Patient focus group report:
congenital hyperinsulinism

This study was completed in the first half of 2016, as part of Findacure’s Drug Repurposing for Rare Diseases Social Impact Bond Development project, with the assistance of the Children’s Hyperinsulinism Charity.
The cover image does not depict an actual focus group event, rather showing another Findacure meeting. The identity of all focus group panellists is purposely kept private.

All of the information in the following report is based on the facts, examples, and opinions expressed in the Findacure focus group. Findacure would like to thank all members of the panel for their valuable participation and insight. We also thank the Children’s Hyperinsulinism Charity for their help in organising this focus group.

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Executive summary

Congenital hyperinsulinism is a rare disease, in which new born infants have permanently high levels of insulin in the blood. This starves the brain of sugar, causing lifelessness, seizures, and even death. In the most severe cases the only treatment is the removal of the pancreas. Findacure ran a congenital hyperinsulinism parent focus group to assess the current treatment and care available to patients, the cost of the disease to affected families, and the parent perspective on clinical trials. The major findings from the focus group, which are detailed below, were used to build an argument for the need for new treatments for congenital hyperinsulinism, potentially funded by Findacure’s rare disease drug repurposing social impact bond.

- Due to the potential for brain damage, delayed diagnosis of CHI is hugely costly, both financially and to the wellbeing of the patient and family.
- Early diagnosis hinges on the completion of a blood glucose test within the first couple of days of life, timed appropriately in the patient’s feeding cycle. This is not currently a standard test for neonates.
- The CHI specialist services, based at Great Ormond Street Hospital and northwest England, is well regarded by CHI families, due to the strong personal relationships they form. There is good communication between the clinical research teams and families.
- The potential of sirolimus to control blood glucose levels in the first years of life, preventing pancreatectomy and life-long diabetes, is well recognised by the CHI community.
- CHI imposes a high financial burden to families in the first few months after birth and diagnosis.
- Young patients struggle with clinical trial involvement, which is invariably stressful. Clear communication between clinicians, families, and where possible, patients themselves is crucial to provide a calm and predictable trial experience. This destresses monitoring, disease treatment, and research.
Rare disease perspectives

In late 2015 Findacure secured a development grant from the Big Lottery Fund’s Commissioning Better Outcomes Fund in order to investigate the potential of a social impact bond to provide a new source of funding for generic drug repurposing in rare diseases. As part of this proposal, Findacure wished to engage with rare disease patients, in order to gain a better understanding of their need for new treatments, and the issues they deal with on a day to day basis.

To achieve this, Findacure decided to run a series of four patient focus groups, to collect the perspectives of rare disease patients. These focus groups helped to provide the personal stories and patient opinion crucial to build a strong argument for the underlying need for Findacure’s proposed drug repurposing programme. The first of the focus groups gathered rare disease patients and advocates from across the spectrum. The other three groups were disease specific, focusing on the three rare diseases which formed the focus of Findacure’s health economic studies: congenital hyperinsulinism, Wolfram syndrome, and Friedreich’s ataxia.

The completed focus group reports have been made available to all of our anonymous focus group participants, our clinical partners for each of our rare diseases, and our patient group partners. They also form a key component of our final presentation to the NHS, designed to discuss the potential of commissioning a rare disease drug repurposing social impact bond to deliver new treatments to rare disease patients in the UK.

Congenital hyperinsulinism

Congenital hyperinsulinism (CHI) is a rare genetic disease of new born infants, where the insulin-producing beta cells in the pancreas are hyperactive. They produce constantly high levels of the hormone insulin, rather than producing it in response to blood sugar levels. Insulin causes sugar, specifically glucose, to be removed from the blood stream and stored in cells. Glucose is the body’s primary source of energy and crucial to normal brain function. Children born with CHI subsequently exhibit severe symptoms from birth. They feed poorly, often appear lethargic or even lifeless, and experience seizures. If not caught early, the low supply of glucose to the brain can lead to permanent brain damage or even death.

