works, how it compares to other standard treatments, and its safety features over a longer period of time.

## So what is GEN-EXTEND?

GEN-EXTEND is the open-label extension study for the Phase 3 trial, GENERATION HD1. Whereas GENERATION HD1 is designed to evaluate the effects of Roche's HD treatment and help decide if it should be made available to patients, GEN-EXTEND evaluates the long-term safety of the same treatment, to understand long-term side effects. Not everyone is able to be a part of this study, only patients who have been involved in the earlier trials in the programme can join an open-label extension.

## Why do we have clinical trials?

Clinical trials enable researchers to answer scientific questions or thoroughly test new treatments and interventions through well-designed, well-controlled and carefully monitored settings. Researchers can accurately compare different approaches to preventing and treating diseases. Without trials, many people living with chronic, rare, and life-limiting conditions would not have access to life-changing treatment.

## Who gets the investigational treatment?

Participants in a trial are chosen at random to receive either the treatment being investigated or a placebo. The number of participants who receive the investigational treatment is dependent on the type and size of the trial. For example, if a trial investigates the effects of several different treatments, it may not be a 50:50 split for 'who gets what'. In each case, groups of participants either receiving the investigational treatment or placebo are chosen at the start of a trial and at random by a computer, to allow the results to be judged independently.

## Why is a placebo used?

Comparing treatment to a placebo means that any improvement in participant health or wellbeing is unlikely to be due to chance. The placebo is administered in the same way as the investigational treatment, to ensure that it really is just the treatment being evaluated.

## Why are clinical programmes set up in different ways?

Every trial is set up differently because every trial has a different purpose, and is designed to answer different questions about diseases or treatments.

Whereas a natural history study may explore the relationship between changes in the body and severity of a disease, a Phase 3 trial investigating treatment for a neurological disorder may require tests on how well the brain is functioning.

Each trial is carefully designed according to a comprehensive plan (protocol), created by doctors, nurses, patients, researchers, trial managers and pharmaceutical companies. In each case, 'inclusion criteria' outline the basic requirements for someone to take part, e.g. age, severity of a condition, whether a patient is taking medication or is living with any other conditions. Not everyone with the disease is able to take part. This is to ensure that the study measures what it is intended to measure, and to minimize the influence of other factors that may make the results difficult to interpret.

The progression of trials through Phases 1–3 may change if they show promising results earlier than expected. Also, depending on the medical need (e.g., a serious disease for which no treatments exist), Phase 1 or 2 may be shortened or skipped altogether. This is also the case for rare diseases, where researchers may first test new treatments in patients, instead of 'healthy volunteers'.

## What is an Independent Data Monitoring Committee?

An independent Data Monitoring Committee (iDMC) is a group of experts outside of a study that reviews accumulating data from an ongoing clinical trial. Safety monitoring is their main focus, while other aspects, such as the design of the trial and its scientific integrity may also be evaluated. Not all clinical trials need an iDMC.

## How long do clinical trials last?

Trials vary in length, depending on what is being studied and when. Normally, the length of a trial increases with each testing phase.

Participants are told how long a trial will last before they agree to take part, and they have the right to withdraw at any time, for any reason. The clock will start only when the last participant is recruited, which could be months after the first participant was recruited

Factors that determine how long a trial lasts include:

- Type of trial
- Type of treatment being studied
- Condition being studied – rare diseases may take longer, as there are fewer patients in the world to recruit to take part
- Number of patients needed – larger numbers may take longer to recruit
- Follow-up period – long-term side effects are essential to understand how the treatment works over a long period, some trials can even continue for more than 10 years

Most trials run as planned, from beginning to end. However, some may stop early because:

- There is clear evidence early on that a new treatment is effective and should be made available as soon as possible
- Participants experience unexpected and severe side effects
- There is clear evidence that the treatment does not work as well as the standard treatment or a placebo
- Not enough volunteers could be recruited to take part
- Results of other trials are published that either answer the trial's research question or make it irrelevant

If the administration of treatment to participants, or 'treatment dosing', stops earlier than expected in a trial, researchers may continue to collect data to fully understand the treatment effects over time. This means that although no one receives treatment, the trial continues.

