Update letter on Valproate clinical trial
Tim Barrett April 2019

Dear friends,

Thank you for the chance to give you an update on the TREATWOLFRAM clinical trial.

First of all, a quick recap. We asked many of you in the Snow Foundation, Wolfram Syndrome UK, French Wolfram Association, and Spanish Wolfram Association, what was your top priority for targeting in a treatment trial. You put vision loss as the number 1 priority. As vision loss is due to the underlying neurodegeneration process, we decided to go after a difficult goal, a treatment for the underlying neurodegeneration in Wolfram. In this study, we are trying to slow down the vision loss.

You all know better than I, how most people with Wolfram get sugar diabetes, and most people get progressive vision loss. The vision loss is a sign of the underlying brain degeneration, which progresses in most but not all people, and sometimes involves problems with other things like balance, taste and smell. Sugar diabetes is a sign that the pancreas is not working, but there are treatments that already work well. However, we do understand that the injections can be difficult, especially when your vision is not so good.

What are we looking at?
We are testing a new use for an old medicine, sodium valproate, to slow down or stop the brain disease in Wolfram. We are doing this because valproate works to protect cells in our models of Wolfram; we have presented our data to the EMA, FDA, and the UK Medical Research Council, and they have given us the go-ahead to test this in people affected with Wolfram. If we can show it is safe, and it works, then it can be prescribed for everybody.

Why will it take so long to get an answer?
Unfortunately, it is incredibly difficult to prove that a medicine stops or slows down progression of neurodegeneration. It takes a long time (2-3 years) to show a change. There are lots of opportunities for data to be confounded by other factors such as measurements being done differently in different centres. There are lots of ways to bias the data, such as the doctor or parent unconsciously wanting to see an improvement when there is none. There is also the danger of unwanted or unexpected side effects.

If a study is not done really carefully, then people will not believe the result even if the medicine works. Alternatively, the medicine works but the effect is missed because the results have been confounded by something else, such as a new treatment for sugar diabetes. If any of these things happen, it can be a disaster because the EMA and FDA may refuse to license the medicine to doctors prescribe it for people in the clinic.

We have gone to great lengths to make the TREATWOLFRAM clinical trial free from bias, so that we will be able to give you a definite answer to the question- does sodium valproate slow or stop the neurodegeneration in Wolfram?

Prof Tammy Hershey has generously allowed us to use the anonymised data on vision tests from the St Louis Wolfram research clinic. This has shown us how long we need to follow people up, to detect an effect on the neurodegeneration. The data from the clinic has been incredibly important to tell us what we should be measuring, such as eye tests, MiniBEST tests of balance, and MRI scans of brainstem volume.

Why do some people need to take the placebo (dummy medicine)?

To reduce bias, we have had to standardise the way tests are done, so that they are exactly the same across each centre taking part. This goes especially for eye tests, and MRI scans. The regulators who will eventually license the medicine if it works, have asked us to have a control group. This is so that we can compare the rate of neurodegeneration in the group receiving sodium valproate, with the rate in people receiving usual standard of care for Wolfram. I know how much families dislike the idea of being in the control group. To minimise this, Mr Kristian Brock our statistician has done a great job with the design of the trial and has been able to ensure that twice as many people will get the sodium valproate, as will get the placebo. At the end of the trial, if the treatment works, everybody on placebo will get the treatment as we will apply for it to be licensed to use in Wolfram.

What does an adverse event mean?

Finally, the regulators have insisted that this is a double-blind study. This means, as you know, that neither the participants nor their doctors will know which treatment they are taking, until the end of the study. This means that we have to report any changes we see in patients, as 'adverse events', even if they are positive changes. So when I refer to adverse events, these include positive outcomes for participants as well as negative ones.

How is the clinical trial going?

As you know, we had many false starts due to bureaucratic and regulatory hold-ups, which have been incredibly frustrating for all the team. There have been lots of issues to content with, including:

1. Brexit- our sponsor has put in place mechanisms to deliver the trial in Europe whatever the outcome of Brexit.
2. Sodium valproate safety concerns relating risks to unborn babies. We have incorporated all the latest advice into the patient information.
3. Complex negotiations on financing- these are now in the final stages, to make sure hospitals that take part have all the support they need to deliver the tests to prove this medicine works for neurodegeneration
4. Many contracts and Quality Of Life Questionnaire licences required (currently we are at 17), to ensure the trial is delivered safely and gathers all the information we need.
5. Experience of key centres- we have been working closely with partners in each centre to support them to deliver what is a complex study.
6. Setting up specialist medical support: we are using this study to help get more hospital resources for people with Wolfram such as adults, who have had limited specialist services in the past.

This is a really important study as it is called a 'pivotal project' – we have only one chance to deliver this, and the health regulators will accept the result from this study without

requiring any more evidence. There will be high levels of scrutiny by our regulators, so we have to be 100% compliant and correct in everything we do.

We recruited our first participant on January 7th 2019. We have held 2 recruitment clinics so far, in January and March, and we have 10 participants. Birmingham Children's Hospital is open as a site for affected children. University Hospitals Birmingham is about to open for affected adults. Almeria, Montpellier, Paris and Lodz are opening this Summer.