In early 2016, Findacure organised a series of group calls and discussions with parents of children with congenital hyperinsulinism (CHI). During these discussions we surveyed the families in order to gain a better understanding of:

- the need of CHI children for new treatments
- what CHI families need from a clinical trial
- the financial burden of CHI to families, as well as its social and emotional impact

The report below summarises the information gathered from our focus group, and a number of subsequent conversations with CHI families. All participants consented to be involved in this study, and have been informed how their thoughts, experiences and opinions will be used.
Current treatment

Journey to diagnosis – CHI is a disease that generally affects children from birth. With a very limited supply of glucose to the brain, early identification of the problem and rapid diagnosis is essential to avoid brain damage in patients. Those children who are born prematurely and placed in specialist baby care units have a good chance that their low blood glucose levels will be noticed. This was the situation for one of our patients, who was subsequently given an intravenous supply of sugar (dextrose) in the first day of life, ultimately reducing the risk of brain damage. Another CHI child, who was less premature, was sent home shortly after birth. They became blue and lifeless on their sixth day of life and were admitted to hospital as an emergency. A diagnosis of CHI was secured quickly in this case, because the clinicians at the local hospital had encountered the disease before, and thus secured a rapid referral to Great Ormond Street Hospital.

Diagnosis is unfortunately not always so rapid. One child’s blood-glucose was tested in the first days of life; however the test was performed just after a feed, meaning that a low glucose level was not identified. This child was discharged and suffered no emergency for their first eight months. Instead the patient fed excessively (every two hours) for that whole period, before experiencing two seizures, the latter of which led to brain damage. After another mistimed blood-glucose test, the final diagnosis of CHI was only secured at the age of 13 months, following a referral to a specialist consultant via a patient support group. This type of patient group mediated referral is not a one-off occurrence the CHI community, and reflects the importance of experience in the successful diagnosis of a rare disease.

Existing treatment – There are a number of different treatments for children diagnosed with CHI. Diazoxide is the frontline drug, but not all patients respond to it and clinicians are often forced to try increasingly high doses of the drug. At least two of the families we spoke to suggested that their children had been given a dose higher than any other patient of their age at the time of first treatment. This dose variation is worthwhile as, when successful, it can help to maintain blood-glucose very effectively throughout early life. One of our patients remained on the drug until aged 10, and has since been able to control his blood sugar level through diet alone.

If diazoxide treatment proves unsuccessful, patients may be moved onto octreotide. However, for patients with diffuse disease who do not respond to this drug, near-total pancreatectomy is standard of care. This invasive surgery is clearly traumatic for patient and family alike, and will almost certainly lead to type one diabetes in later life. Furthermore, surgeries are rarely one off – initial removals may not be sufficient or patients may need feeding tubes implanted. As patients grow up they have to cope with severe diabetes throughout life, which has a huge impact on their day to day quality of life.

However, in the last few years some patients have been trialled on sirolimus, which has proved effective at regulating blood glucose, and thus preventing costly and traumatic surgeries. One of the patients we spoke to remains stable on this drug after almost three years of treatment.

For all patients, almost regardless of treatment type, blood glucose monitoring remains a constant, though frequency of monitoring may vary from treatment to treatment and patient to patient. Furthermore normal illnesses when young can necessitate hospitalisation, as symptoms often reduce appetite or prevent feeding entirely. This makes blood-glucose regulation almost impossible.
Experience of the clinic – There is a generally positive outlook on the CHI clinic at Great Ormond Street Hospital, primarily due to the expertise available there and the willingness of the CHI team to engage with the families and patient groups. This interaction helps to secure further diagnoses for patients around the country and ensures good communication about the progress of new research and treatments. For many families there can be a prolonged and intensive period spent in the clinic after birth, but a relatively limited time there subsequently if the disease is well managed by medication. One of our patients has only visited the clinic a few times since birth. Despite this the CHI clinic were able to arrange a lot of neurological and psychological assessments for them, to ensure that the special needs that resulted from brain damage sustained prior to diagnosis were fully understood. This has proved crucial in securing the correct support for their education.

