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Research update letter about treatment studies in Wolfram syndrome

We would like to share our research with you

- We want to explain our research into treatments for Wolfram.
- Please feel free to share the following information, and discuss with friends and family.
- This is not an information sheet about a particular trial; but an overview of treatment studies that we are developing.
- Ask us if there is anything that is not clear, or if you would like more information.

Important things that you need to know.

- We want to find out if we can slow down the progression of Wolfram syndrome.
- We are testing the use of different medicines.
- These medicines are licensed to treat other conditions, but we don't know whether they are safe in Wolfram, or if they will work in Wolfram syndrome.
- These medicines can cause side effects, and patient safety comes first.
- Each study will include extra visits to hospital.

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How to contact us

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1. Why are we doing these studies?

We are doing these studies because we have no treatment for Wolfram syndrome. We can screen for complications, treat diabetes with insulin, and provide vision aids for the eye problems. However, we have no cure, and nothing that can slow down or halt the progress of the disease. Our current studies will not find a cure for Wolfram; however, we hope that our studies will show whether a medicine can slow down the disease process.

We know that many people with Wolfram syndrome develop sugar diabetes and worsening eyesight. These and other symptoms usually progress over many years. The underlying problem is due to a faulty protein, called Wolfram protein, which is needed to keep the body's cells healthy. When Wolfram protein is faulty or missing, some specialised cells in the pancreas, brain, and other organs, stop working. This causes the diabetes and eye problems.

2. What have we found so far?

Dr Urano's group in St Louis, USA have made cell and animal models of Wolfram in the lab. They have found that the disease in Wolfram is caused by problems with different chemical pathways in cells. These pathways can be targeted by medicines, to try to fix the problem. Prof Urano's group have found a medicine that seems to work on one particular pathway in cell and animal models. The medicine does have side effects, and is not licensed to use in children. We need to find out if it is safe to use, and works, in people with Wolfram.

Dr Barrett's group in Birmingham, UK have also studied cell models of Wolfram in the lab. They have found a different medicine that protects the cells and allows them to carry on working. Other scientists in Estonia have given this medicine to a mouse model of Wolfram, and shown that it helps their symptoms. This medicine works on different chemical pathways to that of Prof Urano's medicine. The medicine is one that is already used to treat other conditions. However, it also has side effects, and we need to find out if it is safe and works in Wolfram syndrome.

3. What are clinical trials?

A clinical trial is a special type of clinical study, in which human volunteers are given a medicine, so that we can learn something new. Clinical trials may compare a new medicine to a placebo (dummy medicine) that contains no active ingredients, or not compare to anything.

When a new treatment is being tried, it is not known whether it will be helpful or harmful. The investigators try and find out if the treatment is safe; and if it works (it is effective). They do this by measuring outcomes, such as side effects, or whether the disease gets better.

Sometimes, clinical trials are described by Phase. **A Phase I study** is usually a study that gives a new medicine to small numbers of patients, to find out if it is safe. A Phase I study does not tell you if a medicine works (is effective) in the disease.

A Phase II study usually compares a new medicine to a placebo or the current standard of therapy, to find out if the new medicine works to treat the disease. Safety is still measured in a Phase II study. Specifically for Wolfram, people are invited to randomly receive either the study medicine, or dummy medicine (placebo). Neither the doctor nor the person taking part, knows which medicine they are taking. People are then followed up with careful measurements. At the end of the study, we check whether people taking the study medicine have had less progression of the disease than those on the dummy medicine.

A Phase III study collects more information about safety and effectiveness by studying different populations, and medicines at different doses and in different combinations.

If we find that a study medicine is safe, and it works, then it will be used to treat people with Wolfram syndrome. If the study medicine is not safe, or if it does not work, then it won't be used.

4. What clinical trials are happening?

The next section describes 2 clinical trials in Wolfram; the Phase I safety trial that has started; and the Phase II efficacy trial that will start in 2017.

A Safety Trial of Repurposed medicine in Child and Adult patients with Wolfram syndrome.

The treatment is:

A medicine used in adults only

This treatment is for 6 months. These are tablets to swallow once or twice a day. This study is in St Louis, USA. 24 people (or more) will take part. They will all receive the medicine.

Stage 1

First visit, up to 28 days before starting

- Ask consent to take part
- Baseline history, examination, blood tests, eye, diabetes, brain function, other tests.
- Check person is eligible to take part

Stage 2

Second visit, start medicine.

- Start treatment- take tablets each day

Stage 3

Safety visits every week for 4 weeks

- Safety visits to check patient is well
- Blood tests

Stage 4

Safety visits at 2 months, 4 months, 6 months.

- Safety checks, blood tests at 2 and 4 months.
- Eye, diabetes, brain function, and other specialist tests at 6 months.