Participants are attending clinic visits and have reported no issues with taking the medication (tablets). It is important to note that Wolfram syndrome is very specific to individuals, and we are not allowed to release any information about effectiveness or potential side effects until the end of the study, unless we are given permission by the independent oversight committee. If there is any new information, released by drug companies, or the medicines regulatory agency, then we will let participants know straight away. We record all possible side effects, whether good or bad, related to the treatment, the condition, or anything else. This is so that they can be closely checked by the study team, and independent regulators. There are 11 visits in total for this study, and several participants have reached visit 5 (12 weeks after starting). Most of the remaining visits will be short (less than 2 hours), for an eye test and safety blood test.

Can I or my child take part?
To take part, participants have to be at least 5 years old. This is so that they can complete the assessments. Participants must have both diabetes mellitus and optic atrophy diagnosed before 16 years of age, and at least one mutation in the Wolfram syndrome gene. Participants must have enough vision left in order for us to measure changes in vision over the course of the study. In practice, this means being able to read better than approximately size 48 font, with glasses. Participants have to be able to travel to one of the trial centres.

There are very few exclusion criteria: most importantly, participants must not have diseases known to be made worse by sodium valproate; must not have active liver disease; or be pregnant, as sodium valproate can harm the unborn child. Participants may not take part in another clinical trial at the same time as this one. All licensed diabetes medicines are allowed in this study, provided they are not being given as part of another clinical trial.

We have learnt that it takes a long time to explain the study properly, to participants and their families. The initial visit, to take informed consent, is quite long (about half a day). I am especially impressed by the questions that children and young people are asking. These are often very perceptive. To give families enough time, I have been sharing this with Dr Renuka Dias, my paediatric endocrinology colleague and local investigator at my hospital. Dr Ben Wright is my adult neurology colleague who is leading recruitment at the adult site.

Every change to a participant has to be recorded, usually as an adverse event, to make sure we detect all effects of the treatment, whether good or bad, and to avoid any bias. Participants are asked to carefully monitor their diabetes and its treatment, so that insulin doses and long term glucose control can be reviewed by the study team on a regular basis.

I think it is critical to acknowledge the help we have received to get this clinical trial up and running. Thanks to the generosity of the UK medical research council, we had the funds to undertake a trial. The CRUK Clinical Trials Unit in Birmingham and their statistician Kristian Brock, put together a trial based on being able to detect a slowing in vision loss. Prof Tamara Hershey very generously shared the anonymous vision tests data from many of the attendees at the St Louis Wolfram research clinic.

The European Medicines Agency protocol assistance committee advised on the design of a trial that would give the strongest possible evidence of an effect. They asked us to undertake a double blind, placebo controlled trial, because it gives the most reliable results, it is protected from bias, and it is the surest way to prove an effect on the neurodegeneration.

Our partners Dr Gema Esteban in Almeria, Profs Agathe Roubertie and Christophe Orssaud in France, Prof Wojciech Mlynarski in Poland, and Drs Renuka Dias and Ben Wright in Birmingham, all kindly agreed to invite their patients to take part. I cannot thank the French Wolfram Syndrome Association enough for funding us to undertake the brain imaging that supported our clinical trial application.

I am also incredibly grateful to the Snow Foundation, Eye Hope Foundation and French Wolfram Syndrome Association for enabling us to find patient reported outcome measures and collect research samples from trial participants, to make available to the whole Wolfram research community.

At Birmingham Children's Hospital, the research nurses, play therapists, pharmacy clinical trials, laboratory technicians, and study coordinator have been absolutely brilliant. Jody Blake, the Wolfram Syndrome Family Coordinator from WellChild, has been wonderful at supporting families to attend. Wolfram syndrome UK and their amazing supporters have been fantastic, and raised over £35,000 to help support participants in the UK with travel costs, to make the visits easier. This support has been a real godsend, and made trips to our hospital much more manageable. Finally, we could not have got this far without the support of the wonderful participants and their families who are supporting them.

We hope to complete recruitment of all 70 patients within the next 12 months We are then governed by a data monitoring committee, who will look at the unblinded data as it comes in. If there is early evidence of effectiveness, or indeed of no effect whatsoever, they will be able to recommend an early end to the trial.

I want to end by offering a source of information to help you all as families; and one request.

The source of information is www.clinicaltrials.gov . If you type in Wolfram, you will get a list of all past and present clinical trials. You will see our sodium valproate trial there (NCT03717909 – unique number), with lots of detail on the assessments, inclusion and exclusion criteria, and potential side effects and risks. When considering any proposed new trial, look to check it is registered on this site; and if it is not, ask, why not?

Secondly, the request. You will hear a lot about possible treatments for Wolfram, and plans for clinical trials. People will give their opinion that a certain medicine is the best available treatment for Wolfram. This is great, but an effect in a few people does not mean a medicine will work for all; and effects on neurodegeneration are very difficult to prove.

The internet is a wonderful data resource but is not regulated and there is the potential for 'fake news' and/or misinterpreted medical breakthroughs. Your clinical team are always happy to discuss any information that you may find on the internet especially in relation to new treatments or other news stories relating to Wolfram syndrome or specific drugs. There may also be a temptation to try different combinations of medicines. This could be dangerous: for instance, a combination of dantrolene and sodium valproate can increase the risk of liver failure. It is important to ALWAYS inform your doctor all the medicines (or herbal / food supplements') that you or your child are taking. I and my colleagues will always be completely honest with you; please always be honest with us; at the end of the day, patient safety is the priority for us all.

If you are still reading, thank you, and I hope you found this article helpful. Please do not hesitate to contact me or any of the study team.

Sincerely

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