# Type 1 Diabetes Research Roadmap

**Identifying the strengths and weaknesses, gaps and opportunities of UK type 1 diabetes research; clearing a path to the cure**

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

**Join us in finding the cure for type 1 diabetes**

**Type 1 diabetes is a chronic, life threatening condition which has a lifelong impact on those diagnosed with it, and their families.** It is caused by a problem with the immune system which triggers the body to destroy the insulin producing cells of the pancreas. Its development is not linked to lifestyle factors.

**Currently there is no way to cure type 1 diabetes, or prevent it from developing.**

**Type 1 diabetes affects about 400,000 people in the UK**; that's over 500 people in each constituency. And in FY11 type 1 cost the UK nearly **£2 billion**. Incidence is increasing by four per cent each year so these costs and numbers will continue to rise.

# Contents


**3** Introduction
**4** Foreword
**6** Executive summary
**8** Survey
**11** Autoimmunity
**16** Beta cell renewal
**21** Complications
**26** Glucose sensing
**31** Hypoglycaemia
**36** Structured education
**41** Glossary
**44** Research funders
**47** Acknowledgemen



**This JDRF Type 1 Diabetes Research Roadmap report has been supported by Novo Nordisk**

Novo Nordisk has had no editorial input into the content of the report

**With individual gifts from JDRF Patrons**
**James and Margaret Cripps**
**Jonathan and Hélène Haw**

# Clearing the path to the cure

I am proud to say that I believe research progress in type 1 diabetes has never been faster than it is today. I believe there are now tangible opportunities for research to transform the lives of people affected by the condition. But I am also concerned that the UK risks losing its place at the cutting edge of type 1 research if certain challenges are not addressed urgently

Despite significant progress in our understanding of the condition, hundreds of new cases of type 1 are diagnosed each year in the UK. Indeed, type 1 incidence is increasing all around the world. With this in mind, the need to support research into type 1 is more urgent than ever. We need to consolidate existing knowledge, define priorities and support the most promising research avenues available.

To address these issues, the 2013 Type 1 Diabetes Research Roadmap project has brought together many of the UK's top type 1 diabetes researchers and key opinion leaders, and their counterparts in Europe. Roundtable meetings were held to discuss these issues in six key aspects of type 1 research: autoimmunity; beta cell renewal; complications of diabetes; glucose sensing; hypoglycaemia and impaired awareness; and structured education.

It is clear from these meetings that there is great excitement about the possibilities to improve the lives of people with type 1 diabetes significantly, in the short, medium and long term. The UK type 1 diabetes research community will play a vital role in delivering these advances to families affected by this life-changing autoimmune condition, not just here in the UK, but all around the world.

In many ways the research infrastructure within the UK is the envy of researchers from outside the UK. Particular praise for Academic Health Sciences Centres, Biomedical Research Centres and the existence of national clinical research networks came across through a number of the roundtable sessions. Many researchers also noted with satisfaction the emphasis successive UK governments have placed on the importance of research to the UK's economy, and the infrastructure and funding mechanisms that have been put in place.

But the workshops also highlighted some areas which are impeding the progress of translating promising research that can benefit people affected by type 1 diabetes as quickly as possible. While opportunities to make improvements and explore new avenues for research have been identified across the pipeline, we believe there is a particular cluster of challenges around the research interface between the clinic and the laboratory.

Overleaf you will find the four cross cutting issues identified through the process of developing this report which we believe provide the greatest challenges in capitalising on the vast potential of discoveries made by UK-based researchers.

If these challenges are resolved, I believe the ability of UK researchers to improve the lives of people with type 1 will be transformed.

Only research can lead to a world without type 1 diabetes – join us to put the UK in the vanguard of the quest for the cure.

**Karen Addington**

Chief Executive
JDRF

# Clinics and collaboration

## Opportunities to transform the UK research landscape

### Clinician scientists are vital to successful translational research

The UK has many world-leading basic scientists and clinicians. And their work is pushing forward our knowledge of type 1 diabetes and how to treat it. But through all of our workshops, researchers highlighted a lack of clinician scientists to support the process of translating laboratory advances into the early phases of clinical testing. The workshops emphasised the need for innovative schemes, like being able to embed clinician scientists in basic science labs.

Reviews such as the Academy of Medical Sciences *Shape of Training* consultation and the Royal College of Paediatrics and Child Health's report *Turning the Tide* demonstrate that this issue is far wider than the field of type 1 diabetes, and needs addressing urgently.

**We call on Government to work with research funders and providers of clinical training to overcome the structural issues that are preventing aspiring clinician scientists from realising their potentially vital role in translating scientific advances into patient benefit.**

### Unintended regulatory barriers must be removed

Clinical trials are the lynchpin of the process of developing new treatments, technologies and practices to help patients and improve efficiency within the healthcare system.

The Health and Social Care Act 2012 places research at the heart of the National Health Service (NHS) constitution and sets out the ambition that any willing patient should be offered the opportunity to participate in clinical research. This is a very positive marker of an objective of the health service, but at present this is being stifled by bureaucracy.

The regulatory steps that must be undertaken to get a clinical trial up and running in the UK are perceived to be some of the most arduous in the world. This reduces the attractiveness of UK research centres and hospitals as settings for clinical trials.

The House of Commons Science and Technology Committee's ongoing inquiry into clinical trials and the use of data is looking closely at these issues.

**We call on Government to study the evidence presented to the select committee in detail and work with researchers, funders and patient groups to implement the recommendations that will allow the NHS to meet the ambition of putting research and innovation at its heart.**

There are also specific regulatory barriers of particular relevance to weaknesses in type 1 diabetes research. For example, beta cell research is vital to the search for the cure for type 1 diabetes, but this field of research is limited by lack of available human pancreas tissue.

Many generous individuals and their families are willing to donate their pancreases for research. But, even with full consent and ethical approval in place, to collect a pancreas for use in research the specific operating theatre in which the surgery is scheduled must have a Human Tissue Act licence to enable post mortem retrieval for this invaluable work.

Although organ donation takes place in many different operating theatres throughout the country, only a handful have this licence in place. This means that, simply as a result of bureaucracy, precious gifts of vital tissue cannot be accessed, slowing research progress.

**We call on Government to work with hospitals and clinicians to address this unintended barrier to research introduced by the Human Tissue Act, and increase the availability of vital human tissue samples for research.**

## ‘Structural issues are preventing aspiring clinician scientists from realising their potentially vital role in translating scientific advances into patient benefit’

### Clinical trials must be designed and presented effectively

Clinical trial design was a hot topic at many of the roundtable discussions, with a number of scientists stating that trials can be much more effectively designed. The National Institute of Health Research has produced an excellent guide to help researchers in designing and correctly planning a clinical trial, the Clinical Trials Toolkit.

**We call on funders, researchers and hospitals to make greater use of the existing Clinical Trials Toolkit in preparing the groundwork for effective clinical studies.**

A recent survey of JDRF supporters revealed that while many families affected by type 1 wish to take part in clinical studies, few have the opportunity to do so. This is despite the implementation of diabetes research networks in England, Scotland and Wales, and in contrast to other fields, such as cancer, where more than 25 per cent of patients participate in clinical research.

At the Roadmap roundtable sessions, a number of researchers commented that only a proportion of diabetes specialists seem to regard promoting research opportunities to patients as a core part of their clinical practice. There is an opportunity for further education of both diabetes clinicians and people with type 1 in the value and benefit of participating in clinical research.

**Diabetes organisations, for both patients and clinicians, must promote discussion of clinical research opportunities within routine clinic visits.**

### Research funding structures must facilitate and nurture collaboration

Many institutions throughout the world provide extensive funding for health research. Scientific enterprise is now truly global and historic barriers to collaboration, such as geographical borders, are of diminishing significance.

The resources present in research centres throughout Europe and around the world, could become even more powerful if they could be harnessed together in the interests of meeting the goals shared by clinicians, researchers and patients globally.

Specific barriers to the implementation of these collaborations exist: one is the lack of access to large-scale long-term funding for major research initiatives, such as birth cohorts. Statutory funding bodies are best placed to support such major research infrastructure undertakings, but when funds are tight and expectations of ‘delivery times’ are high, such projects seem risky for any single funding agency.

**We call on statutory funding bodies throughout Europe and beyond to consider how they can work together to maximise resources for transformative research infrastructure which may be impossible to deliver in national isolation.**

The research opportunities presented by the ability to bring together datasets from many different research teams are powerfully evident. But in order to capitalise on these opportunities, researchers must be able to compare like with like.

The type 1 diabetes research community must come to a consensus as to the core definitions, measures and markers that can and should be used to characterise type 1 diabetes and its complications.

**Diabetes organisations must work together to develop consensus statements on the issues identified in this report and elsewhere to provide a platform for collaboration from which the research community can move as one.**


# Mapping the way forward

The last two decades have seen extraordinary advances in research into type 1 – from genetics and autoimmunity, through beta cell renewal and diabetes' complications, to the care and self-management of the condition. As yet, however, the cure continues to elude us, and there is still no proven method for preventing the condition

The 2013 Type 1 Diabetes Research Roadmap project brought together many of the UK's leading researchers and key opinion leaders in the field of type 1 research, and their counterparts in Europe. The project aimed to:

- identify existing UK research strengths and capabilities relevant to type 1
- find appropriate points of convergence between UK and international type 1 research priorities
- encourage collaboration and communication among academics, clinicians, governments, commercial organisations, funding agencies, the type 1 community and other stakeholders
- recommend areas for future support to accelerate the advance of UK research and enable the translation of research into real clinical outcomes.

Each roundtable event was designed to encourage researchers to participate in an analysis of existing gaps in UK type 1 research, to identify the key research questions that need to be addressed and to discuss the funding streams that need to be in place to allow this to happen.

The roundtable events highlighted several key themes relating to the strengths and weaknesses of UK research into type 1 diabetes.

## Research strengths in the UK

The UK has a well-deserved international reputation for high-quality type 1 research in 'pure science'. In particular, it performs strongly in the fields of immunology and the genetics of type 1. Existing collaborations and consortia have played a key part in enabling developments in this field and have benefited from substantial funding.

Beta cell research is another strength in the UK's research into type 1. In part, this is due to the active islet cell transplantation programme supported by the NHS. This programme has catalysed new research projects in the fields of islet cell survival and beta cell replacement strategies.

The UK also boasts high profile researchers working in basic and clinical research into hypoglycaemia. Substantial research efforts are being devoted to the development of the artificial pancreas and to glucose-sensing technologies.

Finally, structured education for people with type 1 is relatively well embedded across many areas of the UK thanks to the success of the Dose Adjust for Normal Eating (DAFNE) research project. Similarly to islet transplantation, DAFNE is available on the NHS. On-going research in the area is developing related structured education programmes tailored to the needs of different groups of people with type 1, including children and young people.

## Research weaknesses

Despite the strengths outlined above, a relatively balanced basic and clinical research portfolio, and an enviable track record for publishing research papers, type 1 research in the UK still suffers from several significant weaknesses.

Historically, collaboration with European colleagues has been poor – although this is now improving thanks to the advent of European funding mechanisms that encourage cross-border cooperation. There is also a lack of collaboration between more diverse groups within UK type 1 research; for example, between researchers in the autoimmunity field and those working in the wider complications arena.

Lack of access to resources is an issue, and not only in terms of funding for type 1 research. We also suffer from a lack of relevant, established biobanks and repositories. Ongoing collaborations with European and American colleagues could be strengthened further if these resources were made available.

Despite concerted efforts to increase both the quality and quantity of clinical trials running in England, many people with type 1 are still not being routinely offered trials in which to participate. This is particularly pertinent in device trials. As relatively few people in the UK have access to insulin pump or continuous glucose monitoring (CGM) technologies, trials in new devices are hampered by poor recruitment.

## Future research directions

A number of new research strategies could help plug the existing gaps in the UK's type 1 research portfolio and alleviate the weaknesses identified above:

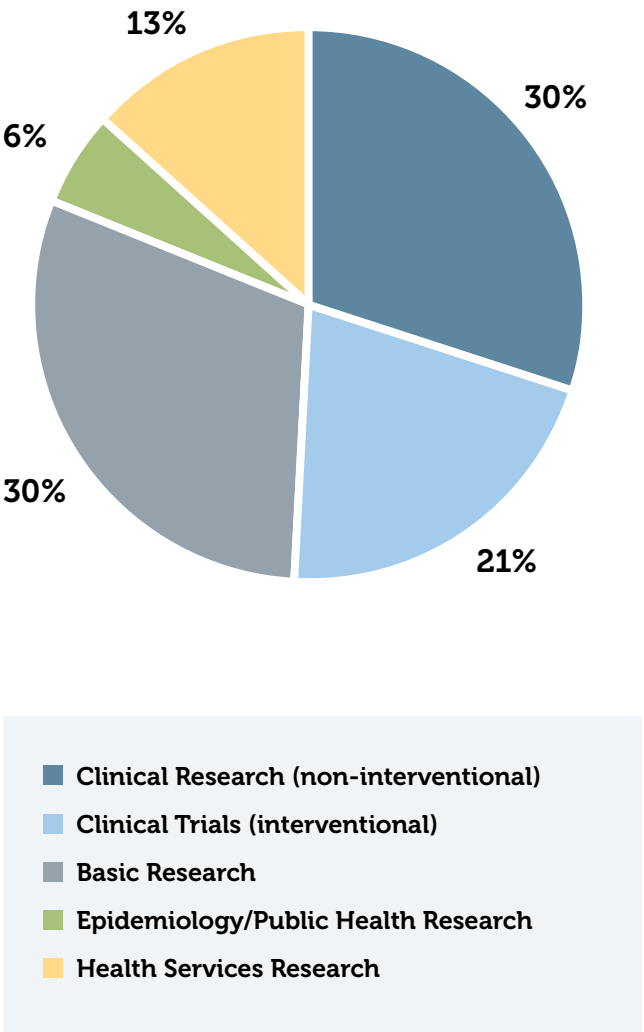
1. Increased funding for research fellowships is needed to encourage more young researchers to engage in the field of type 1 research.
2. A European-wide network for type 1 research is needed to encourage more collaboration between groups and would benefit all areas of type 1 research.
3. A substantial, new birth cohort is needed. This would provide the large-scale, longitudinal data researchers need to monitor the development of type 1, as well as other autoimmune conditions, over time.
4. Innovative, consortia-based funding programmes need to be set up to support the hunt for new biomarkers of early beta cell destruction and of the progression of complications.
5. Small, focused workshops need to be funded. These could enable multidisciplinary researchers from a number of research areas to come together to discuss potential collaborative programmes of work.
6. A new, large-scale clinical study to characterise differences in beta cell function among people with type 1. This would facilitate development of better, more targeted treatments, and would also create a substantial database of blood and tissue samples for other researchers.
7. New animal models need to be created to help researchers develop better treatments for the complications of diabetes and to gain a better understanding of the mechanisms of hypoglycaemia and impaired awareness.
8. Researchers lack a recognised definition of hypoglycaemia and impaired awareness. A consensus statement needs to be written by an expert panel of European researchers.
9. A consensus statement on how to conduct medical device trials is also required to ensure trials are run appropriately and trial results can be meaningfully compared.
10. A pan-European centre of glucose-sensing excellence should be created to encourage rapid translational research.
11. A large, well-characterised cohort of people with impaired awareness should be created to facilitate genetic, biomarker, epidemiological and observational research into hypoglycaemia.
12. New structured education programmes need to be piloted and developed to assess different models of delivery.
13. We need to challenge reliance on a drop in HbA1c as the primary endpoint in most clinical trials in type 1. Research into the development of new evaluation techniques and other measures of success is needed.