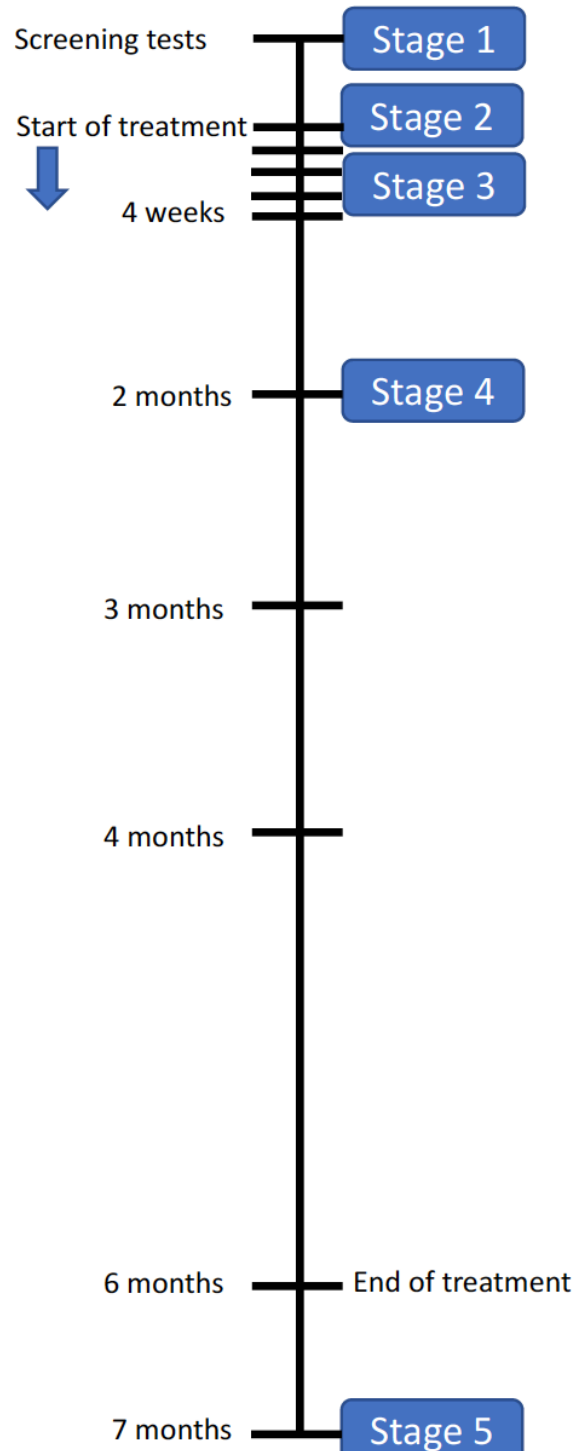
Stage 5

Final visit after treatment finished

- Final safety checks

This trial will tell us if the medicine is **SAFE** in Wolfram. It will **NOT** tell us if **Dantrolene** works in Wolfram. However, we will assess outcome measures, based on the data provided by my colleague, Prof Tamara Hershey. The data will help Prof Urano set up a phase II effectiveness trial.

Treatment Timeline



A Clinical Trial of Treatment to Slow Disease Progression in Children and Adults with Wolfram.

The two possible treatments are:

A- A medicine used in children and adults

This treatment is for 3 years, until final assessments to see if it works. These are tablets.

B- Placebo treatment

This is also for 3 years. The dummy tablets look /taste identical to the real medicine but do not contain the study medication. The patient and doctor will not know which treatment is which.

This study is in Birmingham, UK; Spain; France; and Poland. 70 people will take part. 2 people will have the medicine to every 1 the placebo, decided by chance.

Stage 1

First visit, up to 28 days before starting

- Ask consent to take part
- Baseline tests and brain scan.
- Check person is eligible to take part

Stage 2

Second visit, randomise to medicine or placebo

- Start treatment

Stage 3

Follow-up visit at 6 weeks

- Visit for safety checks

Stage 4

Visits at 6, 12, 18, 24, 36 months.