## What do people do with the results?

Trial results determine the next steps for research or approval of a new treatment. Once a trial ends, the data is evaluated to understand what it means, and whether more testing is needed. For a new treatment, the results assess:

- How well it worked
- Whether it has any side effects
- Whether it works better than another treatment or a placebo
- Whether it works better or worse under specific conditions

For a new treatment, what people do with the results depends on whether the data is 'statistically significant', which means the results unlikely happened 'by chance'. Typically, the next steps are to:

- Move to the next testing Phase, after a Phase 1 or 2 trial
- Stop testing the treatment entirely
- Decide if a treatment should be approved for use in patients, after a Phase 3 trial

If the results are not what the researchers expected, the data is still useful to inform future research.

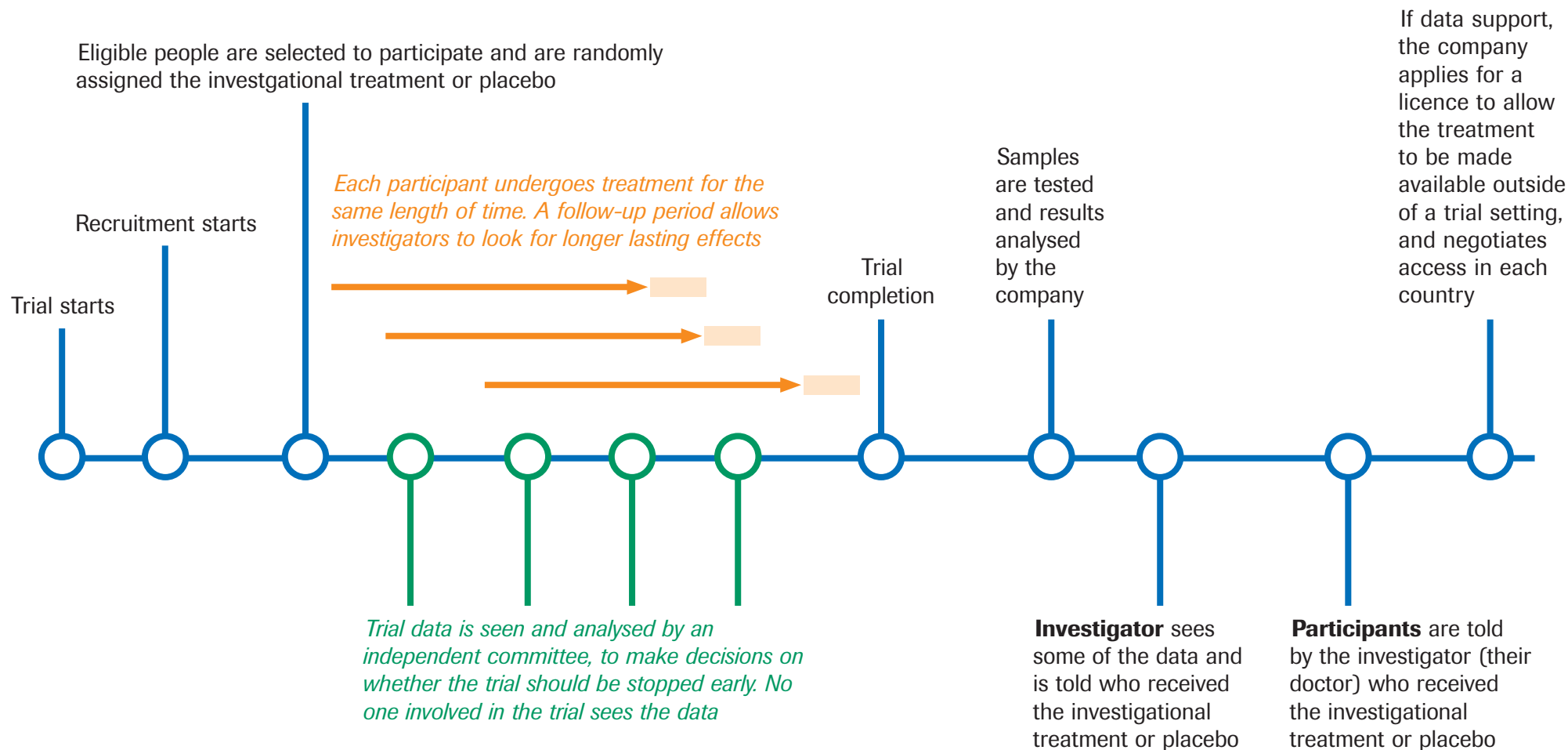
## When are the results shared?

Participants are told as soon as possible about the results by their local trial investigator (the doctor running the trial), after the trial has ended.