# Survey of type 1 research in the UK

To complement the roundtable meetings, a short quantitative review was undertaken. The survey aimed to identify the basic characteristics of the research community involved in type 1 research in the UK

Figure 1

**Principal fields of respondent interest in UK research into type 1 diabetes**




A sixteen-question survey was sent to just under 200 researchers. These researchers were identified in a number of different ways, including:

- funding awards from JDRF
- funding awards from Diabetes UK
- funding awards from the Diabetes Research and Wellness Foundation
- funding awards from the Novo Nordisk Research Foundation
- Web of Science (topic search terms: type 1 diabetes, 2008-2013)
- PubMed (search terms: type 1 diabetes and UK, 2008-2013)

The survey elicited a 36.8 per cent response rate.

This short survey provides a snapshot of type 1 research in the UK today. The spread of researchers who responded was such that the results reflect research in all four devolved nations. Other data, which has not been presented here, outlined existing collaborations, tissue, blood and gene banks and cohorts (i.e. groups participating in research).

The respondents' main field of interest was split relatively evenly across clinical research (non-interventional), clinical trials (interventional) and basic research, with smaller numbers reporting their main area of interest as epidemiology/public health research or health services research. (See Figure 1.)

The respondents' main research area was broken down still further to genetics/epidemiology, islets, pathophysiology/metabolism, clinical science and care, complications (microvascular) and complications (macrovascular). (See Figure 2.)

For those researching genetics and epidemiology, the majority of effort is in the epidemiology or the prediction/prevention of type 1. There is less research into genes and proteins associated with the condition. (See Figure 3.)

In islet research, although respondents reported slightly more research effort devoted to beta cell signalling pathways and islet cell transplantation and inflammation, there was a relatively even split of research conducted across this field.

There is a marked increase in the research being done in animal models and in incretin biology. Incretins are a family of hormones secreted by the gut in response to eating. For diabetes researchers, the most interesting role that these hormones play is in the regulation of the amount of insulin secreted; they are

also potential targets for weight reduction therapies. These results reflect the enormous scientific and clinical effort currently invested in these molecules. (See Table 1 overleaf.)

In the fields of clinical science and care, research efforts are skewed in favour of health care delivery and the technological side of diabetes, with many respondents indicating a research interest in CGM and devices. (See Table 2 overleaf.)

In microvascular complications, research into diabetic kidney disease appeared to dominate. In macrovascular complications, there was a relatively even split of research effort and interest, although interestingly less in hypertension research.

Overall, the results from the survey highlighted a broad range of strengths in type 1 research being undertaken in the UK. These strengths were clearly echoed in the roundtable discussions. Indeed, one

Figure 2

**Main research areas of respondent interest in UK type 1 diabetes**

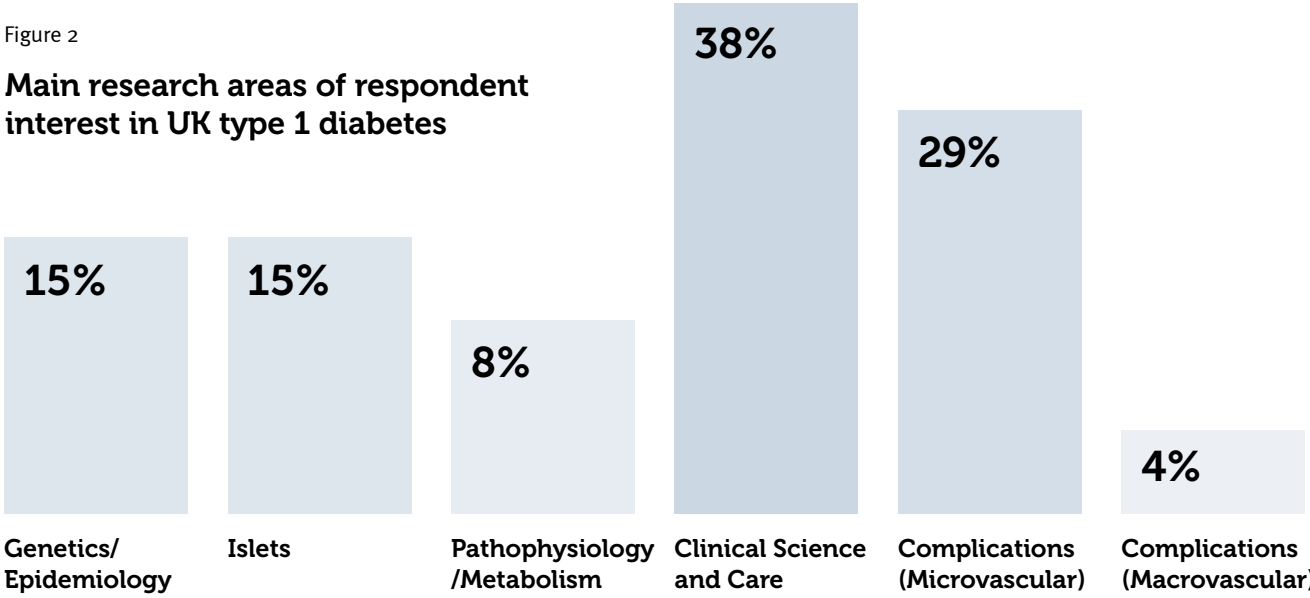
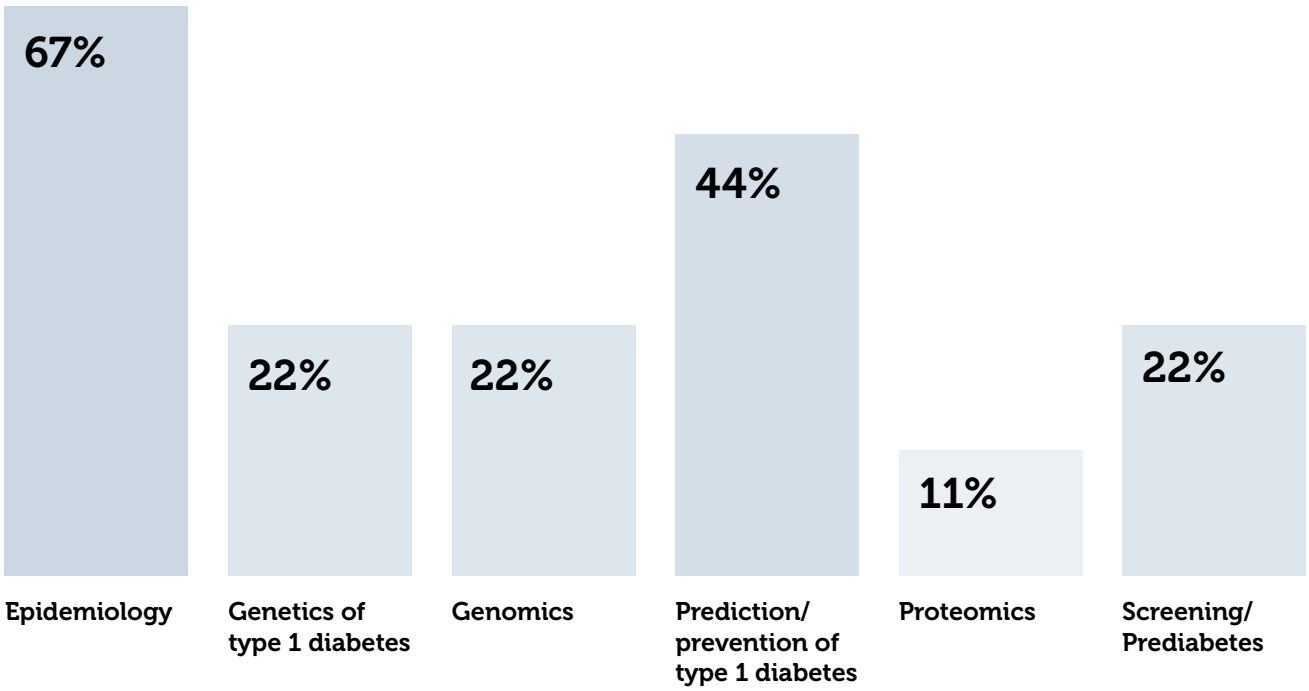



Figure 3

**Principal fields of interest in UK research into the genetics and epidemiology of type 1 diabetes**



## ‘The results from the survey highlighted a broad range of strengths in type 1 research being undertaken in the UK’

theme that emerged from the meetings was how much of the UK’s research is regarded internationally as ‘cutting edge’. However, as you will see reading the following chapters, UK research in type 1 suffers from a number of gaps. Hopefully, the discussions presented below will help identify ways of overcoming these weaknesses in collaboration with European research centres of excellence – and enable the translation of research into real clinical outcomes for people with type 1.

Full results of this JDRF survey of UK research into type 1 are available in the online version of this report **jdrf.org.uk/researchroadmap**
Researchers wishing to contribute further information to the survey, can access the questionnaire on the website

Table 1

### Main focus of current research in the UK into the pathophysiology and metabolism of type 1 diabetes

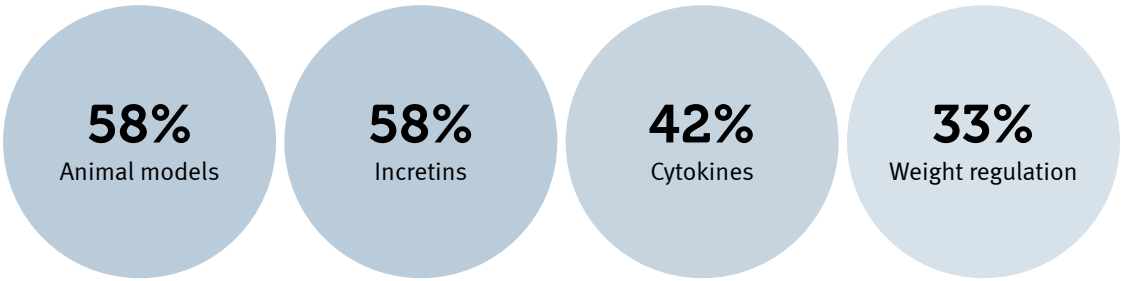
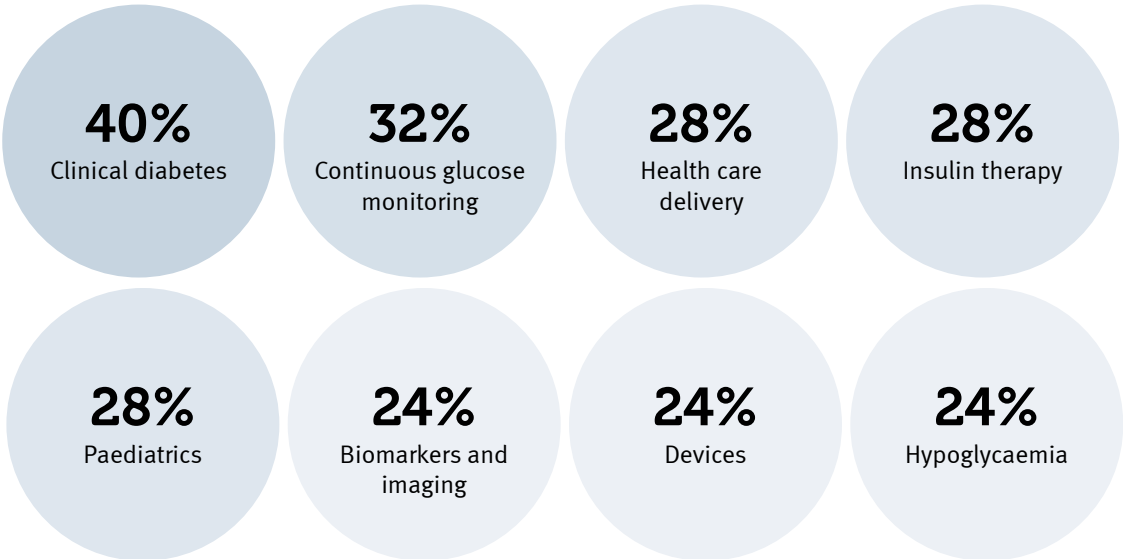
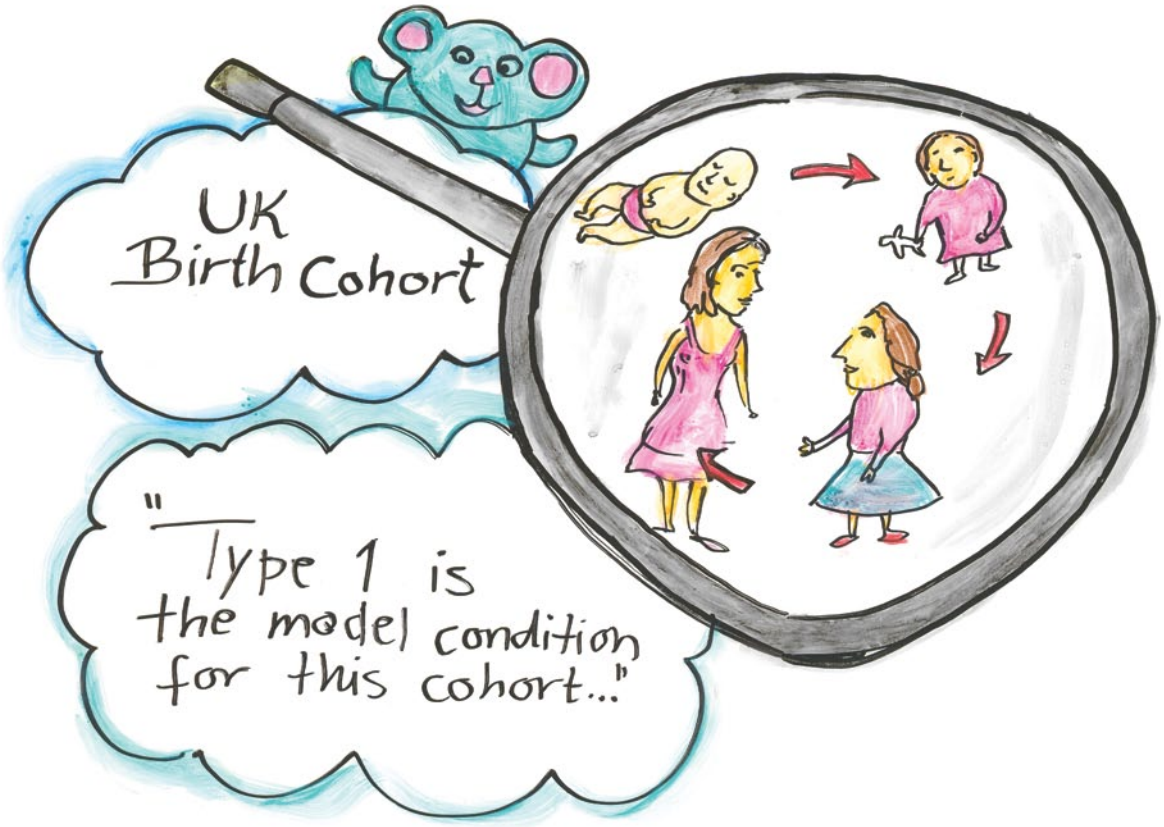



Table 2

### Main focus of current research in the UK into clinicial science and care






# Autoimmunity

The immune system is vital to our well-being, protecting us from invading bacteria, parasites and viruses. Occasionally, however, this complex, delicate system malfunctions and attacks instead our body's own cells – cells that are essential to our health – triggering autoimmune conditions, such as type 1 diabetes. In type 1, insulin-producing beta cells in the pancreas are wholly or partially destroyed, impairing our ability to produce the insulin we need to maintain healthy blood glucose levels

Autoimmune diseases such as type 1 diabetes are the result of a genetic predisposition combined with certain environmental factors thought to trigger them in susceptible individuals. These factors, however, remain poorly defined. Much of the research currently underway in this area aims to determine which genes are involved, the nature of the environmental factors, how the immune system malfunctions, and to design clinical trials intended to reduce the effect of processes that lead to loss of beta cell function – or to prevent those processes entirely.