- Safety checks, blood tests, eye tests
- MRI brain scans at 12, 24, 36 months

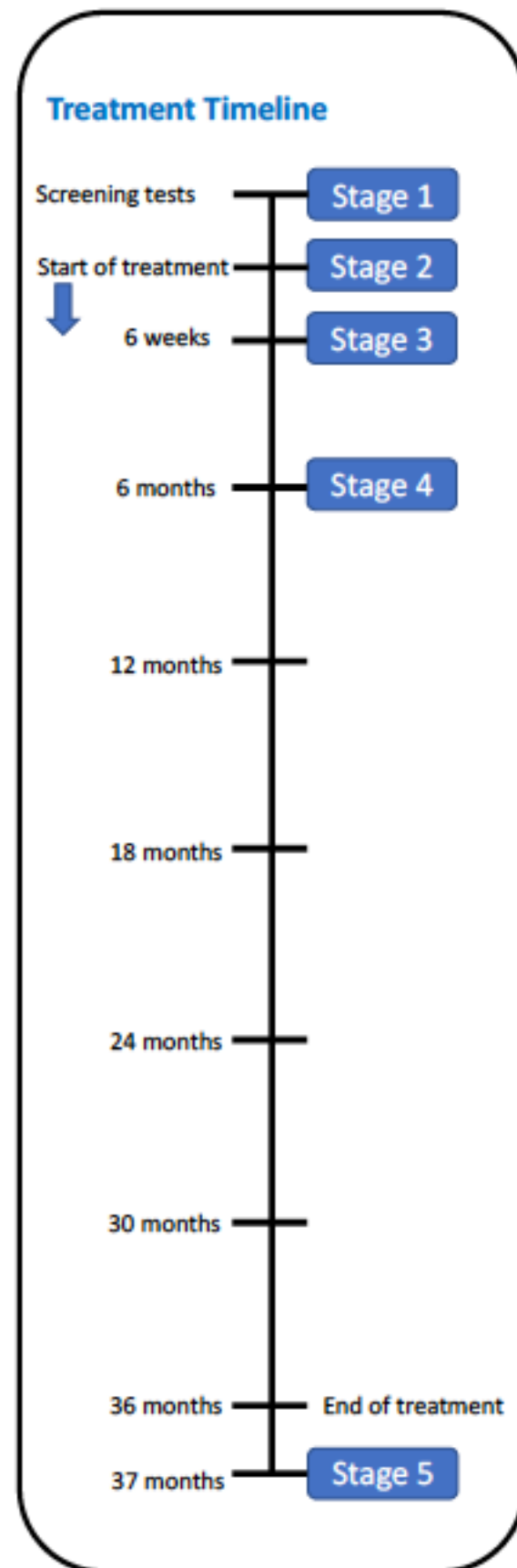
Stage 5

Final visit after treatment finished

- Final safety checks

This trial will tell us if this medicine is **SAFE** and **EFFECTIVE** in Wolfram. If these are shown, then

doctors may prescribe this medicine for almost everyone with Wolfram in any country.



5. Am I eligible to take part?

For the US trial, Prof Urano is currently recruiting patients in the US.

For the European trial, recruitment will start in the UK in Autumn 2017; and in Spain, France and Poland, in Spring 2018.

People will have checks to make sure they have Wolfram syndrome; enough vision at the start of the study to be able to assess the effects of treatment; and safety checks.

6. Possible benefits of taking part

Taking part in a clinical trial can be helpful if the trial medicine works to slow down the progress of the disease. However there is no guarantee that this will happen. There may be benefits in being seen by the study team regularly, as they will monitor the Wolfram disease carefully and treat any complications if they happen.

7. Possible risks of taking part

Any medicine in a clinical trial may not work, and not slow down the disease; and every medicine has side effects. Sometimes these side effects may be serious or life threatening. Before deciding whether or not to take part, always read the participant information sheets carefully, and ask about possible side effects.

8. How will we know if a medicine works in Wolfram?

We asked patient support groups in the UK, USA, Spain, and France, to advise us what are the most important outcome measures for trials of new treatments. Each group ranked vision as the most important. This means that any treatment must slow down or stop the worsening of vision.

Prof Tamara Hershey has shown that in people with Wolfram, parts of the brain slowly get smaller with age. This is related to problems with balance. With her kind help, we are using brain scans, to check that any treatment can slow down or stop parts of the brain getting smaller.

In Wolfram, vision gets worse, and parts of the brain get smaller, over years rather than months. In order to show that a treatment works, we

need to give the treatment for several years. This is why the European treatment trial involves giving people the medicine for 3 years.

If it is clear that a medicine in a clinical trial is working, it is possible to stop the trial early and give everyone the medicine.

9. Can I take these medicines without taking part in a trial?

The medicines being used in the clinical trials are not licensed for use in Wolfram. This means that doctors are not allowed to prescribe them to treat Wolfram syndrome. The reason is that no-one has done studies to show they are safe and to show they work in Wolfram. If a person with Wolfram took one of these medicines outside a trial, and had a serious side effect, the clinical trial would automatically be stopped. If this were to happen, we would never know if these medicines may work in Wolfram.

10. Future plans for studies

If Dr Urano's safety study of his medicine shows that it is safe, he will then apply for a Phase II study to see if it works in Wolfram. The design of this study will be similar to the European trial described above.

We are also seeking European Medicines Agency advice about the design of a Phase III clinical trial comparing both the medicine in the US trial and the medicine in the European trial, in combination in Wolfram. If this is funded, it will start after the current studies have finished. It will recruit up to 140 people with Wolfram worldwide.

We are very grateful to the following people who gave us their time and helped with this research update letter:

- A. Profs Hershey, Marshall, Hamel, Mlynarski, Esteban, Orssaud, Dias, Wright.
- B. Wolfram Study Groups in Washington and Birmingham Universities, Boyd Consultants.
- C. St. Louis Children's, Barnes Jewish, Birmingham Children's, and University Hospital Birmingham
- D. Our fantastic family support groups Snow and Ellie White Foundations, Wolfram syndrome UK, Spanish and French associations, Wellchild.