Treatment hopes and aims

New treatment need – For all families there is a clear burden of CHI, regardless of treatment. They are looking for treatments which can essentially minimise the impact of glucose monitoring on the lives of patients, throughout their whole lives. The development of the drug sirolimus to treat instances of diffuse CHI has captured the imagination of the CHI community, as it offers the chance for patients to stabilise blood-glucose levels while retaining the pancreas. The monitoring while on the drug is generally less than is seen in diabetic patients, and there is a real hope that in sirolimus treated patients the hyperactive beta cells will burn out as the children grow up. If this is the case, monitoring and treatment should decline throughout life, reducing the burden on families and giving patients a hope of a more normal life, not constantly constrained by their blood-sugar levels. Sirolimus, and other similar potential treatments, are therefore a source of hope that patients can live an unconstrained life, while simultaneously providing another treatment option for those patients who may suddenly stop responding to diazoxide.

The patient perspective on clinical trials

None of the families we spoke to have had involvement in clinical trials to date, but some have experience of research and important perspectives on its impact on very young patients.

One parent made a key contribution based on their child’s involvement in a study assessing the neurological impact of brain damage sustained as a consequence of CHI. They made it clear that young patients really struggle when involved in trials. CHI patients often have a lot of experience of a hospital environment from a young age. This is quickly associated with tests, pain, and relatively impersonal investigations, all of which are stressful to the child. Participation in research increases time in this setting, which is innately stressful. This stress is often compounded by uncertainty – children often have no understanding of what is going to happen. This places parents in a difficult situation, as one of our parents explained, “As parents you want to help, you want to do the research, but you don’t want to put you child through the anxiety of it.”

It is therefore crucial that any research or monitoring performed on a paediatric population is explained clearly to the children, when they are old enough to understand. The procedures themselves should be predictable wherever possible. Children like things very definite, uncertainty makes things worse. Predictability of the study, or the clinical process, is therefore paramount. Children should know in advance what is going to happen and this should be delivered. This helps to
build a sense of trust, certainty, and safety for the child, therefore managing anxiety. Finally, the interactions with the patients should not feel rushed. Patience is key – in hospitals things are often done rapidly and with little explanation. Familiarity with the clinician is not necessarily important, but the personality, and level of engagement with the child is. Clinician attitude has a huge bearing on the patient experience and stress. For families with children who have already had to cope with stress and trauma in early life, it is crucial that any voluntary research programme should do everything in its power to minimise this for the patient and their family. Our group felt that patient groups could be involved to assess the impact of any clinical trial on the patients and the parents, to help ensure both enrolment and retention of patients in the research programme.

When we talked specifically about clinical trials for new CHI treatments, like sirolimus, our group reiterated the importance of communication between the medical staff and parents. It is crucial that communication is clear so that parents have an understanding of the research being proposed. Communication between the clinicians and parents destresses monitoring, treatment, and research. Building trust between patient and doctor is crucial to keep patient families engaged in research for the disease. Fundamentally, however, all agreed that in a situation where parents have a choice between pancreatectomy or an experimental drug, such as sirolimus, most will feel that they have nothing to lose. Parents will accept risk and cling to the hope that a treatment will help their child.

**The burden of congenital hyperinsulinism to patients and families**

**Financial Costs** – For all CHI patients, there is a common high cost to families around the point of diagnosis. Establishing the appropriate treatment regime for each individual can be a slow and time consuming process, particularly as patients can take a number of weeks to stabilise. Patients and their parents often spend a period of months in the hospital while treatments are established, and the further down the treatment pathway the child progresses the longer this time will be. One mother of a diazoxide responsive CHI child reported spending an entire month in hospital. Another family, whose child was successfully tested on sirolimus spent roughly five months in three different hospitals from birth. This period of time can be hugely costly. Frequent travel for family members to visit the hospital is essential, while there may be a serious loss of earnings for a parent. One single parent was unable to pay her mortgage during the first months of diagnosis and treatment and only got by financially with parental support.

Many patients experience developmental delays, either as a consequence of brain damage caused prior to diagnosis or other associated illnesses. This is invariably costly to both families, and the government who have to pay out a range of benefits to ensure proper care for the patients. In such cases at least one parent is often unable to work and acts as a carer. Such families often receive higher rate care allowance, while patients receive higher rate disability allowance. Families may also need respite care, which is either provisioned directly or sourced privately using money paid directly to the family. Disabled facilities grants are also used to help modify their homes for their child’s needs. Such funding only tends to be available for one home, which adds either an additional financial or emotional burden to parents who are no longer together. One parent has also received charitable support to purchase a £2000 specialist buggy and a £6000 specialist bed for their child. Some children will also receive additional support at school: one of our patients is a statemented child with exceptional needs funding. This provides one to one support throughout school.