Autoimmune conditions are known to cluster within families. People with type 1 are more likely to have a family member with another autoimmune disease, although not necessarily the same disorder. This has led to the hypothesis that the underlying immune mechanisms of these multiple diseases may be overlapping. Therapies to suppress the autoimmune response may be used to treat multiple diseases.

## Research strengths in the UK

UK research is particularly strong in the pure science areas of immunology and the genetics of type 1, with several teams very active in the field. Another strength is our long-standing cohort studies (i.e. studies of a particular group of participating individuals) of twins and families with diabetes.

One notable strength deriving from the UK's expertise in genetics is the rapid detection of patients with other, rarer forms of diabetes, such as Permanent Neonatal Diabetes Mellitus and Maturity Onset Diabetes in the Young. Although relatively small numbers of people are affected by these conditions, because of UK research such patients can now be screened out of the general type 1 population and treated more appropriately for their condition.

Thanks to the National Institute of Health Research (NIHR), the UK is also becoming increasingly effective

'An effective pan-European clinical research network would put the unity in autoimmunity'


in novel trial design, trials investigating the underlying mechanisms of type 1 – so-called mechanistic clinical trials – with particular emphasis on phase I and phase II clinical trials, statistics, informatics and computing. The NIHR's Biomedical Research Centres are helping to take the results of basic research into clinical trials, a process known as translational research.

In addition, the particular nature of our NHS tends to foster a more altruistic attitude to clinical trial participation among UK patients. Because healthcare delivery at the point of care is not viewed as a financial transaction, patients often seem more inclined to give generously back to the organisation delivering this care.

## Research weaknesses in the UK

Although historically UK research into type 1 has been either nationally focused or has sought collaboration with researchers in the USA, the UK is now looking more and more to its European neighbours for collaboration and funding, particularly in the context of EU funding.

The European research environment has a stronger track record in translational research into type 1 than the UK. Despite recent NIHR initiatives, the UK is regarded as not being as pharma friendly as other countries; big pharma (i.e. the larger multi-national pharmaceutical companies) finds it easier to set up and recruit to their trials in Asia and the USA. This latter preference may be due in part to an arguably more thriving enterprise culture in the USA; the UK research sector remains comparatively risk averse. The USA also benefits from a more buoyant biotechnology sector and a more vibrant venture capital sector, which helps drive translational research. In comparison, the UK is health-service driven and more patient-focused.

Despite its shift towards recruiting trial participants in, for example, South East Asia, the pharmaceutical sector is still keen to work with European researchers. Nevertheless, the UK's research relationships with big pharma remain complex. The bureaucratic hoops involved in setting up large-scale clinical trials continue to be a major issue. Moreover, as budgets have been reduced, funding for researcher-led studies has diminished.

Researchers also often struggle to get ethics committee approval. This may be because they present incomplete explanations of their research to the relevant committee. However, a growing proliferation of rules and regulations mean that undertaking transnational research programmes remains challenging.

## Current research studies

Current research studies range from large-scale clinical trials to smaller, mechanistic studies investigating, for example, ultra-low doses of IL-2 – a molecule that plays a role in signalling the action of the immune system. Across Europe there is a similar mix of small-scale and larger intervention studies. One persistent issue with recruitment into trials is access to people newly diagnosed with type 1. For intervention trials, this cohort will be key.

ADDRESS-2 is an England-wide research project that invites all people identified with newly diagnosed type 1 and their siblings to donate DNA and other information. Funded jointly by JDRF and Diabetes UK, ADDRESS-2 aims to establish a cohort of people aged 5-60 who have been diagnosed with type 1 within the previous 26 weeks, and their siblings. The project is intended to help academic and commercial researchers to recruit NHS patients into clinical studies that require newly diagnosed cases of type 1.

## Research networks

The NIHR Diabetes Research Network (NIHR DRN) supports and delivers high quality clinical research studies across England. Its primary goal is to benefit people with diabetes, or those at risk of developing diabetes, through excellence in clinical research. Thus far, however, much of its work has been on type 2-related trials.


'The cost of running clinical trials in the UK can be prohibitive'

Other research networks exist. TrialNet is an international network resource offering some opportunities for trials and mechanistic studies. The European Clinical Research Infrastructures Network (ECRIN) is a European initiative that supports multicentre clinical trials and research projects. Established across central Europe and with European funding, it has been criticised for its relatively generic approach and for the paucity of type 1-related trials running through it.

In the USA, integrated trial networks have encouraged paediatric centres to get involved and networks have access to very young children for recruitment into trials. Unfortunately, the UK does not benefit from a similar approach. As a result, getting very young children involved in relevant trials remains a challenging prospect for researchers in the UK.

## Birth cohorts

Large, well-funded birth cohorts are a standard part of research across several European countries. Such programmes are most highly developed in Scandinavia. Finland boasts the largest population of pre-clinical type 1 – so-called pre-diabetes – in Europe. The country has exploited this with prospective cohorts that allow researchers to study everything from basic genomic research to environmental factors suspected of triggering the condition.

TEDDY (The Environmental Derminants of Diabetes in the Young) is an international programme that is looking for environmental factors associated with type 1 by tracking its participants' health from birth onwards over several years.

## Existing funding streams

There is a perceived weakness in the amount of funding available for research into type 1. However, a perceived strength within the UK and Europe is the fact that principal researchers do not need to apply for funding to cover their own salaries as this cost is met by their research institution, such as their hospital or university.

It is widely recognised that European funding streams are more diverse than their equivalents in the UK. However, the field is subject to funding agencies' particular focus – with the majority of diabetes research funding being earmarked for issues associated with type 2 in a handful of centres. The fact that type 1 is an autoimmune condition, and shares common pathways with disorders such as multiple sclerosis, systemic lupus erythematosus, and even allergy, is under-recognised by funding agencies.

JDRF is one of the largest funders of type 1 research and many researchers in Europe benefit from JDRF funding. Substantial funding for type 1 research in Europe also comes from the National Institutes of Health in the USA. However, researchers in the USA do not routinely apply to funding agencies in Europe.

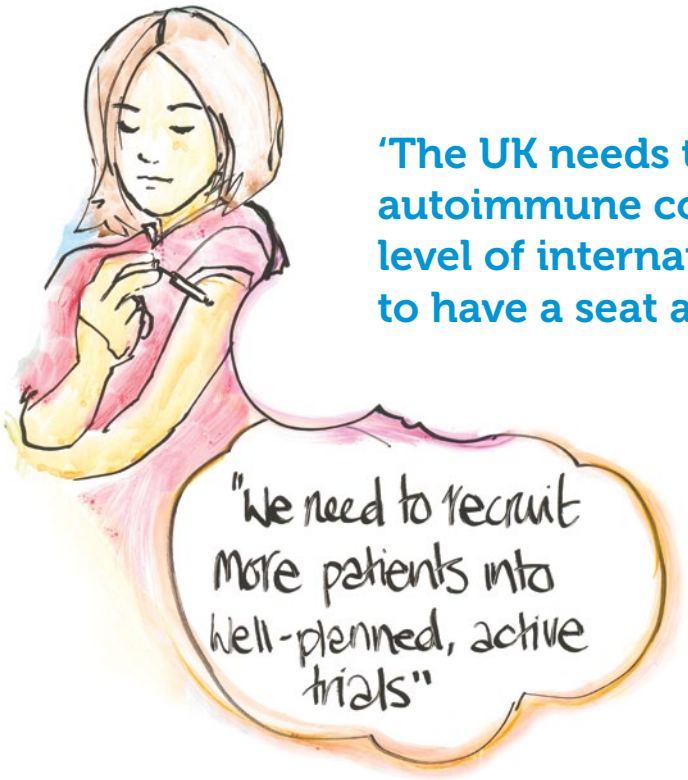
## Future research directions

There is a strong desire within the research community to create a Europe-wide network for type 1 research, one that offers better linkages between paediatric and adult clinicians. Such a network would clearly require substantial funding and an administrative catalyst to get the process started. It is a well-established fact that pan-European initiatives can suffer from language barriers. For example, the need to translate patient-focused literature or websites into all the relevant languages concerned is often challenging and always expensive. A European-wide research network might, however, help facilitate small, mechanistic studies that could be run relatively quickly.

The existence of birth cohorts in other countries, most notably in Scandinavia, has given researchers access to large-scale, longitudinal data. The lack of similar cohorts in the UK is an obstacle to similar research being conducted in this country. Essentially, it means that there is no way of following children from birth onwards to see which factors affect their risk of developing type 1. Such a population sample might also provide opportunities for research into other autoimmune conditions, such as coeliac disease.

Many people with type 1 have expressed interest in participating in clinical studies, but have not been offered the opportunity to do so. We applaud the efforts of the NIHR to increase the opportunities for people to participate in research. The type 1 diabetes research community should aspire to emulate the situation where a significant proportion of UK cancer patients are offered the opportunity to participate in clinical research.

There is also a lack of trained personnel working in the field. Historically the UK has had strong basic and clinical




## 'The UK needs to have a birth cohort for autoimmune conditions to maintain its high level of international research capabilities and to have a seat at the table in the future'

research sectors, but more recently these areas have declined significantly, particularly in the numbers of specialist registrars coming into research. New funding is urgently required to train this group in clinical research and trial management.

The transition from basic to clinical research – the so-called bench to bedside – needs to be marshalled more effectively. It needs to be made easier for researchers to take investigations into the specific compounds or molecules their basic research has identified as potentially valuable, onwards into clinical trials. This approach needs to be matched by strategies encouraging the participation of clinicians and patients, in line with incentives currently made available in the USA.

Looking ahead, a shift to smaller scale studies that investigate the mechanisms by which new treatments work in the body should be encouraged. Such studies would be considerably cheaper to run, could be recruited far more rapidly and should yield benefits more quickly for people living with type 1. New birth cohorts would maximise opportunities and should, in due course, provide researchers with subjects for intervention trials aimed at preventing type 1.

Overall, collaboration with other health scientists, both within the UK and between the UK and Europe, should be encouraged. A particular challenge is the need to highlight type 1 as a model for autoimmune diseases in general. Results in type 1 research may have beneficial synergistic consequences for research into other autoimmune conditions, and also for type 2 diabetes.

## Key steps for the future

- A European-wide network for type 1 research would facilitate more research and foster better links between paediatric and adult clinicians. Such a network could drive the development of small, mechanistic studies, and help to identify robust biomarkers of autoimmune disease.
- New funding should be made available to train researchers in clinical research and trial management.
- New methods are needed to identify type 1 before individuals become insulin dependent.
- We need to encourage people newly diagnosed with type 1 to participate in clinical trials.
- An original birth cohort should be established to support research into type 1 and other autoimmune conditions.

# Researcher overview

Watch **Professor Chantal Mattieu** talk about the strengths and challenges in autoimmunity research

**http://youtu.be/pASdN6xxGQA**

## ‘We need a better understanding of how the immune system recognises the beta cell ’


# Beta cell renewal

Type 1 diabetes is caused by the destruction of beta cells – the insulin-producing cells located in the pancreas. Without these, people with type 1 must inject themselves with manufactured insulin to maintain healthy blood glucose levels. Another treatment option – one that has seen significant advances over the last fifteen years – would be to replace the lost beta cells

Beta cells form part of the islets of Langerhans – discrete clusters of cells, which make up between one and two per cent of the pancreas. The autoimmune response that destroys beta cells leaves other hormone-producing islet cells largely intact.

The challenge for researchers is to unravel the processes underlying beta-cell destruction and discover why and how the immune system targets insulin-producing cells in genetically at-risk individuals. To cure people with type 1 diabetes, it is necessary both to modulate the autoimmune process, and replace lost beta cell function. There is an urgent need to improve the availability, performance and longevity of beta cells for replacement therapy. Principal challenges include finding new sources of beta cells for transplantation, and developing strategies for restoring and preserving sufficient numbers of active beta cells, functional beta cell mass, after type 1 has already developed.

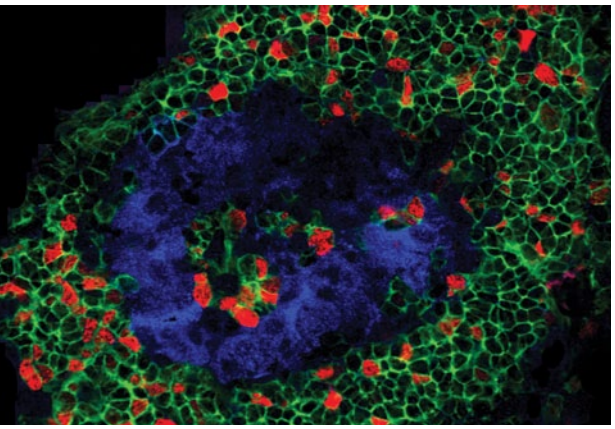
## Research strengths in the UK

The UK has a long-standing international reputation for beta cell research, and an active islet transplant programme. EU Framework Programmes involving many of the UK's islet research centres have helped to develop new systems for generating, characterising and testing cells and tissues suitable for transplantation in type 1. These programmes focus in particular on beta cell regenerative medicine in order to combine expertise, share facilities and avoid research duplication throughout the EU.

Islet cell transplantation enjoys a high profile in the UK thanks to the NHS's commitment to this form of therapy. Since 2008, the treatment has been approved by NICE; the UK now boasts the only national government-funded islet cell transplantation service in the world.

UK research also benefits from forward-looking regulation governing the use of embryonic stem cells, a potential source of cells for beta cell replacement.

The fellowship structure in the UK provides better funding opportunities and access to clinical academic career pathways compared to similar structures in other European countries.



## Research weaknesses in the UK

UK research has only intermittent access to pancreatic tissue from patients with newly diagnosed type 1. Evidence of active autoimmune disease is still present in the pancreas at the time of diagnosis, so such samples would be an invaluable resource for documenting malfunctions in the immune system that lead to type 1. To that same end, appropriately matched control tissues are also required.

