IMPROVING CLINICAL TRIALS TO DELIVER **BETTER** TREATMENTS

Despite decades of research and major breakthroughs in our understanding of Parkinson's, a cure always seems to be 5, 10 or even 20 years away. Today there's a wave of exciting treatments coming through the pipeline that hold genuine potential for slowing, stopping or even reversing the condition. That's why we're working to make sure clinical trials are smarter, faster and more likely to succeed.

All potential treatments need rigorous testing, and clinical trials are the most costly and lengthy part of the whole research process. In recent years, several promising new treatments for Parkinson's have failed to show benefit. We believe the problem may not be that the drugs don't work, but that we're testing them in the wrong way. So we may be throwing away potentially effective drugs because we cannot test them properly.

Parkinson's is a phenomenally complex and varied condition. Different people experience different symptoms, and the condition can develop in varied and unpredictable ways. This makes choosing the right people to participate in trials, and finding the right ways to measure success, extremely difficult. That's why the international community is joining forces to improve clinical trials for Parkinson's.

Right treatment, right patient, right time

To give new treatments for Parkinson's the best chance of success, we need to test them in the right group of people at the right time.

This is the mission of the **Critical Path for Parkinson's** consortium – an international collaboration, led by Parkinson's UK, bringing together pharmaceutical companies, regulatory agencies, universities, charities and people with Parkinson's to share data from major studies and trials.

Our expert partner, the Critical Path Institute, is a world-leading expert in bringing together clinical data and using it to create new tools for clinical trials. They work closely with regulatory agencies like the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA).

This is vital because these agencies are the gatekeepers for the development and approval of new treatments, so any new tools need to be accepted and endorsed by the FDA and EMA before they can be used in clinical trials of potential new therapies.

How it works

This ambitious project is built on 'big data'. Many studies and trials have been conducted in Parkinson's over the past few years – some testing potential new treatments, others collecting detailed information about the condition over time.

Each individual study produces important insights, but if all the data could be combined and analysed together it becomes far more powerful.

This is exactly what the Critical Path for Parkinson's is doing – building a huge and highly sophisticated database that can be used to understand the condition and develop the tools the community needs to improve clinical trials.

The database already includes information collected from more than 3,300 people with Parkinson's from around the world – including from Parkinson's UK-funded studies like Tracking Parkinson's and the Oxford Parkinson's Disease Centre.

It also includes data collected during unsuccessful clinical trials – so even though these studies did not result in a new treatment, the data generated still has huge value.

New tool to select people for clinical trials

In early 2018, the Critical Path for Parkinson's project achieved its first major success. Researchers and drug companies have the go ahead from regulatory agencies to use a new tool – a brain scan – that can be used to select the right people for clinical trials. This is an important step in the search for better treatments for Parkinson's.

Research suggests that up to 15% of individuals taking part in clinical trials may not have Parkinson's. They are extremely unlikely to benefit from the new therapies being tested and their inclusion can affect both the trial results and ultimately the future of the potential treatment.

Because Parkinson's is a progressive condition, caused by the gradual loss of cells in the brain, the best chance to intervene with treatments that can slow, stop or reverse the damage is during the earliest stages of the condition.

However, during these early stages, symptoms tend to be mild, which makes selecting the right people to participate in trials very difficult. Using this brain scan can produce a picture of how dopamine-producing cells – which are destroyed by Parkinson's – are functioning inside the brain.

It can help distinguish between people who have Parkinson's (or a similar progressive condition) and those with a condition like essential tremor, which is unlikely to worsen over time.

These brain scans are sometimes used by doctors to help them reach a diagnosis, but until now they could not be used to select people for clinical trials of new drugs. The use of the brain scan in this way is now encouraged by the regulatory agencies.

Diane Stephenson, Executive Director of the Critical Path for Parkinson's consortium, which led this work, comments:

"These brain scans in themselves are not new, but until now there has not been a clear consensus that they can and should be used to select participants for clinical trials in this way. Through our global project we've been able to bring all the data and expertise together to make a powerful case, so we're delighted that this endorsement from the EMA will improve the quality and chances of success for all future trials. This success is hopefully just the first in a suite of new tools that we hope to deliver for Parkinson's."