"It’s fifteen-ish tests a day, no day is going to be the same, and you never know what is going to happen.”

– Diabetic CHI patient
Costs also directly affect patients and families. Some patients are incontinent at night time – again as a consequence of brain damage – and the families have to bear the costs of nappies for older children. Other families pay directly for additional therapies, such as osteopathy, horse riding, and music therapy for their children (the latter can be as much as £30 for a half hour session). More generally there is a clear cost of travel and accommodation for treatments in London - Great Ormond Street Hospital can afford to pay for the accommodation for one parent, but not two.

Emotional cost – For parents, there is the simple, constant, emotional cost of care. Young children need feeding every two to three hours and monitoring of blood glucose is constant, no matter the time or place. For children who have their pancreas removed this will persist throughout life and lead to a huge loss of sleep for parents, and ultimately for patients. CHI, or diabetes caused as a consequence of pancreatectomy, are illnesses that require constant vigilance and impose a dramatically different lifestyle on families. The main hope of all of them is that other families are saved from this prolonged and stressful way of life, and that the initial period of fear and uncertainty that surrounds diagnosis and identification of an effective treatment is reduced.

Schooling – As with other childhood diseases, CHI does impose a cost on schooling. Even in the most successfully treated cases there is a constant need for blood-sugar monitoring during school. This requires teachers to have specialist training and can necessitate parents spending large amounts of time in the classroom while teachers are brought up to speed. One of our patients who recently started secondary school has waited over seven months for blood-sugar training for school staff. At the time of writing there are still no trained teachers at their school, meaning that the patient is sent home as soon as they feel unwell. This has resulted in a huge amount of lost schooling, as well as stress for the patient and family. This simple medical need, for blood-glucose monitoring, can have a big impact on a child’s experience of school. Parents reported having to go with their children on a residential school trip so that their needs can be met. It is hard for parents to know what level of support should legally be provided by a school and how they can ensure that this is delivered. The educational experience of rare disease children seems to be hugely influenced by the school and its attitude. Another parent reported that every member of their child’s nursery staff has training in blood-sugar monitoring.

Conclusions

A key message from the CHI families was the importance of early diagnosis. The cost of diagnostic delay is huge, lowering patient quality of life, limiting the freedom of their families, and increasing government expenditure to support the complex needs of patients. A simple blood-sugar test delivered prior to a feed, within the first two days of life, has the potential to quickly identify patients with CHI and ensure they secure the treatment they need. Such testing either needs to become standard for all new-borns or doctors need to be encouraged to think outside of the box when dealing with odd, subtle, or unexplained symptoms. Families feel that such symptoms should trigger a blood-sugar test, which should be readily available at GP surgeries.

While genetic diagnoses can be secured for CHI, this is unlikely to dramatically increase diagnostic frequency. A specific test must be requested for such diagnoses, requiring prior clinical suspicion. Furthermore, the disease is complex, and not all the possible mutations have been identified. Children can often present with multiple rare conditions, as is suspected of at least two of the patients whose...
families we spoke to. All this means that while genetic diagnoses are a useful to confirm the underlying cause of CHI, they are unlikely to help to identify CHI patients in the first critical days of life.

Early diagnosis is crucial to prevent life limiting brain damage, which has the most profound effect on the lives of patients and families, as well dramatically increasing cost of care. Once diagnosed, patients and parents simply want to see a faster route to treatment and a treatment with the potential to deliver a life free of the stress of constant blood-glucose monitoring. Pancreatectomy is clearly an imperfect solution, while the repurposing of sirolimus currently offers hope to the CHI community.

A rare disease is defined by the EU as affecting fewer than 1 in 2,000 people.

In the UK, approximately **3.5 million** people live with rare diseases, which can be **chronic**, **life-threatening**, and **isolating**.

Of the **7,000** recognised rare diseases, only **400** have licensed treatments.

The average rare disease patient **waits 4 years** before they receive their final diagnosis, during which time they consult with **5 doctors** and receive **3 misdiagnoses**.

Please contact rick@findcure.org.uk if you’d like to learn more.

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