To date, there has been limited UK research into how interactions between the immune system and beta cells lead to these cells' destruction. Researchers are beset by an incomplete understanding of the interplay between the immune responses we are born with and those we develop through exposure to the environment. This research is, in turn, limited by a lack of biochemical indicators – or biomarkers – specific to beta cell destruction. The presence of insulin is the most obvious biomarker of beta cell function. But as beta cells are destroyed, insulin levels decline progressively to a point where their numbers are so low that insulin is no longer detectable. Alternative beta-cell biomarkers are needed to enable us to monitor type 1's onset. Such biomarkers would also make it feasible to evaluate the impact of potential therapies aimed at protecting or preserving beta cells.


Despite the UK's long tradition of research into general beta cell biology and function, the exact way in which beta cells are destroyed in type 1 diabetes remains poorly understood. The UK suffers from a research silo mentality, with many researchers working in isolation within their own field. Despite recent moves towards more interdisciplinary approaches in the UK, funding is still polarised between basic and clinical science. Type 1 research also suffers from a lack of exchanges between immunologists and beta cell biologists; such interactions should facilitate a better understanding of the disease process in type 1.

A number of issues relating to UK clinical trials in type 1 currently limit their recruitment and effectiveness. Links between paediatric and adult type 1 care need to be developed in order to promote entry into trials – in particular, to recruit people with newly diagnosed type 1. More small trials are needed to understand how treatments work in the body and provide pump priming data for larger clinical trials.

Despite a progressive regulatory environment in the UK, research aimed at identifying alternative sources of beta cells for transplantation is currently constrained by the lack of a unified strategy for stem cell research in the UK and Europe.

## Animal models of diabetes

Research into type 1 often relies on animal models to generate preliminary data. These models, though useful, diverge from human type 1 diabetes in many respects. For instance, the non-obese diabetic (NOD) mouse is a commonly used model. These mice spontaneously develop insulin-dependent diabetes as a result of insulitis – an inflammatory autoimmune reaction within the islet cells. Better models are needed to support research into the molecules involved in the cascade of reactions that result in human beta cell destruction.


## 'The future has to be regeneration'

### Current research studies

The rate and extent of beta cell destruction is known to vary between different parts of the pancreas. Even within a single pancreas, beta cells may be destroyed in one region but survive in others. To further complicate matters, research shows that islet composition can vary; some islets predominantly consist of other islet cell types – such as alpha and delta cells. Other studies have shown that alpha cells, which secrete the hormone glucagon, are able to transform into beta cells. These observations suggest that autoimmune attacks on islets may trigger a defence and repair response, which leads in turn to a compensatory increase in functional beta cell mass. Animal studies have suggested that autoimmune attack on beta cells is associated with regenerative responses, with similar observations in studies of people newly diagnosed with type 1.

One theory as to what triggers type 1 diabetes is that viral infection plays a role in triggering the immune system to attack beta cells. Whilst research in this area is still on-going at a basic level, designing related interventional studies is fraught with difficulties because the exact virus or viruses involved are still largely unknown. An on-going collaborative project is seeking to detect persistent viral infections that lead to inflammation and tissue damage in the pancreas.

Current clinical research includes studies to determine what happens to beta cells during the so-called honeymoon phase in type 1 diabetes. During this period, soon after diagnosis, patients often require less insulin – or no insulin at all – for a short period, suggesting a remission of the condition. Insulin is supplied by the surviving beta cells, but the amounts produced can be unpredictable and the length of this honeymoon phase varies significantly from person to person. Research suggests that this phenomenon may be due to an increase in the number of functioning beta cells. However, owing to the lack of relevant biomarkers, this conclusion is difficult to ascertain definitively.

In 2000, a new approach to islet transplantation was introduced – known as the Edmonton Protocol. The approach proved successful to an unprecedented degree, liberating recipients of the therapy from the need for insulin injections, albeit in a small number of patients. However, even in this small group, long-term insulin independence proved elusive due to a number of factors. Current research seeks to address issues related to cell losses during the process of islet isolation and implantation, and to losses associated with other factors such as the graft site, autoimmunity and immuno-suppression.

### Existing funding streams

Current funding streams for basic beta cell research are relatively limited. A lack of long-term funding often means that experienced scientists and clinicians spend much of their time writing grants in order to maintain their research programmes. As funding opportunities diminish, good, trained staff are often forced to leave – further exacerbating a loss of research momentum.

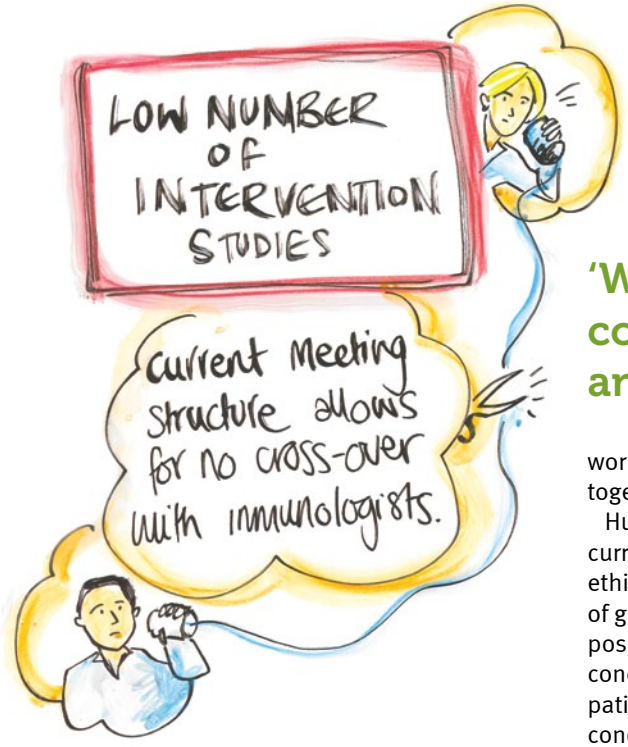
It should be pointed out that in the area of beta cell function, research in type 1 is complementary to research in type 2 diabetes.

### Future research directions

Better, more timely biomarkers are an important requirement for future research. As beta cells are destroyed, possible biomarkers of the underlying disease process may be circulating throughout the blood stream. These need to be studied in more depth. Such biomarkers could identify the autoimmune attack at an earlier stage, enabling beta cell preservation and/or protection. In addition, they could reduce the length of clinical research trials. New imaging techniques are also needed to observe the process of beta cell destruction as it occurs.

Future research needs to involve closer working relationships with researchers investigating other autoimmune diseases to identify areas where such conditions may overlap with type 1 diabetes. The underlying immunological and physiological processes involved are likely to be similar. Stem cell research could play a vital role in finding new ways to replace not only beta cells but other cells damaged by other autoimmune conditions or by chronic high blood glucose.

Collaborative working will be increasingly important for future type 1 research. Novel, consortia-based grant applications that cut across conventional research silos need to be submitted in order to uncover the exact mechanisms of beta cell destruction in people with type 1, and to ensure that the UK maintains its position as a leader in the field internationally. Small, focused



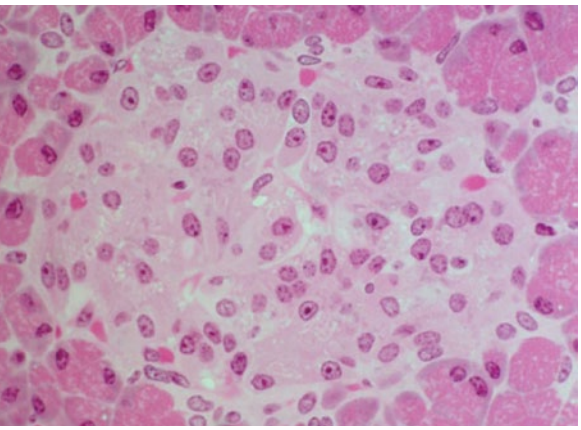

## 'We still need enhanced collaboration between academia and industry partners'

workshops would enable researchers from a number of areas to come together to discuss possible collaborative programmes of work.

Human tissue samples are vital for progress in beta cell research. As current live biopsy techniques are difficult to conduct safely, they are ethically unacceptable. So it is important to make the most efficient use of gifts of pancreas tissue for research, and also investigate whether it is possible to develop new biopsy techniques that could overcome safety concerns and provide useful tissue for research. Islet cell transplant patients have very variable outcomes and much useful research could be conducted to study the way that the islet cell attack process relates to the repair and response process.

A pan-European clinical trial network would be extremely useful, working with industry, to ensure that good, high quality type 1 diabetes interventional clinical trials are conducted to help to address many of these research challenges.

Young clinical scientists need more incentives to specialise in type 1. Job plans incorporating protected research time may prove helpful in this respect.



One of the crowning achievements of UK research into diabetes has been the major cohort study called the UK Prospective Diabetes Study (UKPDS), which established definitively that there is more than one form of type 2 diabetes. Researchers and clinicians have long felt that similarly there may be different forms of type 1 diabetes. There is little information on the status of beta cell function at diagnosis of type 1. It is particularly important for beta cell researchers to understand the course of deterioration of beta cell function during in the honeymoon phase, when there are still sufficient beta cells remaining in the body to make a difference to the person with type 1's ability to regulate blood glucose levels. Better markers of beta cell function, including methods to image the pancreas, would enable large scale studies to understand beta cell function in type 1 diabetes and could lead to new advances in how to preserve beta cell function for as long as possible in a targeted, personalised way for all individuals who develop the condition.

## Key steps for the future

- More collaborative working is needed between immunologists and beta cell biologists. This should be encouraged via small focused workshops. Such interactions should facilitate a better understanding of the disease process in type 1 diabetes.
- Better pancreatic biopsy techniques need to be investigated to allow researchers access to greater numbers of biopsy sections.
- Further stem cell research needs to be encouraged to find new ways of replacing not only beta cells but other cells damaged by autoimmune conditions.
- A large-scale clinical study of people with type 1 is needed to identify different forms of type 1, with the aim of developing more targeted treatments.

# Researcher overview

Watch **Professor Adrian Bone** talk about the strengths and challenges in beta cell renewal research

**http://youtu.be/LXFK4v1JJzE**

**'We need an increased understanding of why the beta cells and not other cells in the pancreas are attacked'**


# Complications

People with type 1 are at risk of a range of long-term complications if their blood glucose is poorly controlled – including diseases of the eyes, kidneys and lower limbs, and increased risk of stroke and heart disease. These exact a heavy toll on the health and well being of people with type 1, as well as significant costs for the NHS

The long-term complications of diabetes (both type 1 and 2) have been clearly linked to poor control of blood glucose levels. Improving diabetes management is vital to their prevention. The Diabetes Complications and Control Trial (DCCT) showed that, even in people with a history of poor glycaemic control, keeping blood glucose levels within a tight, near normal range could slow the onset of and progression to these long-term complications.

Type 1's complications take many forms, but it is the condition's effects on the vascular system that have the most profound effect; these are responsible for the majority of the costs of diabetes to the healthcare system.

Microvascular complications affect the small blood vessels and nerves and lead to damage to the eye (diabetic retinopathy), kidney (diabetic nephropathy) and the lower limbs (diabetic neuropathy).

Macrovascular complications affect the larger blood vessels and include damage to the heart, often leading to myocardial infarction or heart attacks, and to the brain, causing strokes.

The fear of complications is a powerful motivator to people with diabetes. Much research is being done to investigate the biochemical and physiological changes that lead to these complications and to optimise clinical care in order to prevent, treat and manage these conditions.

## Research strengths in the UK

As with many areas of type 1 research, research into complications is relatively strong in the UK. There is much good basic science being done in several centres of excellence in the UK. This means that good cell culture and animal model work is being conducted. The UK also has a well-regarded track record in conducting landmark clinical trials in diabetes.

The development of e-health records, particularly in

Scotland, is strengthening the UK's hand in terms of research in this area. As a consequence of e-health records, parts of the UK research community are in an excellent position to undertake advanced epidemiological studies into type 1 complications.

Screening programmes set up across the devolved UK nations for diabetic retinopathy have led to the development of good photography image capture systems. These have given researchers access to substantial anonymised data with which to track disease progression. However, we need new agreed measures for investigating the progression of small blood vessel disease in the eyes. The current scale by which severity of microvascular damage is graded is skewed towards advanced signs of eye disease.

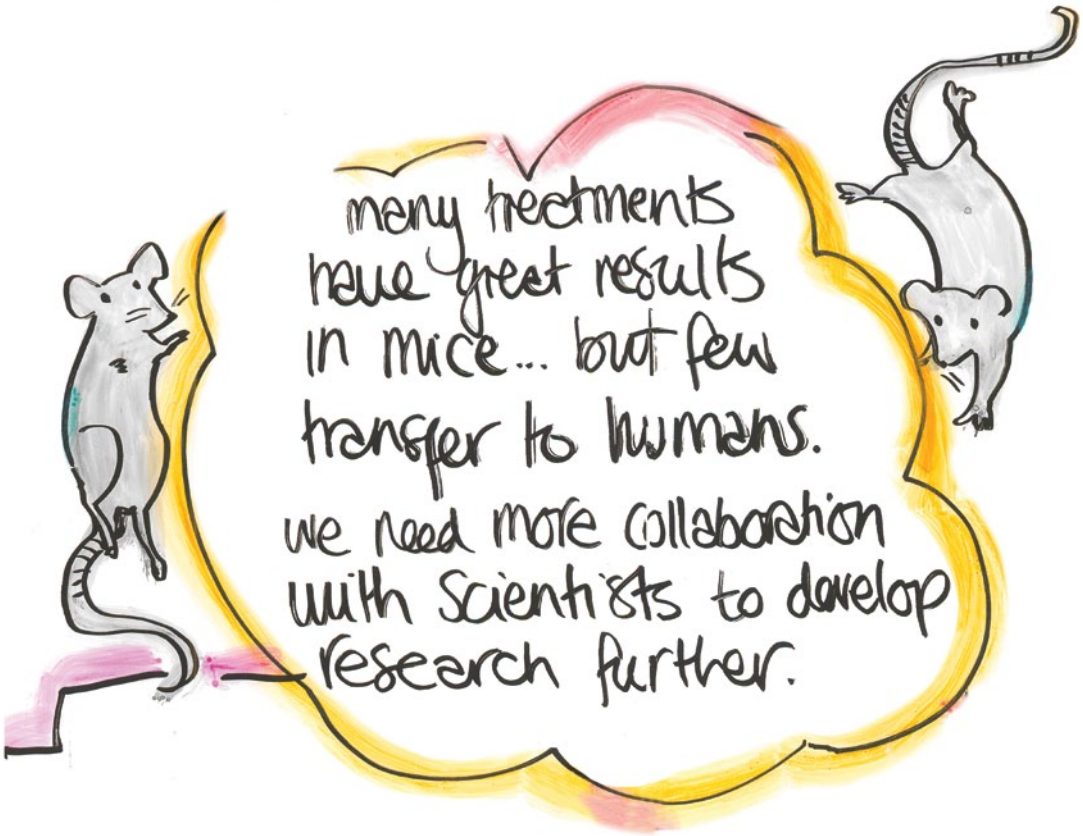
'Biomedical research doesn't attract mathematicians, computer scientists and statisticians but it should'

## Research weaknesses in the UK

The UK healthcare environment is still comparatively slow to adopt some new technologies compared to the rest of the world. This has negative consequences for type 1 research. Even within the UK there are differences among the devolved nations. Compared to Scotland, e-health systems are less well developed in England. As a result, it is more difficult to calculate accurately the numbers of people with diabetes in the country, which frustrates efforts to undertake meaningful epidemiological studies. This is hampered still further by systems that do not talk to one another across England, for example, between primary and specialist care.