Different people join and start treatment in a trial at different times. Once a person has completed their involvement, it takes time for other participants around the world to also complete theirs, and for the trial to end. In addition, the samples taken from each participant are not analysed immediately but are done so in batches. For these reasons, it can take several months to know the trial results.

The research team is responsible for making the data known publicly, usually done by announcing the results at medical conferences, in medical journals, on ClinicalTrials.gov website or to the press. The pharmaceutical company that funds the trial must publish the results within one year after the trial has completed. Where possible, trial participants will be told about the results before they are announced to the public, however publicly traded companies may have a legal responsibility to report results to the media immediately, meaning it may be in the news before all participants are directly informed. This can also be the case if a trial is prematurely stopped.

## What happens, when?



## Who sees my data, when?

# Clinical trial endpoints explained



## *The types of endpoints:*

### Primary endpoints

Primary endpoints describe the main results researchers are looking for, to decide if a treatment worked and its safety features. Most trials have one primary endpoint, but some may include more.

### Secondary endpoints

Secondary endpoints answer other relevant questions about the same treatment. For example, whether the treatment also improves patient quality of life. Most trials will have multiple secondary endpoints.

### Exploratory endpoints

Exploratory endpoints address all other questions about a treatment that researchers may be interested in, but don't determine whether a treatment can be sold or not. For example, does a new treatment work better for one group of patients than another?

## Why are endpoints used in trials?

### Endpoints are used to:

1. Understand how well a new treatment works compared to either: an existing treatment, a placebo (a 'dummy' treatment that has no known physical effect on the body), or to no medical intervention at all
2. Show the benefits and risks of a new treatment

## What are trial endpoints?

Endpoints are used to measure the outcome of a clinical trial. To understand how effective a new treatment is, and any side effects that may occur, it is evaluated against a set of criteria – endpoints. Endpoints measure the effects of treatment on how a disease progresses and how patients feel or function.

In the case of cancer, tumours can be measured; they shrink, grow or stay the same size. Cancer treatment can therefore have a measurable impact on tumour size. For other conditions, where the effect of treatment cannot be easily measured, endpoints are typically used to assess changes in a symptom or everyday abilities, such as being able to perform certain movements, or the ability to learn or think. This is the case for Huntington's disease.

In a single trial, many endpoints are needed to properly evaluate a treatment's effectiveness and safety, some being more important than others.

In Huntington's disease, disease progression (the rate at which the disease gets worse) is slow, as shown in natural history studies that measure the development of the condition without treatment.

Therefore, endpoints must be sensitive enough to identify small and meaningful changes in patient health or functioning over short periods of time, and in small groups of patients.

## How are endpoints chosen?

Each endpoint in a trial is carefully chosen to ensure it is :

- **Clinically relevant** – important and relevant to the disease or condition
- **Reliable** – provide consistent measurements over time
- **Sensitive** – responsive to change
- **Specific** – unaffected by other factors or influences

Because different trials answer different questions about a treatment, endpoints also differ between trials. Trial investigators work with groups who would later license the treatment to choose acceptable endpoints, before a trial begins.

The chosen endpoints should also be considered as true benefits by patients themselves, such as symptom relief, slowing down the progression of a disease or improvements in quality of life – a patient's sense of wellbeing and ability to carry out day-to-day activities. Patients are increasingly involved in the endpoint selection process through groups such as patient councils, which often focus on how to include impactful 'quality of life' measurements in trials.

Some endpoints may be more difficult to measure than others. For example, measuring the clinical effects of new treatments for a complex neurological disease such as Huntington's disease is more challenging than measuring the impact of cancer drugs on tumour size.

## What happens if an endpoint is not reached?

If a primary endpoint (the most important one) is not reached, the trial is not considered a success and is unlikely to progress to the next testing phase. If only the secondary or exploratory endpoints are not reached, the trial may still be a success – it depends on what the endpoints are, and more research may be required to explore the safety and efficacy of the new treatment. In each case, data will be used to inform the endpoints for the next trial.

Different endpoints can be reached at different times in a trial. Many are reached only at the end of a trial, but some may be reached part-way through.

In Huntington's disease, usually all endpoints are time-dependent, to be reached (or not) by a set time. Because disease progression is slow, trials may last several years before endpoints are reached.

# Endpoints explained in Huntington's disease



## What type of endpoints are used in Huntington's disease?

As with other disease areas, Huntington's disease (HD) trials use a mixture of primary, secondary and exploratory endpoints to understand the safety profile of a new treatment, and how well it works compared to another treatment or the natural progression of the disease.