Next steps for the Critical Path for Parkinson's

Our mission with the Critical Path for Parkinson's is to take the guesswork out of planning clinical trials. This first success is a great step forward but there is still much more work to do.

Next, we plan to use all the data we've collected to build sophisticated computer models that can be used by researchers across the world to make the right choices when planning clinical trials for Parkinson's.

These choices include things like how many and what kind of people to recruit to Parkinson's trials, as well as deciding on the best dose and how long to run the trial for.

Ultimately we hope to create a computer platform that functions like a flight simulator – but for trials.

Researchers will be able to test-run their trials using our platform to predict outcomes, fine-tune plans and maximise chances of a successful outcome.

All the tools we create through this groundbreaking collaboration will be shared with the global community so that all clinical trials for Parkinson's can benefit, and have the best possible chance of producing new treatments.

Measuring new treatments against what matters most

As well as being able to ensure that the right individuals take part in studies, we also need to make sure that the way we assess treatments is meaningful and truly reflects the experience of people with Parkinson's.

The main way we measure Parkinson's and the effects of treatments in clinical studies and trials today is using a scale called the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

This assessment is composed of 50 questions about both movement (motor) and non-movement (non-motor) symptoms.

Each question is rated from 0 (normal) to 4 (severe), and then the marks are added up to give a total score, which is intended to provide an overall indication of the severity of the condition.

Although this assessment can provide a helpful snapshot of symptoms, it does not allow for variation and can struggle to capture the real impact on everyday life.

Lesley Gosden, a person with Parkinson's and clinical trial participant, comments:

"Research into Parkinson's needs to move up a gear, improve clinical trial outcomes and focus

on treatments in years not decades. Those of us unfortunate enough to have the condition do not have the luxury of time on our side. I recently took part in a trial and found the assessments used to measure my Parkinson's frustratingly inadequate and artificial.

"The severity of symptoms varies enormously in response to stress, constipation, general health and many other triggers. Assessing participants can only accurately reflect the efficacy of the treatment under trial if all factors are identical on each occasion – but this is clearly not reproducible.

"Therefore, participants need to be monitored more frequently with provision for recording symptoms and reactions not covered within the rigidly defined assessment scales. Asking me to assess my walking ability generally is meaningless – it can vary from immobility or a slow shuffle to a brisk walk. In my Parkinson's there is no general state.

"One of my most debilitating symptoms is dystonia – cripplingly painful muscle spasms in my feet and legs that have a huge impact on my ability to do things like drive or walk. The trial assessments failed to test the factors that most adversely affect my daily life while concentrating on symptoms that I do not experience. Multiplied across the test group this will clearly distort the overall result.

"Everyone's Parkinson's is different and variable and we need assessments that acknowledge improvement in quality of life, which is ultimately what we are all striving for."

Creating better ways to measure Parkinson's

First and foremost, if we want to develop better ways to measure the impact of treatments, we need to work with people affected by Parkinson's to understand what benefits they value most.

This year we plan to work with people affected by Parkinson's who have taken part in clinical trials, like Lesley, to hear their feedback and ideas on how we can better capture their experiences.

To get clinical trials right, people with the condition need to be involved in developing and testing all these new methods and scales to ensure they measure the right things and that they are practical to use in clinical trials.

The development of new technologies represents a huge opportunity to develop better ways to monitor Parkinson's much more objectively and in real time.

Wearable technologies, like pedometers and wrist sensors, are being developed that can collect and analyse vast amounts of data around the clock to produce a much more meaningful and comprehensive picture of Parkinson's symptoms.

We plan to work towards standardised and accepted ways to use these technologies to monitor and measure Parkinson's in clinical trials – and input from people living with the condition is crucial to this.

We are taking all of these issues into account when reviewing the way we fund clinical trials and we are determined to make sure that we support only studies that are designed in the best possible way to deliver treatments to people who need them as quickly as possible. ■