This problem is well illustrated by the retinopathy screening programme. Because of the different screening and grading systems used across England, the English Screening Programme for Retinopathy struggles to get different regions to pool their data. These difficulties are exacerbated by the lack of unifying standard ways of practice or definitions of what counts as a case of retinopathy and what does not. As a result, the programme lags behind similar programmes in Scotland and Wales.

Retinopathy researchers are also poorly integrated with the screening service. Relatively few groups are doing basic and clinical research and there is no robust mechanism for evaluating the effectiveness of a particular drug or intervention. The failure of recent trials in retinopathy has demonstrated a disconnect between basic and clinical research. New drugs across a range of complications may be more effective if they are tested on patients with less advanced disease. Interventions are routinely being tried in people at very late stages so it is more difficult to slow or prevent progression to the most severe stages of these complications.




'Complications research offers so many opportunities for academia, the pharmaceutical industry and the funders to work together'

There is a need for larger patient cohorts, more trials and more routine and systematic sample collection, along with greater integration of epidemiology into studies. New methods of early complications detection need to be studied. At present there is a lack of cross-working between groups investigating diabetes complications. In addition, physiology expertise is being lost from the research community. Both situations need to be reversed if meaningful, collaborative research is to be conducted in the future.

Finally, the genetic factors or indicators of complications lag behind other genetic research. So far genetic research has failed to discover genetic markers that could be used to predict a person's risk. More complex information is required characterising the individual participants within a cohort – i.e. phenotyping. There is a huge potential for discovery but it will only work if we use appropriate samples taken from appropriate cohorts.

## Current research studies

The UK boasts several large clinical trials at present, looking at various aspects of diabetic complications.

The REMOVAL study is investigating the use of metformin, a drug traditionally used to treat type 2, in addition to regular insulin treatment in a cohort of people with type 1 to see whether this intervention can protect blood vessels from being damaged.

The AdDIT trial is recruiting adolescents with type 1 who have early signs of diabetic kidney disease. They are investigating the effect of ACE inhibitors and statins. The aim is to provide cardio-renal protection in young people at high risk of developing complications. The study should also yield new information on early clinical markers.

Another study is looking at other uses for images captured by corneal confocal microscopy, a method used to screen for eye disease. The researchers hope that these images could be used to identify early signs of nerve damage (diabetic neuropathy). This study has already identified one of the earliest detectors for microvascular damage.

## Research environment, funding streams and industry interest

Funding for research has been maintained at a strategic level. In the UK, the NIHR has succeeded in engaging government and policy makers in the importance of funding health research. The NIHR's clinical research networks have already recruited large numbers of patients into trials. However, as yet the number of trials in type 1 that are run using this NIHR infrastructure is limited.

Recent difficulties with rosiglitazone, a drug used to treat type 2, have led the US's Food and Drug Administration to introduce new regulations surrounding drug trials. Companies are now required to undertake long-term outcome trials. Such trials can add up to USD$400 million on to the costs involved in bringing new drugs to market. As a result, the research environment is becoming more risk-averse in terms of funding innovative complications studies.

It is increasingly difficult to obtain funds for smaller, targeted pilot studies, particularly to test new technologies. Such funding is vital. Moreover, even when funds for smaller studies are found and promising results are obtained, a lack of funds means they are not followed up or scaled up.

## Future research directions

There is a continuing need for better surrogate end points; new, more accurate biomarkers; and for such biomarkers to have a predictive value. The diabetes research community needs to work more closely together to design better trials capable of finding ways of detecting complications at an earlier stage. To do this, funding needs to be made available for interdisciplinary groups of basic and clinical researchers to come together to write grant applications, and to encourage effective translational research.

There is also a need for more funding for research fellowships in the field of complications research. There are opportunities to co-fund such awards with a number of


funding agencies whose interests lie in the wider complications arena.

New animal models of complications need to be created. There are relatively few robust current models and, although the progression to disease is compressed into approximately six months compared to the decades of progression in humans, molecules accessed from industry could be rapidly tested and moved into new trials where appropriate.

Complications research is hampered by a lack of large, accurately phenotyped and genotyped cohorts. In order to predict the risk of complications in type 1 accurately, researchers need access to cohorts and follow-up data that would allow study of changes in disease progression at regular intervals.

One way this could be accelerated would be if basic and clinical researchers had access to the pharmaceutical industry's biobank data – i.e. the data companies have taken from trial participants. Companies could also work more effectively with academia by making available molecules that have failed in phase I and phase II clinical trials. Drugs that have been developed specifically to treat one complication may be useful in treating another.

More accurately phenotyped and genotyped population samples are needed. Such cohorts would make possible shorter, more powerful and more pragmatic trials. More clinical trials could also be carried out to investigate the impact of drugs used to treat type 2 on blood glucose control in a type 1 population.

Studies of the mechanisms of diabetes' microvascular complications using a type 1 cohort would be extremely informative as the outcomes would not be confounded by other factors, such as diet or hypertension – common confounders in similar studies investigating type 2.

## Key steps for the future

- A long-term cohort of accurately phenotyped and genotyped patients is needed to facilitate the discovery of new biomarkers of disease progression.
- Closer working relationships with the pharmaceutical industry should be fostered. Researchers should be given access to pharmaceutical companies' trial biobank data to help them conduct innovative retrospective analyses of type 1 prediction and progress.
- More research fellowships need to be established in the complications area.
- New animal models of the complications of diabetes are needed to test new molecules. Molecules from phase I and phase II trials which have not been progressed may prove valuable in the wider complications field.

# Researcher overview

Watch **Professor John Petrie** talk about the strengths and challenges in complications research

**http://youtu.be/2ezAipLo9W8**

## ‘We have a good collaborative spirit between research centres’


# Glucose sensing

Managing blood glucose levels is a tricky business for people with type 1, and many struggle to replicate our bodies' natural systems for achieving a healthy balance – sometimes with devastating results. But what if technology could provide the means of doing this for us, some device for sensing our requirement for glucose and administering insulin according to need?

People with type 1 are required to replicate the body's natural systems to maintain healthy blood glucose levels – monitoring the levels of glucose in their blood and adjusting their intake of food and injections of insulin accordingly, with reference to levels of exercise and numerous other factors. It's a complicated business. And one that demands considerable diligence and expertise.

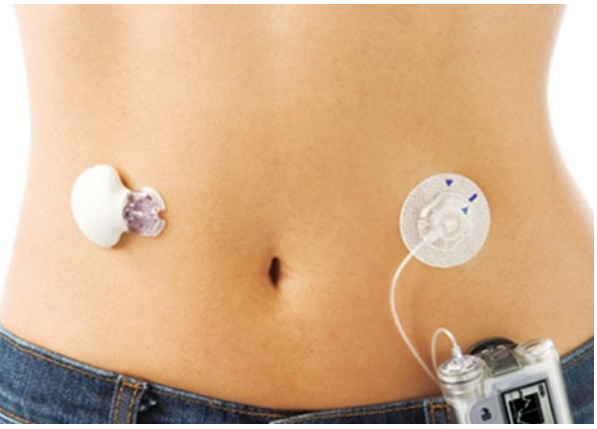
Not surprisingly, many struggle to achieve a healthy balance; if they control their blood glucose too tightly, they put themselves at risk of hypoglycaemia (see page 27); if they don't, they risk long-term complications (see page 19). A device combining the capability to sense a person's blood glucose levels with the ability to administer appropriate amounts of insulin has become something of a holy grail for research into type 1 management. Such a device would, in effect, function in much the same way as an artificial pancreas.

These systems – generally referred to in diabetes research circles, as the closed loop system – have generated considerable interest in recent years, as hopes for an artificial pancreas loom ever nearer.

There have been significant advances in combining insulin pump technology with CGM – and in developing algorithms to link the two. However, at present, closed loop systems are still beset by a number of difficulties. Foremost amongst these is glucose sensing. Current technology for measuring blood glucose – including commonly used blood glucose meters – is capable of giving patients information they can act on and has clear benefits. However, today's sensors are considered by many experts as insufficiently accurate to be relied on as part of a closed loop system, where the technology takes over the role played by people with diabetes in measuring and correcting their blood glucose levels. The glucose-sensing component needs to give consistent, accurate data for the systems to function safely. This is one of the foremost problems holding up progress in development of closed loop technology.

The ONSET trial recently reported that CGM, used in combination with insulin pump therapy in newly diagnosed children with type 1 diabetes, could significantly improve blood glucose control compared

'We need all the august organisations to work together and to realise that there is a problem with diabetes technology'




to conventional self-monitoring of blood glucose and pump therapy.

However, after one year, only 50 per cent of the children who were given the sensor were still using the device. This finding suggests that, as yet, this technology does not perform to acceptable levels for routine and long-term use in people with type 1 or insulin-treated diabetes. The study also showed significant variation in glucose sensing reliability between individual participants. A lack of accuracy and predictability may explain why many people had stopped using the sensor by the end of the trial. Other factors that contribute to people stopping using CGM are alarm fatigue (desensitisation to, or ignoring of, alerts to high or low blood glucose) and the considerable education and training required to enable people to use CGM without being overwhelmed by the enormous amount of data such devices generate.

In the USA, patient advocacy has helped to make CGM more widely available than it is in the UK and most of Europe. So far, in the UK, CGM has not been reviewed by NICE. The number of people with access to them is limited, and has largely depended on self-funding and individual case-by-case applications by healthcare professionals to local health organisations. Only about seven per cent of the diabetes population in the UK currently use insulin pumps, a technology with which CGM is most frequently used. This low uptake contrasts starkly with a recent priority-setting exercise for type 1 diabetes research conducted by the James Lind Alliance. Three of the top priority questions defined by this exercise were clearly focused on the development of technology:

- Is it possible to monitor blood glucose levels constantly and accurately, in people with type 1 with a discrete device (non-invasive or invasive)?
- Is insulin pump therapy effective?
- Is an artificial pancreas for type 1 (closed loop system) effective?

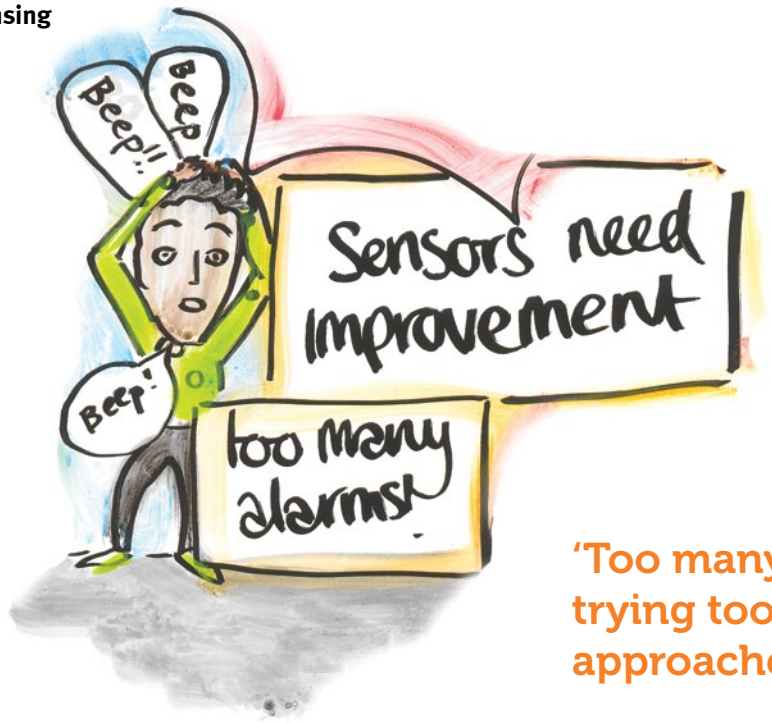
## Research strengths in the UK

The UK has made impressive contributions in developing and testing novel diabetes technologies over the past three decades, including insulin pumps and glucose sensors. Some examples of current glucose sensor research include developing smart tattoos – micro- or nanoscale devices implanted under the skin, which respond to tissue glucose changes with a change in fluorescent light that can be measured outside the body with a hand-held monitor.

UK researchers are also developing re-implantable fibre-optic probes for glucose sensing based on fluorescence, and these promise to have improved stability and accuracy compared to existing electrochemistry-based glucose sensors. Other new technologies are being investigated in the UK to improve sensor reliability and reduce insertion pain.

Current commercially available CGM systems used in clinical practice depend on the enzyme glucose oxidase to detect glucose, employing a mechanism similar to the blood glucose meters people with type 1 routinely use to test their own blood glucose levels. Here, glucose interacts with oxygen, catalysed by the enzyme glucose oxidase, which coats an electrode. The reaction is monitored by a change in current. Such systems are subject to interferences from alterations in oxygen and various substances in tissues under the skin that affect accuracy. UK researchers are therefore investigating glucose detectors other than glucose oxidase for use in CGM. One such technology is a glucose-binding protein isolated from bacteria, where responses can be detected by alterations in fluorescence.

The UK has a record of innovation in biosensors stemming from the 1980s to the present. Several centres are researching new sensing technologies that might lead to completely non-invasive glucose sensing. Amongst these methods are variations of Raman spectroscopy, a technique involving measuring the scattering of light by molecules of interest – in this case, glucose.




'Too many groups are trying too many different approaches'

## Research strengths in Europe

Europe has been particularly active in pioneering clinical trials into the clinical effectiveness of insulin pumps and CGM, as well as the analysis of the combined or average outcomes of several trials (meta-analysis).

Several European groups, as well as NICE, have published economic analyses establishing the cost-effectiveness of insulin pump therapy, and are now considering similar studies on CGM. This has contributed significantly to more widespread uptake of diabetes technology.

New education systems for sensor users are being put in place at European centres and substantial European Union funding is helping new sensor development and its potential combination with insulin pumps in closed-loop systems. An example is the Artificial Pancreas (AP)@Home project (see current research studies, below). Single-port glucose sensor-insulin catheters are also the subject of the EU-funded SPIDIMAN project (again, see below).

## Research weaknesses in the UK

Despite a wealth of basic research and early testing of novel and improved glucose sensors in the UK, it has proved difficult to translate this activity into commercially available devices. Several factors account for this. One is the relative paucity of UK-based small-to-medium sized enterprises in biosensing and related technologies who are available and willing to collaborate with academia.

A second problem is the lack of funding for translation of research into commercial products. Often, research is regarded by agencies as high-risk and high-cost, early stage, and unsuitable for existing translational funds without collaboration and significant co-funding from industry.