## Why are HD endpoints important?

Endpoints in HD trials are not selected at random. They are selected because they are important to patients, representing many different factors that play a role in how a patient feels over time and importantly, how people can carry out everyday tasks. The endpoints and tools used to measure them help researchers understand disease progression during trials.

## When are endpoints specific to HD reached?

HD trials are designed so that endpoints are usually time-dependent, to be reached (or not) by a set number of months or years, to assess how much the disease progresses in that time.

It is difficult to measure the impact of treatment in complex neurological conditions such as HD as disease progression is slow, meaning trials may last several years before endpoints are reached.

## Biomarkers as endpoints

The hope is that in the future, more and different types of endpoints are accepted to better assess HD. One area that researchers are particularly interested in is using biomarkers as clinical endpoints.

Biomarkers are molecules found throughout the body that show whether bodily processes are taking place as they should. They can be used to assess how well a body responds to a treatment. Some biomarkers can also be digitally recorded (see section on 'Using wearable technology').

Several HD biomarkers have already been identified, including:

- The mHTT fluid biomarker – the mHTT (mutant huntingtin) protein is associated with the development of HD, found in the fluid that surrounds and protects the brain and spinal cord, called the cerebrospinal fluid.
- An imaging biomarker – using brain scans, pictures of a person's brain structure can be used to identify the severity of HD.

Through understanding more about biomarkers in relation to changes in HD, researchers hope to better measure if the progression of the disease is being slowed down.

## Using wearable technology

Digital monitoring techniques may be used to complement current ways of monitoring HD progression and as such, may form new endpoints (sometimes referred to as 'digital biomarkers') in the future. Digital measurements can be captured by using wearable technology (e.g. smartphone or smartwatch), so they can be taken continuously throughout the day. It means activities of 'daily living' are captured. Measurements also appear to be more sensitive than traditional methods such as the Unified Huntington's disease Rating Scale (UHDRS).

For several natural history studies, the primary outcome is to explore the presence or absence of 'something' in HD patients. To learn about the natural course of disease and how it relates to different patient characteristics and biomarkers. In these cases, blood and urine samples are often used to test for DNA and biological 'signs' of HD.

*In Phase 1 and 2 trials, endpoints are often similar...*

*In Phase 3 and some open-label trials, which are used to inform decisions as to whether a treatment should be licensed for use in patients...*

## Primary endpoints

Most importantly, early-stage trials evaluate **safety** and **tolerability** of a new treatment, based on the presence and severity of side effects. In addition, the number of patients who withdraw from a trial due to side effects is measured.

The **Unified Huntington's disease Rating Scale** (UHDRS) is not a score or an endpoint, but a collection of measures and assessments that are commonly used in HD. The individual measures are often used as endpoints.

The **composite UHDRS** (cUHDRS) is a scoring system that combines four of these UHDRS measures into a single score, for use as a clinical trial endpoint, including: Total Functional Capacity (TFC), Total Motor Score (TMS), Symbol Digit Modalities Test (SDMT) and Stroop Word Reading (SWR). The TFC assesses a person's ability to perform typical daily activities and the level of care support they receive. The TMS is an assessment of the person's motor skills (ability to perform or carry out movements). The SDMT and SWR assess cognitive ability, including how quickly someone can process information.

Both the cUHDRS and the TFC were used as primary endpoints by Roche.

## Secondary endpoints

Most often, early stage trials measure the **pharmacokinetics** of a new treatment – how the human body deals with a drug, in terms of how it is absorbed, travels round and exits the body.

Endpoints to assess a person's ability to carry out everyday tasks may also play a role, such as **Total Functional Capacity** (TFC) scoring.

While also forming part of the UHDRS, **Total Motor Score** (TMS) is often used as a secondary endpoint in HD trials. This tool assesses a person's motor skills (ability to perform or carry out movements), which get worse in people with HD over time, so it can be a useful measure of disease progression.

## Exploratory endpoints

**Magnetic Resonance Imaging** (MRI) may take place to further explore how a new treatment affects brain function.

One example of an explorative question is the **effect of a new treatment on innate (what you are born with) immune markers**.

Our natural immune system, which fights against harmful germs or viruses, plays an important role in HD. Many different molecules make up the human immune system, some of which can be called 'markers' – people with HD often have abnormal levels of markers. Therefore, changes in immune markers can indicate whether a disease is getting worse, and evaluate the effect of a new treatment on disease progression.