A significant hindrance in bringing new technology to patients is the lack of funding and facilities for testing new devices that have been introduced by industry and establishing their efficacy and best use. Thus, whilst pharmaceuticals will reach market with their effectiveness and best use already defined by industry-sponsored trials, devices are commonly introduced first, with investigators only later undertaking trials to determine their value to clinical practice. Similarly, technologies such as CGM require extensive training in their use and instruction in interpretation of data and therapeutic action in response; there is a lack of funds and facilities for researching best education and training.

## Current research studies

Several large-scale clinical glucose-sensing trials are currently underway.

The AP@Home project is a European Union Framework 7 funded, multi-centre study to improve treatment of patients with diabetes at home by improving closed-loop algorithms for the artificial pancreas. This four-year study involves academic and industry partners in seven European countries and aims to improve CGM performance so that an artificial pancreas can be used at home. This will be achieved by better CGM software and by developing a single probe that combines both the glucose sensor and the insulin delivery catheter from the insulin pump, thereby significantly increasing patient acceptance.

The Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) is an on-going trial investigating whether CGM can improve blood glucose control in pregnant women with type 1 without substantially increasing their rate of hypoglycaemia.

The HypoCOMPaSS study, which is comparing different methods of blood glucose control, will report later this year. Participating patients are randomised to one of four intervention groups:

- multiple daily insulin (MDI) injections
- MDI with real-time CGM
- insulin pumps
- combination of insulin pumps and CGM.

The study also aims to find out if optimised conventional management in patients with severe hypoglycaemia and/or impaired awareness can help restore hypoglycaemia awareness.

## 'Glucose sensing is not a panacea'

Finally, the SPIDIMAN study is another European Union Framework 7 award. The researchers aim to create a single-port device, blending existing technology into one delivery system. Reducing the number of catheters involved from two to one may play a vital role in encouraging very young patients to use the system.

### Current funding streams and industry interest

Funding is available for research leading to an artificial pancreas – including substantial investment from the European Union. However, few companies appear willing to enter into partnership with academia to bring such devices to market. The market is dominated by a few industry players, which dissuades others from participating.

Little funding from other funders has been made available to obtain vital pilot data. Grant reviews frequently state that applications in this area are either overly ambitious or too early. Funding for nanotechnology is available; but in many cases, such funding is insufficient to develop its potential fully.

### Future research directions

Researchers understand the need to develop implantable devices that are accurate and can be left *in situ* for prolonged periods of time. However, extensive toxicology work is required to make this a reality. Work is required across the whole spectrum of the product development process, including expensive animal work and at the clinical interface.

In order to create an environment that is conducive to the development of diabetes technology, we need to centralise the various efforts that are currently scattered across Europe. A pan-European centre of excellence – virtual or real – would help to encourage rapid translational research, including new single-port sensors, improved insulin delivery systems, implantable insulin pumps, and viable alternatives to glucose oxidase.

A national or international consensus statement is also needed on glucose sensing.

To obtain robust cost-effectiveness data, a large, multicentre randomised clinical trial is needed, involving people who have been unable to achieve good blood glucose control using conventional therapies. In order to facilitate this, a consensus statement on the best way to conduct medical device trials needs to be drafted. Such a statement should enable research centres to carry out device trials in a standardised way that allows direct comparisons to be made. Achieving this would require input from both academia and industry and could focus international efforts on high-quality device trials. Simple head to head trials of CGM devices need to be conducted in clinically relevant populations.

A large study comparing the outcomes of CGM use by different population groups could support the adoption of CGM and closed loop technology by NICE. including new single-port sensors, improved insulin delivery systems, implantable insulin pumps, and viable alternatives to glucose oxidase.

## Key steps for the future

- A consensus statement is needed on the best way to conduct medical device trials.
- A pan-European centre of excellence (virtual or real) should be established to encourage rapid translational research.
- Funding is needed to identify viable alternatives to glucose oxidase for use in glucose sensing devices.
- More clinical trials of CGM devices should be supported to ensure that robust data can be presented to NICE.

# Researchers overview

Watch **Dr Nick Oliver** and **Professor Thomas Pieber** talk about the challenges in glucose sensing research

**http://youtu.be/gbdrINpyEKs**

## ‘We need to get good ideas quickly into the patient’


# Hypoglycaemia and impaired awareness

Hypoglycaemia is a complication of insulin therapy that occurs when the brain is starved of glucose. The symptoms can be alarming in themselves. But they play a crucial role in telling us when we need to eat or drink something to correct our blood glucose levels. Over time, however, some people with type 1 lose these symptoms, leaving them without these vital warning signs

The brain depends on glucose as its principal source of energy and rapidly malfunctions if deprived of glucose. Hypoglycaemia is a state of a low blood glucose concentration. The symptoms that ensue – which come under the general heading of neuroglycopenia – can range from non-specific anxiety, sweating, feelings of hunger and tiredness and a loss of concentration. These vary in intensity from person to person and according to the severity of the hypoglycaemic attack.

Nearly one in five people with type 1 or type 2 diabetes regularly experiences disruption to their day because of hypoglycaemia and reports increased levels of both stress and depression as a consequence. Despite improvements in insulin therapies and blood glucose monitoring techniques, the frequency of reported hypoglycaemia among people with diabetes has remained fairly steady for the past two decades.

Impaired awareness of hypoglycaemia is a common complication of insulin therapy in people with type 1 and less commonly occurs in people with insulin-treated type 2. The ability to recognise the onset of hypoglycaemia can weaken progressively and, in some individuals, this ability is lost completely. It is estimated that between 20 and 25 per cent of people with type 1 are affected by impaired awareness. However, we lack a standard, internationally recognised definition of impaired awareness, making exact figures difficult to estimate.

In the clinical setting it is often very difficult, if not impossible, to reverse impaired awareness, and hypoglycaemia and impaired awareness represent major barriers to the clinical management of type 1. It is complicated further by the fact that symptoms differ between patients; even for an individual, symptoms may differ significantly between events. Finally, people may be reluctant to report hypoglycaemia or impaired awareness because it can have implications for their employment opportunities or right to drive.

Relatively few clinical interventions are available to minimise the risk of hypoglycaemia or to treat impaired

'Hypoglycaemia isn't a complication of diabetes. It's a complication of therapy'


awareness. To a large extent, a robust scientific and medical understanding of impaired awareness of hypoglycaemia remains elusive. What is evident is that the costs of emergency treatment of hypoglycaemia to the NHS and the indirect costs to society in terms of loss of productivity would be significantly reduced if this situation were reversed.

## Research strengths in the UK

The UK boasts a number of international opinion leaders in the field of both basic and clinical hypoglycaemia research.

Science in the UK is revealing the role of the hypothalamus in glucose sensing, as well as demonstrating the key roles played by other regions of the brain – including the brain stem and the part of the brain known as the amygdala. This research demonstrates that a complex network of brain centres and neuronal circuitry is involved in glucose sensing. Work using cell cultures and animal models is key to giving researchers surrogate measures of what may be happening in human brains during hypoglycaemia.

Clinically, the UK is also recognised to have significant strengths. Neuroimaging studies with positron emission tomography of small numbers of participants have indicated that impaired awareness is characterised by altered responses in the brain's hedonistic and reward centres. These are related to the addiction regions in the brain. Studies have also been done to investigate the way the brain finds alternative sources of fuel when faced with a shortage of glucose.

Small studies on a pharmaceutical intervention called modafinil have demonstrated its potential use as a means of improving hypo awareness for people with type 1. Other drugs, such as caffeine and benzodiazepines, have also been investigated to look at possible mechanisms for targeting blood flow in the brain.

Islet cell transplantation, another strength in the UK, has shown the restoration of symptomatic awareness in transplant patients. This restoration has also been reported in whole-pancreas transplant recipients.

Finally, the Dose Adjustment for Normal Eating (DAFNE) cohort has given researchers access to a large database of people with type 1 and has stimulated research into the spectrum of hypoglycaemia and impaired awareness. This cohort could provide a platform for further detailed characterisation, including genotyping and hypoglycaemia phenotyping, which could in turn increase the research opportunities for using this cohort.

## Research strengths in Europe

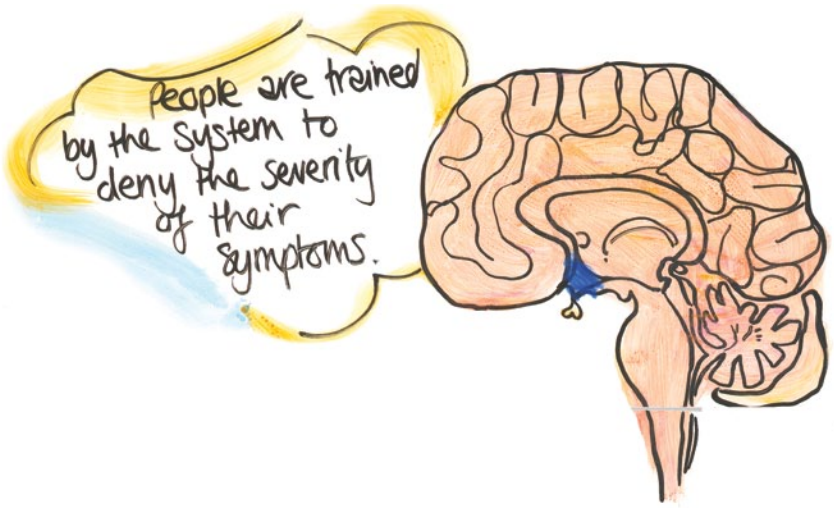
Small studies have suggested that there is a genetic component to susceptibility to hypoglycaemia and impaired awareness. It will be necessary to coordinate patient cohorts and to provide adequate resources to conduct a comprehensive genetic study to identify the pathways that play a role in impaired awareness and hypoglycaemia.

European research is also focusing on the role played by a hormone called glucagon in raising blood glucose when the body needs it. This hormone's action has the opposite effect to the action of insulin. The glucagon-insulin axis is of considerable interest to scientists. Although this basic research has not yet been translated into the clinical setting, work in animal models indicates that this, along with work on glucose transporters, may have implications for treatment in the future.

## Research weaknesses in the UK

As yet, no genes have been identified as being associated with increased risk of hypoglycaemia. It is also difficult to get a good animal model of impaired awareness.

The significant interactions with reward centres in the human brain also remain largely unexplored and there is a lack of an understanding of brain mechanisms at a molecular level. There is limited understanding of the




**'Impaired awareness of hypoglycaemia can be very disruptive to everyday life'**

role of glucose sensors, how hypoglycaemia is sensed within the brain and how this may be altered by recurrent exposure to hypoglycaemia. A lack of funding to do large-scale neuroimaging studies is a major restriction on research in this area.

An additional weakness in the UK research landscape is that very few clinical trials and studies are being done in this area. There is no access to well-defined, large cohorts. Because some people conceal the frequency of their hypoglycaemia from their healthcare professional team, it is difficult to identify suitable patients for recruitment into studies, or to determine exactly how many people are having severe hypos.

Finally, psychological interventions may be effective in treating at least some people with impaired awareness. However, there is no psychologically trained workforce to help design and conduct such psychological interventions.

## Current research studies

The HypoCOMPaSS study is a randomised clinical trial aims to prevent recurrent severe hypoglycaemia by comparing optimised multiple daily injections of insulin or insulin pump therapy with or without simultaneous real-time CGM. The study has recently been completed and will shortly be reporting its results. A questionnaire has been developed and validated as part of this intervention and appears to identify with accuracy people who have developed impaired awareness.

The DAFNE-HART study has been designed to support those who continue to experience problems with hypoglycaemia even after a DAFNE course. (For more on DAFNE, see page 32.) This cognitive behavioural therapy and motivational interview-based intervention is educator-led. Its aim is to help people with type 1 to recognise and modify any unhelpful or destructive behaviour that may be stopping them from achieving optimal self-management of their condition, and to retrain awareness into those whose awareness is impaired.

Other small studies are looking at the interaction between psychology and technology at the clinical interface, including a cohort who experience severe hypoglycaemia, and investigating the role that CGM may have in reducing the frequency and severity of their hypos.

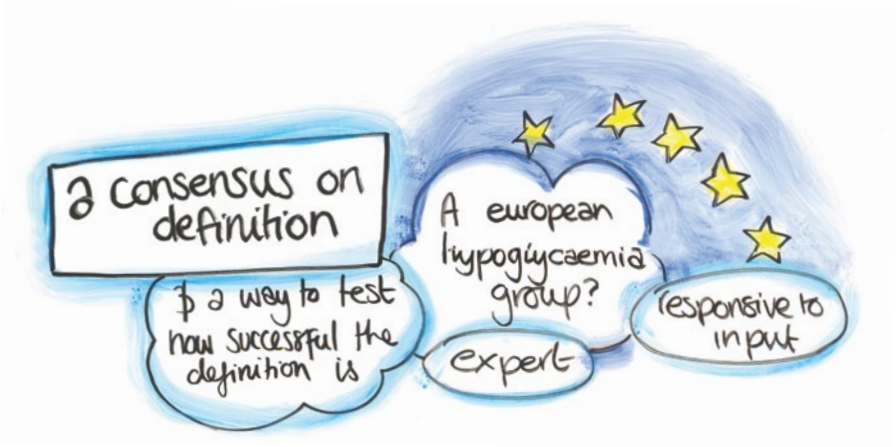
## Current research funding streams and industry interest

Although there is significant interest in hypoglycaemia and in impaired awareness research, there is no recognised intervention or pharmacological treatment. This is partly due to the fact that, in most clinical trials run by the pharmaceutical industry, people with hypoglycaemia or with impaired awareness are excluded, despite a recognition that such patients could benefit from new insulin trials. New insulin or insulin-analogue clinical trials are not conducted with this problem in mind, and a lack of sufficient meaningful collaboration between academia and the pharmaceutical industry is delaying progress.

## Future research directions

There are several very pertinent future directions for hypoglycaemia and impaired awareness research. However, without a recognised definition of hypoglycaemia and impaired awareness, this research will not be standardised and runs the risk of not being able to compare results between centres and across borders. An agreed definition and quantification system for hypoglycaemia awareness and its impairment needs to be established via a committee consensus statement in collaboration with European colleagues. This expert panel should include clinicians, scientists and psychologists. Its aim would be to develop a methodology for quantifying hypoglycaemia and impaired awareness, thereby enabling the construction of a tool for measuring the effectiveness of interventions.

Currently, interventions cannot be compared as there is also a gap in the availability of standardised questionnaires to establish levels of self-reported impaired awareness. Some do exist but, though adequate for internal validation, they are not sensitive to improvements in hypoglycaemia awareness. The validated HypoCOMPaSS questionnaire needs to be translated and used more widely across Europe. However, this is designed only for use in adults, not for use in children; further work on establishing questionnaires for use in paediatric populations is also required. There




may also be a need to examine this further in elderly people; awareness of hypoglycaemia is affected by ageing, and elderly people exhibit a different symptom profile.

There needs to be a large, well-characterised cohort of people with impaired awareness. A multicentre cohort of around 10,000 people is needed to undertake a meaningful genetics study. Some people may be genetically predisposed to impaired awareness whilst others are more psychologically predisposed. Such subgroups among people with type 1 may have identifiable biomarkers.

There are many theories as to why people develop impaired awareness and as to why some people may also be more prone to losing consciousness during hypoglycaemia. Some people are reluctant to acknowledge their problems with hypoglycaemia – a resistance which is, to a large extent, rooted in psychology. There is, therefore, an urgent need to encourage a bigger role for psychology in impaired awareness research. A multicentre cohort on this scale would also help to address the need for more robust epidemiological and observational studies.

Better clinical trials need to be undertaken that include people with impaired awareness rather than excluding them, as often currently occurs. Studies could include investigation of the effects different insulins appear to have on appetite, and the relationship between exercise and hypoglycaemia. Better neuroimaging studies need to be undertaken in collaboration with relevant areas of addiction science that may feed into this field, and further psychological interventions need to be designed. Finally, there is a significant gap in the understanding of the physiology of the hormones involved in regulating blood glucose. To encourage translational research in this area, better animal models are needed to study the various signals sent by the brain and the pancreas.

Carefully designed studies of whether hypoglycaemia and impaired awareness have any lasting effects on the brain should be conducted. Issues surrounding long-term cognition problems after periods of prolonged hypoglycaemia are hugely emotive areas for people with type 1 and more research is clearly needed in this area.

## Key steps for the future

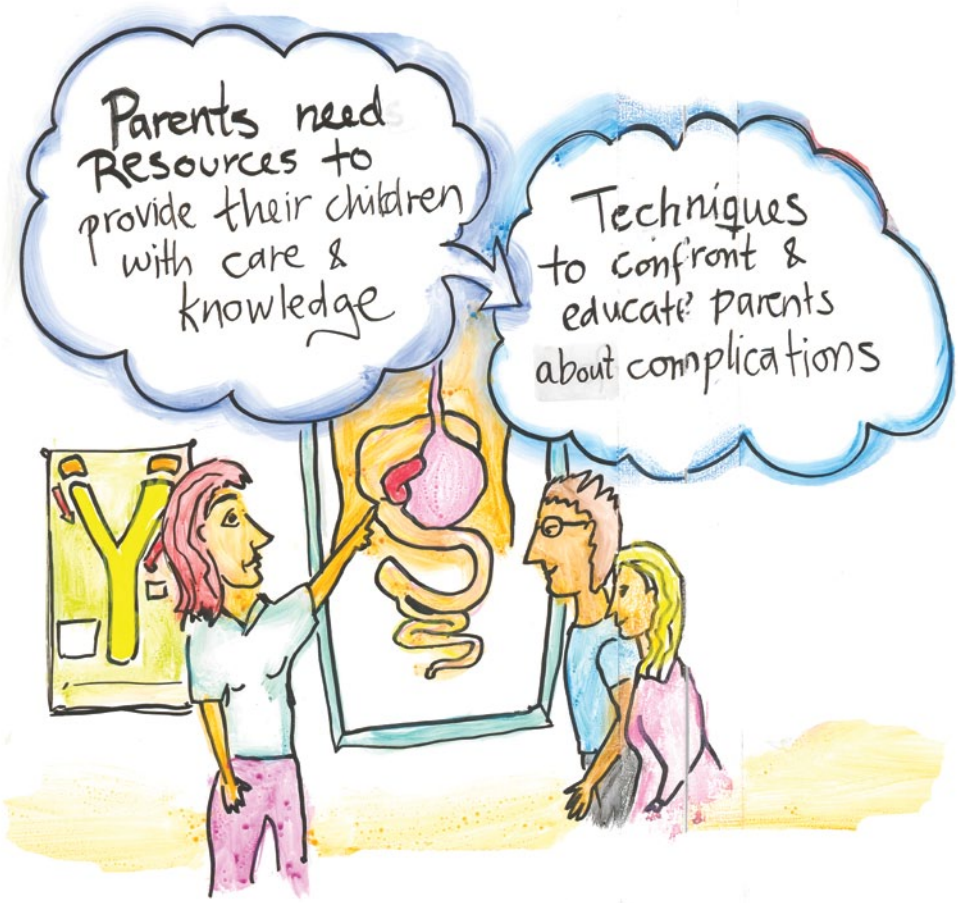
- We need an agreed definition and quantification system for hypoglycaemia awareness and its impairment. This should be established via a committee consensus statement drawn up in collaboration with European colleagues.
- Standardised, validated questionnaires to establish levels of self-reported impaired awareness need to be made available across Europe to allow meaningful research to be conducted.
- A unique cohort of people with impaired awareness needs to be established in which the physiological and psychological, basic and clinical subtypes of hypoglycaemia and hypoglycaemia unawareness are systematically captured.
- Carefully designed studies involving people with impaired awareness need to be conducted to investigate the lasting effects of hypoglycaemia and impaired awareness on long-term cognition and to conduct more robust neuro-imaging studies.

# Researcher overview

Watch **Professor Brian Frier** talk about the strengths and challenges in hypoglycaemia research

**http://youtu.be/jKl1YpDogLw**

## ‘There isn’t a suitable way of managing hypoglycaemia’




# Structured education

The role people with type 1 play in their condition's day-to-day management has a profound effect on their health. To do this well, they need education structured in a way that enables them to manage the complexities of life with diabetes

Clinical research is a particular strength in the UK. However, research findings often fail to translate into the care people with type 1 receive in the clinic or into their on-going day-to-day management.

Healthcare professionals have often adopted a paternalistic view of management and care. More recently, though, empowering patients by offering structured education programmes has provided a paradigm shift in how people might be enabled to manage their diabetes. These programmes, which are widespread in Europe and the USA, are now accepted as an essential part of diabetes management by many in the UK.

NICE has recognised this crucial element of diabetes healthcare. Its guidance on structured education states that there should be: "evidence of local arrangements to ensure that people with diabetes and/or their carers receive a structured educational programme that fulfils the nationally agreed criteria from the time of diagnosis, with annual review and access to on-going education." However, in many areas of the country, high quality self-management training programmes are not available either to adults or to children and their families.

Although some patients cope well with their condition and are highly motivated to achieve good glycaemic control, many more do not. Education programmes are vital if self-management skills are to be improved, although many fail to sustain effective diabetes self-management following the course. Despite an increasing volume of research and the availability of appropriate programmes, change in practice has been relatively slow and many units offer truncated and unevaluated programmes, which may be less effective. Furthermore, it is increasingly realised that, in addition to initial training, both adults and children and their families require on-going professional support. Training models need to be developed and evaluated.

The UK is regarded as an international leader in the field. Nevertheless, in order to ensure that the very best education programmes are available, much research has to be done.

'Structured education is often seen as an optional extra in the UK'


## Research strengths in the UK

The Dose Adjustment for Normal Eating (DAFNE) programme was piloted in the UK in late 1990s and was based on an innovative German model.

The programme aimed to provide people with type 1 with the skills necessary to estimate the amount of carbohydrate in each meal and inject the correct dose of insulin accordingly. The pilot study's success meant that the programme was rapidly embedded into many centres. DAFNE is now an integral part of the structured education offered to people with type 1 and has had a profound effect in shaping structured education guidelines. Funded mainly by the NIHR, the DAFNE consortium has led to the development of programmes designed to improve self-management among young adults, and has also been successful in supporting on-going research. Successful research programmes include teams of researchers from a number of disciplines including clinicians, diabetes educators, health economists and social scientists, qualitative researchers and experts in behaviour change. These are necessary to develop complex educational interventions capable of ensuring more effective diabetes self-management.

The UK, like other countries, is trying to incorporate social media, telemedicine and e-learning platforms as innovative ways to improve structured education programmes in the future. These are being developed to offer core modules plus optional other modules that can be selected – thereby tailoring education to an individual's needs. As yet, however, there is only limited evidence to suggest that they improve biomedical outcomes.

## Research strengths in Europe

German researchers have for many years led the way in developing and implementing successful structured insulin training programmes for both adults and children with type 1. This has been delivered in in-patient settings immediately after diagnosis, as well as to those who have had the condition for some time. In many centres, similar programmes are taught by fully trained, engaged multidisciplinary healthcare teams. They are expert in teaching methodology and techniques which facilitate educational approaches and effective delivery using age-appropriate tools and language. In Germany, structured education appears to be facilitated by a healthcare insurance system which only reimburses local healthcare providers on condition that quality skills training for people with diabetes, their families and carers is in place.

The important outcome of this nationwide initiative is that, in Germany, the mean HbA1c values achieved in both adults and children are lower than the corresponding figures in other countries in Europe, including the UK; the progression to long-term diabetic complications is also much slower.

## Research weaknesses in the UK

In the UK, structured education remains poorly integrated with diabetes management. As a result, people with type 1 living in the UK have worse outcomes than their European counterparts. Both adults and young people with type 1 would benefit from research that identifies more effective ways of engaging and maintaining successful diabetes self-care.

Structured education is currently delivered to substantial numbers of children and adults in relatively few centres. Roll-out is often hampered by a lack of funding and unenthusiastic senior clinicians. Moreover, both staff and patients sometimes regard structured skills training in insulin self-management as an optional extra; this may explain why in many centres only 30 per cent of those eligible undertake training. There is a lack of understanding as to why people are either not offered a structured education course or choose not to do it. There are recognised ethnic and social deprivation biases.



## 'You need a local champion to ensure the very best care is offered'

There are also questions around difficulties in persuading patients to take time off work to attend such courses. This may require the development of more flexible programmes. Many people demonstrate substantial behavioural changes during a structured education course, but these improved self-management behaviours are not always maintained afterwards. How to embed behavioural changes in the long-term is not well studied. In DAFNE and other programmes, more work needs to be done on developing effective ongoing structured support.

There are substantial research weaknesses in terms of education at the point of diagnosis. Most people with type 1 are diagnosed in childhood, adolescence or young adulthood. Models for educating people straight after diagnosis are being developed but research is still in its infancy, and it is unknown whether the paediatric education model used in Germany can be easily transferred to the UK. There is also more to be learned in terms of how to present information to children; as their motivators and cognitive needs are very different. This particular research weakness is exacerbated by the relative lack of paediatric consultants working in the UK.

Finally, the quality of research grant applications being submitted for research into structured education often falls short of the basic and clinical research applications that are more routinely received by funding agencies. As a result, psychosocial research applications seem weaker in comparison and the research viewed as less competitive. Research grant applications are also hampered by the fact that the primary endpoint for research in this area is often a drop in HbA1c. This quantitative measure is well recognised as a gold standard, but it is a difficult endpoint to demonstrate and one which these complex interventions often fail to meet.

### Current research studies

Structured education for healthcare professionals and for children and young people and their families has only attracted research funding over the last decade and has not yet progressed into a national programme. However, the need to develop a national approach to improving the educational skills of diabetes healthcare professionals and to develop national education programmes for healthcare professionals and people with diabetes has been clearly identified. Over the last decade there has been substantial interest in examining specific components of education. Several recent large-scale randomised controlled trials in adolescents have focused on education. These have now finished and are due to report. Unfortunately, although the trials showed benefits in some secondary outcomes, none of them succeeded in meeting all of their defined endpoints.

### Existing funding streams

The National Institute of Health Research (NIHR) is interested in funding research on structured education to improve diabetes management. Following NICE recommendations, the NIHR Health Technology Assessment programme will be looking to fund psychosocial research that promises obvious benefits to the NHS. In the meantime, many adults and young people and their families will continue to struggle to manage their condition effectively.

### Future research directions

A skilled workforce is key going forward. Without training in structured education many busy healthcare professionals will see it only as an optional extra. There needs to be an accredited programme of structured education for healthcare professionals. All members of the multidisciplinary healthcare team need to be trained and enthusiastic in delivering structured education to people with type 1.

There is also a need for specialised training or educationalist input into this team learning. Healthcare professionals' acquisition of skills in this area currently depends on self-directed learning and enthusiasm. Consequently, though there is learning, teaching and delivery skills may not match this learning and innovation may fail to materialise.

There is a research gap in terms of encouraging transformational leadership qualities and developing a clear career pathway for people in the structured education field; practice would benefit from accreditation


## 'One size fits nobody'

of key skills and competencies. There is a need to consider what skills are needed within a multidisciplinary team and how much educational skills training each individual team member needs.

A paradigm shift is required to get the whole family involved in structured education. More research is needed investigating the patient context. Patients come from very different backgrounds and structured education programmes need to cater more effectively to this diversity.

Research into transformational change in children's diabetes services is needed to investigate how appropriate behaviours can be instilled at the point of diagnosis and maintained over time. There have been excellent examples of education studies done in small groups or in single centres. Such research needs to be extended to encompass larger groups and multiple settings.

Education needs to be offered at the point of diagnosis. Because of the honeymoon phase and a reliance on a primary endpoint of a drop in HbA1c, most studies and trials are conducted in people at least one year post-diagnosis. Research into structured education at the point of diagnosis needs to examine the very different and complex relationships involved – e.g. between the person with type 1 and their condition; the person, their condition and their parents; and all of these with the healthcare professional team.

In order to compete internationally, researchers need to collaborate to write the very best grant applications. Applications cannot be single centred and need to involve multidisciplinary teams of enthusiasts. They need to be innovative and should consider novel evaluation techniques – not just a drop in HbA1c – including measures such as knowledge, psychological well-being and quality of life. Knowledge can be assessed by formal assessment but several outcome measures will undoubtedly be required if a programme is to obtain accreditation.

Across England, even though their care is delivered by the same healthcare system, HbA1c levels achieved by people with type 1 vary widely. Researchers need to discover why. There has been little research into why patients choose to do a structured education course and how issues about numeracy and literacy are dealt with in existing programmes. Research into different models of delivery should also be considered, e.g replacing face-to-face education with internet-based education tools, or delivering education in a non-clinic setting.

## Key steps for the future

- Research should be conducted investigating how appropriate behaviours can be instilled at the point of diagnosis and maintained over time.
- The structured education research community needs to collaborate with diverse, multidisciplinary team members in order to submit competitive grant applications to funding agencies.
- New outcome measures that do not rely solely on a drop in HbA1c need to be investigated.
- Further work on the patient context is needed to develop appropriate structured education programmes for different patient groups. There need to be accredited programmes of structured education for healthcare professionals, children and young people and their families.

# Researcher overview

Watch **Dr Katherine Bernard** talk about the strengths and challenges in structured education research

**http://youtu.be/yhMVPIpWgho**

## ‘We need to know how we can structured education more accessible’

# Glossary of terms

**Alpha cells**. A type of cell found in the pancreas. Alpha cells make and release a hormone called glucagon. The body sends a signal to the alpha cells to make glucagon when blood glucose falls too low. When glucagon reaches the liver, it tells it to release glucose into the blood for energy.

**Autoimmunity**. The system of proteins and various cells types, including antibodies and macrophages, which the body uses to protect itself against invading bacteria, parasites and viruses.

**Autoimmune disease**. A disorder in which a person's own autoimmune system destroys their own body tissues, such as the beta cells in the pancreas.

**Antibodies**. Proteins produced by the body to fight off foreign substances such as bacteria, viruses and transplanted organs.

**Beta cells**. Insulin-producing cells found in areas of the pancreas called the islets of Langerhans.

**Biobank**. A systematically organised collection of biological samples, such as blood or DNA, taken from a defined population.

**Biomarker**. A molecule or gene that can be used to identify individuals at risk of a given disease or to track the progress of disease.

**Blood glucose**. The main sugar that the body makes from food.

**Blood glucose meter**. A small, portable machine used by people with diabetes to check their blood glucose levels.

**Blood glucose monitoring**. The way people with diabetes determine how much glucose is in their blood.

**Blood sugar**. A term used interchangeably with blood glucose.

**Carbohydrate counting**. A method of meal planning for people with diabetes based on counting the number of grammes of carbohydrate in food.

**Coeliac disease**. An autoimmune digestive disease that damages the small intestine and interferes with absorption of nutrients from food.

**Cohort studies**. A group of people who, for example, were all born in the same time period, and in whom cause and effect can be monitored with age. For research purposes, this can involve investigating the group's genetic background and exposure to environmental factors that may trigger disease.

**Complications**. Harmful effects of diabetes such as damage to the eyes, heart, blood vessels, nervous system, teeth and gums, feet and skin, and kidneys.

**Continuous Glucose Monitor (CGM)**. A CGM automatically measures blood glucose levels at set intervals. It will usually consist of a small disposable sensor placed under the skin, a non-implanted transmitter attached to it, and a separate electronic receiver. Sensors need to be changed every few days.

**Dose Adjustment For Normal Eating (DAFNE)**. This is an educational course for managing type 1 diabetes and provides the skills to estimate the carbohydrate in each meal and to inject the right dose of insulin.

**Embryonic stem cells**. Cells formed when an egg is fertilised.

**Endocrine gland**. A group of specialised cells that release hormones into the blood. For example, the islets in the pancreas, which secrete insulin, are endocrine glands.

**Endpoint**. A measure used in clinical research to define how successful the intervention has been.

**Epidemiology**. The study of disease in populations.

**Genome**. The complete set of genetic material found in a single organism.

**Genotype**. The genetic map of an individual.

**Glucagon**. A hormone produced by the pancreas that stimulates the liver to break down glycogen and release it into the bloodstream as glucose. It can be given by injection to treat hypoglycaemia.

**Glucose**. A simple form of sugar that acts as fuel for the body. It is produced during digestion of carbohydrate and carried to the cells in the blood.

**Glycaemic control**. Control of the levels of glucose in the blood.

**Glycogen**. The main carbohydrate storage material, which is stored in the liver and muscles for use when energy is required.

**Glucose oxidase**. An enzyme used in blood glucose monitors to measure the amount of glucose in the blood.

**Haemoglobin A1c (HbA1c)**. A test that reflects the average amount of glucose in the blood over the previous three months. This test is frequently used as the target endpoint for diabetes research trials.

**Honeymoon phase**. The period of time after the diagnosis of type 1 diabetes when the dose of insulin may need to be reduced due to remaining or recovered insulin secretion from the pancreas. This period can last weeks, months or years.

**Hormones**. Substances released into the bloodstream from a gland or organ. Hormones control growth and development, reproduction, sexual characteristics, blood-glucose levels and influence the way the body uses and stores energy.

**Hypoglycaemia**. A condition in which blood-glucose levels drop too low. Symptoms may include sweating, trembling, hunger, dizziness, moodiness, confusion, blurred vision and coma.

**Hypothalmus**. A region of the brain thought to play, among other functions, an important role in glucose sensing.

**Immunology**. The study of the immune system.

**Immuno-suppression**. The act of inhibiting or restricting the action of the immune system.

**Impaired awareness of hypoglycaemia (IAH)**. A state in which a person does not feel or recognise the symptoms of hypoglycemia. People who have frequent episodes of hypoglycaemia may no longer experience the warning signs.

**Insulin**. A hormone manufactured by the pancreas, which helps glucose leave the blood and enter the muscles and other tissues of the body.

**Insulin analogues**. Genetically engineered forms of insulin that are still recognised as insulin by the body but which may, for example, be designed to act more quickly than naturally produced insulin.

**Insulin pumps**. Small computerised devices that deliver a slow continuous level of rapid-acting insulin throughout the day.

**Interventional research/studies**. Studies or trials which usually involve giving research participants a drug and therapy.

**Islets**. Groups of cells located in the pancreas that make hormones that help the body break down and use food. For example, alpha cells make glucagon and beta cells make insulin. Also called islets of Langerhans.

**Islet transplantation**. A procedure in which islets are moved from a donor pancreas into a person with type 1 diabetes.

**Longitudinal study**. A study conducted over a period of time, which takes repeated measurements or observations at regular intervals.

**Mechanistic clinical trials**. Trials looking at the underlying mechanisms of a particular medical condition.

**Macrovascular disease**. Disease of the large blood vessels, such as those found in the heart.

**Microvascular disease**. Disease of the smallest blood vessels, such as those found in the eyes, nerves and kidneys.

**mmol/L**. The abbreviated form of millimoles per litre, a term used to describe how much glucose is present in a specific amount of blood.

**Myocardial infarction**. A heart attack.

**Nephropathy**. Diabetic kidney disease.

**Neuroglycopenia**. A shortage of glucose in the brain.

**Neuroimaging**. A non-invasive technique that allows researchers to look at images of the brain.

**Neuropathy**. Diabetic nerve damage.

**Pancreas**. A fish-shaped gland that secretes various substances such as digestive fluid, insulin and glucagon.

**Peripheral neuropathy**. Nerve damage that affects the feet, legs or hands.

**Phase I and Phase II trials**. Phase I trials are clinical trials whose main objective is to find out whether the drug being tested is safe for use in humans and how the body's reaction to it may change its effect. Phase I trials tend to be carried out in small groups of people, a few dozen, who are in good health and do not have the condition the treatment will eventually target. Phase II trials are conducted once a drug has been proved safe in a Phase I trials. These are intended to show whether the drug is effective and safe to use to treat people who have the condition the drug is targeted at. They are carried out on between 200-500 people who have the condition in question.

**Phenotype**. Often used with genotype, an individual's phenotype refers to characteristics that can be readily observed e.g. height and eye colour.

**Positron emission tomography**. A specialised form of neural scanning, which can produce images of a brain's anatomy and function.

**Prospective birth cohort study**. A study whose participants are observed from birth onwards over several years.

**Proteinuria**. The presence of protein in the urine, indicating that the kidneys are not working properly.

**Renal**. A renal disease is a disease of the kidneys. Renal failure means the kidneys have stopped working.

**Retina**. The light-sensitive layer of tissue that lines the back of the eye.

**Retinopathy**. A disease in which the small blood vessels, capillaries, in the back of the eye, retina, may bleed or form new vessels.

**Translational research**. Often referred to as bench to bedside, such research links basic research through to drug discovery and development.

**Type 1 diabetes**. A condition in which the body's immune system destroys the cells in the pancreas that produce insulin. Insulin allows glucose to enter the cells of the body to provide energy. People with type 1 diabetes must take daily insulin injections or use an insulin pump.

**Type 2 diabetes**. A condition in which the body either makes too little insulin or cannot properly use the insulin it makes to convert blood glucose to energy. Type 2 diabetes may be controlled with diet and exercise, but may require oral medications and/or insulin.

# Research funders

| Research Organisation | Focus | Relevant grants |
|---|---|---|
| **JDRF** | JDRF is a global organisation working towards the cure. Internationally, we are the world's leading charitable funder of type 1 diabetes research. We work with academia, industry and governments to make sure that the research we fund has the greatest possible impact on the lives of people with type 1 now and in the future | Clinical and basic post doctoral fellowships, early career awards, innovative grants, bridge grants, travel awards, strategic research agreements, industry discovery and development partnerships, project grants |
| **Diabetes UK** | Committed to improving the care and treatment of diabetes, preventing it from developing in those at risk and, ultimately, finding a cure | Project grants, clinical and basic research fellowships, PhD studentships, equipment grants, small grants, AHP nurse and midwife fellowships, travel fellowship |
| **Wellcome Trust** | Supports research into all aspects of biomedical science: from molecules and cells vital to life, through the spread of diseases or the vectors of disease across the globe, to clinical and public health research to improve the quality of healthcare | PhD studentships, fellowships, strategic awards, investigator awards |
| **Medical Research Council** | Dedicated to improving human health. By supporting research across the entire spectrum of medical sciences | Studentships, fellowships, partnership grants, programme grants, biomedical catalyst grants, new investigator research grants |
| **Biological and Biotechnology Science Research Council** | Investing in world-class bioscience research and training on behalf of the UK public | Studentships, fellowships, new investigators, strategic awards, industry partnerships, international collaboration grants |

| Research Organisation | Focus | Relevant grants |
|---|---|---|
| National Institute of Health Research | Commissions and funds research focusing on improving outcomes for health and social care | Programme grants |
| European Research Council | Encourages high quality research in Europe through competitive funding | Starting grants, consolidator grants, advanced grants, synergy grants, proof of concept grants |
| European Foundation for the Study of Diabetes | Since its inception, EFSD has committed €88 million to diabetes research in Europe by various funding means. In the last five years, the Foundation has become a significant European funding agency for diabetes research, and is continually striving to enhance awareness in Europe of the severity and magnitude of this devastating disease | Programme grants |
| Diabetes Research and Wellness Foundation | Research programme is designed to support bright young researchers, as well as established institutions, as they strive to make the kind of life-changing break-through our members and supporters are hoping for | Research projects, pilot studies, exchange fellowships |

# Resources for type 1 diabetes researchers

The **Diabetes Research Network (DRN)** intends to provide a world-class health service infrastructure to support clinical research in diabetes. It is a network of primary and secondary care centres throughout the UK supported by the Department of Health for the purpose of conducting high quality clinical research in both the commercial and academic sectors.

**ADDRESS-2** is a database of people who have been newly diagnosed with type 1 and their siblings, that have consented to be approached to take part in research studies.

Both JDRF and Diabetes UK have structures in place to help researchers recruit people with type 1 diabetes to take part in clinical research

## JDRF supported research resources

**Samples for biomarker studies**

**Human Pancreatic Islets for Basic Science Studies**

**The Pancreatic ß-Cell Functional Differentiation Analysis Laboratory**
This Core laboratory at the University of Chicago provides a service to evaluate the function of candidate surrogate ß-cells (obtained from alternative sources including stem cells) and isolated human islets that may or may not have undergone various treatments.

**T1D-Base**
Network for Pancreatic Organ Donors with Diabetes (nPOD)
http://www.jdrfnpod.org/

*This list will be updated periodically, if you would like any resources to be included email info@jdrf.org.uk

# Participants in the type 1 research round-table discussions

## Autoimmunity

**Professor David Leslie** (chair)

Professor Christian Boitard
Dr Claire Bradford
Ms Mary Dang
Professor Colin Dayan
Professor Steve Gough
Dr Chiara Guglielmi
Professor David van Heel
Professor Mikael Knip
Professor Ake Lernmark
Dr Fun Liu
Professor Chantal Mathieu
Professor Mark Peakman
Professor John Todd
Dr Tom Van Belle
Dr Frank Waldron-Lynch
Dr Tim Tree
Dr Jennie Yang

## Beta cell renewal

**Professor Adrian Bone** (chair)

Dr Yasser Abdel-Wahab
Mr Diego Balboa
Dr James Bowe
Dr Mariya Chhatriwala
Mr Scott Clarke
Dr Miriam Cnop
Professor Peter Flatt
Dr Fiona Gribble
Dr Terry Herbert
Professor Peter Jones
Professor Thomas Mandrup-Poulson
Professor Piero Marchetti
Dr Wendy Macfarlane
Professor Noel Morgan
Professor Timo Otonkoski
Dr Dan Ploug Christensen
Dr Frank Reimann
Dr Sarah Richardson
Professor Patrik Rorsman
Professor Jim Shaw
Dr Paul Squires
Dr Ludovic Vallier
Dr Olatz Villate
Mr Michael White

## Complications of diabetes

**Professor David Matthews** (chair)

Professor Rudy Bilous
Professor Helen Colhoun
Dr Gemma Currie
Professor Michaela Diamant
Professor Tim Frayling
Professor Luigi Gnudi
Dr Janaka Karalliedde
Dr Helen Looker
Professor Sally Marshall
Dr Reinhold Medina
Professor John Petrie
Professor Angela Shore
Professor Alan Stitt
Dr Mitra Tavakoli

## Glucose sensing

**Professor Thomas Pieber** (chair)

Professor Carine de Beaufort
Dr Pratik Choudhary
Professor Thomas Danne
Dr Ahmed El-Laboudi
Dr Roman Hovorka
Dr Markus Laimer
Dr Lalantha Leelarathna
Dr Andreas Melmer
Dr Helen Murphy
Dr Revital Nimri
Dr Nick Oliver
Professor John Pickup
Dr Ulrike Schierloh

## Hypoglycaemia and impaired awareness

**Professor Brian Frier** (chair)

Professor Stephanie Amiel
Dr Craig Beall
Dr Pratik Choudhary
Dr Mark Evans
Dr Bastiaan de Galan
Dr Peter Lommer Kristensen
Dr Sankalpa Neupane
Dr Ulrik Pedersen-Bjergaard
Professor Thomas Pieber
Dr Bas Schouwenberg

## Structured education

**Professor Simon Heller** (co-chair)
**Dr Sheridan Waldron** (co-chair)

Dr Kath Barnard
Ms Kay Bottrell
Professor Helen Cooper
Ms Carole Gelder
Dr David Hopkins
Ms Isobel Howarth
Dr Nicky Kime
Ms Julie Knowles
Dr Rebecca Lewin
Professor Jane Noyes
Dr Kath Price
Dr Heike Sassman
Ms Liz Webster
Ms Kate Wilson


## Special thanks to

**Dr Eleanor Kennedy** – Project manager

**Cathy Jamieson MP** for hosting the Parliamentary launch event

**Peter Meeus**, Managing Director, Novo Nordisk for supporting the project and launch event

**Amanda Simonds**, Strategic Alliances Manager, Novo Nordisk for supporting the project and launch event

**ING**
for hosting the research roundtable meetings

**Macquarie**
for hosting the research roundtable meetings

**Slaughter and May**
for hosting the research roundtable meetings

**This JDRF Type 1 Diabetes Research Roadmap report has been supported by Novo Nordisk**

Novo Nordisk has had no editorial input into the content of the report

**With individual gifts from JDRF Patrons James and Margaret Cripps Jonathan and Hélène Haw**

JDRF gratefully acknowledges; Rob Saunders as editorial consultant; Ada Jusic, Isolde Godfrey, Sine Skovsen and CreativeConnections for the visual minute illustrations in this report.

19 Angel Gate, City Road, London EC1V 2PT
T: 020 7713 2030 F: 020 7713 2031
E: info@jdrf.org.uk W: jdrf.org.uk



**This JDRF Type 1 Diabetes Research Roadmap report has been supported by Novo Nordisk**

Novo Nordisk has had no editorial input into the content of the report

**With individual gifts from JDRF Patrons**
**James and Margaret Cripps**
**Jonathan and Hélène Haw**